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Editorial

Importance of COVID-19 Vaccine Among HIV Patients

Mohsin Masud Jan

Editor

WHO analysis reveals that HIV is a significant independent risk factor for severe COVID-19 illness at hospitalization and in-hospital death.

International AIDS Society (IAS) – calls upon all countries for people living with HIV to be included in priority populations for COVID-19 vaccine rollout. The studies highlighting new evidence on HIV and TB drug resistance updates on acceptability of HIV prevention tools and increased risk faced by women and girls under COVID-19 lockdowns.

The IAS featured five studies preview scientific highlights, showing important progress in HIV prevention, treatment and cure efforts despite major disruption to HIV programmes and research during the COVID-19 pandemic.

WHO study underscores the importance of countries including all people living with HIV in the list of priority populations for national COVID-19 vaccine programmes.

The global community must also do more to bring COVID-19 vaccines to countries around the world with high prevalence of HIV and other diseases. It is unacceptable that as of today, less than 3% of the entire African continent has received a single dose of the vaccine and less than 1.5% have received both doses.

The previous evidence regarding the impact of HIV infection on the severity and mortality of COVID-19 has been limited and sometimes conflicting, and most analyses have been based on relatively small cohorts of individuals in specific settings. In this report, WHO researchers analysed clinical data submitted to the WHO Global Clinical Platform for COVID-19 from 24 countries on more than 15,500 people living with HIV who were hospitalized for COVID-19.

A study highlights improved strategy to treat highly drug-resistant TB. The positive results from ZeNix, a Phase 3 trial seeking to improve a key treatment strategy for highly drug-resistant TB, could lead to changes in TB treatment guidelines and have real benefits for people living with TB. The study enrolled 181 people with highly drug-resistant TB in South Africa, Russia, Georgia and Moldova. A high relapse-free cure rate was observed in all study arms.

We will mark 100 years since the BCG vaccine for tuberculosis was first administered. This vaccine has saved many lives – but unfortunately, it has very limited effectiveness and it is still the only TB vaccine we have," IAS 2021 Local Co-Chair Hendrik Streeck, director of the Institute of Virology and Professor of HIV Research at the University of Bonn in Germany, said.

This anniversary is a reminder of the urgent need for improved prevention and treatment options, including for highly drug-resistant TB.

The study from the Global Evaluation of Microbicide Sensitivity (GEMS) project found high rates of drug resistance in individuals who were diagnosed with HIV while participating in HIV pre-exposure prophylaxis (PreEP) rollout programmes. The project implemented drug resistance monitoring for PreEP users who were diagnosed with HIV.

Drug resistance in PreEP breakthrough infections could threaten treatment effectiveness, contribute to spread of resistance and undermine efforts to prevent HIV," Prof Streeck said.

These findings reinforce the need for PreEP rollout programmes to check acute infections before starting people on PreEP and to conduct ongoing HIV drug resistance monitoring.

Another study observed promising adherence to oral PreEP and the dapivirine vaginal ring among adolescent girls and young women in Africa. The study assessed safety, adherence and acceptability of both products among adolescent girls and young women.

Acceptability varied, with about 88% liking the ring and about 64% liking oral PreEP. Only one HIV acquisition was reported among study participants. Both products were well tolerated and highly acceptable. "Adolescent girls and young women account for most of the new HIV infections in sub-Saharan Africa. These findings should accelerate efforts to make these two prevention options available to all those who can benefit," Prof Kamarulzaman said.

A study also observed sexual violence and HIV exposure during COVID-19 lockdown. The research team concluded that investment in unhindered, flexible and adaptable gender-based violence mitigation is important during pandemics.

"There has been a lot of concern about the potential for COVID-19 lockdowns to fuel what UN women have called the 'shadow pandemic' of increased gender-based violence and unintended pregnancy. This study confirms that the HIV risk is also a major concern that should be taken into account when designing pandemic response plans.

Original Article

UTI in Diabetic Males

Frequency of Urinary Tract Infection in Diabetic Males

Muhammad Abas Khan

ABSTRACT

Objective: To find out the frequency of urinary tract infection in diabetic males.
Study Design: Cross sectional study
Place and Duration of Study: This study was conducted at the Lady Reading Hospital Peshawar Medical A ward from December 2020 to May 2021.
Materials and Methods: 150 patients were involved in study. These patients had type one and type two Diabetes mellitus and they did not take medicines for any illness. on microscopic examination of urine those patients who had >5 pus cells per high power field (phf) were selected and their mid stream urine (MSU) sample was than referred for culture and sensitivity. The culture results urine samples having colony forming units equal to 10^5/ml of urine were considered as positive.
Results: 150 male diabetic patients comprising of (120 type 2 DM & 30 type1 DM) were included in study. Leukocyturia >5/hpf was found in 58/150 (38.66%) cases.in these 58 cases, cultures of urine whose results were positive was noted only in 36 (62.1%) patients. It was noted that frequency of urinary tract infection was 24% and the Ecoli was most common bacterium noted in 18 cultures of urine.In patients having type 2 diabetes mellitus, it was noted that Leukocyturia >5/hpf was present in 47/130 (43%) cases and in 29/47(61.7%) patients culture of urine was noted positive. Patients, Leukocyturia >5/hpf was present in 11/30 (36.66%) and positive urine culture was found in 7/11 (63.64%) cases in type 1DM
Conclusion: It was found that in both Type 1 and type 2 diabetes mellitus urinary tract infection occurs commonly.

Key Words: Diabetes mellitus type 1, Diabetes mellitus type 2, urinary tract infection, culture and sensitivity, male.

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INTRODUCTION

There is increased risk for urinary tract infection in both type 1and types 2 DM [1]. in diabetic females Urinary Tract Infection (UTI) occur more commonly but males have increased risk of uti because of local and host risk factors. The main causative organism accounting for 85% of cases of UTI are enteric gram negative bacteria[2-4]. Less common bacteria are streptococci, enterobacteria, klebsiella,, and staphylococcus saprophyticus[5].The fungal infection is most frequently caused by candida. Viruses can also cause uti[6,7]. Urine can be inhibitory or even bactericidal against minute inoculi of uropathogens in some situation[8].In Diabetes mellitus change in chemical composition of urine can change the ability of urine and promote the growth of microorganisms.

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Experimental studies in animals showed that glycosuria can cause E coli infection[9].In diabetes mellitis autonomic neuropathy impairs emptying of bladder causing UTI[10]. We conducted this study to find the frequency of urinary tract infection (UTI) in diabetic males.

In men Urinary tract infections are not very common because the length of the male urethra is long, less periurethral colonization in men and as the prostatic fluid is antibacterial. In males whose age is less than 50 years the incidence is 5 to 8 per 10,000 in an year. The lifetime prevalence of UTI is reckoned to be 13,000 to 14,000 per 100,000 male population and there is increase in frequency of urinary tract infection in males as the age increases[11]. Although in women majority of urinary tract infections can be treated with antibiotics empirically without urine culture, but when men present with urinary tract infection a urine culture should always be obtained. UTIs in Diabetic patients are multifactorial in origin. There is increased risk for infection with greater severity or longer duration of the disease[12].The symptom which is most common for Urinary tract infections is dysuria in both women and men[11,13,14].Bacteria which are gram-negative live in colon also start colonizing the skin in periurethra are the main reason for UTI. The bacterium found mostly commonly in urinary tract infections in both males and females is E coli. Conditions such as Diabetes mellitus

and human immunodeficiency virus that suppress immune function also predispose men to recurrent urinary tract infection. The location of the infective process in the urinary tract may give a hint to the background etiology. For example pyelonephritis occurs due to obstruction in urinary tract due to a stone or a tumor. In contrary to this, lower urinary tract infections (e.g. urethritis, cystitis) occur due to infection due sexually transmitting diseases. The bacteria in the urinary tract infection give idea into the underlying predisposing condition e.g. Esheriecha coli, Proteus mirabilis, Pseudomonas aeruginosa and Klebsiella pneumoniae are mostly noted in individuals having anatomic obstruction[15-17].In one of the study it was noticed that nearly 24% individuals having stone had urease-splitting bacteria[18].Contrary to this Neisseria gonorrhoeae, Ureaplasma urealyticum, or Trichomonas vaginalis and Chlamydia trachomatis are sexually transmitted[15-17]. Infection with Candida (e.g. yeast) shows immunosuppression such as diabetes or corticosteroid use[15-17]. High number of resistant bacteria occur in patients with catheterization e.g. Pseudomonas species.[19]

In male patients UTI needs a urologic assessment as an underlying cause is expected to be established[14,21]. In men symptoms like dysuria, frequency and urgency are having a positive predictive value of 75% for a urinary tract infection[11,13]. Although flank pain is suggestive of pyelonephritis, pain in suprapubic suggests a diagnosis of cystitis. In Diabetic patients there is a high incidence of UTI than in non-diabetics leading to complications like dysuria, organ damage and can lead to death due to complicated UTI (e.g. pyelonephritis)[22].

Evaluation include urinalysis alongside microscopy on a clean-catch, midstream urine sample. Positive Gram staining is 80% specific and 90% sensitive for an infection.[1] But a negative urine Gram staining report, especially on unspun urine, will not exclude a urinary tract infection. An uncentrifuged urine has a specificity and sensitivity 90% and 94%, respectively, when 100,000 colony-forming units (CFUs) per milliliter have been separated.[23] The gradation of pyuria has a sensitivity of 85% to 90% if more than 10 white blood cells per milliliter are existing on urine analysis. Dipstick testing has high specificity but very low sensitivity for the diagnosing infection. The standard gauge for diagnosing infection is a culture and sensitivity of urine. The precise count of bacteria needed for diagnosing a urinary tract infection in is debatable in men. Some advice treating any man with bacteriuria irrespective of the count, others give recommendation for treating for number higher than 10,000 CFUs. Men with history of recurrent urinary tract infection, suitable assessment via imaging, urologic testing, analysis for immune-deficiency states (for example diabetes, deficiency of immunoglobulin, HIV infection, lymphoma) ought to be followed.

Decision for treating an individual ought to be established on the culture and sensitivity. For infections which are uncomplicated, the first-line agents are trimethoprim-sulfamethoxazole and fluoroquinolones. The treatment duration is usually 7 to 10 days.[12,14]

MATERIALS AND METHODS

This study was conducted on 150 male patients in Medical "A" Unit of lady Reading Hospital, Peshawar. Regarding duration of diabetes there were no specific criteria to find true frequency of uti in men. Microscopic examination of urine was done in the hospital laboratory. In order to quantify the number of leucocytes in urine sample glass slide microscopy was used whereas the numbers of pus cells were counted per high power field (hfp) in resuspended sediment of centrifuged urine. Patients who had higher than 5/hpf leukocyte in urine were carefully chosen for culture of urine. The collection of mid-stream urine samples (M.S.U) was done in culture bottles and then referred to lrh laboratory. Those culture reports who were having colony forming units more than 10^5/ml of voided urine were considered positive. The usual count of random blood sugar <200 mg was adopted as the standard for reasonable glycemia control.

Inclusion Criteria; Type 1 and type 2 Diabetes mellitus patients.

Exclusion Criteria; Numerous conditions that may prompt men to urinary tract infections for example blockade due to benign prostatic hyperplasia, stone formation, stricture due to trauma, tumor may cause stasis of urine with an increase in danger of infection were excluded. Instrumenting the urinary tract for a lot of aims (for example, assessment of voiding, catheterization and cystoscopy) is additional danger that can lead to UTI were excluded. Patients taking antibiotics were excluded.

RESULTS

Overall 150 patients were included in the study, in which 30 patients had Type 1 diabetes mellitus whereas 120 had Type 2 diabetes mellitus. Leucocyturia which was defined as more than 5/hpf occurred in 47 males (43%) having Type 2 diabetes mellitus and 11 males (36.6%) having Type 1 diabetes mellitus (Table I). Individuals having leucocyturia more than 5 per hpf were than choosed for culturing of urine. Forty seven patients having type 2 dabetes mellitus had leucocyturia more than 5 per hpf (Table 2). In these 47 patients, 29 (61.7%) had positive cultures for urine whereas 18(38.3%) cases were having no significant growth of any micro-organism. In a Similar way in 11 patients having Type 1 diabetes mellitus**,** 7(63.64**%**) had positive cultures for urine and 4 (36.36%)were having negative culture(Table II).Overall, 29/120 (24.16%) Type 2 diabetes mellitus patients, had UTI with positive cultures whereas 7/30(23.33 %) patients having Type 1

diabetes mellitus had UTI with positive cultures (Table 3). Overall 36(24%) patients had UTI, in which 29(80.55%) were having TYPE 2 diabetes mellitus and 7 (19.44%) had TYPE 1 Diabetes mellitus. The most common organism found from urine culture was Easchrica. coli (Table 4). Easchrica coli was found in 18 (69.6%) cultures of urine. Enterobacteria in 3(11.11%), Pseudomonas in 2 (7.41%) and Staphylococcus in 3 (11.11%) positive cultures and C.albicans noted in 1 (3.7%) cultures which were positive.

Table No.1: Microscopic Examination Outcomes in Diabetic Males

Urine microscopy	Type 2DM (n=120)	Type 1DM (n=30)
Leukocyturia >5/hpf n=58	47(43%)	11(36.66%)
Leukocyturia <or=5/hpf n=92	73(60.83%)	19(63.33%)

Table No.2: Result of urine cultures in diabetic males having pus cells >5 / hpf

Result of urine cultures	Type 2 DM n=47/120	Type 1DM n=11/30
Culture results positive	29(61.7%)	7(63.64%)
Culture results negative	18(38.3%)	4(36.36%)
Total	47	11

Table No.3: UTI frequency in diabetic males

Urinary tract infection UTI	Type 2 DM n=120	Type 1 DM n=30
Patients with UTI	29(24.16%)	7(23.33%)
Patients without UTI	18 (15%)	4(13.33%)
Total	47	11

Table No.4: Types of microorganisms isolated

Organism isolated	Type 2 DM	Type 1DM	Total
Pseudomonas	2	0	2(7.41%)
Staphlyococcus	2	1	3(11.11%)
C.albicans	0	1	1(3.7%)
E.coli	14	4	18(66.66%)
Enterobacter	3	0	3(11.11%)
Total	21	6	27

DISCUSSION

In our study which was done in 150 male diabetic patients, 120 had Type 2 diabetes mellitus while 30 patients had Type 1 Diabetes mellitus. Leucocyturia more than 5 pus cells/hpf was noted in 47/150(43%) of the Type 2 Diabetic patients. Cultures of urine were positive in 24.16% (n=29/120) Type 2 diabetic patients and nill growth seen in 15% (N=18/120) of patients with Type 2 Diabetes mellitus. In 30 patients having Type 1 diabetes mellitus, leucocyturia more than 5 per high power field occured in 36.66% (n=11/30) patients and cultures for urine were positive having significant bacteriuria in 23.33% (n=7/30) of patients. Our study can be matched with the Sewify M, et al[24] study including a total of 722 patients including both males and females. Which have shown frequency of leukocyturia as 35%.Patients having UTI were 7.5 times more expected to be having leukocyturia, whereas a leukocyte count <5cells/hpf has anticipated the nonexistence of urinary tract infection in 96% of the females[24]. Similarly this study showed a relationship between leucocyturia >5 cells/high power field and positive culture results. In our study whole number of patients who had UTI were 24 (24%).So our study is comparable with the study of Patel JC[25] which was a prospective study of 14 years in 8793 hospitalized cases. He notified acute and chronic UTI in 31.4% of diabetic patients. These minute variations in results are because of a lot of factors. Our study was done on lesser number of patients; culture was not done on urine of all patients hence the precise number of UTI were not sensed. In a different study conducted by Brauner A et al host factors and virulence of bacteria was studied in 514 out-patients having DM and 405 controls who were non-diabetic. It was noted that the frequency of bacteriuria was not greater in women having diabetes (8/236, 3.4%). Whereas according to Brauner–A et al, the UTI frequency is almost equal in diabetic and non-diabetic women. In Brauner-A et al study, the standard for glycaemic control was HbA1C. In our study random blood sugar was used and it is not precisely depandable, but we did not perform HbA1C because of affordability.in EL-Kebbi IM et al[27] study it was noted that while blood glucose levels may not replace HbA1c findings, measuring fasting or random plasma glucose can be consumed to recognize improperly controlled type 2 DM patients with reasonable certainty in clinical enviroment. The most common bacteria found in our study was Escherica.coli. in 27 cultures which were positive, E.coli was isolated from 18 cultures with frequency of 66.66%.The additional bacteria isolated were staphylococcus aureus with a frequency of 3(11.11%) Enterobacteriaceae 3(11.11%), c.albicans 1(3.7%) and pseudomonas with frequencies of 2(7.41%).Our study is comparable with Ramrakhia S et al[26], which told frequency of 60% of Escherica.coli in cultures of urine in diabetic females. In Lye–WE et Al[28] study, a total of 287 diabetic patients (66 males) having nosocomial and community acquired UTI were considered. The commonest organism was E coli in community acquired urinary tract infection, but its incidence in diabetics was fewer as matched to non-

diabetic. Klebsiella species leading to community acquired urinary tract infection in diabetics was high as compared to non-diabetics. Our study showed that klebsiella was not found in culture of urine because our study group was trivial and culture of urine was done merely in 27 patients.

CONCLUSION

1. Urine culture should be advised and diabetic patients ought not to be started treatment for urinary tract infection merely on the base of Leucocytouria.
2. Urinary tract infection is commonly found in type 1 and type 2 diabetic patients.

Recommendations: Extensive studies are needed to study relation of glycemic control of diabetes mellitus with UTI.

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Author's Contribution:

Concept & Design of Study:	Muhammad Abas Khan
Drafting:	Muhammad Abas Khan
Data Analysis:	Muhammad Abas Khan
Revisiting Critically:	Muhammad Abas Khan
Final Approval of version:	Muhammad Abas Khan

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Original Article

Frequency and Association of Subclinical Thyroid Disorders with Poor Obstetric Outcome

Sumaira Yasmin and Farnaz Zahoor

ABSTRACT

Objective: To determine the frequency and association of subclinical thyroid disorders in patients with poor obstetric outcomes.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynecology, Lady Reading hospital Peshawar from August 2019 till July 2020.

Materials and Methods: Women of reproductive age with a bad obstetrical history during her visit in the outpatient department of the hospital were enrolled. Obstetrical details including previous miscarriages, stillbirths, neonatal deaths and congenital anomalies were recorded by interviewing the patient as per questionnaire. patients fulfilling the inclusion criteria were subjected to thyroid function tests. Data was analyzed on SPSS version 18.

Results: Out of the 549 women presenting with a poor obstetric outcome, 103women were recruited for the study. subclinical thyroid disorders were found to be 24.27%, with subclinical hypothyroidism more prevalent (21.35 %) in patients with poor obstetric outcome. significant weak positive correlation was reported between neonatal deaths and TSH levels (r= 0.200; p= 0.043).

Conclusion: Subclinical thyroid dysfunction is more prevalent in patients with poor obstetric outcome. various adverse fetal and neonatal outcomes are expected to be encountered in patients with subclinical thyroid dysfunction.

Key Words: Subclinical hypothyroidism, thyroid stimulating hormone, miscarriage, stillbirth

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INTRODUCTION

Thyroid hormones have an important role in neurophysiologic development of the fetus. Subclinical thyroid dysfunction implicates an abnormal serum thyroid-stimulating hormone level (normal TSH reference range: 0.45 to 4.5 μU per mL) in clinically asymptomatic patient. Serum TSH 0.1-0.45 mIU/L will denote subclinical hyperthyroidism and serum TSH 4.5-10.0 mIU/L will demarcate as subclinical hypothyroidism. Some studies recommend against routine treatment of patients and free thyroxine(T4) and triiodothyronine(T3) levels within their normal ranges[1]. thyroid disease represents the second most recurrent endocrine condition that might affect females in the reproductive age[2].

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The risk of hypertension, miscarriages, fetal growth restriction, abruption and preterm births has been increased if thyroid disorder is not treated in pregnancy[3].In order to reduce these risks, Screening has to be performed during the first trimester of pregnancy. It has been recommended by American Association of Endocrinologist, but European and American Thyroid Association experts do not recommend the universal screening of all pregnant population, though testing in case of high risk is suggested[4]. Females with the history of stillbirth, neonatal death, three or more abortions are considered as poor obstetrical history[5]. The causes of poor obstetric outcome are varied including diabetes, hypertension anaemias, uterine factors, cervical incompetence, prelabour ruptured membranes, antepartum hemorrhage or intrapartum adverse incidents. Some studies revealed an association of these poor obstetric events with subclinical hypothyroidism or thyroid autoimmunity[6]. Others have reported a relationship with a higher rate of stillbirth in the second trimester of pregnancy with subclinical hypothyroidism[7].

The present study is, therefore, being conducted to assess the frequency and association of subclinical thyroid dysfunction with obstetric outcomes in women of reproductive age group and to evaluate patients with poor obstetrics outcome for any underlying subclinical thyroid dysfunction.

MATERIALS AND METHODS

This cross sectional study was done at the department of obstetrics and gynecology, Lady Reading hospital Peshawar over one year from August 2019 till July 2020.

Patients were selected by non-probability convenient sampling after taking ethical approval from the institutional review board of the hospital. Women of reproductive age who had a previous history of poor obstetric outcome were included in the study. Patients with any underlying comorbidities such as diabetes, hypertension which per se would increase likelihood of increased fetal and perinatal mortality and in turn lead to poor obstetric outcome were excluded from the study. clinically proven thyroid disorders, previous history of thyroid surgery was also excluded from the study.

After informed consent detailed history was taken regarding maternal age, parity, previous miscarriage, still births and early neonatal deaths etc., as per attached questionnaire. Blood samples were then taken for thyroid hormones i.e. thyroxin(T4) and thyroid stimulating hormone (TSH) levels on their visit in the outpatient department. Patients were also inquired about personal and family history of thyroid disease; those patients who come up with deranged TFTS (thyroid function tests were thus retrospectively diagnosed to be have subclinical thyroid dysfunction which led to a poor obstetric outcome.

Data analysis: The collected data was entered into SPSS version 18.0 and analyzed. Descriptive statistics were presented as frequency and percentages and were calculated for qualitative variables. Pearson correlation was applied to assess the association. P-values less than 0.05 were considered as a level of significance.

RESULTS

Out of the 549 women presenting with a poor obstetric outcome, 446 women had known risk factors for their poor obstetric outcome. These patients were thus excluded. Rest of103 without any identifiable cause for their bad obstetric history were enrolled for the study. The mean age was noted to be 28.94±4.07years. Mean parity was 3.47±1.70 in which 7(6.8%) were nulliparous (although they had recurrent miscarriages) whereas 96 (93.2%) were multiparous women, (as shown in Table-1).

48(46.6%) had 2 miscarriages. 38 (36.9%) of them had previous 1 still birth. 10 (9.7%) women had a history of abnormal babies, 6 (5.82%) had babies with cerebral palsy (CP), 2(1.94%) women had 2(1.94%) growth retarded child births, whereas 2 (1.94%%) had congenitally abnormal baby with one having skeletal dysplasia and other having polydactyly. 27 (26.2%) had previous 1 neonatal death.

78(75.5%) patients had normal thyroid function tests. Frequency of subclinical thyroid disorders was found to be 24.27% out of which subclinical hypothyroidism was found in 22 (21.35 %) who have normal T4 levels but elevated TSH, whereas subclinical hyperthyroidism in 3 (2.9%) patients with poor obstetric outcome. (As shown in Table-2)

Table No.1: Maternal demographic characteristics and variables of poor obstetric outcome

Variable	Mean±SD
Age (years)	28.94±4.07
Parity	3.47±1.70
Miscarriages	2.37±1.2051
Stillbirths	0.65±0.73
Neonatal Deaths	0.32±0.52

Table No.2: Adverse fetal outcomes of maternal thyroid dysfunction.

Variables of poor obstetric outcome		Number of patients	%tage
Previous Miscarriages	1 miscarriage	10	9.7
	2 miscarriage	48	46.6
	3 miscarriage	26	25.2
	4 miscarriage	7	6.8
	5 miscarriage	3	2.9
	6 miscarriage	3	2.9
	No miscarriage	6	5.8
Previous Still Births	1 Still Birth	38	36.9
	2 Still Births	13	12.6
	3 Still Births	1	1.0
	No Still Births	51	49.5
Abnormal Babies	No abnormality	93	90.29
	Cerebral Palsy.	6	5.82
	Growth Restriction	2	1.94
	Congenital anomaly	2	1.94
Previous Neonatal Deaths	1 Neonatal Death	27	26.2
	2 Neonatal Deaths	3	2.9
	Nil	73	70.9

Table No.3: Correlation of demographic variables and obstetric outcomes with TSH levels.

Variable	TSH Levels	
	P	p-value
Age (years)	-.057	0.564
Parity	0.058	0.559
Miscarriages	0.016	0.874
Still Births	0.037	0.713
Neonatal Deaths	0.200	0.043

An insignificant correlation for TSH levels was reported with age (r= -0.057; p=0.564), an insignificant correlation was reported with parity (r=0.058; p=0.559), with miscarriages (r= 0.016; p=0.874), with stillbirths (r= 0.037; p= 0.713) whereas a significant weak

positive correlation was reported between neonatal deaths and TSH levels (r= 0.200; p= 0.043), as shown in Table 3.

Table No.4: - TSH Levels of patients presenting with poor obstetric outcome

TSH Levels	Number of patients =N	Percentage (%)
Reduced(hyperthyroid)	3	2.9
Normal (euthyroid)	78	75.7
Increased(hypothyroid)	22	21.4
MeanTSH Values	3.34±2.26	

DISCUSSION

Thyroid dysfunction is the second most common recurrent endocrine disorder faced by 2 to 3% of women during pregnancy[8]. Adverse or poor obstetrics outcome as detected in overt hypothyroidism may also be encountered in subclinical hypothyroidism. Our study showed prevalence of subclinical hypothyroidism in patients with poor obstetric outcome to be 21.4% whereas subclinical hyperthyroidism was observed in 2.9% cases which shows a relatively higher percentage of subclinical hypothyroidism in patients with poor obstetric outcome. Subclinical thyroid dysfunction in females in reproductive age group fluctuates from 2%-10%[9,10]. A study conducted in Jordan showed 3% pregnant women to have hypothyroidism during pregnancy[11]. A much higher prevalence of subclinical hypothyroidism 65.2%in pregnant women with a bad obstetrical history was revealed by a study[12].The reason could be the iodine deficiency in the population which is unmasked and potentiated in a physiologically hyperactive thyroid gland in pregnancy.

The effects of Subclinical (SC) thyroid dysfunction on poor obstetrics outcome have still not been clearly known. Certain studies[13] reported that SC Hypothyroidism did not lead to any consistent adverse maternal and prenatal outcomes, while other showed that SC Hypothyroidism is associated with a number of obstetric complications, which include abruption of placenta, GDM, and IUGR[14]. Our results showed a weak positive significant correlation between TSH levels with neonatal deaths (r= 0.200; p=0.043) while insignificant association was observed in terms of miscarriages, parity and still births.

Women with hypothyroidism were more prone to miscarriages during their first trimester, which is comparable to the outcomes of earlier studies. Our study results were in agreement with the above mentioned studies and revealed that 48(46.6%) had 2 miscarriages during pregnancy whereas 26(25.2%) had 3 miscarriages but there was an insignificant association between miscarriages and TSH level (p=0.874).

A study by Su and colleagues[15] showed greater risks of deformities of circulatory system (11.1%) and musculoskeletal (4.7%) in fetuses of women with hypothyroidism. As far as our study is concerned, it is in compliance with the above mentioned studies in way that maternal thyroid disorder led to deliver abnormal babies as skeletal dysplasia and polydactyly were noted in 1.94%. Moreover, our results have shown Cerebral Palsy in 5.82% and growth retarded babies were reported in 1.9% cases of subclinical thyroid dysfunction

Study by Casey as mentioned earlier demonstrated that the rate of stillbirth was more among those women with SCH than women with euthyroid in the second trimester, but no statistically significant differences were seen. Though higher rate of stillbirth in women with hypothyroid with TSH levels 0.10mU/L has been earlier stated, SCH (described by much lesser amount of TSH levels) appears to have small impact on stillbirth[16].Our findings are in agreement with those reported in the literature and indicated that stillbirth rate was higher in women hypothyroidism 38(36.9%) but there was an insignificant correlation observed between stillbirth and TSH levels. (r= 0.037; p= 0. 713. Therefore, thyroid screening in women with poor obstetric outcome may be useful to predict its prior incidence. Further, timely management of subclinical thyroid dysfunction might reduce the morbidity and mortality related to poor obstetric outcome.

CONCLUSION

Various adverse fetal outcomes can be correlated with subclinical thyroid dysfunction in patients with poor obstetrical history. Subclinical hypothyroidism in reproductive age group may increase the risks of miscarriages and neonatal deaths.

Recommendations: Routine screening of women with poor obstetric outcome is essential to rule out subclinical thyroid dysfunction to improve fetal and perinatal outcome.

Author's Contribution:

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Original Article

Frequency of C Shaped Canals in Permanent Mandibular 2nd Molar in Pakistani Population

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ABSTRACT

Objective: Evaluation of C-shaped canal frequency and its types in permanent mandibular 2nd molars in patients presenting with irreversible pulpitis.

Study Design: Cross Sectional study

Place and Duration of Study: This study was conducted at the Operative Dentistry department, Punjab Dental hospital, Lahore from January, 2019 to July, 2019 for a period of six months.

Materials and Methods: 100 patients were examined suffering from irreversible pulpitis, C-shaped canals and its types were assessed using Min's classification system by using Dental loupes with 3.5 magnification and recorded information. SPSS Version 20 used for entering/analyzing data.

Results: In the 100 individuals, 42% were males and 58% females. 19% according to Min's classification had a C-shaped canal in mandibular second molar. Of these, 21% had type-1 (a peninsula), 47.4% had type II (a buccal), and 31.6% had type III (only one mesial) C-shaped canal. The major number was among 16-25 years, 08 (42.1%) but statistically insignificant differences was observed (p-value = 0.138). Similarly, maximum no of C-shaped canal was found among females, 11 (57.9%) but statistically insignificant difference was observed (p-value = 0.992).

Conclusion: There are a significant percentage of C-shaped canals among 2nd molars mandibular in Pakistani people. Thus treating dentists need to know C-shaped root canal systems their presence as well as configuration so that endodontic treatment success rate increases.

Key Words: C-shaped canal, Mandibular permanent 2nd molar, Irreversible pulpitis

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INTRODUCTION

The variability among mandibular molars is related to their shape as compared to other teeth and these teeth have complex internal anatomy[1,2]. C shaped canal is one such variation occurring in 2nd molar mandibular which is not only easily neglected, it is also difficult to prepare and obturate which is required for optimal endodontic treatment.[3,4] In a study, it has been further noted that age, gender or tooth position has no effect on prevalence of C shaped canals. If C shaped canals exists bilaterally then they will be symmetrical up to 81% of the cases.[5]

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They can be with simple C shape with no separation or division or they can resemble a semicolon resulting in discontinuation of C shaped outline or at times in two canals or three canals types or lastly as one round canal variation.[6]

The occurrence of these forms of root morphologies reaches up to 41.27% percentage in Asian population which is very high and are challenge in dental practice only a thorough knowledge of C shaped canals morphologies will enable a dental practitioner to treat these variations properly.[7] Cleaning of C shaped canals after identifying them is essential for endodontic treatments success.[3,6] Four types were classified by Min et al regarding orifice and pulp floor based on the pulp, chamber floor shape and the dentin fusion location.[7]

The frequency of C shaped mandibular 2nd molar is between according to Mandana Naseri et al 6.96% and up to 41.27% in accordance to Yan Wang et al in populations across the world.[3,8] Yan Wang et al found mandibular 2nd molar C shaped canals were 41.27% in Chinese population. Cases on the basis of clinical examination showed C-shaped canal as 22.94% were C1; 48.11% were C2; whereas 15.59% had C3a; 13.36% showed C3b.[1] The C-shaped root canal among mandibular 2nd molar showed prevalence that ranged from 2.7% - 44.5%.[9]

Various studies showed that gender based differences was not found regarding its distribution and in addition maxillary 2nd deciduous molars showed this root canal system.[10-12] While, permanent teeth had been reported predominantly incurring this condition. Developed countries individuals like Americans and Europeans had relatively lower numbers of these systems as compared to developing countries such as Asians.[13] All types of the tooth could have this condition especially the 02 unusual features in their structure. Three types of these C-shaped canals had been reported in a study.[14] The higher incidence of these canals was reported using combination of various methods such as if used examination using microscope there was 41.27% occurrence seen, using clinical examination alone showed 39.18% while radiography reported 34.64%[15-17]. The crown morphology of teeth with C-shaped anatomy does not present with any special features that can aid in the diagnosis. A longitudinal groove on lingual or buccal surface of the root with a C-shaped anatomy may be present.[18] Such narrow grooves may predispose the tooth to localized periodontal disease, which may be the first diagnostic indication. [19-20]

Data regarding frequency of C shaped canals in mandibular 2nd molar among Pakistani population is scarce and in order to help local dental practitioners and endodontists for understanding how often they would come across these canals during root canal treatment to the patients. So, this study was planned to know the C-shaped canal frequency among irreversible pulpitis patients of Punjab dental hospital, Lahore**.**

MATERIALS AND METHODS

All patients with irreversible pulpitis were assessed for C-shaped canal presence during specified time period (30-01-2019 to 30-07-2019) at Punjab dental hospital, Lahore. 100 patients were examined to confirm the irreversible pulpitis presence, then C-shaped canals were assessed and also types of these canals on the basis of Min's classification system by using Dental loupes with 3.5x magnification and information was recorded on predesigned questionnaire. The data was reviewed and entered on questionnaire was analyzed using SPSS Version 20.0. Frequency along with percentages was calculated for categorical variables and Mean±SD was calculated for quantitative variables. Chi square test was used for association between socio-demographic and certain factors. Statistically significance was set as p-value ≤ 0.05.

RESULTS

Among all patients requiring endodontic treatment for permanent 2nd mandibular molars presenting with irreversible pulpitis, 100 patients were selected and enrolled for this study. Among these 42(42.0%) were males and remaining 58(58.0%) were females, age ranged from 16 - 45 years. The mean age of the patients was 32.78 ± 9.25 years. In the 100 individuals, 19 (19.0%) people according to Min's classification had a C-shaped canal in 2nd molar in mandibular region. Among these, 04 (21%, n= 19), had type-1 (a peninsula), 09 (47.4%, n=19) had type II (a buccal), 06 (31.6%, n=19) had type III (only one mesial) C-shaped canal and no one had type IV C-shaped canal.

Table No.1: Frequency distribution of characteristics and C-shaped canal system among patients

Variables		Frequency	%age
C-Shaped Canal	Yes	19	19
	No	81	81
C-Shaped Type (n=19)	type-1(A peninsula)	04	21
	type-2(A buccal)	09	47.4
	type-3(Only one mesial)	06	31.6
Gender	Males	42	42
	Females	58	58
Age (Years) 32.78 ± 9.25*	16-25	25	25
	26-35	28	28
	36-45	47	46
Total		100	100

*Mean±SD

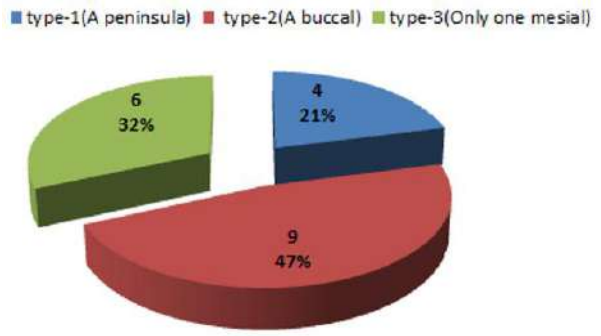

Figure No.1: C-Shaped Canal Type among Patients

There were 32% patients with C-shaped canal system that were having age 16-25 years, 17.8% were having age 26 to 35 years and 13% had age 36-45 years (p-value = 0.138). Regarding gender, there were 19% male patients with c-shaped canal system as compared to 18.9% female patients suffering from the disease (p-value = 0.992) as shown in table no: 2.

Table No.2: Age and Gender association with C-shaped canal system

Variable		C-Shaped Canal System		p-Value
		Yes (%)	No (%)	
Age (Years)	16-25	08 (32%)	17 (68%)	0.138
	26-35	05 (17.8%)	23 (82.2%)	
	36-45	06 (13%)	41 (87%)	
Gender	Males	08 (19%)	34 (81%)	0.992
	Females	11 (18.9%)	11 (81.1%)	
Total		19 (19%)	81 (81%)	

DISCUSSION

During endodontic treatment, C-shaped canal poses difficult situations while performing the procedure.[21] The individual canals are connected via isthmus characterized by the anatomical variants of the root systems. Asians are mostly affected by these morphological types especially in region of 2nd molar mandibular. So, dentists must be known about the importance of this complex system.[22] The incidence is affected by the ethnic origin of the individuals, Asians showed highest rate up to 44.5% as compared to other regions.[22]

Yin et al results demonstrated that among Chinese population enrolled in their study, 32% had condition of such root system (i.e. the radiograph cross sectional looked alike the 'C' letter), although of these, the actual problem was present among 14% of the respondents. [23] Whereas, in another Chinese study done in 2011 by Zheng O et al, the prevalence of such condition was 39% in the respondents. The differences seen might be attributed to operational definition of the studies, sampling sources, study methodology and anatomy of 2nd molar mandibular.[6] However, in the present study, 19% of the Pakistani population was affected. The difference from the other studies was attributed to geographical location of the in particular Pakistan and in general the South East Asia.

A study described classification for the C-shaped roots that was used to check its frequency in our population.[7] In our study out of 19 patients with C-shaped canal; type-I (a peninsula) was found in 4(21.1%) patients, type II (a buccal) was in 9(47.4%) and type-III was observed in 6(31.5%) mandibular permanent 2nd molar. In a recently published study from Pakistan showed that single-rooted (18%), double-rooted (80%) and three roots were present only in 2% of the respondents. The canal types seen were category I and II (3 each) while category III (07) individuals out of 100.[24] A study also reported that category III systems occurred most frequently, which is not in agreement with our study.[24]

In our study C-shaped canal of the second molar was more common among females than males but statistically insignificant differences were observed between C-shaped canal and its types with respect to age and gender. In the literature, it is stated that among Asians, the Korean population showed highest prevalence ranging from 31-45 percent.[25] The study results demonstrated that females had two times more single root canal than males thus describing gender as an important factor for evaluation for non-surgical randomized control trials.[25] The contrary results from our study showed that almost 70% individuals had C-shaped canal found in opposite tooth if it is previously present on one side. Recent study done on Korean population demonstrated that C-shaped canals were present in 74.4% on both sides.[26]

The morphology of tooth specifically regarding pulp determines the variation in canal system and thus accessing obturation and cavity for the teeth.[26] The techniques used might be needed to modify them such as distal and mesial spaces could be prepared as well as obturate being standardized canals; but if only lateral condensation is used the difficulty lies in sealing of lingual or buccal isthmus; therefore, certain other procedures like plasticized gutta-percha is recommended.[27]

CONCLUSION

The conclusion drawn from this study showed that significant percentage of C-shaped canals occurs in permanent mandibular 2nd molars in Pakistani people, therefore treating dentists need to know C-shaped root canal systems their presence as well as configuration so that they can first identify and perform endodontic treatment properly in these challenging cases.

Author's Contribution:

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Original Article

Technology Addiction and Phubbing Behaviour in the Generation Z of Pakistan

Impact Of Internet Addiction And Smartphone

Ruqia Safdar Bajwa[1,2], Haslinda Binti Abdullah[1,3], Wan Munira Wan Jaafar[1] and Asnarulkhadi Abu Samah[1,3]

ABSTRACT

Objective: To check the impact of internet addiction and smartphone addiction on phubbing behavior in Generation Z.

Study Design: Cross-sectional survey research study

Place and Duration of Study: This study was conducted online at University Putra Malaysia on the students of two public sector universities in Pakistan (Bahauddin Zakariya University, Multan and Islamia University, Bahawalpur) from June 2020 till August 2020.

Materials and Methods: Students from two public universities in Pakistan's Southern Punjab province were sampled with a multistage cluster sampling technique. Internet addiction, smartphone addiction, and phubbing behavior were measured with reliable and valid instruments, and IBM-SPSS-23 was used to analyze the data of 794 students. A Chi-square test of independence and linear regression were used to check statistical significance.

Results: Results from the Chi-square test of independence in the relation between technology use patterns and gender (47% males and 53% females) were significant ($p < .001$). The regression results show that model was fit $F(2,791) = 35.786$, $p < .001$, and internet and smartphone addiction predicted phubbing behavior significantly ($b = .072; .131$, $p < .001$).

Conclusion: Individuals differ significantly in technology use patterns according to gender. Internet addiction and smartphone addiction play a significant role in eliciting phubbing behavior.

Key Words: Internet Addiction, Smartphone Addiction, Phubbing, University Students, ICTs, and Behavioural Addictions, Generation Z.

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INTRODUCTION

"Humans," being social species, have always been inclined to be together, act together, and unite since the dawn of civilization. When two people experience the same situations and settings, they impact each other. In this condition, people born, grew up and lived in the same period share comparable traits. To characterize features of individuals, scientists applied the word "generation" and conducted studies on it[(1)].

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The Internet emerged in 1995, and Generation Z (Gen Z) was born around this period and is frequently named technology generation[(2, 3)].

Generation Z has been profoundly shaped by the advent of technology [(2)]. Youngsters of Gen Z have had more access to knowledge than any prior generation at their age; everything they need to know is just a few clicks away. Along with all the benefits, this huge accessibility to intent and smartphones brings technology addiction and negative consequences [(4, 5)].

Internet and smartphone addiction are a type of technological addiction that has become a major global social issue. Griffiths [(6)] operationalized technological addiction as a sort of non-chemical behavior addiction involving human-machine interaction. Internet addiction(IA) has the same impacts on behavior, perception, and physical fitness as the use of habit-forming substances[(7)]. DSM-5 defined internet addiction as compulsive, impulsive, obsessive, and addictive behavior, but this definition requires further research[(8)]. Its prevalence ranges from 0.7 to 27.7%, depending on research designs, methodologies, and population, as reported in various studies [(9)]. A recent study about the prevalence of IA reported 12.5% of students had addiction [(10)]. The evidence from Pakistan said 28% of students had internet addiction [(11)], which is

prevalent among young people [12]. Internet addiction brings a plethora of consequences for youngsters, even severe like depression [13], procrastination [14], and academic performance [15].

A smartphone uses the same technology like the Internet, and it is predicted to have the same or even more enormous impact hence considered a disorder. The more people use their smartphones, the more they get reliant on them and develop difficulties [16]. Literature has shown multiple worldwide patterns of smartphone addiction [17]. For instance, smartphone addiction rates in European countries, such as Switzerland (16.90%) [18], France (21.59%), Spain (12.50%),[19], and UK(10%) [20], are less as compared to the Middle Eastern and Asian countries, notably Saudi Arabia(48%)[21], India(55.70%)[22], and South Korea (35.20%) [23]. A study was conducted in Pakistan and found smartphone addiction in 60% of students [24]. When individuals keep themselves busy with a smartphone all the time, this is not without consequences ranging from cognitive, social, psychological, physiological, and behavioral issues [17, 25-29].

Despite triggering so many negative consequences, Internet and smartphone addiction give birth to further problematic behaviors like phubbing. Viewing your phone and ignoring others during a conversation is known as "phubbing" [30], and this behavior is quite prevalent among Gen Z. The word "phubbing" is the combination of two phrases phone and snubbing[31]. Phubbing is the convergence of several addictions because smartphones are structured to provide bundles of temptation [32]. Phubbing is more widespread than previously believed, and its possible repercussions can be more damaging. This phenomenon is relatively new; very little research has been conducted to check its predictors in Pakistan. Among little available literature, all is dedicated to understanding phubbing at the workplace [33] and close and intimate relations [34]. The current study aims to check whether internet and smartphone addiction predict phubbing behavior in the young Pakistani population as found in other cultures.

MATERIALS AND METHODS

A multistage cluster random sampling procedure was employed to reach study participants from 2 public sector universities: Bahauddin Zakariya University and Islamia University, for a cross-sectional study. At the first stage, the province was chosen, later universities and faculties were divided, and departments were selected randomly from each faculty. In the last phase, classes were randomly picked from departments as a stratum. Study approval was obtained from University Putra Malaysia. Participants were approached in their virtual classrooms through the class instructors; informed consent was a part of the online survey questionnaire, and participants were debriefed. Seven hundred ninety-four responses were analyzed who met the inclusion criterion: must meet the age requirements of Gen Z, must be internet users, and must have a smartphone.

Internet addiction was measured with the "Problematic Internet Use Questionnaire" 9-items version [35]. The response format is a 5-point Likert scale with a minimum score of 9 and a cut-off score of 22. The ten-item short version of the Smartphone Addiction Scale (SAS-SV) was used [36], and responses were anchored on a Likert-type scale. The authors reported excellent reliability (Cronbach's alpha: 0.91) for this scale. Phubbing was measured with the five items of the "communication disturbance" subscale, and the response format was anchored from 1-5 on a Likert scale[30]. All the scales exhibited very good reliability scores in the current study (α = .94; α = .91; α = .88) respectively.

RESULTS

Among 794 participants, 373(43%) were males, and 421(53%) were female students aged 18 to 24. The relation between gender and internet use patterns has been represented in Table 1. A significant association was found between the frequency of internet use and gender among students. A Significate relation was found in gender and hours of internet use. Most females reported using the internet daily (94.7%) and above 4 hours (51.8%) than males. A vast majority of females were using the Internet at home (90.3%) than 78% of males. More males were using the Internet at university (15%) than females (7.4%). More females were using the Internet for educational (37.5%) and entertainment purposes (20.4%) while boys preferred internet use for social networking 13.9% than females who reported 8.4 percent use for social networking.

Participants told about their opinion on internet addiction, and a significant majority responded as may be (38.3%) and yes (36.9%). Less than one-third (24.8%) of participants responded that they do not think internet use is addictive (Figure 1).

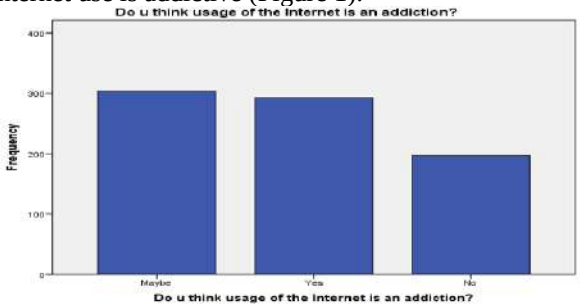

Figure No.1: Frequency of participants' opinions about internet addiction

Two hypotheses were framed to investigate whether internet addiction and smartphone addiction significantly impact phubbing behavior. The dependent variable phubbing was regressed on the predicting

variables internet and smartphone addiction to test the hypothesis. Internet addiction and smartphone addiction significantly predicted phubbing behaviour, F (2,791) =35.786, p< .001, which indicates that internet addiction and smartphone addiction can play a significant role in shaping phubbing behaviour (b= .072; .131, p= .000; .000) respectively. Moreover, the R^2 depicts that the model explains 8.1% of the variance in phubbing behavior. These results direct the positive effect of internet addiction and smartphone addiction. Table 2 shows the summary of the findings.

Table No.1: Internet use Patterns and Gender Differences among Generation Z

Questions	Response Options	Male (373)	Female (421)	Total (794)	Pearson Chi-Square	P=Value
Frequency of internet use?	Everyday	341(91.4%)	399(94.7%)	740(93.2%)	X^2= 3.509[a]	.042
	More than once a week	32(8.6)	22(5.3%)	54(6.8%)		
Hours of internet use?	Up to 4 hours daily	235(63%)	203(48.2%)	438(55.2 %)	X^2= 18.219[a]	.001
	More than 4 hours daily	138(37%)	218(51.8%)	356(44.8%)		
Preferred place for internet use?	home	292(78%)	380(90.3%)	672(84.6%)	X^2= 23.663[a]	.000
	University	56(15%)	31(7.4%)	87(10.9%)		
	Others	25(7%)	10(2.3%)	35(4.5%)		
The primary purpose of using the Internet?	Education	120(32.1%)	158(37.5%)	278(35%)	X^2=36.020[a]	.000
	entertainment	74(19.8%)	86(20.4%)	160(20.2%)		
	Social networking	52(13.9%)	35(8.4%)	87(10.9%)		
	others	127(34.2%)	142(33.7%)	269(33.9%)		

Table No.2: Regression Results

Regression Weights	Beta Coefficient	R^2	F	t-value	p-value	Hypothesis supported
IA-PB	.072	.081	35.786	4.775	.000	yes
SPA-PB	.131			6.796	.000	yes

Note: p<0.001. IA: internet addiction, SPA: Smartphone Addiction, PB: Phubbing behavior

DISCUSSION

The current study figured out the technology use patterns among Gen Z and found the impact of the internet and smartphone addiction on phubbing behavior. Technology has become a life necessity, but its excessive use can also damage human cognition and behavior. First of all, results from the descriptive statistics were obtained, and a significant association was found between gender and intent use patterns. Results were in line with current findings where considerable gender differences were found in the purpose of internet use [(37)]; females' preferred purpose was educational assistance that is in line with the current findings. Support comes from the Studies that found gender differences in the purpose and patterns of internet use [(38-40)].

This study measured the existence and predictors of phubbing among Gen Z. A key hypothesis was to check the effect of internet addiction on phubbing behavior. Results informed that internet addiction significantly and positively predicted phubbing behavior. These findings are in the same vein as reported by Karadağ et al., who provided evidence that internet addiction is one of the primary determinants of phubbing behavior [(30)].

The following hypothesis was to check the impact of smartphone addiction on phubbing behavior. Results showed a positive effect of smartphone addiction on phubbing behavior. Smartphone addiction leads to phubbing behavior, and it is a stronger predictor of phubbing than internet addiction. These findings are consistent with Karadağ et al., who reported that smartphone addiction is the strongest predictor of phubbing behavior than other variables [(30)]. The person with smartphone addiction gets absorbed in the device and ignores the surroundings. Another large-scale study on 17 countries, including Pakistan, informed about the impact of smartphone addiction on phubbing [(41)].

Existing literature [24] and the current research provide enough evidence about technology addiction and phubbing in youngsters. Besides the addiction to technology, there are many other personal and situational factors related to phubbing behavior [42] that must also be considered in future research in Pakistan.

CONCLUSION

To conclude, there are pretty apparent gender differences in the internet use patterns among Gen Z. It is inferred that internet and smartphone addiction predict phubbing behavior, and smartphone addiction is the stronger predictor. Based on these findings, it is recommended that policymakers consider technology addiction seriously, and remedies must be sought out. Behaviourism explains technology addiction as a learned behavior subject to the "stimulus-response-reinforcement" principle (SRR) that can be unlearned like any learned behavior. Thus, internet addiction, smartphone addiction, and phubbing behavior can be modified to avoid detrimental consequences[43, 44].

Author's Contribution:

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Original Article

Diagnostic Accuracy of Magnetic Resonance Cholangiopancreatography in Diagnosis of Choledochal Cyst Taking Surgery as Gold Standard

Sadia Riaz, Sarah Nisar, Kamran Naseem, Fariha Mumtaz, Naima Mujahid and Arshad Faheem

ABSTRACT

Objective: To establish diagnostic accuracy of MRCP (Magnetic resonance cholangiopancreatography) in detecting choledochal cyst, considering surgical findings as gold standard.

Study Design: Descriptive, cross sectional study

Place and Duration of Study: This study was conducted at the Department of Diagnostic Imaging, Bahawal Victoria Hospital, Bahawalpur from January, 2019 to January, 2020 for a period of one year.

Materials and Methods: There were total 122 patients with age range of 1-20 years, with complaints of jaundice or cystic mass of any size in the right upper quadrant. Patients with any bleeding disorder, hepatocellular carcinoma and contraindication to MRI were excluded. All the patients got their MRCP done and findings were correlated with the operative findings.

Results: Mean age in the study; 10.19 ± 4.86 years. Amongst the 122 patients, 64 (52.46%) male and 58 (47.54%) female presented with ratio of 1.1:1(male; female). In MRCP positive patients, 64 true positive while 09 turned out to be false positive. While in 37 MRCP patients with negative findings, 07 came out to be false negative while 42 as true negative. The overall sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of magnetic resonance cholangiopancreatography (MRCP) in detecting choledochal cyst, taking surgical findings as gold standard came out to be 90.14%, 82.35%, 87.67%, 85.71% and 86.88% respectively.

Conclusion: The current research concluded that magnetic resonance cholangiopancreatography (MRCP) is an effective modality of choice with high diagnostic accuracy in diagnosing choledochal cyst, non-invasively.

Key Words: choledochal cyst, magnetic resonance imaging, sensitivity.

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INTRODUCTION

Choledochal cysts are rare congenital abnormality with exact etiology still unclear. Choledochal cysts usually present during the early first year of life with a slight female predilection. The Adult presentation presents relatively less and mostly associated with other complications. Usual symptoms at presentation includes intermittent pain abdomen and sometimes with right sided abdominal mass or jaundice.

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The cystic dilatations of the biliary tree have a variable form that may involve the extrahepatic and/or the intrahepatic biliary channels[1]. Todani classification is used globally. There are 5 types of Choledochal cysts. Types I and IV being the most common. Various imaging modalities such as ultrasound abdomen, computed tomography scanning, radionuclide imaging and even endoscopic retrograde cholangio-pancreatography (ERCP) are being used to visualize the dilatation of ducts and their anatomical variations. For the past few years, increasing attention has been gained by the magnetic resonance cholangiopancreatography (MRCP), as the primary diagnostic study due to its noninvasive nature and quality imaging [2]. Complications like recurrent cholangitis, pancreatitis, biliary cirrhosis, biliary strictures, liver abscess, portal hypertension, pancreatic stones, choledocholithiasis, cyst rupture, and portal aneurysm, are presented very often[3]. Cholangiocarcinoma risk is associated with a ductal remnant and un-resected choledochal cysts. The optimal treatment available is total surgical excision or if possible biliary diversion[4].

MATERIALS AND METHODS

Study Design: Descriptive, Cross-sectional study.
Setting: Department of Diagnostic Imaging, Bahawal Victoria Hospital, Bahawalpur.
Duration of Study: 20 January 2019 to 20 January 2020
Sample Size: Sample size calculated of 122 with 95% confidence level, 9.6% desired precision for sensitivity of 81%, 7.8% precision for specificity of 90%[12] and taking expected prevalence of choledochal cyst as 53.57%[5].
Sample Technique: Non-probability, purposive sampling.
Sample Selection:
Inclusion Criteria:
a. patients presenting with cystic mass of any in right upper quadrant (on ultrasonography).
b. Obstructive jaundice on lab analysis (raised bilirubin > 2 mg/dl, markedly raised alkaline phosphatase > 140IU/L).
c. Patients 01-20 years of age.
d. Both genders.
Exclusion Criteria:
a. Patients with any bleeding disorder.
b. Patients having Hepatocellular carcinoma.
c. Patient not fit for anesthesia.
d. Patients with contraindication to MRCP i.e. cardiac pacemaker, claustrophobia
e. Patient not willing for surgery.
f. patients not willing to participate for study.
Data Collection Procedure: After the hospital ethical review approval, a total of 122 patients were referred after fulfilling inclusion/exclusion criteria to the radiology department, of Bahawal Victoria Hospital. After taking informed written consent, magnetic resonance cholangiopancreatography (MRCP) was performed on a 1.5 Tesla MR System using phased-array coil. All MRCP films were interpreted by a trained qualified radiologist (05 years post-fellowship experience). MRCP findings were correlated with the surgical findings. Data was recorded on a proforma (Annexure-I).
Data Analysis Procedure: Through computer software SPSS 23.0, collected data was analyzed. Age and duration of disease were presented as mean and standard deviation. Gender as well as presence or absence of choledochal cyst on MRCP and surgery were also expressed in the form of frequency and percentages. 2×2 table was applied to calculate sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of MRCP in diagnosing choledochal cyst, considering surgical findings as gold standard.
Effect modifiers and confounders were controlled through stratification. Post-stratification chi square was applied to analyze effect on outcome and p-value ≤0.05 was considered significant.

RESULTS

In this study age ranged from 1-20 years, mean age 10.19 ± 4.86 years. Most of the patients 63 (51.64%) in range between 11 to 20 years. In 122 patients, 64 (52.46%) were male and 58 (47.54%) females with male: female ratio 1.1:1. Mean disease duration was 5.09 ± 2.23 months. MRCP showed the choledochal cyst in 73 (59.84%) patients. Surgical findings confirmed choledochal cyst in 71 (58.20%) cases where as 51 (41.80%) patients' revealed no choledochal cyst. In MRCP positive cases, 64 true positive while there were 09 false positive. Among MRCP negative patients, 07 false negative while 42 true negative were present. The calculated sensitivity 90.14%, specificity 82.35%, positive predictive value 87.67%, negative predictive value of 85.71% and diagnostic accuracy 86.88% of magnetic resonance cholangio-pancreatography (MRCP) in detecting choledochal cyst, taking surgical findings as gold standard was found.

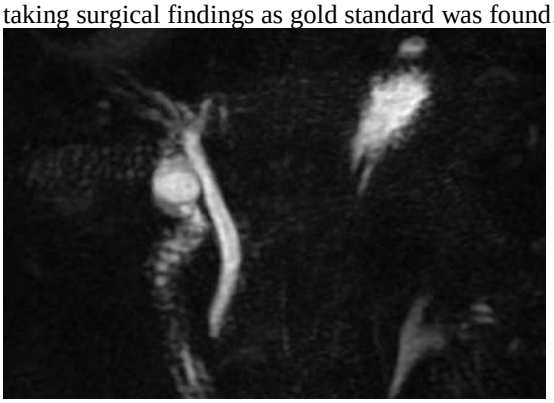

Figure No.1: MRCP of a choledochal cyst, type II

Figure No.2: Coronal 3-D magnetic resonance cholangiopancreatography image showing Type IV choledochal cyst

Table No.1: Distribution of patients according to Age

Age(years)	No. of patients	%age
1-10	59	48.36
11-20	63	51.64
Total	122	100

Mean ± SD = 10.19 ± 4.86 years

DISCUSSION

The preferred imaging modalities are Ultrasound (US) and MRCP in pediatrics hepatobiliary and pancreatic systems as compared to the computed tomography (CT) due to nonionizing properties.[5] MRCP is an emerging relatively newer technique added to the diagnostic tool. Apart from being noninvasive, MRI allows detailed assessment of the biliary tract in a (3D) projection just like endoscopic retrograde cholangiopancreatography (ERCP) providing with a better patient tolerance for the technique.[6] MRCP was used in limited cases initially and used for extremely cooperative patients. However, with the respiratory control along with non-breath holding techniques, it has allowed MRCP to be equally good for less cooperative patients as well as children[7].Rapid imaging sequences such as HASTE/single-shot FSE or single-shot turbo spin echo (TSE) have markedly reduced acquisition time. [8]Eventually, MRRCP has literally replaced and superceeded. [9]ERCP as the primary investigation in biliary tract imaging .[10] The study is specifically designed to establish the diagnostic accuracy of magnetic resonance cholangio-pancreatography (MRCP) in detecting choledochal cyst in young patients, while taking surgical findings as confirmatory gold standard.[11]

For current study the age range was from 1-20 years and mean age calculated was of 10.19 ± 4.86 years. Most of the cases 63 (51.64%) were in range between 11 to 20 years. [12] Out of these 122 patients, 64 (52.46%) male while 58 (47.54%) females with male to female ratio of 1.1:1. MRCP showed the choledochal cyst in 73 (59.84%) patients. [13]Surgical findings confirmed choledochal cyst in 71 (58.20%) cases where as 51 (41.80%) patients' revealed no choledochal cyst.[14] In 73 MRCP positive patients, 64 true positive whereas 09 were false positive. Amongst, 37 MRCP negative patients, 07 false negative and 42 true negative were found.[15] The detection rate for diagnosing choledochal cysts on MRCP in a study [8] was found to be 96%.With sensitivity, specificity, positive predictive value, and negative predictive value of MRCP for classifying choledochal cysts according to Todani's classification were found to be 81%, 90%, 86%, and 86% for type I, respectively; 73%, 100%, 100, and 95% for type III, respectively; 83%, 90%, 80%, and 91% for type IVa, respectively; 100%, 100%, 100%, and 100% for type IVb, respectively; and 100%, 100%, 100%, and 100% for type V, respectively[16].

In another study[9], MRCP showed variation in intrahepatic ductal branches, variation in common hepatic duct, variation in gallbladder or (CBD) common bile duct, especially in children. [17]Cystic duct was often visible, although in younger children. Main pancreatic duct in head and body portions was visible in 65% of patients, while in tail in 17% of cases. Irie H et al[10] in a study came to conclusion that MRCP serves to be an important noninvasive diagnostic tool for choledochal cysts detection, however, it should not replace ERCP[18]. In his study 16 patients diagnosed were choledochal cyst. MRCP could however define the proximal bile duct better but distal common bile duct defects were missed with MRCP in 2 pediatric patients. [19]On the whole, it showed MRCP has high diagnostic accuracy of magnetic resonance cholangiopancreatography (MRCP) in detecting choledochal cyst, taking surgical findings as gold standard.[20]

CONCLUSION

The study concluded that magnetic resonance cholangiopancreatography (MRCP) non-invasively diagnoses choledochal cyst with a higher accuracy .It not only improves ability to diagnose in children pre-operatively but also helps surgeons in proper decision making. It is recommended that magnetic resonance cholangiopancreatography (MRCP) should be done routinely in all suspected cases of choledochal cyst especially in children to prevent complications and for accurate assessment pre-operatively leading to proper and timely surgical intervention.

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Original Article

Pattern of Microorganisms Isolated from Endotracheal Swabs of Neonates and Determination of Their Antibiotic Susceptibility

Identification of Microorganisms That Colonize the Trachea of Intubated Neonates

Shreekrishna Devkota[1], Sarfaraz Alam[2], Mimpal Singh[1], Muhammad Jareer Alam[3], Amrit Dhungel[1] and Maryam[1]

ABSTRACT

Objective: The aim of this study was to identify the microorganisms that colonize the trachea of intubated neonates at 1st, 24th, 48th and 72nd hours of intubation and find their antibiotic sensitivity pattern.

Study Design: Descriptive case series study

Place and Duration of Study: This study was conducted at the Department of Pediatric Medicine Unit II, Mayo Hospital Lahore. Study duration was 2 years from August 2014 to July 2016.

Materials and Methods: This study was conducted on 189 neonates who remained intubated for more than 72 hours at the hospital. After data collection, data were processed and analyzed using statistical software SPSS, version 20.

Results: When total sample collection events (1st, 24th, 48th and 72nd hours) were considered to be 100%, the majority showed no growth (65%), whereas in positive cultures Pseudomonas topped the list with 19% positive cultures followed by E.coli (6%) and Coagulase positive Staph aureus (6%). Antibiotics resistance was most commonly seen for ampicillin and cefotaxime, 5.2% each, while most bacteria were sensitive to vancomycin, tanzo and meropenem (5.2%) each.

Conclusion: Pseudomonas is the most common bacteria causing ventilator-induced pneumonia among neonates.

Key Words: ventilation, pneumonia, sensitivity, neonates, endotracheal intubation

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INTRODUCTION

Nosocomial infections which include surgical site wound, lower respiratory tract and urinary tract infection are leading public health problems in hospital worldwide[1]. The risk of these infections increases considerably with the modern invasive medical procedures in the intensive care settings[2,3]. Ventilator-associated pneumonia poses a great risk to patient safety. More ever the use of endotracheal tube is one of the most common ways of transmission of nosocomial infections.

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The risk of pneumonia is increased by up to 6 to 20 folds among patients who require mechanical ventilation after endotracheal intubation and in such cases, the mortality rates reach up to 20 to 40 percent[4,5]. The burden of hospital-acquired infection is significant in the developed countries were 5 to 15% of the patients who are hospitalized in the wards and this burden is estimated up to 50% or even more in intensive care unit patients. In contrast to this in the developing countries, the degree of this problem is still underestimated or not known as hospital-acquired infection diagnosis is complicated and there are not enough resources and expertise for surveillance measures to guide interventions[1].

Gram-negative bacilli infections in the lower respiratory tract are a leading complication in patients with tracheal intubation and ventilator assistance.[6] VAP is the commonest hospital-acquired pneumonia. VAP represent an episode of pneumonia which develops after 48 hours or more after initiating mechanical ventilation in a patient. Aspiration of the colonized respiratory secretions in the nasopharynx has been seen as the major cause of VAP[7-15]. The colonization of trachea by such possible pathogenic organisms predispose the patients to infections and these patients present with signs and symptoms like fever, lower

respiratory signs and polymorphonuclear leucocytes in the examination of sputum[16].

There has been an unrestricted use of antibiotics especially in the ICU settings which is a major cause of development of nosocomial infections caused by resistant gram-negative organisms[17]. The main aims of this study are to see the pattern of microorganisms isolated from endotracheal tube and their antibiotics sensitivity pattern and to compare whether we are using correct antibiotics or we have to modify according to culture susceptibility. A similar study was done in Iran (2012) showed Enterobacter species, Pseudomonas aeruginosa, Escherichia coli, Coagulase negative Staphylocooci, Staphylocoocus aureus and Proteus species respectively. Antibiotic susceptibility testing has shown that P. aeruginosa was the most resistant gram negative organism with the highest resistance against Cefixime and Coagulase-negative staphylococcal were the most resistant gram-positive with the highest resistance against Oxacillin[1]. Another similar study done in Iran showed mostly Acinetobacter, Pseudomonas aeruginosa, Proteus mirabilis. Antibiotics resistance was seen mainly against Acinetobacter, Staphylococcousaureus, and Kleibsella[17]. No similar study is done in Pakistan in the last 5 year.

Every year nearly 45% of all under 5 child deaths are among newborn infants, babies in their first 28 days of life or neonatal period. Three-quarters of all newborn death occur in the first week of life. In developing countries, nearly half of all mothers and newborns do not receive skilled care during and immediately after birth.[18]

In the Southeast Asia region around 52% of under-five mortality is contributed by deaths during the neonatal period. Some factors that impact newborn consequences include the health status and care received by the mother before and during pregnancy, during childbirth and postnatal care of the mother and neonates.[19]

There are two relatively distinct syndromes of Neonatal sepsis which are based on the age of performance, early-onset and late-onset sepsis.[20]

Early-onset sepsis (EOS) boons in the first 3-5 days of life. Typically, from the maternal genital tract, the infant has acquired the organism during the antepartum or intrapartum period. Procurement of other organism is associated with the birth process. With rupture of membrane, vaginal flora or various bacterial pathogens may ascend to reach the amniotic fluid and fetus. Chorioamnionitis develops leading to fetal colonization and infections[20].

MATERIALS AND METHODS

It is a descriptive case series study. Place of the study was Mayo hospital Lahore, department of paediatrics medicine. Duration of study was 2 years.

Operational definitions:

Nosocomial infections (hospital-acquired infection) refer to infections that a patient acquires after hospital admission and these infections were not present at admission. In this study nosocomial infection refers to those which occur after at least 48 hours of admission.

Ventilator-Associated Pneumonia (VAP) was defined as pneumonia that develops more than 48 hours after initiation of mechanical ventilation.

Antibiotics sensitivity: Antibiotics sensitivity was defined as the susceptibility of bacteria to antibiotics. Antibiotics susceptibility testing (AST) usually carried out to determine which antibiotics were most successful in treating a bacterial infection in vivo. Testing for antibiotics sensitivity was done by Kirby Bauer Method.

If the bacteria are sensitive to the antibiotics a clear ring or zone of inhibition was seen around wafer indicating poor growth.

The study aimed to identify the microorganisms that colonize the trachea of intubated neonates at 1st, 24th, 48th and 72nd hours of intubation and find their antibiotic sensitivity pattern. This study was conducted on 189 neonates who remained intubated for more than 72 hours at the Department of Pediatric Medicine Unit II, Mayo Hospital Lahore. Informed written consent was taken from parents or guardians. Endotracheal swabs were collected after following aseptic measures and were immediately submitted for culture and sensitivity to the hospital laboratory. All samples were analysed separately by the one laboratory person to avoid subjective variation in the analysis. The analysis was done following hospital laboratory protocols. Possibility of error was reduced by avoiding delay in submission of samples and multiple laboratories. After data collection, data were processed and analyzed using statistical software SPSS, version 20.

RESULTS

The overall findings of the study are described under the following sections:

4.1 Age

4.2 Gender

4.3 Indication for Intubation

4.1 Age: Mean±SD of neonates was 41.6±93.0 hours (1.7±3.9 days). Median age of the neonates was 15 hours (0.6 days), whereas age ranged from 1-480 hours since birth (0.04-20 days) (Table 4.1).

4.2 Gender: In terms of gender distribution, there was male predominance with 122 (64.6%) males and 67 (35.4%) females (Figure 4.2).

4.3 Indication for Intubation: The majority were indicated for intubation due to apnea (n=95, %=50.3), whereas bradycardia (n=6, %=3.1) was the least indication for it. After apnea, respiratory distress (n=61, %=32.3) was another major reason to intubate the neonates (Figure 4.2).

Table No. 4.1: Age

Time	Mean	Standard Deviation	Median	Range
In hours	41.6	93.0	15.0	1-480
In days	1.7	3.9	0.6	0.04-20.0

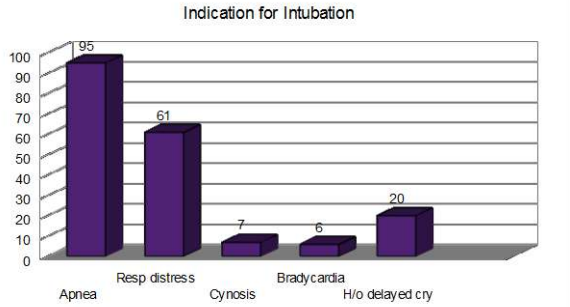

Figure No. 4.2: Indication for intubation

Table No. 4.2: Organisms Isolated

Organisms	1st hour of intubation	24th hour of intubation	48th hour of intubation	72nd hour of intubation
No growth	179 (94.7)	136 (72.0)	91 (48.1)	88 (46.6)
Pseudomonas	6 (3.2)	37 (19.6)	49 (25.9)	49 (25.9)
E coli	0 (0.0)	3 (1.6)	21 (11.1)	24 (12.7)
Coagulase positive Staph aureus	0 (0.0)	10 (5.3)	19 (10.1)	19 (10.1)
Proteus	4 (2.1)	0 (0.0)	6 (3.2)	6 (3.2)
Coagulase negative Staph aureus	0 (0.0)	3 (1.6)	3 (1.6)	3 (1.6)
Total	189 (100.0)	189 (100.0)	189 (100.0)	189 (100.0)

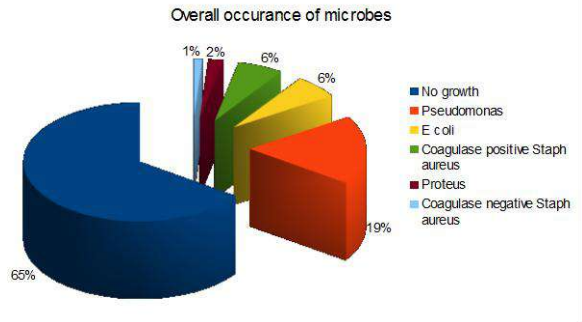

Figure No. 4.3: Total percentage of Microbes when overall (1st, 24th, 48th and 72nd hour) taken as 100%

4.4 Organisms isolated at different hours (1st, 24th, 48th and 72nd): At different times, different microorganisms were isolated from the tracheal swab of the intubated neonates. After 1st hour of intubation nearly 95% (n=179) showed no growth whereas 10 patients had growth with Pseudomonas (n=6, %=3.2) and Proteus (n=4, %=2.1). After 24th hour of intubation, no growth was seen in 136 (72.0%) neonates. Majority of the neonates had Pseudomonas growth (n=37,%=19.6), coagulase-positive Staph aureus (n=10, %=5.3) was 2nd to the list in terms of growth in 24th-hour post-intubation. Growth of microbes continued to increase after 48th hour of intubation with only 91 (48.1%) having no growth. The list was again topped by Pseudomonas (n=49, %=25.9) and the least culture-positive microbe was coagulase-negative Staph aureus (n=3, %=1.6). After 72 hours of intubation, more than 55% samples showed culture-positive samples among which Pseudomonas (n=49, %=25.9) has 49 positive cultures followed by E.coli (n=24, %=12.7) and the least was coagulase-negative Staph aureus (n=3, %=1.6). There was not much difference in culture positive status of 48th and 72nd hour post intubation (Table 4.2).

Table No. 4.3: Antibiotic sensitivity at 1st hour

Antibiotics	Sensitive n (%)	Resistant n (%)	Not done n (%)
Cefotaxime	0 (0.0)	10 (5.2)	0 (0.0)
Ceftriaxone	6 (3.2)	4 (2.1)	0 (0.0)
Ceftazidime	6 (3.2)	4 (2.1)	0 (0.0)
Gentamycin	3 (1.6)	7 (3.7)	6 (3.2)
Vancomycin	10 (5.2)	0 (0.0)	3 (1.6)
Ampicillin	0 (0.0)	10 (5.2)	24 (12.7)
Meropenem	10 (5.2)	0 (0.0)	0 (0.0)
Tanzo	10 (5.2)	0 (0.0)	3 (1.6)
Amikacin	6 (3.2)	4 (2.1)	0 (0.0)
Sulzone	3 (1.6)	7 (3.7)	73 (38.6)
Not required (culture negative)	179 (94.7)		
Sensitive to none of Antibiotics	0 (0.0)		

4.5 Total percentage of Microbes (1st, 24th, 48th and 72nd hour)when overall is taken as 100%: When total sample collection events (1st, 24th, 48th and 72nd hours) were considered to be 100%, the majority showed no growth (65%), whereas in positive cultures Pseudomonas topped the list with 19% positive cultures followed by E.coli (6%) and Coagulase positive Staph aureus (6%)(Figure 4.3).

DISCUSSION

Nosocomial infections including surgical wound, urinary tract infection and lower respiratory tract infection are major public health problems in hospital worldwide[1]. Invasive medical procedures in the intensive care unit remarkably increase the risk of such infections[2,3]. Ventilator-associated pneumonia has been shown to cause the greatest risk to patient safety. More ever the use of endotracheal tube is one of the most common ways of transmission of nosocomial infections. Intubation with mechanical ventilation increases the risk of pneumonia 6 to 20 folds more among patients and is associated with a case mortality rates of 20 to 40 percent[4,5]. The burden of hospital-acquired infection is already substantial in developed countries where it affects from 5% to 15%of hospitalized patients in regular wards and as many as 50%or more of patients in intensive care units. In developing countries, the magnitude of the problem has remained underestimated or even not known mostly because hospital-acquired infection diagnosis is complex and surveillance measures to guide interventions require expertise and enough resources[1].

CONCLUSION

This study allowed us to find out the pattern of microorganism colonizing the trachea after 48 hrs of intubation and determine the antibiotics sensitivity pattern. The results of this study would help us to know the percentages of gram-positive and gram-negative microorganism and their sensitivity pattern, the resistant pattern if presence, to change or adjust antibiotics according to sensitivity and the result can be used as a reference in primary and secondary health care where laboratory facilities are lacking.

Author's Contribution:

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Original Article

The Presentation and Management of Thoracic Trauma in a General Surgical Ward

Presentation & Management of Thoracic Trauma

Gul Sher Khan, Abdul Ghafoor, Asif Mahmood and Alam Zeb

ABSTRACT

Objective: To evaluate the various modes of presentation of thoracic trauma and to assess the adequacy of management in a surgical ward of a tertiary care hospital.

Study Design: A retrospective study

Place and Duration of Study: This study was conducted at the Surgical Department Khalifa Gul Nawaz Teaching Hospital Bannu from July, 2016 to April, 2018.

Materials and Methods: A total of 220 patients with thoracic trauma, including both blunt and penetrating thoracic trauma presented to the emergency unit of KGN hospital were included in this study.

Results: Out of the 220 patients, 48% (105) were with blunt thoracic trauma and 52% (115) with penetrating thoracic trauma. Rib fracture was detected in 70% (154) cases, haemopneumothorax in 40% (88) of patients, pneumothorax in 28% (61), haemothorax in 18% (40), flail chest in 6% (13) of the cases, traumatic rupture of diaphragm in 7% (15) of the cases. Pure thoracic trauma was present in 62% (136) patients, thoracic trauma with associated injuries presented in 38% (84) patients and out of these 84 cases, 15.5% (13) cases had polytrauma. During treatment, 77.7% (171) of the patients were treated either non operatively or with chest tube thoracostomy. 16.5% (36) developed complications. 8.18% required thoracotomy. The overall mortality was 8.18% (18).

Conclusion: Penetrating chest trauma is increasing with time due to gunshot injuries although blunt trauma is commoner worldwide. Most of the chest trauma patients can be managed in the general surgical wards satisfactorily and only a few patients need surgical intervention in their management.

Key Words: Thoracic trauma, penetrating injuries, blunt injuries, complications, mortality and morbidity

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INTRODUCTION

Thoracic trauma is the 3rd leading cause of death after head and spinal injuries[1]. It accounts for 20-25% deaths due to trauma. Isolated thoracic trauma is found in 60-65% of the cases while associated chest trauma is found in 35-40% of the cases. Pure thoracic trauma has a mortality rate of 4-8%, in associated cases 13-15% and in poly trauma cases 25-30%[2].

Road traffic accidents are the commonest causes of blunt trauma accounting for more than >70% while in penetrating trauma gunshot wounds account for more than 60% of the cases. Although blunt thoracic trauma is generally commoner than penetrating thoracic trauma but in our setup in KPK the penetrating trauma is commoner, mostly due to gun shots, stray bullets, stab wounds and blast injuries.

Early diagnosis and prompt treatment of various life threatening conditions, better resuscitative measures, perioperative care and effective surgical procedures have significantly improved the outcome of thoracic trauma patients[3]. Gunshot wounds to the heart have been found with a high rate of mortality. Perioperative death from thoracic injuries is due to great vessel injury and exsanguinations, cardiac tamponade, tension pnuemothorax and bilateral flail chest with deep refractory hypoxia[4].

The outcome and prognosis for a vast majority of chest trauma cases are excellent. More than 80% of patients require either non-invasive therapy or at most tube thoracostomy[5]. However, about 10-15% of blunt trauma and 15-30% of penetrating chest trauma require open thoracotomy[6,7].

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MATERIALS AND METHODS

220 patients with chest trauma either alone or in association with other organ injuries presented to the accident and emergency department during July 2016 to April 2018 were included in the study, with the age ranged 15-75 yrs with the mean 38±12 yrs. All these

patients after proper resuscitation in the emergency were admitted to the surgical unit. On presentation to the emergency, clinical history and physical examination including primary and secondary survey according to the ATLS protocol were taken. Resuscitation of these patients went hand in hand with the assessment. Blood samples drewed for complete blood picture and arterial blood gases and serum viral profile. Chest x-rays were taken for every case. Chest and abdomen u/s and CT scan were done for complicated cases. Patients who were looking ill and on examination and investigations diagnosed as having life-threatening injuries e.g. immediate tube thoracostomy for tension pneumothorax, emergency room thoracotomy for massive haemothorax were done. Patients having pnuemothorax, haemopnuemothorax and haemothorax were shifted to the main operation theatre for tube thoracostomy. All these patients after resuscitation and stabilization were shifted to the surgical wards for further management. Of course, there were some patients with mild thoracic trauma received in the A/E department were straight forward transferred to surgical ward for observation for the next 24hrs. However, the few patients with flail chest who needed ventilatory support were shifted to ICU.

The records of all the above patients were reviewed and the data were collected retrospectively. The demographic features, type of trauma, clinical and radiological findings, associated organ injuries, management of the chest pathologies, surgical intervention, morbidity and mortality were analyzed and recorded.

Statistical analysis: Data were fed to the computer, were analyzed using software package for social sciences version 22 IPSS. Mean and standard deviation was used for continuous, while frequency and percentages for discrete variables. The difference in proportion was estimated by Pearson's chi square (x^2) and Fischer exact test, with the threshold for significance $p<0.05$.

RESULTS

A total 220 patients were studied for various chest injuries during the 21 months duration. Age ranged 15-75 yrs with the mean age 38±12 years. More than 50% patients were in their 2nd and 3rd decades of life. 90% (198) were males and 10% (22) were females.

Table No.1: Mode/mechanism of chest trauma

Blunt trauma		Penetrating trauma	
Road traffic accident	75	Gunshot	65
Assault	15	Stab Wounds	25
Fall from a Height	12	Blast injuries	20
Animal Related	3	And others	5
Total	105	Total	115

Table No.2: Pattern of chest injuries

Type of injury	Blunt thoracic trauma	Penetrating thoracic trauma
1) Haemopneumothorax	60	28
2) Pneumothorax	61	0
3) Haemothorax	25	15
4) Rib fracture	120	34
5) Clavicle fracture	15	8
6) Chest wall injuries	4	6
7) Lung contusion	8	7
8) Traumatic diaphragmatic rupture		
9) Flail chest	10	5
10) Surgical emphysema	13	0
11) Tension pneumothorax	20	10
12) Open pneumothorax	30	23

Table No.3: Associated injuries (n=84)

Injuries	Number
1) Head injuries	35
2) Limb long bone fractures	12
3) spinal injuries	12
4) Pelvic fractures	9
5) Spleenic injuries	4
6) Liver injuries	6
7) other abdominal visceral injuries	6

Table No.3: Various treatments offered

Treatment instituted	Blunt thoracic trauma	Penetrating thoracic trauma
1)Conservative or observation	30	6
2)tube thoracostomy	55	80
3) Laparotomy	10	11
4)Mechanical ventilator	8	0
5) Thoracotomy	0	6
ER(emergency room) Elective	0	12

Table No.4: Morbidities in the management of chest trauma

Morbidities Patients (%)	
Pneumonia	8 (3.6)
Respiratory failure	12(5.5)
Acute respiratory distress syndrome	8(3.6)
Empyema	6(2.37)
Septicemia	4(1.8)
Wound infection	10 (4.4)
Overall morbidities	21.73

Table No.5: Mortality in the management of thoracic trauma

Chest trauma mortality Patients deaths (%)	
Thoracic injury with neurosurgical trauma	4 (1.8)
Mortality in thoracic polytrauma	8 (3.64)
Flail chest mortality	6 (2.73)
Overall mortalities	18 (8.15)

DISCUSSION

Thoracic trauma continues to be a major public health issue in the world. It constitutes 20-25% of all the 50% deaths due to trauma. Road traffic accidents (RTA), fire arm injuries(FAI), stabbings and falls are the frequent causes of thoracic trauma. Young males in their 2nd, 3rd and 4th decades of life are the usual sufferers. RTA account for >70% of all the causes of blunt thoracic trauma. Among these more than 50% are either by motor car or motor bike accidents. Among the causes of penetrating chest trauma, gunshot wounds (homicidal, suicidal, stray bullet, blast injuries) constituted more than 60% of the causes.

Worldwide the incidence of blunt trauma is more than the penetrating chest trauma but in many urban hospitals in America, the incidence of penetrating trauma is higher than the blunt one[8].The same was the situation in this our study where the incidence of penetrating chest trauma was more than blunt trauma. (52% versus 48%).

Internationally males outnumber females by a large ratio because of their greater exposure to outdoor activities and rivalries etc[9]. In our study the male to female ratio was 198 versus 22.

The time of incidence of trauma and arrival of patients in the hospital (Golden Hours) is considered critical in the patient management. Patients arrived to the hospital with in the Ist 30-60 mints after the occurrence of major thoracic trauma, the patients chance of survival are increased[10].

Surgical intervention is required in about 10-15% cases of blunt thoracic trauma and 15-30% cases in penetrating thoracic trauma[11,12]. Many western studies suggest, observation or chest tube placement, adequate volume replacement, chest physiotherapy, occasional respiratory support, pain and infection control (by analgesics and antibiotics) and serial chest x-rays are the only treatments required in 80-85% cases of thoracic trauma[13]. Adding respiratory support, the success rate of management is increased to 92% without major thoracic surgery. In our study the success rate of management was 82% and the overall surgical intervention rate was 8.18%.

Thoracotomy can be early emergency one (emergency room thoracotomy) for unstable patients e.g. patients with heavy intrathoracic bleed, cardiac tamponade and cardiac message[13]. In our study, 6 cases of severe thoracic trauma (with intrathoracic bleed from intercostal arteries) underwent emergency room thoracotomy (the bleeder were ligated).

In our study rib fracture was present in 70%(154) of cases of thoracic trauma while in many local studies the value ranges from 44%-64% and it has been reported as the most common injury in the thoracic trauma[14,15].

Chestintubation is the most frequent surgical procedure in thoracic trauma patients and in our study it was in 61.4% (135) cases for the purpose of re-expansion of collapsed lungs, complete drainage of pleural cavities and monitoring of the injured lung for any continued blood loss. Also many international studies have reported its insertion rate upto 70%.

Head injury was the most frequent extra thoracic trauma followed by extremities trauma. The common involvement of this structure have been reported to be associated with a high mortality which is in conformity with this study[14,15].

In our series, pure thoracic trauma was present in 62% of patients and associated injuries in 38% of cases. The international statistic expresses the values for pure thoracic injuries from 60-70% and associated injuries in 35-40% of cases.

Flail chest was present in 5.91% of cases in our series while many local studies have reported it between 6.6-20%[16,17]. The mortality for flail chest was 2.73% while in literature it is between 4.5-20%.

8 out of 13 patients of flail chest were put on ventilator in ICU. Many western studies have shown a high mortality due to ventilator support from conditions like barotraumas and volutraumaending up in ARDS[18,19].

The overall morbidity in our study was 21.26% while the international figures for it vary between 20-30%. The overall mortality rate in our series was 8.18% while in the literature it varies from 5-15%. In literature the mortality rate for isolated thoracic injuries is 4-8%, for associated injuries 13-15% and for polytrauma it is 25-30%[2]. The mortality from thoracic trauma was more in old patients than the young ones.

Morbidities in the management of chest trauma.

Morbidities patients (%)
pneumonia 8 (3.6) Respiratory failure Acute respiratory distress syndrome Empyema Septicemia 4 (1.8) Wound infection
Overall morbidities

Chest trauma in association with extra thoracic injuries makes the presentation and management of such patients a complicated and difficult with a high rate of mortality and morbidity.

The average hospital stay was 7.8 (1-14) days. Patients were discharge from the hospital and followed for the next 2-3 months with almost no uneventful incidence.

Mortality in the management of thoracic trauma.

Chest trauma mortality
Thoracic injury with neurosurgical trauma Mortality in thoracic polytrauma Flail chest mortality
Overall mortalities

Thoracic surgeons are not usually a part of the initial thoracic trauma emergency management in most of the trauma centers worldwide. In North America thoracic surgeon is present in 1 out of 16 level 1 trauma centers. This is due to the presentation of injuries, many of which do not need the specific knowledge of thoracic surgeon in each patient. Thoracic surgeon intervention in operating theatre was required in only 5.4% of cases. This paper expresses that thoracic surgeons are occasionally required in the management of the thoracic trauma patients. Many deaths can be prevented by prompt diagnosis and aggressive treatment. Thoracic trauma patients are generally managed in the emergency (resuscitation) and general surgical ward by the general surgeons in more than 90% of cases.

CONCLUSION

Blunt thoracic trauma is generally commoner than the penetrating thoracic trauma and that surgical interventions are required occasionally. Thoracic surgeons are not usually part of the trauma team in most of the trauma centers. Most of thoracic trauma cases are dealt in the surgical wards by the general surgeons with good outcome and only a minor number of patients are referred/dealt by the thoracic surgeons.

Author's Contribution:

Concept & Design of Study:	Gul Sher Khan
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Revisiting Critically:	Gul Sher Khan, Abdul Ghafoor
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Frequency of Anemia in Chronic Kidney Disease Patients Presenting at Civil Hospital Quetta

Anemia in Chronic Kidney Disease

Zohra Samreen[1], Muhammad Tahir Zehri[2], Shah Wali[3], Nazeer Ahmed Sasoli[4], Abdul Sadiq[6] and Ashiq Hussain[5]

ABSTRACT

Objective: The management and assessment of anemia is poorly understood in Balochistan. To determine frequency of anemia associated with chronic kidney disease patients admitted in Tertiary Care Hospital at Quetta Balochistan.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Medicine Department Sandeman Provincial Hospital Quetta, from January, 2019 to June, 2019 for a period of six months.

Materials and Methods: 106 patients who met the diagnostic criteria were included. Mean age in our study was 48.38±7.89 years. Mean duration of CKD in our study was 3.89±1.66 days.

Results: Out of 106 patients who developed chronic kidney disease patients, 26 (24.52%) had anemia and 80 (75.47%) did not have anemia. The data result shows that the anemia due to chronic kidney disease was more in male 18(16.98%) as compared to female patients 8(7.54%). Frequency distribution of age showed that 06 (5.66%) were in age group 30-40 years, 12 (11.32%) patients were in age group 41-50 years and 8 (7.54%) patients were belonging to age group 51-60 years with anemia in chronic kidney disease. The anemic patient's distribution in different stage of CKD showed that, 02 (1.88%), 3(2.83%), 6 (5.66%), 8 (7.54%) and 7 (6.60%) were in CKD stage 1, 2, 3, 4 and 5 respectively.

Conclusion: Anemia arise severe problems of chronic kidney disease. Correction of anemia may improve renal and is a significant middle marker of CKD so it might be valuable to measure hemoglobin even at overall screening. Early discovery of CKD is of highest position to stop the development of renal failure.

Key Words: Chronic kidney disease, anemia and end stage renal disease

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INTRODUCTION

Chronic Kidney Disease (CKD) recognized worldwide public health problem and anemia is the complex complication of progressive CKD.[1]The prevalence of CKD in India in diff erence populations is about 0.16% and further renal illness is about 0.7%.[2]. The current population grounded study evaluated the frequency at 150-200 cases per million populations each year in India.[3]

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A lack of iron in red blood cells diminishes tissue oxygen transport, increments cardiovascular output, and may bring about ventricular expansion and hypertrophy, whenever left untreated. The primary reason of iron inadequacy is expanded interest for iron, iron misfortune, and often case in chronic kidney disease diminished iron absorption, or incendiary iron block.[4]

Anemia of chronic kidney illnesses might be because of deficient creation of erythropoietin by unhealthy kidneys, decreased RBC endurance, iron or nutrient insufficiencies, bleeding bruise, chronic inflammation, hyperparathyroidism as well as comorbidities.[5] Iron inadequacy likewise can create in hemodialysis patients getting erythropoiesis animating agents, create cause an expanded interest for iron; blood misfortune from dialysis is another reason for iron lack.[6] Patients with diabetes have an increased hazard of anemia, in addition anemia itself is an autonomous danger factor for persistent kidney infection .[7-8]

Symptoms of iron lack incorporate weakness, exhaustion, anorexia, a sleeping disorder, tachycardia, dyspnea, angina, diminished mental and actual performance, and perhaps cardiac failure. In spite of the fact that weakness remedy in CKD has been displayed to moderate the movement of renal illness and progress

complete worth of life, iron deficit anemia leftovers undiagnosed and under treated.[4,9,10]

Since both beginning phase anemia and CKD are generally asymptomatic, kidney and hematologic research facility esteems ought to be checked yearly in patients at risk.[2,3,8] Because the glomerular filtration rate (GFR) diminishes with reformist CKD, the danger of anemia increments by about 27% in stage 1 to stage 5 (GFR <15 ml / min) becomes 76%.[7,11]

Anemia was existing in 68% of all patient's initial hemodialysis. Iron deficit was a common feature happening in 29% of patients pleasing erythropoietin and 26% of patients without erythropoietin.[12] In another study in USA, the current anemia prevalence was 15.4% patients with CKD. The global prevalence of anemia augmented through stage of CKD, since 8.4% at 1 stage to 53.4% at 5 stage. The anemia prevalence in individuals without CKD were 6.3%.[13]

Therefore, this study is designed to generate local data and to estimate the current magnitude of iron deficiency anaemia in CKD cases. If the burden will be found to be high, then screening will be recommended in all subjects prior to initiation of dialysis then timely decision could be taken for treatment and thereby preventing further morbidity.

MATERIALS AND METHODS

Study Design: Cross sectional study.

Study Setting: This Study was conducted at department of Medicine, Sandeman provincial Hospital, Quetta.

Sample Size: Anemia in patients with CKD[13] was 15.4%, confidence level 95%, absolute precision 7% and the required sample size came out to be 103 patients meeting the inclusion criteria.

Sampling Technique: Cross sectional study

Sample Selection: The patients with chronic kidney disease for more than 3 months were included. Male and female of age 30-60 years were included in data. The patients with known bleeding disorder were excluded from trail. The patient with sickle cell anemia, multiple and myelodysplastic syndrome were excluded from trail.

Data Collection Procedure: Consecutive patients with findings fulfilling the inclusion criteria visiting outpatient department of Medicine Civil Hospital Quetta was included. Determination and procedure of this study was described; confidentiality was assured and knowledgeable consent was taken for the inclusion in the study. A phlebotomist drew 2 cc venous blood after taking aseptic measures and the sample was send for hemoglobin estimation from the institutional laboratory. Presence of hemoglobin level ≤ 13 g/dL in male and ≤ 11g/dL in female was labeled as anemia positive. This information along with demographics like age, gender, stage of CKD and duration of CKD was noted in the proforma.

Data Analysis Procedure: Statistical analysis was performed on SPSS version 18 software. Continuous variables like age and duration of CKD was presented by mean +/-SD (standard deviation). Similarly, the categorical variables like gender, stage of CKD and anemia was presented by frequency and percentages. Effect modifiers like age, gender, duration of CKD and stage of CKD was taken care by stratification. Post stratification chi square test was useful taking p value of ≤ 0.05 as significant.

RESULTS

A total of 106 patients with CKD patients visiting Department of Medicine, civil Hospital, Quetta who met the inclusion and exclusion standards were comprised in this study.

Out of 106 patients lowest age of the patient was 37 while extreme age of the patients was 58 years. Mean age in present study was 48.38 years thru the standard deviation of ±7.89. Mean duration of CKD in our study was 3.89±1.66 days as shown in Table-1.

Table No.1: Described Statistic of Patients Admitted in Hospital

Variable	Mean	Standard Deviation	Min-max
Age (years)	48.38	±7.89	37-58
Duration of ckd (years)	3.89	±1.66	1-5

Out of 106 patients who developed chronic kidney disease patients, 26 (24.52%) had anemia and 80 (75.47%) did not have anemia as shown in Figure 1.

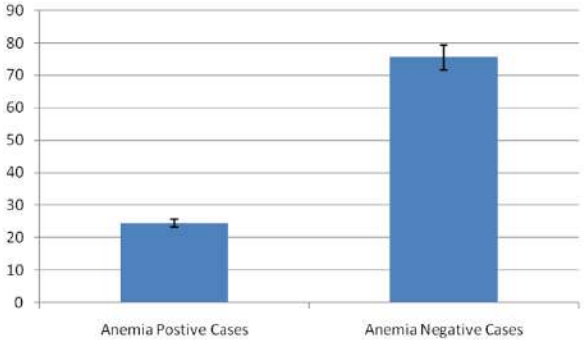

Figure No.1: Overall percentage of Anemia patients in CKD

The data result shows that the anemia due to chronic kidney disease was more in male 18(16.98%) patients as compared to female patients 8(7.54%) as shown in Table-2.

Table No.2: Detail of gender with anemia

Gender	Anemia	
	Yes	No
Male	18 (16.98%)	35 (33.01%)
Female	8 (7.54%)	45 (42.45%)
Total	26 (24.52%)	80 (75.46%)
P-value 0.46		

Frequency distribution of age of patients showed that 06 (5.66%), were age group 30-40 years, 12 (11.32%) patients have age group 41-50 years and 8 (7.54%) patients were in age group 51-60 years with anemia in chronic kidney disease as shown in Figure-2.

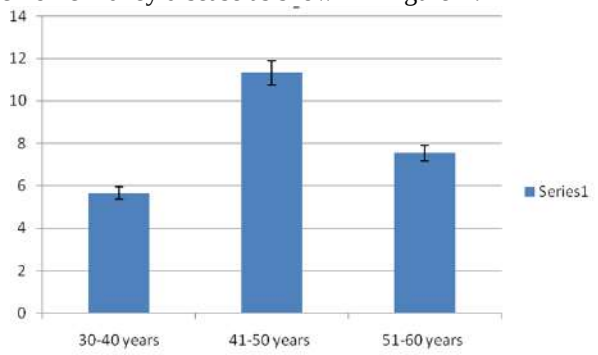

Figure No.2: Age wise distribution of Anemia patients in CKD

The anemic patient's distribution in different stage of CKD showed that, 02 (1.88%), 3(2.83%), 6 (5.66%), 8 (7.54%) and 7 (6.60%) were in chronic kidney disease stage 1, 2, 3, 4 and 5 correspondingly as shown in Figure-3.

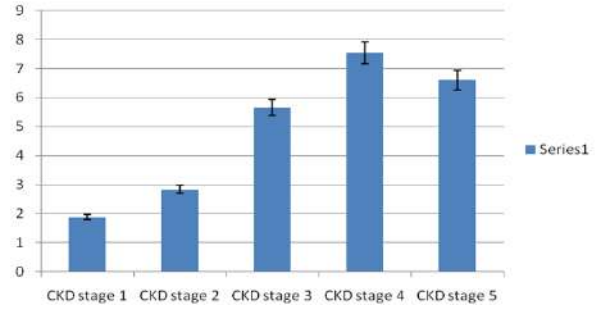

Figure No.3: Anemia distribution in different stage of CKD

DISCUSSION

Chronic kidney illness is a universal public health problematic. Main consequences of CKD comprise the development of CKD for the elimination of stage renal disease, the development of various difficulties due to kidney failure and the increase danger for development of cardiovascular sickness. Quite possibly the most common difficulties of CKD are anemia associated with augmented risk for cardiovascular illness, affects patients and deaths due to an increased risk especially in the high-risk group.

A total of 106 patients with chronic kidney disease patients visiting department of Medicine, Sandeman Provincial Hospital, Quetta were included. Mean age in our study was 48.38±7.89 years. Mean duration of CKD in our study was 3.89±1.66 days.

Out of 106 patients who developed chronic kidney disease patients, 26 (24.52%) had anemia and 80 (75.47%) did not have anemia. A study done in USA revealed that an assessed 14.0% adult people of US had CKD. Anemia stood twofold as predominant in individuals with CKD (15.4%) as in the overall population.[13]

The data result shows that the anemia due to chronic kidney disease was more in male 18(16.98%) patients as compared to female patients 8(7.54%). Contrast with our study Anemia was recognized in 51.3% men and 48.7% women. The occurrence of anemia augmented associated progressing CKD stage.[14] Frequency distribution of patients age showed that 06 (5.66%), were age group 30-40 years, 12 (11.32%) were age group year 41-50 and 8 (7.54%) patients were in age group 51-60 years with anemia in chronic kidney disease. Gunaseelan et al reported that 24.7%. prevalence of cases was age group of 51 - 60 years.[15]

The anemic patient's distribution in different stage of CKD showed that, 02 (1.88%) CKD stage 1, 3(2.83%) CKD stage 2, 6 (5.66%) CKD stage 3, 8 (7.54%) CKD stage 4 and 7 (6.60%) CKD stage 5. Previous study showed the incidence of anemia in CKD stage I (17.64%), Stage II (27.78%), Stage III (48.38%), stage IV (74.19%), stage V (80%).[16]

Early identification of anemia in CKD retards the development of end stage renal disease and consequently improves morbidity and mortality**.**

CONCLUSION

Anemia is one of the many complications of chronic kidney disease (CKD). Correction of anemia may improve renal and significant middle indicator of CKD hence it could be suitable to degree hemoglobin smooth at overall screening. Primary discovery of CKD is of highest position to stop the development of renal failure. Our study found high occurrence of anemia in to entirely stages of CKD. Hemoglobin lower 9 g/dl, would be needed treatment. Nevertheless, we must evade ignoring patients with severely anemia (10 g/dL hemoglobin).

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Effect of Nigella Sativa on Platelets in Organophosphorus Induced Toxicity in Albino Rats

Muhammad Sajid Khan[1], Raheela Adil[1], Sabahat Gul[4], Farheen Hameed[2], Mohammad Sair[2] and Muhammad Adnan Sadiq[3]

ABSTRACT

Objective: To evaluate the effect of Nigella Sativa on Platelets functions in Organophosphate induced toxicity in Rats.

Study Design: Experimental Study

Place and Duration of Study: This study was conducted at the Al Tibri Medical College Isra University Karachi Campus from January 2015 to July 2015.

Materials and Methods: Thirty albino rats were selected through random sampling and divided into three groups. Group A was the control group, Group B the group that was induced with Chlorpyrifos, whereas Group C was the interventional group in which the Chlorpyrifos and Nigella Sativa was given. At the end of the experiment, the rats were sacrificed and blood samples were collected via cardiac puncture, after which Platelet count was assessed. Data was analyzed using SPSS. To compare the mean values one-way ANOVA, followed by Post Hoc Tukey's test was done.

Results: The mean platelet count of the groups were $185x10^3/m^3$ for Group A, $95x10^3/m^3$ for Group B, and $115x10^3/m^3$ for Group C. Significant difference was seen in the mean platelets count between Group A and B (P-value ≤0.01), and Group B and C (P-value ≤0.01). No significant difference was seen between Group A and C.

Conclusion: Nigella Sativa had a protective effect on Platelet count and hence function when Albino rats were subjected to Organophosphorus Poisoning.

Key Words: Nigella Sativa, Platelets, Organophosphorus Induced Toxicity, Albino Rats

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INTRODUCTION

Nigella sativa L is one of the most effective herbal plants that are derived from their seeds. It is well placed under the classification of edible plants with basic composition of fatty acids (polyphenols and tocopherols) along with major content of water- soluble vitamins and adequate quantity of minerals that are essential for maintenance of healthy environment of the body.[1] Their anti-inflammatory and antimicrobial activity are main functional part of the seeds. The seeds and oil both having essential components that can establish the antioxidant status of the body.[2]

Kalongi is the common name of these seeds, and they are the part of daily cuisine on our society especially in Asian Countries. This plant belongs to the family of Ranunclaceae, and specie Sativa. Multiple studies establish the evidence regarding various benefits of the seeds.[3-4] Organophosphate is one of the poisons that creates oxidative stress in the body. They can over stimulate the cholinergic system and generates the oxidative stress, and alter the pathophysiology.[5] In developing countries the ratio of poisoning increases due to its excessive use, and lack of awareness regarding potential use of that product. Common site or exposure is its industrial usage as pesticides.[6] Most affected site is South Africa according to the report of epidemiology.[7] According to some case reports the thrombotic complication may occur due to acute poisoning.[8] Acute poisoning also alter the blood indices.[9] The poisoning also reports the deformation of the erythrocytes membrane due to inflammation, and also change the size and morphology of erythrocytes.[10] The basic purpose of this study is to evaluate the effect of black seeds in treating organophosphate poison and their influence on platelet count.

MATERIALS AND METHODS

The experimental study was designed at Al Tibri Medical College Isra University Karachi Campus from January 2015 to July 2015. After taken an ethical

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approval from the concerned authority, total 30 numbers of rats were randomly selected from the animal house. The animals were divided into three groups on the basis of treatment plan, and each group having 10 numbers of rats with weight of 150-250 gms. Group A (Control) given normal saline and normal diet with 12 hours light and dark cycle. Group B (toxic) group given orally with Chlorpyrifos daily for 6 weeks (The dose was given 4.2 mg/kg b.w. - 1/20th L D_{50}). Group c (treated) group Chlorpyrifos with Nigella sativa for 6 weeks. (The dose was given 4.2mg/kg b.w. - 1/20 LD_{50} + 500mg/kg b.w. The Nigella seeds extract were washed under tap water. The seeds were placed and spread properly on cotton cloth. The room temperature was maintained between 35°C - 40°C in day time and 25°C - 30°C at night. This procedure was done continuously for 6 weeks, till the seed were completely dried. After dryness the seeds were converted into powder by using grinder. The desired compound was concentrated in the distillation flask, and made the ethanol based extract. Each animal was anaesthetized by giving deep ether anesthesia then dissected through midline abdominal incision. Thoracic cage was retracted. The heart was exposed, and blood samples were collected via cardiac puncture from each rat with the help of syringe. Blood was collected in heparinized tubes for the assessment of blood parameter. The data was analyzed through SPSS. To compare the Mean values one way of ANOVA was applied followed by post hoc Tukey's test, and the p value was considered significant at <0.05**.**

RESULTS

Figure 1 shows the Mean Platelets values among the different therapeutic groups

Table 1.1 shows the comparison of Mean with level of significance among different therapeutic groups.

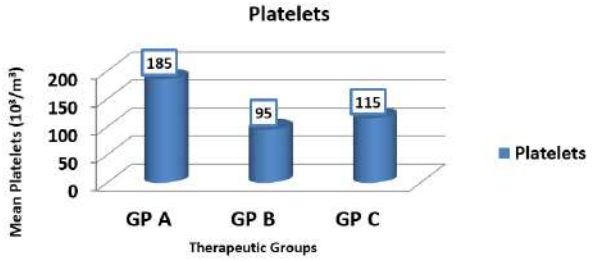

Figure No.1: The Mean Platelet count among the different Therapeutic groups

Table No.1: Comparison of Mean platelet values among the therapeutic groups

GP B vs A	GP B vs C	GP A vs C
≤0.001	≤0.001	0.005

DISCUSSION

Organophosphate compounds are commonly used as agricultural insecticide. However, its use has been directly proportional to global morbidity and mortality, with a greater predilection in developing countries [11]. With Organophosphate accounting for three million cases annually, it is important to control its use and find treatment modalities that might reverse its life threatening effects. Organophosphate inhibit the enzyme acetylcholine esterase (AChE) which in turn results in accumulation of acetylcholine, overexciting acetylcholine receptors and the parasympathetic pathway[12]. Organophosphate poisoning in the acute setting has a potentially of inducing thrombotic abnormalities [13]. Cohort studies have shown to increase prothrombotic diathesis in patients with organophosphate intoxication[14]. Many studies have gone onto show that Organophosphorus poisoning effects the platelets by inducing thrombotic events such as Deep vein thrombosis and pulmonary thromboembolism [15-16]. Nigella Sativa is hailed as a miracle herb, due to its miraculous therapeutic properties such as antihypertensive, liver tonics, diuretic, digestive, anti-bacterial, and analgesic[17]. Nigella Sativa was studied to see if it had any effect on the platelet levels in Organophosphorus pesticides. The interventional group C proved to show positive result when given Nigella Sativa, preventing significant reduction in the platelet levels. Although the platelet count wasn't as high or greater than Group A, the control group, it still managed to produce appreciable results showing off the miraculous properties of this herb. In another study, Nigella Sativa's preventive features were studied when rats were exposed to Diazinon, an organophosphate insecticide similar to the one in our study. The study showed that administration of Nigella Sativa attenuated the hematological changes that are caused by Diazinon [18]. Nigella Sativa also had a protective role in reproductive and hormonal alterations when induced by Chlorpyrifos, the same agent we used in our study [19]. This shows that not only does *Nigella Sativa* has a protective role on the hematological parameters of the body, which is also proven from our study, but cab exhibit protective efforts on other organs as well. We only went onto evaluate the platelets in our study, future studies can be done on other hematological parameters such as Red Blood Cell Count, Hematocrit, Mean Corpuscular Volume, Hemoglobin, Mean Corpuscular Hemoglobin Concentration, and White Blood cells as done in various studies [20]. However, uniqueness of our study is that Platelet count has not been studied often and knowing the fact that Organophosphate compounds can cause thrombotic events, more research needs to be done here.

CONCLUSION

Our study can concluded that Nigella Sativa prevented a decline in platelet count in Organophosphorus induced poisoning, thereby exhibiting a protective effect on the platelets.

Author's Contribution:

Concept & Design of Study:	Muhammad Sajid Khan
Drafting:	Raheela Adil, Sabahat Gul
Data Analysis:	Farheen Hameed, Mohammad Sair, Muhammad Adnan Sadiq
Revisiting Critically:	Muhammad Sajid Khan, Raheela Adil, Sabahat Gul
Final Approval of version:	Muhammad Sajid Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Anti-Oxident Effects of Cinnamon Extract in Alloxan-Induced Diabetic Rats

Raheela Adil[1], Muhammad Sajid Khan[1], Sabahat Gul[4], Farheen Hameed[2], Mohammad Sair[2] and Muhammad Adnan Sadiq[3]

ABSTRACT

Objective: To evaluate the antioxidant effects of cinnamon extract in alloxan induced diabetic rats.
Study Design: Experimental Study
Place and Duration of Study: This study was conducted at the Al-Tibri Medical College Isra University Karachi Campus during the period of December, 2012 to June, 2013.
Materials and Methods: Experimental study was designed with total 32 numbers of male rats, and the animals were randomized selected from the animal house after taken an ethical approval from the concerned authority. Animals were divided into four groups on the therapeutic basis. Diabetes was induced in rats by using alloxan and the antioxidant effects were evaluated through antioxidant enzymes. The data was analyzed through SPSS by applying One-way ANOVA to compare the mean difference between the groups. The level of significance was considered P=<0.05.
Results: Antioxidant level was maintained among the diabetic rats after utilization of cinnamon extract.
Conclusion: The result indicates that in diabetic conditions, oxidative stress is induced that causes peroxidative damage to membrane lipids. Cinnamon extract helps in restoration of antioxidant enzyme activity and their transcription.
Key Words: alloxan-induced diabetes, oxidative stress, antioxidant enzymes, cinnamon

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INTRODUCTION

Diabetes is one of the comorbidities among the infected peoples. The prevalence of the diabetes is still unknown, and different metaanalysis established the prevalence ratio of 10.3% and Mean age was reported around 49.5.[1] Metabolic disorders induced multiple underlying stress that can alter the different organic functional and chemical compositions, results in establishing an oxidative stress.[2] The cellular reduction-oxidation difference leads effects the oxidative levels that can alter the cell signaling process of β-cell dysfunction and insulin resistance. The numerous factors create an influence, that can cause the various functional defects especially in reducing the solubility, storage insufficiency, and this impair systematic regulation can affect the pharmacokinetics and their availability. [3] Short-lived reactive species (free radicals) that contains the one or more pair of electrons that can damage the cell by an oxidation. Diabetes provoke the oxidative stress and results in cell damage.[4] Reactive oxygen species stimulated by non-enzymatic glycoprotein and glucose oxidation and the activity of glucose transportation leads to insulin resistance.[5] Lipid peroxidation increased with the alteration in oxidative level of the body, and influence by target the defensive function against enzymatic and non-enzymatic antioxidants. [6] In diabetes the oxidative stress mainly changes the biochemical composition of cellular integrity and simultaneously become dangerous for insulin producing cells of pancreas. Free radicals induce alteration in cell signaling pathway inside the cell, like extra cellular signal regulated kinase pathway.[7] The purpose of the study to assess the effects of cinnamon extract in restoration of antioxidant levels, that are essential to maintain the integrity of β cells of pancreas in diabetic rats, as now in our community the diabetes is one of the common metabolic disorder that needs importance from heath care providers in controlling this health issue.

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MATERIALS AND METHODS

The experimental study was designed at Al-Tibri Medical College, Isra university karachi campus from

December 2012 to June 2013 After taken an ethical approval from the concerned authority, and total 32 numbers of male albino rats were randomized selected from the animal house with weight of 150 to 250mg. All rats were divided into four groups on the basis of therapeutic design. The cinnamon barks were purchased from the market, then these barks were washed with distilled water, and then dry to form the powder from these barks. 8 grams of powder was dissolved in 100ml of distilled water and then incubate at 60°C for an hour. This extract was administered with gavage tube daily for 4 weeks once daily. Group A (control Group) received normal saline, Group B (normal saline +cinnamon extract), Group C (diabetic group) induced by alloxane, and Group D (alloxane + cinnamon extract). The antioxidant enzyme was evaluated by preparing the lysate followed by centrifuging the blood sample. We observe the following antioxidant enzymes like catalase, superoxide dismutase (SOD) and glutathione reductase (GR). Data was collected from the alloxane based group to establish the confirmation of the diabetic status. After receiving the cinnamon extract for 4 weeks the blood sample were collected to compare the level of antioxidant enzymes. The data was analyzed through SPSS, the Mean value of each enzyme were compare through One-way ANOVA followed by post hoc Tukey's test, to ananlyze the significance difference between the groups.

RESULTS

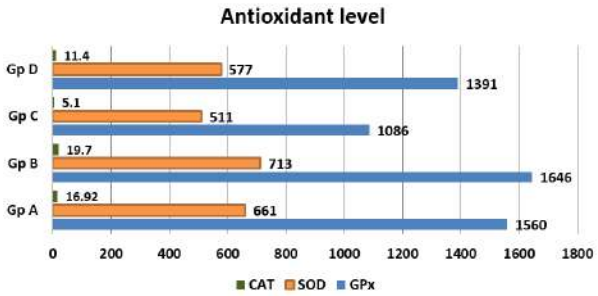

Figure No.1: Mean level of antioxidant enzyme among different therapeutic groups. CAT: catalase enzyme, SOD: superoxide dismutase, GPx: Glutathione peroxidase enzyme

Table No.1: Level of significance among the different therapeutic groups

Groups	Glutathione peroxidase	superoxide dismutase	catalase
Group C vs A	≤0.001	≤0.001	≤0.001
Group C vs B	≤0.001	≤0.001	≤0.001
Group C vs D	≤0.001	≤0.001	≤0.001

One-way ANOVA followed the post hoc Tukey's test applied P=<0.05

Antioxidant level was maintained among the diabetic rats after utilization of cinnamon extract.

Figure I shows the Mean values of antioxidant enzymes among different therapeutic groups.

Table 1 shows the level of significance among the different therapeutic groups.

DISCUSSION

Cinnamon extract used commonly around the world especially as herbal component especially in Asian countries for different therapeutic purpose. It mainly composed of hypoglycemic agent and simultaneously reduces the insulin sensitivity. Similarly, in the present study, cinnamon shows efficient role in reducing hyperglycemia and control the insulin sensitivity. In accordance with the study results, there was no significant role of cinnamon extract with the dose of 8gms for 8 weeks, and there was no reduction in glucose levels. Now in the present study the effects of cinnamon extract show remarkable effects in lowering the blood glucose levels.[9] The results of the study that was conducted to analyze the effects of cinnamon extract to improve the oxidative stress induced by the acrylamide in animal model. The extract shows significant restoration of antioxidant levels after inducing acrylamide toxicity as in the resent study, the positive effects was shown by the similar extract.[10] This herbal extract recovers lipid profile by inhibiting the ß-hydroxy-ß-methylglutaryl-coenzyme-A (HMG Co-A) reductase and evidence the restoration of oxidative stress. As per results of the present study, the same herbal product minimizes the injurious effects of free radicals resulting due to underlying diabetes.[11] One of the metaanalysis or a systemic review regarding usage of cinnamon extract as a supplement in reducing the lipid profile, as per results of that study shows the significant reduction in lipids levels and also covers the lipid peroxidation, that may leads to diminish the oxidative stress and maintain the bioavailability of antioxidant enzymes to establish the cell signaling pathway and restore the physiological and biochemical activity of enzymes.[12-13] In accordance with the study results the utilization of cinnamon oil as a potent protector against oxidative stress in mice, and they conclude the effective role of oil in reducing the oxidative stress like in the present study.[14] According to the study that was designed to induced acetaminophen induced liver toxicity that produces apoptosis and oxidative stress. They conclude the hepatoprotective role of cinnamon oil in restoring the liver injury and regulate the oxidative pressure along with boost up the antioxidant enzyme activity and enhance the anti-inflammatory response, as shown in present study the regulation of antioxidant enzyme activity produced by cinnamon extract application in diabetes rats.[15] In one

of the study the combination therapy was introduced to the type 2 diabetic rats for the purpose to maintain the glycemic control and lipid metabolic disturbance along with reduction in body weight. They induced the combination of ginger, cinnamon extract and turmeric for the hyperglycemic control in animal model. The results reveled the amazing facts by using this regime, control the complications results due to diabetes by overcome the oxidative stress, inflammatory conditions and manage the lipid serum levels.[16] All these facts combine establish the positive evidence regarding the usage of cinnamon extract or oil as an herbal product in the treatment of oxidative stress, and maintain the metabolic imbalance of the body.

CONCLUSION

The study conclude the antioxidant role of cinnamon extract when apply in diabetic rats. The level of antioxidant enzymes shows remarkable balancing in cinnamon feed groups by reducing the production of reactive oxygen species and restore the oxidative stress along with maintain the cellular integrity.

Author's Contribution:

Concept & Design of Study:	Muhammad Sajid Khan
Drafting:	Raheela Adil, Sabahat Gul
Data Analysis:	Farheen Hameed, Mohammad Sair, Muhammad Adnan Sadiq
Revisiting Critically:	Muhammad Sajid Khan, Raheela Adil, Sabahat Gul
Final Approval of version:	Muhammad Sajid Khan

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Outcome of Strict Peri-Operative Glycemic Control in Diabetic Patients Following Open Heart Surgery

Syed Imran-ul-hassan[1], Sharyar[1], Muhammad Rashid[2], Maryam Liaqat[1], Javairia Saleem[1] and Taiba Zulfiqar[1]

ABSTRACT

Objective: To compare the outcome in terms of post-operative complications and early morality of strict glycemic control among diabetics having open heart surgery with control group following open heart surgery.

Study Design: Prospective Cohort Study

Place and Duration of Study: This study was conducted at the Department of Anesthesia, Punjab Institute of Cardiology, Lahore from November 2020 to April 2021.

Materials and Methods: In this study, 60 patients were randomly assigned to two groups (30 patients in each group) according to a computer-generated allocation table. All the diabetic patients of 18 years to 60 years old with ASA II and III planned for cardiac surgery during this study period was included. In the control group no insulin was given to the patient unless blood glucose level exceeded 180 mg/dl. While in the study group glucose level between 80 and 110 mg/dl was targeted using continuous infusion of insulin in saline. Cardiac, Pulmonary, Renal and Neurological problems were noted. Early mortality was also documented.

Results: Mean duration of diabetes in the strict control of diabetes group was 13.57$\pm$6.32 years and in conventional group it was 12.89$\pm$5.88 years. Complications or poor outcome due to occurrence of complications or early mortality was seen in 29 patients in the conventional glycemic control group while only 8 patients in the strict glycemic control group. Cardiac complications were three times less in the tight control group. Early mortality was observed in the control group in 2 patients as compared to none in the strict / tight control group, difference was statistically significant p value <0.0001.

Conclusion: Intra-operative tight glycemic control can help in controlling post-operative morbidity after open heart surgery. With control of post-operative complications, the recovery process can be improved. All types of complications are decreased with strict glycemic control.

Key Words: Peri-Operative, Glycemic Control, Diabetic Patients, Open Heart Surgery

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INTRODUCTION

Diabetes is one of the common endocrine disorders with disturbed metabolic pathways, leading to significant morbidity. Patients of cardiac surgery also having diabetes can affect the outcome and lead to many post-operative complications. These include diabetic peripheral neuropathy, renal dysfunction, fatty liver, optic neuropathy and atherosclerosis.

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Glycemic control and hyperglycemia can impact the course of anesthesia and surgery.[1]

Review of literature shows that a strict control of sugar can be beneficial in prevention of post-operative on reducing neurological and infectious complications yet this was offset by the possibility of hypoglycemia which is more dangerous in case of general anesthesia in the short term view.[2,3]

Diabetes or impaired glucose tolerance is common state of the body of candidates of cardiac surgery. Few of them are even undiagnosed diabetics with hyperglycemia leading to further increase in the chances of development of post-operative complications. Increase in the hospital stay leads to further increase in the cost of the treatment.[4]

Studies have concluded that the glycemic control in perioperative period is a key factor in determining the outcome of surgery and complications, especially during open heart surgery. But the extent of control is still debatable, whether the strict control of blood sugar can further improve the outcome as compared to the patients with normal or below average control.

Most of the studies concluded in the favor this notion, still few have shown the difference to be in-significant.[5,6]

Various societies of surgeons have recommended a controlled blood sugar level of less than 180 mg/dl during the surgery and in the ICU. No local study is available in our region regarding assessment of outcome in terms of post-operative complications of cardiac surgery with strict control of blood sugar. Can the extent of glycemic control in cardiac surgery patients affect the outcome of cardiac surgery and its complications? The aim of the study was to determine the association between perioperative glycemic control and the outcome of patients following open heart surgery. With continuous strict control of sugar, significant morbidity can be prevented, thus improving the outcome.

MATERIALS AND METHODS

In this cohort study done at the Punjab Institute of Cardiology, Lahore, Pakistan between November 2020 to April 2021 (6 months), after the ethical clearance of the Hospital Research Review board. Informed consent was signed from the patients to asking them regarding the use of data for the purpose of study.

We conducted this study on 60 patients randomly assigned to two groups (30 patients in each group) according to a computer-generated allocation table. All the diabetic patients included were of 18 years to 60 years old and were falling in the ASA - American Society of Anesthesiologists class II and III, and were planned for cardiac surgery during this study period.

Sample size calculation was done using WHO sample size calculator, assuming the incidence of adverse events in tight control of blood sugar group was 14% and 42% in the control group, taking power of the study of 80% and level of significance of 5 %.

All of these enrolled cases were put on insulin therapy two days before the operation following the routine of the hospital protocol for all the patients. All the patients with a fasting (8 hours fast) blood glucose level of more than 140 mg/dl were declared as diabetic.

Any patient with impaired renal functional renal impairment (creatinine level more than 1.6 mg/dl) in whom hyperkalemia may be present that may require insulin – glucose for correction of hyperkalemia, patients with poor glycemic control (HbA1c ≥9%), having emergency surgery, having surgery with off-pump bypass, age less than 18 years, on dialysis due to renal failure, and having history of cerebral vascular accident/transient ischemic attack (CVA/TIA) within the last six months were excluded from the study.

For all patients included in the study, medical record (MR) numbers were obtained, files were retrieved from medical records, and data were collected on a predesigned data collecting form by one of the investigators.

The day before surgery, pre-operative evaluation of patients was done which included medical history, clinical examination, chest X-ray examination, ECG, data of cardiac catheterization, echocardiography and laboratory investigations (complete blood count, bleeding time, clotting time, prothrombin time, partial thromboplastin time, blood sugar, Hemoglobin A1c, liver function tests, renal function tests, and urine analysis. Then the study protocol was explained to every patient.

The anesthetic technique was the same for all patients in the study, starting by pre-operative re-examination of the patient, and re-checking his file. On arrival to the operating room, in the fasting patient a venous cannula (22 Gauge) was inserted in the non-dominant forearm under complete aseptic technique and 1–2 mg midazolam was injected through it. The non-dominant radial artery cannulation is performed under local anesthesia using lidocaine 2% after doing modified Allen's test, followed by insertion of thoracic epidural catheter. The patient was put in the sitting position, the anesthetist wearing sterile gloves painted the patient's back with antiseptic solution, the site of epidural needle entry (mid-line – at the level of the line joining the lower angle of the two scapulae) was infiltrated with 2 ml lidocaine 2% using sterile fine needle of insulin syringe (least painful) before advancing the epidural needle with loss of resistance test applied till reaching the epidural space.

After intubation, patients were mechanically ventilated through volume-controlled ventilation with 100% O2 to maintain the end-tidal CO2 at 30–35 mmHg. We continued with isoflurane 0.5–1% (aided by the epidural morphine) and proceeded for central line cannulation of the right internal jugular vein with a 2-way CVP catheter.

Blood glucose was measured (venous blood samples with-drawn and sent to the hospital lab for blood glucose level) just before induction of anesthesia, before skin incision, before initiation of cardio-pulmonary by-pass, every 20 min after start of by-pass till the patient was transferred to the intensive care unit where blood glucose level is measured every 2 h until extubation is done. After extubation blood glucose was monitored every 4 h routinely.

In the control group no insulin was given to the patient unless blood glucose level exceeded 180 mg/dl. If so, we initiated an infusion of rapidly acting insulin (act rapid) in saline of 6–9 units/h using syringe pump and adjusted the rate of infusion to keep glucose level between 110 and180 mg/dl.

While in the study group where tight glycemic control of glucose level between 80 and 110 mg/dl was targeted we gave a continuous infusion of insulin in saline (50 units of rapidly acting insulin (act rapid) in

50 ml syringe) at a rate of 1–2 units/h if blood glucose between 110 and 150 mg/dl. If blood glucose level was between 150 and 200 mg/dl, we increased the rate of insulin infusion to 4–6 units/h. And if it exceeded 200 mg/dl then the insulin infusion rate was 6–9 units/h.

Delayed recovery was defined as extubation done in the next day of operation after 18 hours of intubation. Cardiac problems noted were atrial fibrillation or acute myocardial infraction. Pulmonary problems noted were prolonged bronchospasm, pneumothorax, bronchitis, atelectasis and pleural effusion. For all these serial X-rays of the chest were done. Renal problems were defined as doubling of serum creatinine level by 2nd day of operation. Neurological problems were defined as any episode of post-op stroke within 4 days of operation or any episode of post-op delirium (POD). Early mortality was defined as mortality of the patient in the cardiac ICU.

RESULTS

In this prospective cohort study, 60 patients were enrolled and randomly assigned to two groups. Mean age of the patients included in the study was 54.76+8.32 years. Male and female ratio was almost the same in both the groups. In the strict control group, 17 were male and 13 were females while in the control group on conventional treatment strategy 18 were male and 12 were females.

Mean duration of diabetes in the strict control of diabetes group was 13.57±6.32 years and in conventional group it was 12.89±5.88 years. Table 1 showing the comparison of outcome / complications like pulmonary complications, cardiac complications, Renal problem, Neurological problems, Surgical problems and early mortality among the patients having cardiac surgery.

Complications or poor outcome due to occurrence of complications or early mortality was seen in 29 patients in the conventional glycemic control group while only 8 patients in the strict glycemic control group. Table no. 1 below is showing various outcomes / complications of cardiac surgery with strict versus conventional peri-operative glycemic control.

Cardiac complications were three times less in the tight control group. Similarly, pulmonary complications were reduced almost two times; renal, neurological and surgical complications were reduced by 4-5 times than those in the control group.

Early mortality was observed in the control group in 2 patients as compared to none in the strict / tight control group, difference was statistically significant p value <0.0001.

Table No. 1: Comparing the various outcomes / complications of cardiac surgery with strict versus conventional peri-operative glycemic control

Outcomes	Control Group		Strict Control		P value
	No. of patients	%	No. of patients	%	
Pulmonary problem	5	16.67	2	6.67	0.23
Cardiac Problem	6	20	2	6.67	0.13
Renal Problem	5	16.67	1	3.33	0.08
Neurological Problem	4	13.33	1	3.33	0.16
Surgical Problem	7	23.33	2	6.67	0.07
Early Mortality	2	6.67	0	0	0.0001
Total	29		8		

DISCUSSION

Patients of cardiac surgery are mostly diabetic and diabetes is a major factor in deciding the outcome of the cardiac surgery. A patient of cardiac surgery with controlled diabetes may have a better outcome as compared to the patient with un-controlled diabetes. Diabetes can be a major medico-economic problem, especially in the developing and under-developed countries. Can a better control of diabetes affect the outcome of cardiac surgery? It's still a matter of debate and research. This study was designed to determine the outcome of cardiac surgery in terms of various complications in the post-operative period between patients with strict glycemic control and those with poor control. Only adult patient of CABG were included.

Mean duration of diabetes in the strict control of diabetes group was 13.57±6.32 years and in conventional group it was 12.89±5.88 years. Complications or poor outcome due to occurrence of complications or early mortality was seen in 29 patients in the conventional glycemic control group while only 8 patients in the strict glycemic control group. Cardiac complications were three times less in the tight control group. Similarly, pulmonary complications were reduced almost two times; renal, neurological and surgical complications were reduced by 4-5 times than those in the control group. Early mortality was observed in the control group in 2 patients as compared to none in the strict / tight control group, difference was statistically significant p value <0.0001.

In a similar study, complications were seen more frequently among the patients with poor glycemic

control. Patients with strict control of sugar during the operation had less frequent postoperative complications (23.2% vs 34.1%), although the mean blood glucose was not significantly different (6.6 ± 0.7 vs 6.7 ± 0.8 mmol/L, P < .001).[7]

Siddiqui KM, et al reported in a local study including 129 patients in 2 years. Male to female ratio was 3:1. Majority was of CABG (95.3%); few were of CABG plus valve replacement. Mean fasting blood sugar (FBS) was 154.6 ± 55.6 g/dl and mean duration of diabetic was 12.3 ± 5.5 years. Data analysis showed that no intraoperative and postoperative complications were seen among these patients.[8] In our study, both the groups had complications but these were much reduced with strict glycemic control.

In a study on 100 patients of cardiac surgery, all the features related to intra-operative and post-operative complications of all the patients were noted. Among the control group of patients 21 (43%) had complications and 7 (14%) cases in the group of patients with strict glycemic control group. P = <0.05.[9]

Unlike the results of our study and many others like those mentioned above, Chen CP, et al studied cardiac surgery patients with diabetes. Duration of ventilation, stay in ICU, blood transfusion, postoperative infection, hypoglycemic events were not significantly different between case and control groups (p>0.05).[10]

In a study published in 2005, open heart surgery patients having poor glycemic control had poor outcome. Among all these cases, poor intra operative glycemic control was seen in 18% cases. Frequency of patients with poor intraoperative glycemic control was more in patients with severe postoperative morbidity (37% vs. 10%; P < 0.001).[11] This was almost similar to our data analysis.

A review study was published in 2018, in which it was concluded that a higher sugar level before the surgery and during the surgery is associated with poor outcome. A strict control of blood sugar for patients with diabetes and moderate control for pre-diabetic patients can improve outcome.[12]

Intensive insulin therapy for strict control in diabetic patients of cardiac surgery was done in the peri-operative period. 82 of 185 (44%) cases in this group and 46% in the conventional therapy group had compilations. This raised mortality and incidence of stroke with strict control of blood sugar through insulin therapy, unlike the results of other studies, can raise a concern for cardiac surgeons.[13]

Studies have proved with evidence from clinical data that perioperative control of hyperglycemia in cardiovascular surgery patents, can affect the outcome. Guidelines should be made regarding the control of blood sugar for all the cardiac surgery patients with history of diabetes and those without diabetes.[14]

It has been reported previously that the variable diabetes and hyperglycemia in patients of cardiac surgery are associated with severe outcomes. And by improving the control of the patients of cardiac surgery can improve the success rate and overall morbidity of the patients.[15]

CONCLUSION

Intra-operative tight glycemic control can help in controlling post-operative morbidity after open heart surgery. With control of post-operative complications, the recovery process can be improved. All types of complications are decreased with strict glycemic control.

Recommendations: Study should be planned with a longer follow-up with a larger sample size to see the impact of tight control of blood sugar of diabetic patients having open heart surgery, on the outcome and post-operative complications along with length of hospital stay and 30 days mortality. With that it can be recommended to all the diabetic patients of open heart surgery with monitoring of blood sugar for any episode of hypoglycemia no fear of hypoglycemia if close monitoring of blood glucose level is done to maintain eu-glycemic stability.

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Original Article

Awareness of Breastfeeding Among Nursing Students of Al-Tibri Medical College & Hospital

Nighat Seema[1], Bushra Zulfiqar[2], Erum Saboohi[1], Shagufta Perveen[1], Amna Khan[3] and Ume Kulsoom[3]

ABSTRACT

Objective: To provide the awareness of breastfeeding among nursing students.
Study Design: Descriptive case study.
Place and Duration of Study: This study was conducted at the Al-Tibri Medical College & Hospital, Al-Tibri School of nursing, Karachi between the duration of November 2020 to April 2021.
Materials and Methods: A total of 42 responses were received including 30 male and 12 female nursing students. A survey of 28 close- and open ended questions was developed after extensive literature review.
Results: Among 42 responses, majority of students were male 71% and 29% were female with mean age of 20.18 ± 0.13. The maximum numbers of our nursing students have basic knowledge of breastfeeding and were familiar about its benefits but less aware about the transmission of communicable diseases (such as HBV, HCV, HIV, and TB) through breast milk. Moreover there is need to emphasize the nursing curriculum to advance their knowledge against breastfeeding.
Conclusion: These studies revealed that majority of the female nursing students were more aware about the breastfeeding and its benefits than male nursing students. There is no statistical association observed between the gender and awareness regarding breastfeeding.
Key Words: Breast feeding, awareness, bacterial infections, viral infections.

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INTRODUCTION

Malnutrition of child, low literacy and high infant mortality are most common public health problems found in Pakistan. The leading cause for child morbidity and mortality is malnutrition. The reason is the lack of exclusive breastfeeding. World Health Organization declares breastfeeding is the best source of nutrition for infants and children and it is enthusiastically working to increase the rate of exclusive breastfeeding from the baseline of 37 per cent to at least 50% by year 2025 among the world.[1] Unfortunately more than 800,000 global deaths of children and cumulative loss of 302 billion USD is attributed to not breastfeeding according to the recommended guidelines[2].

Breastfeeding provide protection from innumerable illness like diarrhea and pneumonia which remains to be the leading cause of death of infants globally, in addition, breastfeeding increases IQ level of growing child, promote better neurodevelopment and growth of children and most importantly upholds the bonding of mother and children. Moreover, it also reduces the risk of breast cancer, ovarian cancer and diabetes in women[3,4]. For this instance, breastfeeding can prevent annually 823,000 child and 20,000 breast cancer deaths[5].

Every mother has her own decision, how to feed her child but this decision is greatly influenced by the economic, community and other factors such as counselling from healthcare facilities, workplace and available marketed infant foods. For this purpose, WHO also offers training program for healthcare professionals to care breastfeeding mothers and overcome their problems regarding growth of children and make sure that the every children have the opportunity to thrive[6,3].

With investment in enhancing the children's strength and health, breastfeeding also supports the economy of a country by investing in manpower development that absolutely benefits the economy of country. It is one of the best investments in global health which counter that every $1 invested in breastfeeding generates $35 in economic returns[2,7].

According to Keith E. Hansen (the World Bank Country Director for Kenya):

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"If breastfeeding did not already exist, someone who invented it today would deserve a dual Nobel Prize in medicine and economics" [8].

The aim of the study is to educate them about the benefits of breastfeeding and to investigate about how much they actually know about the phenomenon.

Breastfeeding promotion remains an intervention of enormous public health potential to decrease global mortality and promote better growth and neurodevelopment in children**.**

MATERIALS AND METHODS

The cross sectional study was conducted after ethical approval from concerned authority. The study was conducted at ATMC&H and Al-Tibri school of nursing between the duration of November 2020 to April 2021. A total of 42 participants (30 male and 12 female students) were included in this study.

Only Nursing undergraduate students were included in the study. Other students from medical and health sciences were excluded, data was presented in the form of frequency and percentage to evaluate the gender based awareness. Chi-square test was applied to assess the association between the variables at $p \leqslant 0.05$.

Data Collection: A self-designed questionnaire was distributed among the students of Nursing and before the data collection the questionnaire was explained to the participants. The questionnaire includes 28 questions comprises of three parts. The first part has 15 questions regarding their basic knowledge of breastfeeding. The second part had 5 question targeted their beliefs about benefits of breastfeeding. The third part consisted of 8 questions regarding their knowledge of breastfeeding in chronic condition/illness. The data analysis was carried out by using SPSS Software (version v24)

RESULTS

In this study, the total numbers of respondents were 42 nursing students out which majority of students were male 71% and29%were female (Fig. 1) with mean age of 20.18 ± 0.13 (Table1).

Table 2 showed the responses against their basic understanding about breastfeeding which accounts for about 90 percent correlations between the answers of male and female nursing students. Exceptions were found for the question no. 8 "Nothing should be given to exclusively breastfed babies" and "expressed Breast milk can be given to preterm babies with improper sucking", however, the chi-square test value indicates that there is no statistically significant (i.e. $p<0.005$) difference between gender based responses against the questions asked.

Table 3 summarized the responses about benefits of breastfeeding, which impact on mother and children both. The responses showed that only 38% – 42% percent nursing staff were aware from reducing risk of breast and ovarian cancer in breastfeeding mother with no statistically significant difference (i.e. $p<0.005$). Furthermore, about 90% students were agreed to the benefits of breast milk, but the correlation among the variables was found to be insignificant and weak.

Table 4 emphasized upon the participant's knowledge of breastfeeding when mother or child is suffering from bacterial or viral infections like Hepatitis (HBV & HCV), HIV, TB, diarrhoea, mouth ulcers and respiratory illness etc.

In this study, we found that there is a lack of awareness among nursing students about breastfeeding. Certain misconceptions were found regarding transmission of viral infection like Hepatitis B (HBV), Hepatitis C (HCV), and other infectious disease like Tuberculosis (TB) through breastfeeding. It was observed that only 28% and 35% participants were aware that there is no association between the transmission of these viral infections (HBV, HCV respectively). Similarly, only 23% participants already knew that bacterial infections (like TB) would not spread nor it has anything to do with breastfeeding. Almost 83% students were aware about the transmission of HIV through breast milk however, the chi-square test value indicated insignificant correlation (i.e. $P>0.05$), except that the response generated in the question no. 7 i.e. "Breast feeding should be continued if baby develops respiratory infection" showed that the relationship between the tested variables is weak positive ($P=0.0175$).

This study revealed that 52% & 42% of participants believed that breastfeeding should be discontinued if child develop respiratory illness and oral ulcers respectively. Although, to some extent breastfeeding helps in reducing respiratory illness[9].

Table No.1: Frequency of Age and Gender

Age and Gender Distribution		
Male	**Female**	**Mean Age**
30	12	20.18 ± 0.13

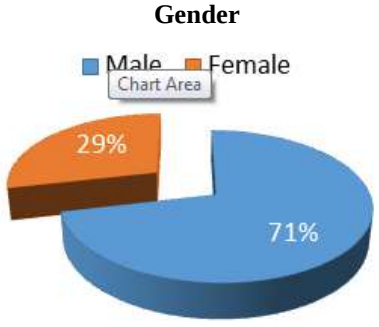

Figure No.1: Ratio of Male & Female

Table No.2: Participants basic knowledge regarding breastfeeding

		Male		Female		% YES	% NO	P-Value	χ^2
		Yes	No	Yes	No				
Q1	Breast feeding should be started within half an hour after delivery	27	3	11	1	90.48	9.52	1.000	0.028
Q2	Breast feeding helps mother in reducing gestational weight gain	23	7	9	3	76.19	23.81	1.000	0.013
Q3	Breast feeding helps in birth spacing	23	7	9	3	76.19	23.81	1.000	0.013
Q4	Breast feeding should be continued exclusively for a period of 6 months	21	9	11	1	76.19	23.81	0.233	2.218
Q5	Colostrum should not be discarded	25	5	9	3	80.95	19.05	0.668	0.386
Q6	Colostrum is beneficial for babies	27	3	10	2	88.10	11.90	0.613	0.363
Q7	Breast feeding should be continued for 2 years	27	3	10	2	88.10	11.90	0.613	0.363
Q8	Nothing should be given to exclusively breastfed babies	17	13	8	4	59.52	40.48	0.731	0.356
Q9	Weaning should be started at 6 months of age	22	8	10	2	76.19	23.81	0.696	0.472
Q10	Breast milk is always sterile	27	3	8	4	83.33	16.67	0.088	3.36
Q11	Breast milk is easier to digest	26	4	9	3	83.33	16.67	0.387	0.84
Q12	Bottle feeding should be discouraged	21	9	10	2	73.81	26.19	0.464	0.788
Q13	Bottle feeding has many adverse effects	26	4	11	1	88.10	11.90	1.000	0.204
Q14	Twin babies should be breastfed	27	3	11	1	90.48	9.52	1.000	0.028
Q15	expressed Breast milk can be given to preterm babies with improper sucking	9	21	9	3	42.86	57.14	0.14	7.088

Table No.3: Knowledge of Participants on benefits of breastfeeding

		Male		Female		% YES	% NO	P-Value	χ^2
		Yes	No	Yes	No				
Q1	Breast feeding protects mother from ovarian cancer	13	17	3	9	38.10	61.90	0.316	1.222
Q2	Breast feeding protects mother from breast cancer	15	15	3	9	42.86	57.14	0.180	2.188
Q3	Breastfeed infants are more intelligent	27	3	10	2	88.10	11.90	0.613	0.363
Q4	Breast feeding protect babies from infection	28	2	10	2	90.48	9.52	0.565	0.995
Q5	Breast feed is ideal nutrition for babies	28	2	8	4	85.71	14.29	0.046	4.978

Table No.4: Awareness of breastfeeding during chronic condition or illness

		Male		Female		% YES	% NO	P-Value	χ^2
		Yes	No	Yes	No				
Q1	Breast feed should be started immediately after caesarean section	9	21	4	8	30.95	69.05	1.000	0.045
Q2	Breast feeding should be continued with maternal Hepatitis C infection	12	18	3	9	35.71	64.29	0.495	0.84
Q3	Breast feeding should be continued	8	22	4	8	28.57	71.43	0.715	0.187

	with maternal Hepatitis B infection								
Q4	Breast feeding should be continued with maternal HIV infection	5	25	2	10	16.67	83.33	1.000	0.000
Q5	Breast feeding should be continued with active maternal Tuberculosis	7	23	3	9	23.81	76.19	1.000	0.13
Q6	Breast feeding should be continued if baby develops diarrhea	24	6	10	2	80.95	19.05	1.000	0.062
Q7	Breast feeding should be continued if baby develops respiratory infection	12	18	10	2	52.38	47.62	0.017	6.453
Q8	Breast feeding should be continued if baby develop oral ulcers	10	20	8	4	42.86	57.14	0.84	3.889

DISCUSSION

Efforts have been made to promote breastfeeding throughout the world. Despite these efforts, lack of awareness regarding breastfeeding has been documented. According to Statistics by WHO, about 44% children of Pakistan are under weight and height, having poor physical and intellectual performance. This percentage can be reduced by exclusive breastfeeding for a period of 6 months, later on complimentary breastfeeding for about 2 years. The global health care organization like PAIMAN, USAID, and UNICEF have initiated in services trainings and breastfeeding awareness programin a few districts of Pakistan[9-10].

The majority of our participants valued breastfeeding as an important feed for infants and familiar about the basic knowledge of breastfeeding however, they are against in favour of feeding expressed breast milk to preterm babies with improper sucking. This has been summarized in Table 2.

Majority of nursing students were less familiar with major benefits of breastfeeding (Table 3.) comprising reduce risk of breast and ovarian cancer which accounts for being the most invasive malignancy in women, and having a prevalence of 36.8% when accounting for all female malignancies, ultimately leading to a high mortality rate[11]. Centers for Disease and Control, declares that there is no data documented regarding transmission of HBV and HCV through breast milk, therefore, HBV and HCV positive mother can continue breastfeeding, and hence HBV and HCV infection is not contraindication to breastfeeding[12,16].

Breast-feeding is strongly not recommended to mothers infected with human immunodeficiency virus (HIV), and type 1 human T-cell leukemia virus because this pathogen can transmit postnatally from breast milk to infants[13]. On the Other hand, Tuberculosis (infection caused by Mycobacterium tuberculosis) is considered safe for feeding mothers as comparison to other infectious diseases. Therefore, breastfeeding consider compatible for mother infected with TB[14]. Unlike, most of the nursing students were not aware of breastfeeding during chronic condition or illness like HBV, HCV & TB with exception of HIV but majority were up to date about the breastfeeding during respiratory illness, diarrheal condition and upon development of oral ulcers in children.

According to a systematic review by (yang et.al), there is need to emphasize the nursing curriculum and specialized program that can advance the limited knowledge of nursing students regarding breastfeeding and to enhance their confidence in guiding breastfeeding mothers[15-16].

CONCLUSION

This is a very important finding that the majority of the female respondents were well aware about the breastfeeding and its benefits in comparison to male respondents. Moreover, there is a need for changes in existing nursing syllabus in institutions to promote awareness that support successful breastfeeding among students of nursing.

Author's Contribution:

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Original Article

Screening of Young Adults Using HbA1c for Evaluating Pre-Diabetic Status

Huma Ahsan, Moin Ud Din Ahmed and Tooba Khan

ABSTRACT

Objective: HbA1c is usually used a useful biomarker for monitoring glycemic control but also in predicting and identifying diabetic patients. The objective of this study is to determine the incidence of diabetes in pre-diabetic adults by using HbA1c.

Study Design: Cross Sectional Observational Study

Place and Duration of Study: This study was conducted at the Naz Memorial Hospital Karachi Sindh Pakistan from June, 2019 to December, 2020.

Materials and Methods: After ethical approval, patients attending the medicine clinic of the hospital between 18 and 50 years of age, previously undiagnosed with diabetes, having HbA1c in between 5.4-6.4 and agreed to participate were included. Diabetic patients or with an HbA1c below 5 and above 7 were excluded. SPSS version 23.0 was used for analysis of data. Chi-square and independent t tests were applied between qualitative and quantitative variables keeping p-value of <0.05.

Results: In 100 patients with mean age 33.59 ± 6.68 years, 38 males and 62 females. Mean weight and height was 77.2 ± 12.17 kg and 1.62 ± 0.09 m respectively. 28 patients were between 18.5-24.5 kg/m^2 of BMI while 26 between 24.5-30 kg/m^2 and 46 were above 30 kg/m^2. Mean fasting blood glucose was 110.52 ± 5.63 mg/dl, mean HbA1c 5.87 ± 0.35 %. 54 patients had HbA1c below 6.5 while 46 had above 6.5 but less than 7%.

Conclusion: Significant differences between nationalities, weight, BMI, smoking, family history of diabetes and fasting blood sugar levels were reported in patients having an HbA1c greater than 6.5 %.

Key Words: Pre-diabetes, Glycosylated hemoglobin, Screening

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INTRODUCTION

Diabetes is a chronic endocrine disorder that becomes a serious problem in developing world. It occurs when either pancreas does not produce enough insulin in body or body does not use insulin actively to regulate blood glucose which is produce by pancreas [(1)]. Non-insulin dependent or adult onset diabetes also known as diabetes type II in which body fails to secrete ample amount of insulin to fulfill body requirements, the risk of diabetes include, family history, metabolic factors, ethnicity and a sedentary lifestyle[(2,3)].

On the global health care system, a large economic burden imposes due to increase cases of diabetes, in future low-middle income nations will carry larger population effected with diabetes[(4)]. The eight most common reason behind mortality in either gender and fifth most commonly observed reason of death amongst women was diabetes[(5)]. Prevalence of diabetes has risen in the past few decades throughout the world among all socio-economic status especially in low and middle income population. Such populations have also reported an increased number overweight or obese people[(6,7)]. Recent researches show that obesity's prevalence amongst children as well as adolescents is rising at alarming rates. Most of adult diagnosed with diabetes are found to be overweight, with positive history of diabetes in family, demonstrating insulin resistance [(8)]. Diabetes is increasingly being reported among females as well as specific ethnicities. Detecting diabetes in the early phase might help in reduction of disease's impact especially in-between young adults. Therefore, analyzing aspects attributed with impairment of glucose metabolism may result in improved understanding of present increase in diabetes in young adults [(9)]. HbA1c (Glycosylated hemoglobin) has recently been advocated as standard approach in confirming diabetes. HbA1c is utilized as screening tool in detection of diabetes [(10)]. First isolation of HbA1c was accomplished by Huisman. Characteristics were noted by Bookchin and Gallop, regarding HbA1c under glycoproteins. It is used as biomarker in monitoring blood glucose levels, initially being proposed by Koenig et al [(11)].

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The expression of HbA1c is done in percentage. More percentage mean greater blood glucose levels in previous 2-3 months. HbA1c levels in-between 5.7-6.5%, denote pre-diabetes status wherein levels 6.5% or higher, means a patient is diabetic[12]. HbA1c was directly associated to diabetes risk progression in glucose intolerant individuals. HbA1c percentages are measured at the same time as oral glucose tolerance tests to evaluate if HbA1c should be utilized to diagnose diabetes instead of oral glucose tolerance test [13]. It is found that the oral glucose tolerance test could identify approximately 90% patients having HbA1c greater than 7 percent as being diabetic. Race / ethnicity amongst diabetic people with "borderline diabetes," and people with no diabetes have been shown to be substantially co-related to HbA1c[14]. A growing number of countries have rapidly embraced the use of HbA1c as a screening marker in clinical practice where it can provide an excellent cost-effective approach to diabetic mellitus screening, provided it is demonstrated to have adequate sensitivity and specificity. The aim of this study is to evaluate incidence of diabetes in pre-diabetic adults by using HA1c. People with family history of diabetes or other predisposing risk factors will benefit. Early diagnosis or prediction helps them to change their lifestyle or pharmacological intervention to prevent or delay onset of diabetes.

MATERIALS AND METHODS

This cross sectional observational study was done using non-probability convenient sampling technique from June 2019 to December 2020 at the Naz Memorial Hospital Karachi Sindh Pakistan. After ethical approval, patients attending the medicine clinic of the hospital between 18 and 50 years of age who were previously undiagnosed with diabetes mellitus, having an HbA1c between 5 -7 and agreed to participate in the study were included. Diabetic patients or patients with an HbA1c below 5 and above 7 were excluded from the study.

HbA1c cut off values for pre-diabetes were used as recommended by the American Diabetes Association (ADA) were patients having HbA1c above 5.4 and below 6.5 were treated as pre-diabetes if checked for the first time, while HbA1c above 6.5 was check again and if still found above 6.5, were excluded been diagnosed with diabetes. Demographic characteristics of the patients included their age, gender, nationality, weight, height, BMI, history of hypertension, asthma, thyroid disorder, family history of diabetes in family, fasting blood sugar, HbA1c, lipid profile including total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein. For laboratory investigation, a fasting blood sample of five ml venous blood was taken using aseptic technique and fasting for about 12 hours.

SPSS version 23.0 was used for analysis of data. For qualitative variables, frequency and percentages were reported and for quantitative variables, mean and standard deviation were reported. Patients were divided into two groups, one group being those having HbA1c levels below 6.5 % and another group having HbA1c levels above 6.5 %. To test for significance between groups, chi-square and independent t tests were applied between qualitative and quantitative variables. A p-value of <0.05 was considered as statistically significant.

RESULTS

From the total of 100 patients in the study, the mean age was 33.59 ± 6.68 years. 38 were male and 62 females 80 percent patients were Sindhi. Mean weight and height of patients was 77.2 ± 12.17 kg and 1.62 ± 0.09 m respectively. 28 patients were between 18.5-24.5 kg/m^2 of BMI while 26 between 24.5-30 kg/m^2 and 46 were above 30 kg/m^2. 38 patients gave a history of hypertension while 20 of asthma and 38 of a thyroid disorder. 12 patients reported positive history of smoking. Mean fasting blood glucose was 110.52 ± 5.63 mg/dl, mean HbA1c 5.87 ± 0.35 %, mean total cholesterol 200.1 ± 23.15, mean triglycerides 170.9 ± 13.73 mg/dl, mean HDL 48.16 ± 7.25 mg/dl while mean LDL was 92.1 ± 19.23 mg/dl [Table I].

Table No.1: Baseline demographics of study participants

Variables		Mean ± SD / Frequency (%) n=100
Age (years)		33.59 ± 6.68
Gender	Male	38 (38%)
	Female	62 (62%)
ethnicity	Sindhi	80 (80%)
	Balochi	10 (10%)
	Pathan	04 (4%)
	Punjabi	04 (4%)
	Siraiki	02 (2%)
Weight (kg)		77.2 ± 12.17
Height (m)		1.62 ± 0.09
BMI (kg/m^2)	<18.5	0
	18.5-24.5	28 (28%)
	24.5-30	26 (26%)
	>30	46 (46%)
Hypertension		38 (38%)
Asthma		20 (20%)
Thyroid disorder		38 (38%)
Smoking		12 (12%)
Family History of Diabetes with relation	Father	18 (18%)
	Mother	32 (32%)
Fasting Blood Sugar (mg/dl)		110.52 ± 5.63
HbA1c (%)		5.87 ± 0.35
Total Cholesterol (mg/dl)		200.1 ± 23.15
Triglycerides (mg/dl)		170.9 ± 13.73
High Density Lipoprotein (mg/dl)		48.16 ± 7.25
Low Density Lipoprotein (mg/dl)		92.1 ± 19.23

With regards to the demographics of patients according to HbA1c, a significant difference of 0.04 was observed between different ethnicities. A substantially higher mean weight was observed among patients having an HbA1c greater than 5.5. A higher BMI was reported among patients with higher HbA1c. Patients with a family history of diabetes were observed to be more prone to diabetes as well as reported higher HbA1c levels [Table 2].

Table No.2: Demographics of study participants according to HbA1c

Variables		HbA1c <6.5 n=54	HbA1c >6.5 n=46	p-value
Gender	Male	20	18	0.83
	Female	34	28	
Nationality	Sindhi	42	38	0.04
	Balochi	06	04	
	Pathan	0	04	
	Punjabi	04	0	
	Siraiki	02	0	
Weight (kg)		75.44 ± 14.33	79.26 ± 8.73	0.04
Height (m)		1.63 ± 0.09	1.61 ± 0.08	0.34
BMI	<18.5	0	0	<0.001
	18.5-24.5	24	04	
	24.5-30	6	20	
	>30	24	22	
Hypertension		18	20	0.3
Asthma		12	08	0.55
Thyroid disorder		16	22	0.06
Smoking		02	10	0.006
Family History of Diabetes with relation	Father	06	12	0.001
	Mother	12	20	
Fasting Blood Sugar (mg/dl)		98.3 ± 6.06	103.13 ± 3.69	0.003
Total Cholesterol (mg/dl)		198.63 ± 25.16	201.83 ± 20.68	0.78
Triglycerides (mg/dl)		169.26 ± 15.03	172.74 ± 11.92	0.66
High Density Lipoprotein (mg/dl)		48 ± 6.73	48.35 ± 7.89	0.34
Low Density Lipoprotein (mg/dl)		91.89 ± 19.12	92.3 ± 19.57	0.62

DISCUSSION

HbA1c is usually used a useful biomarker for monitoring glycemic control but also in predicting and identifying diabetic patients which were either previously undiagnosed or prone to become diabetic, being at a greater risk of diabetic complication if left undiagnosed. Therefore, a single HbA1c test can provide vital information about a patient which can be used to prevent, manage and treat chronic disorders [(15)]. A study not only evaluated HbA1c for predicting glycemic index of patients previously undiagnosed with diabetes, however in addition the study also evaluated HbA1c in terms of lipid profile (including total cholesterol, triglycerides, high density lipoprotein and low density lipoprotein) and BMI of patients. The study concluded that total cholesterol and triglycerides were significantly higher while HDL substantially lower in patients with a higher HbA1c level [(16)]. Similarly, in our study as well we evaluated the levels of HbA1c in terms of patient demographic and also included lipid profiles and anthropometric features such as weight, height and BMI.

Elevated levels of HbA1c especially among undiagnosed diabetics can be more harmful than known diabetics owing to the fact that in undiagnosed patients, the status of not only diabetic but also cardiovascular, neurological and ophthalmic complication status remains unknown [(17)]. Especially among young adults, HbA1c predicting diabetic status can help in preventing diabetic among those having high or pre-diabetic levels of HbA1c. Another important aspect of pre-diabetic control among young adults is that their metabolic status can easily be altered as compared with older adults [(18)]. In addition, individuals with higher BMI are also reported to be prone to diabetes, as reported in studies [(19)]. Likewise, in our study as well, individuals with higher HbA1c were found to have higher BMI values. Nonetheless, lipid profile of patients with high or optimum HbA1c levels were not reported to be significantly different, however they were slightly higher among group having HbA1c above 6.5 %.

HbA1c, a test which can reflect the levels of blood glucose for about 120 days, stands in itself a standardized and valuable test in assessment of glycemic control. On the contrary, it is debated that if for every individual, HbA1c levels are optimal biomarker for observing glycemic index, control and assess level of complications associated with diabetes[(20)]. The only factor postulated in observing discordance between HbA1c among different populations is because of inter-individual variations in red blood cells life span differing among different races and populations [(21)].

In our study, individuals having an HbA1c level above 6.5 % were observed to have higher weight and BMI than individuals with normal HbA1c or below 6.5 %. Similarly, individuals with a family history of diabetes in either parent were observed to have higher levels of HbA1c. Other researchers have also reported similar results where individuals having pre-diabetic status [(22)]. They have observed that a wide range of possible levels exist for mean glucose levels for a given HbA1c value which means that for some individuals, HbA1c might not be as a reliable for glycemic control. Additionally, HbA1c only denotes information about hyperglycemia

and not hypoglycemia, glycemic variability or daily pattern of glucose levels [23]. The benefits of HbA1c include an accurate and easily administered test having on-the-spot availability of results and help not diagnosing, managing and maintaining diabetic control especially in low and middle income countries and in hard to reach populations.

CONCLUSION

According to the results of the study, a significant difference of nationality, weight, BMI, smoking, family history of diabetes and fasting blood sugar levels were reported in patients having an HbA1c greater than 6.5%. Additionally, values of lipid profile were not significant in patients with HbA1c above 6.5 % or below 6.5 %.

Author's Contribution:

Concept & Design of Study:	Huma Ahsan
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Original Article

Relationship Between Previous Cesarean Section Scar, Subsequent Implantation of Gestational Sac and Abnormal Invasive Placenta

Bushra Zulfiqar[1], Shagufta Perveen[1], Kausar Parveen[1], Eraj Abbas[2] and Najma Parveen[1]

ABSTRACT

Objective: To analysis the relationship between previous caesarean scar and subsequent implantation site of gestational sac and abnormal invasive placenta.
Study Design: Prospective Cohort Study
Place and Duration of Study: This study was conducted at the Al-Tibri Medical College and Hospital, Isra University and Fatima Bai Hospital from November, 2019 to November, 2020.
Materials and Methods: 79 Pregnant women were enrolled in the study and examined the transvaginal ultrasound and abdominal Doppler ultrasound in 1st trimester for the implantation of gestation sac, placental localization, placental myometrial interface and inter-placental lakes at the first, second and third trimmers by ultrasound.
Results: Among 79 patients the mean age was 26.25± and the odd ratio was 0.0128 at $P < 0.0001$. R value in Regression model was to be found 0.698.
Conclusion: Previous caesarean scars showed weak positive association with placenta accrete diagnose 1st trimester. Higher the number of CS scar more susceptible to the placenta accrete.
Key Words: Placenta accrete, caesarian scar

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INTRODUCTION

The placenta initially develops during blastocyst stage and is expelled with the fetus at the time of delivery. The fetus depends on the placenta for its development and growth. Abnormalities of placenta may effect embryonic and fetal development badly.

Placenta accrete spectrum (PAS) is an abnormally invasive placenta (AIP), encompasses a spectrum of disorders where placenta attaches in a pathological manner to the myometrium[1]. It is described by an abnormal adhesion to and abnormal trophoblastic annexation through the Utrine serosa and myometrium[2,3]. Abnormal Placental invasion (previously called as morbidly adherent placenta) is split into increta, precreta and placenta accreta when placental villi is attached and invades into myometrium, this lead to the inward and outward development of the serosa and surrounding structure, respectively.[4,5] Incidence of AIP includes 75% as accreta, 18% as increta and 7% as percreta[6].

With the increasing rate of placenta accreta syndrome, the peripartum hysterectomies, neonatal complication, maternal haemorrhage and maternal morbidity and maternal mortality has been risen[7]. The common risk factors for PAS encompass placenta previa, prior caesarean section or uterine surgery[3, 8]. Additional risk factors are progressive maternal age, multiparity, previous uterine curettage and Asherman's syndrome [9].

Caesarean section have increased from 4.5 percent in 1965 to 33 precent now, with parallel rise in occurrence of placenta accreta from 1 in 2510 pregnancies to 1 in 333 pregnancies in the past decades[7].

Prenatal diagnosis of PAS has been seen to decrease mortality and morbidity occurred in these conditions because it facilitates planned intervention[10]. Early 1st Trimester ultrasound (Five -Seven weeks) has been advised to detect the likelihood of developing PAS disorder in women at high risk of these anomalies[11]. Other modality of imaging includes MRI, however definitive diagnosis of the condition is depended on the pathological evaluation after hysterectomy[6].

The classic ultrasound findings of PAS or AIP have been elucidated including the:

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Dropping of normal uteroplacental interface (clear zone)[2]

1. Extremely thin underlying myometrium (less than 1mm thick)
2. Vascular alterations within the placenta (lacunae) and placental bed (hypervascularity)[2].

Ultrasound findings are correlated with these pathophysiology[2]. Imperfection of the endometrium-myometrial interface favours a defective or abnormal decidualization and causing the infiltration of trophoblastic tissue within the myometrium, sometimes to serosa and neighboring organs[2].

It important to examine or evaluate the chances and liklehood of the PAS during the ultrasound in the pregnant women having previous cesarean scar[12]. A review in which 551 risk pregnancies were analyzed and their 1st trimester ultrasound finding includes 82% low implantation of gestational sac, 63 % reduced myometrial thickness, and 46% lacunae[13]. Low implantation of gestational sac in pregnancies made the women more susceptible to the AIP[13].

Cecarean scar and gestational sac position relationship can be classified as the following

a) Cross-over[14,15] sign(cos)
   COS 1 : The size of the sac above endometrial line is 2/3 diameter
   COS 2 : The size of the sac above endomet line 2/3 diameter
b) The implantation of the sac in dehiscent scar, (Implantation on cured scar versus "niche") [16]
c) Above versus below implantation from the the utrerine midline.
   COS 1 below the utrine mid line implantation "in the niche" are positively correlated with the acute type of PAS
   COS 2 Above the utine mid line implantation on the scar exhibits mild types of PAS

We aimed to study the relationship between previous caesarean scar and subsequent implantation site of gestational sac and abnormal invasive placenta.

MATERIALS AND METHODS

This multicentered prospective cohort study was performed in the Al-Tibri Medical College and Hospital, Isra University and Fatima Bai Hospital. This particular study and its protocol was approved by Local ethical committee. Informed consent had been taken from the participants. This study was done for the period of one year. Inclusion criteria was the pregnant patients 20—40 years of age, having singleton intrauterine pregnancy with gestation age 6—11 weeks and past history of one or two previous uterine lower segment cesarean section. All the patients were examined by the transvaginal ultrasound and abdominal Doppler ultrasound in first trimester for the implantation of gestation sac, placental localization, placental myometrial interface and inter-placental lakes then followed by ultrasound in second and third trimester. The patients with the age of above 40 years and having multiple pregnancies with no scarred uterus were excluded. Sample size was calculated by convenient sampling method.

RESULTS

Table I: Shows Mean age of the patient enrolled in the study lies in the range of 20-40 years with mean value of 26.25±.

Table II: Shows frequency and percentage of Previous cesarean history 45 subject were having one cesarean and 34 subjects were had two cesarean procedures.

Table III: Shows Best fit regression model between the previous caesarian and the Placental Accreta, **R** value showed positive significant co-relation i.e., 0.698, and it reflects that the patients with previous cesarean history made them more susceptible increases the chances of Placental Accreta

Table IV: Shows the Odd ratio 0.0128. The results show that the cesarian scar patients are 0.01 time more susceptible to have placental accrete.

Table V: Shows frequency and percentage of diagnosed case with Placenta Accreta during third trimester among 79 subjects was 1(1.26%) with history of cesarian section.

Table No.1: Age Distribution among the patients

	N	Minimum	Maximum	Mean	Std. Error
Age	79	20	40	26.25	.613

Table No.2: Frequency and Percentage of History of Pervious Cesarian Scar among the patients

	Frequency	%
One C/S	45	57.0
Two C/S	34	43.0
Total	79	100.0

Table No.3: Regression Model Third Trimester and Placental Accreta

Model	R	Std. Error of the Estimate
	.698[a]	.366

Table No.4: Odds Ratio

Odds ratio	0.0128
Significance level	P < 0.0001

The Odd ratio was calculated through online tool Medcals.

Table No.5: Frequency of Placenta Acreeta Diagnosed Patients in their Third Trimester

		3rd Trimester		
		Normal	Placenta Accreta	Total
Pervious_Cesarian	One C/S	44	1	45
	Two C/S	34	0	34
Total		78	1	79

DISCUSSION

According to the studies the anterior low lying or major placenta previa with a previous CS scar are highly predictive to the susceptibility of the PAS[18-19], which is to be evaluated by ultrasound screening from 18th week gestation. As this study also showed the week positive association between previous CS scar and PAS. According to the study there is a 2 fold increased risk of PAS disorder after the CS and which is contracted with the results of this study 0.06 fold increased risk of PAS after the CS[20]. A systematic review reported that the PAS incidence in women with no CS scar is around 3.3% to 4 % and around 50-70% with three to more scars. As in this study all the subject were not having more than 2 CS scar and incidence of the PAS is 1.26% -1 in 79- this also seconds the results of the study[21]. Study published in USA reported tha incidence of the PAS and prior CS was 67%, 61%, 40%, 11%, and 3% for five, four, three, two and one previous CS deliveries[22]. Multiple studies reported the complications like hemorrhagic shock, rupturing of utrine, postpartum hemorrahage(PPH) before the labour in PAS women[23-26].

As per the reported studies PAS is contributing factor to increase in maternal death but influenced by the early diagnosis and following intervention[27] PAS may lead to Peripartum hysterectomy(PH). Reported study in US 38% PH patients were having PAS[28].

The gradually increment in the frequency and the hurdle in the management of PAS. We felt the need to of this study which reflected the positive association of PAS with the previous CS scar which leds to the other complication in pregnant women and mostly lead to maternal death during the deliveries. Early detection and proper management of the condition can help mitigating the effects of PAS. However, there is a rising interest in and practice of expectant treatment of PAS, firstly to reduce fatal and very morbid complications associated with rapid hysterectomy, and, secondarily, to maintain the uterus when indications and preconditions are met. The roughly, a quarter of pregnancies that are successful.

CONCLUSION

In pregnant women previous caesarean scar is biologically as well as statistically showed weak positive association with the occurrence placenta accrete.

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Original Article

Evaluation and Comparison of Coefficient of Thermal Expansion of Esthetic Restorative Materials

Zartashia Arooj[1], Varda Jalil[4], Shahlisa Hameedi[5], Anila Errum[2], Marryam Riaz[3] and Aneela Amjad[6]

ABSTRACT

Objective: This study was performed to compare the co-efficient of thermal expansion of three esthetic restorative materials.

Study Design: Experimental Study

Place and Duration of Study: This study was conducted at the PCSIR, Lahore from April 2015 to September 2015 for a period of six months.

Materials and Methods: A thermodilatometer was used to measure CTE at temperature range 25-70°C under both dry and wet conditions. 40 study blocks of specified dimensions of each restorative material i.e. a flowable composite, a resin modified glass ionomer cement and a compomer and were randomly divided into two groups of twenty tested in dry and wet atmospheric conditions respectively.

Results: Results obtained were that under dry and wet conditions, at temperature range 25-50°C the mean CTE value of all the three restorative material differed significantly. Resin modified glass ionomer was observed to have different pattern from the group tested under dry conditions it did not undergo contraction it showed expansion and its values were closest to tooth structure as compared to other two materials.

Conclusion: Flowable composite and Compomer both showed expansion as similar in dry and wet.

Key Words: Thermal Expansion, Restorative Materials, Tooth Tissue.

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INTRODUCTION

Temperature extremes inside the oral cavity may affect the adhesive bonding between the tooth and restorative material in the long run (Majety and Pujar., 2011)[1]. When temperature of a material is raised it expands due to molecular vibrations (Karch, 2014)[2]. If the expansion of restorative material and tooth structure mismatch the adhesive bond between tooth and restorative material will be broken and hence failure of restoration (Lohbauer et al., 2009)[3]. For long clinical life of a restoration the value of CTE should closely match that of tooth structure (Powers et al., 1979)[4].

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A variety of tooth colored materials and their modifications have been introduced in order to produce a material which is closest to tooth structure in properties.

The chemical nature and structural formula have a strong impact on thermal properties of composite material, these materials have high CTE when compared to values of tooth structure (Narsimha, 2011)[5].

Flowable composites have improved handling properties and its viscosity allows it to closely adapt to tooth structure (Prabhakar et al., 2003)[6]. The flowable composites have higher polymerization shrinkage, coefficient of thermal expansion and inferior mechanical properties. Higher polymerization shrinkage may lead to disruption of adhesive bond finally leading to microleakage (zartashia et al. 2019)[7]. For GICs no or negligible change in dimensions occur between 20˚C and 50˚C in wet environment (McCabe et al., 2011)[8]. GICs have porous structure which resulted in gain or loss of loosely bound water and the dimensional changes were compensated (Mc cabe et al., 2011)[8]. Resin-modified glass ionomers (hybrid) are used for restorations in low stress-bearing areas and for patients with high caries risk. (Sakaguchi and Powers, 2012a)[9]. They follow the same trends when heated in dry environment as conventional GICs but when heated in wet environment they expand owing to their HEMA content which has highest affinity for water and thus

absorb water from surrounding environment (Yan et al., 2007)[10]. Compomers are light activated to cause setting by polymerization (Jedynakiewicz and Martin, 2001)[11]. The thermal expansion behavior of compomers is close to resin composite material (Sidhu et al., 2004)[12]. CTE of the restorative material and tooth structure should have close possible values to avoid microleakage and disruption of the adhesive seal (S.K.Sidhu et al; 2004)[12]. When the adhesive seal between restorative material and tooth structure is disturbed clinical life of the restorative material is affected (Didron et al., 2013)[13]. The materials with higher values of CTE expand more than tooth tissue on increasing temperature while materials with values closer to tooth tissue are more compatible with tooth tissue (Sakaguchi and Powers, 2012)[9].

MATERIALS AND METHODS

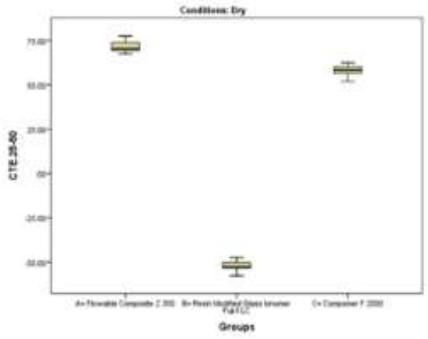
Three tooth colored materials were used. The dimensions of specimens were according to the specifications of the dilatometer used in the study. The flowable composite Filtek ™ Z350 XT Flowable restorative (3M ESPE Dental 3M ESPE Dental Products. St. Paul, Mn.U.S.A). The Resin Modified Glass Ionomer Cement, FUJI II LC(GC Corp,Tokyo Japan)and a Compomer; F2000 Compomer Restorative (3M ESPE Dental Products. St .Paul ,Mn.U.S.A)

It was experimental study with purposive sampling. Total specimens were 120 as calculated by sample size formula. Forty specimens of each restorative materials were made. They were named as flowable composite (FC) GROUP A, Resin modified glass ionomer cement (RMGIC) GROUP B, Compomer(Co) GROUP C. 20 specimens from each material were tested under dry conditions and 20 were tested under wet conditions.

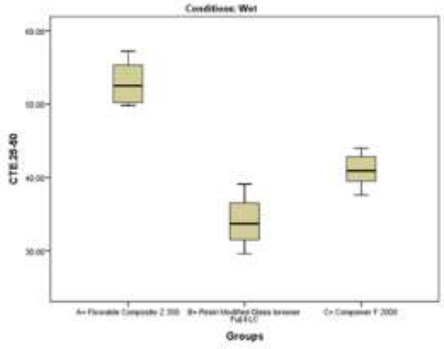
Each specimen was manually prepared with the dimensions 25mm×10mm×2mm. Dimensions were prepared by pouring the material into an open-ended stainless steel mould and light cured. Specimen was then removed from the mould and the previously unexposed surfaces were cured for 40 seconds each. The specimens were stored in distilled water for 24 hours before testing in dilatometer. The specimens of each material were further divided into two groups: group 1 & 2 each having twenty specimens. Specimens from all three materials from group 1 were tested in dry conditions and those from group 2 were tested under wet conditions. Distilled water was injected into the cotton. This ensures that these specimens were tested under wet conditions to simulate saliva rich environment of oral cavity. Specimens from each group were placed in Thermo-dilatometer (model 2016 STD, ORTON USA). Each specimen was introduced to this device for two times. The temperature was raised from 25°C to 70°C at a slow rate of 5°C/ min. Any dimensional changes in specimen were transmitted to the probe that was connected to LVDT–transducer, which allowed vertical movement of the probe to be monitored on y-axis of the recorder. Temperature variations were recorded on x-axis. CTE was measured using heating rate of 5˚C/min. CTE from second run was considered to obtain final results. While calculating the results the temperature was divided into two: 25-50℃ and 50-70℃. The values of CTE were obtained from software of dilatometer. All the collected data was entered in Statistical Package for Social Sciences (SPSS) version 18. ANOVA Tukey's pair wise comparisons of mean CTE of three restorative materials was done. A P-value < 0.05 was considered as statistically significant.

RESULTS

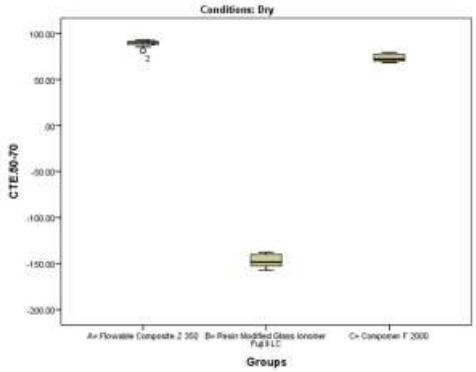
In dry conditions at 25-50°C and 50-70°C highest CTE value was seen for FC followed by Co and RMGICs. In wet conditions mean CTE value of all 3 restorative material differ significantly. In the temperature range from 25 to 50°C the FC showed expansion but the values were lower as compared to dry values. It was followed by compomer which also showed expansion, but it was lower as was shown in dry conditions. RMGIC was observed to have different pattern from the group tested under dry conditions it did not undergo contraction it rather showed expansion, but values were lowest as compared to other two materials and closest to tooth structure as compared to other two materials. In higher temperature range, 50 –70°C expansion was found in all three materials. The mean values for CTE in higher temperature range in wet conditions were closest to tooth structure in our study.



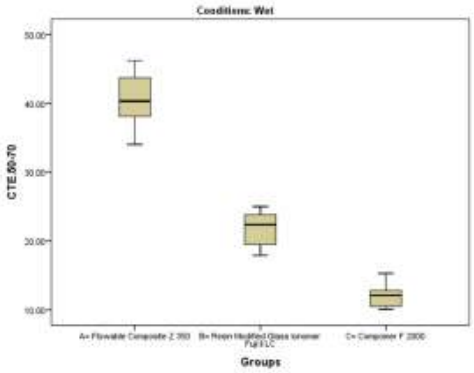
box and whisker plot CTE in dry condition at 25-50°C



box and whisker plot CTE values in wet condition at 25-50°C.



Box and whisker plot CTE values for in dry condition at 50-70°C



Box and whisker plot for CTE values for in wet condition at 50-70°C.

Table No.1: Comparison of CTE in Restorative Materials in Dry Condition at 25°-70°C

temperature	Groups	Mean± SD	Minimum	Maximum	p-value
DRY 25-50	A=FC Z 350	71.28±3.02	67.50	77.40	0.000
	B=RMGICFuji II LC	-52.36±2.92	-57.80	-47.30	
	C=Com F 2000	58.13±2.94	51.90	62.50	
DRY 50-70	A=FC Z 350	89.17±3.36	81.20	93.00	0.000
	B=RMGICFuji II LC	-147.58±6.64	-157.10	-137.80	
	C=Compomer F 2000	73.17±3.78	68.50	79.20	

Table No.2: Multiple Comparison Test to See the Difference of CTE in Between Restorative Material

Dependent Variable	(I) Groups	(J) Groups	Mean Difference (I-J)	p-value
CTE.25-500C	A=F C	B= RMGIC	123.64 (*)	0.000
		C= Comp	13.15 (*)	0.000
	B= RMGlC	A=FC	-123.64 (*)	0.000
		C= CoMP	-110.49 (*)	0.000
	C= Comp	A=FC	-13.15 (*)	0.000
		B=RMGIC	110.49 (*)	0.000
CTE.50-700C	A=FC	B= RMGIC	236.75 (*)	0.000
		C= Comp	16.00 (*)	0.000
	B= RMGIC	A=FC	-236.75 (*)	0.000
		C= Comp	-220.75 (*)	0.000
	C= Compomer	A=F C	-16.00 (*)	0.000
		B= RMGIC	220.75 (*)	0.000

Table No.3: Comparison of CTE of Restorative Material on Wet Condition

Atmosphere	Groups	Mean± SD	Minimum	Maximum	p-value
Wet (25-500C)	A= Z 350	52.96±2.86	49.80	57.20	0.000
	B= Resin Modified Glass Ionomer Fuji II LC	34.11±3.04	29.60	39.10	
	C= Compomer F 2000	40.94±2.03	37.60	44.00	
Wet (50-700C)	A=Flowable Composite Z 350	40.81±3.67	34.00	46.20	0.000
	B= Resin Modified Glass Ionomer Fuji II LC	21.83±2.39	17.90	25.00	
	C= Compomer F 2000	12.09±1.56	10.10	15.30	

Table No. 4: Multiple Comparison Test to See the Difference of CTE in Between Restorative Material

Dependent variable	(I) Groups	(J) Groups	Mean Difference (I-J)	p-value
CTE.25-500C	A=Flowable Composite	B= Resin Modified Glass Ionomer	18.85 *)	0.000
		C= Compomer	12.02 (*)	0.000
	B= Resin Modified Glass	A=Flowable Composite	-18.85 (*)	0.000

		C= Compomer	-6.83 (*)	0.000
	C= Compomer	A=Flowable Composite	-12.02 (*)	0.000
		B= Resin Modified Glass Ionomer	6.83 (*)	0.000
CTE.50-700C	A=Flowable Composite	B= Resin Modified Glass Ionomer	18.98 (*)	0.000
		C= Compomer	28.72 (*)	0.000
	B= Resin Modified Glass Ionomer	A=Flowable Composite	-18.98 (*)	0.000
		C= Compomer	9.74 (*)	0.000
	C= Compomer	A=Flowable Composite	-28.72 (*)	0.000
		B= Resin Modified Glass Ionomer	-9.74 (*)	0.000

DISCUSSION

The response of restorative materials to varying thermal stimuli do affect the long term clinical stability of the restorative material in the mouth (M.B. Lopes et al; 2012)[14]. Ideally the thermal expansion should be low to maintain an adequate bond between tooth and restoration to ensure long clinical life of a restoration. The extent of dimensional changes in a material in response to temperature variations are measured as coefficient of thermal expansion of that material (Santos et al; 2008)[15]. It is a fractional change and is given as a coefficient per unit of temperature. CTE of the restorative material and tooth structure should be as close as possible. (S.K.Sidhu et al; 2004[12], Powers et al; 1979[4], A. Tezvergil et al[16]). Microleakage can be avoided if two materials have almost same rate of contraction and expansion (Tolidis et al., 2012[17], Bullard et al., 1988[18]).

This study is performed in sequel to our previous study which was conducted to evaluate coefficient of thermal expansion of composites with low filler content (flowable composites) under both dry and wet conditions and it was concluded that CTE of flowable composites was at great variance with tooth structure due to its lower filler content which can affect its clinical stability as a restorative material (Zartashia et al., 2019)[7]. In present study we compared the effect of temperature changes on three esthetic restorative materials.

Sanbir K. Sidhu in his study assessed the Coefficient of Dimensional Change (CDC) of tooth-colored restorative materials. Similar pattern of thermal expansion was observed for all materials except for conventional glass ionomer cements which showed contraction (Sidhu et al., 2004)[12]. A study was conducted by Lopes et al in 2012 in which CTE of human and bovine teeth was compared. When tested under dry environmental conditions both human and bovine teeth showed contraction. (Lopes et. al.,)[14]. A research was carried out by Sindhu et al in 2004[12] in which he measured the values of thermal expansion of tooth colored filling materials and mentioned that temperature changes may bring about expansion of material by not merely by expansion or contraction of the materials but there may be a role of fluid content in dimensional changes of few materials.

In present study, the values of CTE of flowable composites were found to be highest amongst the three materials when tested in dry and wet conditions as well as compared to tooth structure. These higher values may be attributed to low filler content of these materials. Many studies have tested this fact. Different factors affect the CTE of these materials as mentioned in previous research work i.e. ratio of filler particles to resin matrix, bonding between fillers and resin matrix and extent of polymerization (Sidhu et al., 2004[12]; Sideridou et. al. 2004)[19]. CTE is inversely proportional to filler content.

It was previously mentioned by Yan et al in 2007[10] that RMGICs when heated in dry conditions showed greater contraction in higher temperature range i.e. above 35°C. Same pattern was observed in this study. Another study by Tolidis et al in 2013[16], where dilatometer was used to measure the CTE of three different types of glass ionomers a conventional, a resin modified and a one with modified polyacrylic acid in temperature range of 20-60°C. The result of this study was that RMGIC showed expansion when temperature was increased.

CONCLUSION

CTE of three dental esthetic restorative materials; the flowable composite, compomer and resin modified glass ionomer cement was observed. Flowable composite and compomer showed expansion under both dry and wet conditions. The behavior of resin modified glass ionomer was similar to the other two materials under wet condition, while it showed contraction under dry conditions. Under dry conditions none of the materials have CTE close to dentin and enamel while under wet conditions values of RMGIC and Compomer are closer to tooth tissue.

Co-efficient of thermal expansion is a single property, many other properties define the behavior of a restorative material and effect microleakage and hence clinical longevity of a restorative material. To prefer a material a clinician must keep other factors in mind and choose most appropriate material to ensure clinical longevity.

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Author's Contribution:

Concept & Design of Study:	Varda Jalil, Zartashia Arooj
Drafting:	Varda Jalil, Shahlisa Hameedi
Data Analysis:	Anila Errum, Marryam Riaz, Aneela Amjad
Revisiting Critically:	Zartashia Arooj, Varda Jalil
Final Approval of version:	Zartashia Arooj

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Effect of Different Curing Modes on the Degree of Conversion and Vickers Microhardness of Commercial Composites

Varda Jalil[1], Zartashia Arooj[3], Shahlisa Hameedi[2], Pulwasha Tanveer[6], Fariha Fayyaz[4] and Anila Errum[5]

ABSTRACT

Objective: The aim of this study was to evaluate and compare the effect of different curing modes (soft start, ramped and delayed polymerization modes) on the degree of conversion and Vickers micro hardness of commercial composites.

Study Design: Experimental study

Place and Duration of Study: This study was conducted at COMSAT, Lahore in October 2015 till April 2016 for a period of six months.

Materials and Methods: Two commercially available hybrid and nano-hybrid composite i.e. Te-Econom plus (Ivoclar vivadent, Liechtenstein) and Coltene NT Premium (Whaladent, Altstätten, Switzerland) respectively were evaluated. All samples were prepared in brass molds by using three different modes of polymerization. Degree of conversion and Vickers micro hardness of the samples was evaluated by FTIR (Thermo Nicolet P6700 USA) technique and Vicker's hardness indentor (MicroMet 6040, Buehler, Germany).

Results: Degree of conversion and Vickers microhardness of both dental composites showed the sequence, delayed curing > ramped curing > soft start curing. However, Coltene NT Premium showed better results comparatively.

Conclusion: Delayed mode of curing showed better degree of conversion and Vickers micro hardness comparatively. However, there was insignificant difference between the findings of both composites.

Key Words: Dental Composites, Degree of conversion, Vickers microhardness, Modes of curing

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INTRODUCTION

In restorative dentistry, light-cured composite resins have been regarded a material of key importance owing to their aesthetic properties. However, several factors, mainly polymerization shrinkage and stress are the main issues that reduce the longevity of the restoration. Researchers have focused on bringing up novel composites based on changing the chemistry of organic matrix (hyperbranched resins and ring opening polymers) and by throwing light on different curing techniques that decreased the polymerization shrinkage and stress to a significant level [1-3]. Three main phases *i.e.* pre-gel, gel point, and post-gel take place in the curing process of composite resins. During the pre-gel phase, there is a prevalence of linear polymer chains and the material may flow and undergo molecular readjustment to compensate for the shrinkages forces. Following pre-gel phase, the gel point of resin material is established during which the resin passes from the flow state (pre-gel) to the viscous state (post-gel) and movement of molecules is no longer possible. Thereafter, in the post-gel phase, the resin loses its flowing ability presenting a high modulus of elasticity and predominance of cross-linked polymeric structure. At this stage, the stress generated by polymerization shrinkage is transmitted to tooth-restoration interface [4, 5].

In the past, various studies have demonstrated that curing technique may influence the polymerization shrinkage of resin based composite materials [6, 7]. The clinical performance of composite resins is directly related to the degree of monomer conversion after photopolymerization and incomplete curing may lead to reduction in hardness, biocompatibility, bond strength between tooth and restoration and increased possibility of marginal leakage, pulpal damage, solubility and

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water sorption[8,9]. Therefore, different curing techniques have been suggested to minimize the effects of polymerization contraction especially sensitivity and marginal leakage [6, 10].

The techniques used in this study were step technique, soft start or ramped curing, and pulse-delay technique. In step technique (2 stages), exposure of low light intensity is given for a determined period followed by exposure with high light intensity for a certain additional period [11]. The soft start or ramp technique (progressive) has low initial intensity in the first few seconds, which is gradually increased for a certain period until it reaches a high final value that is maintained for the remaining curing time [12], whereas, in pulse-delay technique (delayed pulse) a short exposure of low light intensity is given for a certain period, followed by a period without exposure and then final curing step is performed [13]. The aim of these techniques is to decrease the shrinkage stress by allowing the occurrence of a more prolonged pre-gel phase, which as a result would allow the material to maintain its plasticity and flow for an extended period, thereby, reducing internal stresses and providing good marginal adaptation. Complete curing or a proper degree of conversion at the final stage of these techniques with high light intensity would provide satisfactory physical and mechanical properties [14].

The measurement of microhardness (MH) is an indicator of physical, mechanical, and biological properties of a restorative material and the degree of curing of a material can be indicated indirectly by the hardness test [11, 15]. Vickers hardness test (VHS) has been considered a valid tool for evaluating the hardness, viscoelastic properties, and other responses of rigid polymers [16].

Fourier transformed infrared spectroscopy (FTIR) is a direct method used to measure the degree of conversion (DC). It utilizes molecular vibrations to quantify the ration of monomer conversion into polymers by determining specific band positions to compare the unpolymerized aliphatic C=C stretching band at 1640 cm^{-1} to the aromatic C=C stretching band at 1610 cm^{-1} [13].

The aim of the present study was to determine and compare the in vitro effects of different curing techniques on the depth of cure by VH testing and measuring DC by using two different resin composites and to find out if a different composite material would respond differently under the same curing technique.

MATERIALS AND METHODS

Total 52 samples were prepared in a disc shaped brass mold, out of which 36 samples of dimension 8×4 mm were prepared for hardness testing, 18 samples of dimension 8×2 mm for degree of conversion evaluation. The mold was placed on glass slab and each sample was poured in a mold carefully. Single increment layer of 2mm was cured from both sides using high intensity blue light (LED, Woodpecker) for 60s at the constant distance of 1mm by applying three different modes of curing. The samples were removed carefully from the mold and were polished with different sized grit papers and further processed for testing.

Fourier Transform Infrared Spectroscopy (FTIR) was conducted before and after curing of all samples to evaluate the degree of conversion using the FTIR (Thermo Nicolet 6700, USA). The spectra were collected over the region 4000–400 cm^{-1} at a resolution of 8 cm^{-1} and averaging 256 scans. The data was analyzed by using OMINIC software and degree of conversion was calculated by using the following formula:

$$DC\ \% = 100 \times [1 - (R_{polymerised}/R_{unpolymerised})]$$

Where, DC denotes degree of conversion and R is the ratio of peak height of polymerized aliphatic to polymerized aromatic and unpolymerized aliphatic to unpolymerized aromatic groups of samples. DC was calculated by analyzing the changes in the ratio of the absorbance intensities of aliphatic C=C peak at 1638 cm^{-1} and that of an aromatic C=C at 1608 cm^{-1} of the uncured and cured samples[3].

Vicker's hardness was measured by applying 200 gf load for 10 s by Vicker's hardness indentor (MicroMet 6040, Buehler, Germany). Three indentations were made on each specimen; the mean values of all three indentations were calculated. The HV values will be calculated according to ASTM E384-11e1 by using following formula:

$$VH = 1.854\ F/\ d_o$$

Where VH denotes Vicker's hardness number, F denotes indentation load and d_o denotes indentation diagonal[3].

The mean and standard deviation values were calculated and One-way ANOVA analysis was performed for all characterizations by using SPSS version 24. The result was considered significant with p-value ≤ 0.05.

RESULTS

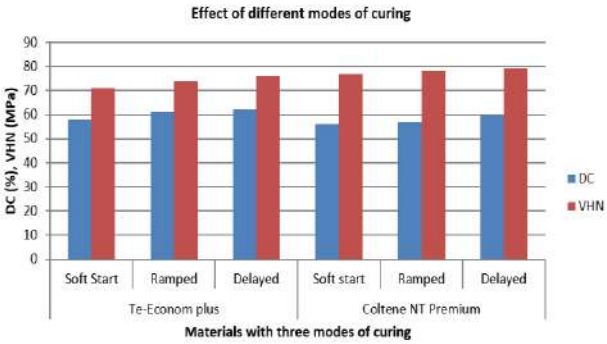

Figure No.1 Graphical presentation of degree of conversion and Vickers microhardness values

No statistical difference was observed between degrees of conversion and micro hardness of both materials. However, delayed curing mode showed better results than ramped and soft start curing modes. Vickers microhardness showed high values for Coltene NT Premium.

Two commercially available dental composites of A1 shade were used in the study. Description of the composites has been elaborated in Table 1.

Table No.1: Composition of the materials

Materials	Composition (Wt %)
Te-Econom plus (Ivoclar vivadent, Liechtenstein)	A1 Shade Hybrid resin based dental composite[17] Dimethacrylate based resins (BisGMA, UDMA, TEGDMA – 22 wt %), Filler (Barium glass, Ytterbium trifluoride, silicon dioxide -78 wt %)
Coltene NT Premium (Whaladent, Altstätten, Switzerland)	A1 Shade Nanohybrid resin based dental composite[18] Dimethacrylate based resins (BisGMA, BisEMA, TEGDMA – 25 wt %) Filler (Silica nanoparticles & aluminosilicate glass – 75-80 wt %)

Table No.2: Degree of conversion and Vickers microhardness values

Materials	Modes	Degree of Conversion	Vickers microhardness
Te-Econom plus	Soft Start	58%	71 ± 1.5
	Ramped	61%	74 ± 0.9
	Delayed	62%	76 ± 3.7
Coltene NT Premium	Soft start	56%	77 ± 3.9
	Ramped	57%	78 ± 0.5
	Delayed	60%	79 ± 2.0

DISCUSSION

In this study effect of different modes of curing on degree of conversion (DC) and hardness of two commercially available composites was evaluated. Results showed insignificant difference in hardness as well degree of conversion of both the tested RBC's and these results are in accordance with previous studies done by[19] and [20] in which the authors reported no statistically significant difference in hardness and degree of conversion of a commercially available dental composite after curing with different modes of polymerization. However, as the Coltene NT Premium has more filler loading by weight %, it showed high values of micro hardness comparatively.

DC is a very important parameter of resin based composites (RBC's) as final mechanical, physical and biological properties are influenced by it and are greatly enhanced by increased DC[21,22]. A low degree of conversion may affect the longevity of restorations by RBC's as unreacted monomers may dissolve in wet environment due to incomplete conversion and also act plasticizers consequently reducing mechanical properties[23]. Moreover, the degradation of material might take place due to oxidation or hydrolyzation as the double bonds present in uncured resin are reactive[24]. The minimum DC required for clinically acceptable restoration has not been established precisely[25]. The DC of commercially available RBC's reported in literature is found to be in range of 50% to 75%[26]. The findings showed that both composites in all the tested modes had DC within that range. In delayed mode both the DC and hardness was more by ramped mode and soft start mode respectively. The difference in DC and hardness as a result of different curing modes made be due to difference in cross linking of monomers and setting reactions within RBC's[27]. Delayed curing had positively impacted degree of conversion by allowing monomers ease of settlement & reaction[23]. The more DC and hardness by pulse delay mode may be due to fact that this mode provides higher amount of energy to RBC's every time because according to[28] the maximum intensity by light source is achieved at 0.55 s and then decreases significantly as time progresses. As in pulse delay mode the material is given intermittent light and dark cycles[29], so it is supplied with maximum energy every time which increased both DC and hardness as both are dependent on supply of energy for conversion of double bonds to single[30].

The lower DC and hardness of RBC's in soft start mode may be due to fact that a lower intensity of energy is supplied at the start which results in less polymerization rate. Moreover, viscosity of RBC's is increased in initial soft start curing which interrupts supply of free radicals and consequently polymerization is limited in the end although supply of energy is increased[31,32]. In another study[33] also evaluated the effect of different cures modes on hardness and DC and results showed maximum hardness and DC was shown by Delayed mode, followed by ramped mode and soft start which are accordance with this study.

CONCLUSION

Based on the results of the study, it is concluded that different curing modes affect degree of conversion and micro hardness slightly. No significant difference was observed between two materials however delayed curing showed better results than ramped curing followed by soft start mode. Clinicians prefer technique based on several factors and literature has mixed findings in report.

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Original Article

Extracorporeal Shock for Tennis Elbow

Extracorporeal Shock Wave Therapy for Tennis Elbow; A Double Blinded Randomized Clinical Trial Comparing Two Different Energy Levels

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ABSTRACT

Objective: The objective was to compare the two ranges of energy flux density for treatment of tennis elbow using ESWT technique.

Study Design: Quasi experimental study

Place and Duration of Study: This study was conducted at the Kanaan physiotherapy & spine clinic from February 2020 till July 2020.

Materials and Methods: A convenient sample of 50 was calculated by epitool software. Patients were divided into 2 groups of 25 patients in each group. Group A received shockwave therapy with an intensity of 0.3mJ/mm2 and Group B received intensity of 0.2mJ/mm2. The outcome variables are pain, maximal grip strength and Upper Extremity Functional Index.

Results: Shockwave at 0.3mJ/mm2 was found to be more effective in improving pain and maximal Grip strength at the post-treatment level while both 0.3mJ/mm2 and 0.2mJ/mm2 were found equally effective on Upper Extremity Functional Index.

Conclusion: This Study concluded that the patients who were treated with 0.3mJ/mm2 intensity of shockwave had better outcomes of Maximal Grip strength at 6th Month.

Key Words: Tennis elbow, Extracorporeal Shock Wave Therapy

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INTRODUCTION

Tennis elbow which is also called lateral epicondylitis in medicine language is considered as one of the common and most observed injuries of the arm and especially observed among professional population.[1] This injury is a considered a challenge as it is challenging to treat, susceptible to recurrence.[2,3] Tennis elbow may be observed at any age but it is most common within age group of 40 to 65 years with higher incidence among women.[4] Prolonged exposure to vigorous and repetitive activities have been reported as main cause to tennis elbow.[5]

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The choice of treatment mainly depends on the common practice of physiotherapists and doctors which may include surgical or physiotherapy treatment.[6] There are different treatment options in physiotherapy i.e. electrotherapeutic and non-electrotherapeutic.[7,8] Electrotherapeutic therapy includes laser therapy, ultrasound and extracorporeal shockwave therapy (ESWT) etc.[9,10] Electrotherapeutic treatment results in cell activity which results in therapeutic benefits and reliefs.[11] Non-electrotherapeutic therapy includes acupuncture, exercise, bracing, manipulation treatment, and taping.[12,13]

The use of extracorporeal shockwave therapy is emerging as popular treatment method for treating tennis elbow.[14] Extracorporeal shockwave therapy is a non-invasive technique that uses pressure waves of different intensities to treat various musculoskeletal disorders.[15]

The purpose of the present study was to assess the outcomes of extracorporeal shockwave therapy in the treatment of tennis elbow. Two different ranges of energy flux density were compared for the treatment of tennis elbow with ESWT.

MATERIALS AND METHODS

A quasi experimental study design was used in the study, in which all the patients participating in the study were divided in to two separate groups by lottery method. Convenient sampling was used. After sampling, participants were allocated to two categories of intervention and treatment groups. The study was conducted in Kanaan Physiotherapy & Spine clinic. A sample size of 50 patients was taken in this study by Epitool software. But 55 patients were included in this study in order to maintain an adequate follow up. The duration of the study was 06 months from February 2020 till July 2020. The participants were allocated into 02 groups using lottery method. In Group A ESWT treatment with energy level of 0.30 mJ/mm2 was used for subjects in Group A, Patient were asked to sit with pillow under elbow. Before application of ESWT, Heating pad was applied for 10 mints and Ultrasound was used. After application of ESWT, cryotherapy was applied for 7 minutes. Total 27 patients were allocated in group A. In Group B, ESWT treatment with energy level of 0.20 mJ/mm2 was used for subjects in Group B, comparatively low intensity energy level than that used for subjects in Group A. Patient were made to sit with pillow under elbow. Before application of ESWT, Heating pad was applied for 10 mints and Ultrasound was used. After application of ESWT, cryotherapy was applied for 7 minutes. Total 28 patients were allocated in group B. Each patient had 2 sessions in one week and the treatment lasted for 3 weeks. The patients were assessed at pre-treatment level to confirm the baseline comparability and at post –treatment level to check the efficacy of treatment provided. Follow-ups assessment were maintained at 3rd and 6th month by phone calls. Patient Selection Criteria included patients with Age 20-60 years and were having chronic tennis elbow, more than 3 months. Exclusion Criteria included those Patients who were not willing to participate for the mentioned study, Patients who do not have chronic tennis elbow illness. (Less than 3 months) and patients having Red flags i.e. Rheumatoid arthritis, Osteo-arthritis, neoplasm. Written informed consent was taken. Visual Analogue Scale was used to assess the level of pain of patients, UEFI (Upper Extremity Functional Index) to assess the Functional Status of patients and Hand grip strength of patients was assessed using the Dynamometer. Visual Analogue score was taken at pre-treatment, post treatment level, Follow up sessions at month 3 and month 6. The hand grip strength of patients of both groups was assessed by the Hand Dynamometer was assessed four times and for each reading, an average of three readings was calculated and recorded. The study was approved from ethical review committee of Kanaan physiotherapy & spine clinic. The data was analyzed using SPSS for Windows software, version 20.

RESULTS

Amongst 27 patients of group 0.30mJ/mm 19 were males and 8 were females whereas amongst 28 patients of group 0.20mJ/mm, 16 were males and 12 were females. Amongst males, many of them were painters, bankers and masons whilst the females were chefs. House maids and knitters. The reason of having this complaint was repetitive use of the extensor compartment of the forearm. Amongst 55 patients, had 54 had Right side affected whilst only 2 of them had left Hand affected and P-value was found to be 0.98. Amongst 27 patients of group 0.3mJ/mm, 15 had normal BMI, 12 were obese and none were underweight from this group. Amongst 28 patients of group 0.2mJ/mm, 18 had normal BMI, 9 were obese and 1 was found to be overweight and p value was found to be 0.26 i.e. Non-significant as mentioned in table 1.

Table No. 1: Group statistic data

Demographic details	Group A	Group B
Male/Female	19/8	16/12
Mean age± SD	33.81(6.7)	32.86(6.31)
Dominant arm affected	26	27
Body Mass Index	Normal 11 Obese 14 Underweight 0	Normal 14 Obese 10 Underweight 1

Table No.2: Visual analogue scale results

Group of the patient	Pre-Treatment Value (Mean ± SD)	Post-Treatment Value (Mean ± SD)	Follow up 3 Month (Mean ± SD)	Follow up 6 Month (Mean ± SD)	P-Value
0.3mJ/mm^2	10 ± 0.00	5.36 ± 0.90	3.72 ± .979	1.96 ± .790	<0.001
0.2mJ/mm^2	10 ± 0.00	6.52 ± 0.82	3.44 ± .583	2.32 ± 1.145	<0.001

Table No.3: Upper extremity functional index

Group of the patient	Pre-Treatment Value Mean ± SD	Post-Treatment Value Mean ± SD	3 Month Follow Up Mean ± SD	6 Month Follow Up Mean ± SD	P-value
Group 0.3mJ/mm^2	52.84 ± 1.40	67.52 ± 2.14	70.92 ± 2.01	70.16 ± 1.62	<0.001
Group 0.2mJ/mm^2	52.88 ± 1.76	64.2 ± 6.07	66.56 ± 6.65	66.85 ± .5.89	

Table No.4: High Grip Strength Results

Group of the patient	Pre-Treatment Assessment Mean value ± SD	Post-Treatment Assessment Mean value ± SD	3 month Follow up Mean value ± SD	6 Month Follow Up Mean value ±SD	P-value
0.3 mJ/mm^2	31.62 ± 5.1	41.4 ±6.06	46.5 ± 5.8	50.42 ± 6.18	<0.01
0.2 mJ/mm^2	26.25 ± 8.1	41.2 ±9.33	43.6 ± 9.17	45.80 ± 8.7	<0.01

The results of visual analogue scale were presented in table 2 and concluded that the patients who were treated with 0.30 mJ/mm2 had their pain between a range of 6 and 4 soon after their treatment whilst those who were treated with 0.20 mJ/mm2 had it in between 6 and 7. Later at 3 and 6 month follow up, the pain was less in those patients who received Shockwave therapy at 0.30 mJ/mm2. In independent sample t test, the p-value for the patient after they had been treated was found to be .00 which means that the treatment which was provided was effective and patients of both groups had their pain treated, thus significant.

The results of Upper Extremity Functional Index were presented in table 3 and Independent sample t-test was applied to compare the groups at pre-treatment and post-treatment level and the p-value was found to be <0.05 post-treatment which means both groups i.e. those who were treated with 0.2 mJ/mm2 and those who were treated with 0.3 mJ/mm2 both had improved upper extremity functional Index.

The results of hand dynamometer were presented in table 4 all the patients who were included as subjects were asked to hold the dynamometer and the average of 3 recordings was taken. The patients Grip strength was found to be improved for both the groups at post-treatment level but at week 6 follow up, the results showed that the patients who were treated with 0.3 mj/mm2 had better grip strength outcome than those treated with shockwave at an intensity of 0.2mj/mm2, p-value at this level of assessment was 0.03, thus significant i.e. <0.05.

One way Repeated Measured Analysis of Variance abbreviated as ANOVA was conducted to assess the null hypothesis that 0.2 mJ/mm2 is more effective is treating patients with chronic lateral epicondylitis when measured before, after and in follow up treatment sessions. The results of ANOVA indicate a significant time effect, Wilk's Lambda, 0.48, F (3, 46) =301.7, p<0.01,n2=.50.Thus there is a significant evidence to reject the Null Hypothesis.

Follow up comparisons indicates that each pairwise difference was significant, i.e. p-value< 0.01. There was a significant increase in scores over time suggesting that the patients who were treated with 0.3mJ/mm2 had better grip strength at week 6 than the group that was treated with 0.2 mJ/mm2, i.e. alternate hypothesis proved.

DISCUSSION

This is the first study that compared the treatment effects of two different intensities of Shockwave therapy in cases of Lateral epicondylitis. The results showed that both the treatments were effective in treating the patients and the pain was relieved after 3 weeks (2 sessions per week). Significant improvements were also found in both groups of Maximum Grip Strength and the Upper Extremity Functional Index. In this study, significant improvements were found in the pain score of patients at pre-test and post-treatment level. No significant differences were found at the follow up sessions rather the Grip strength was found to be better at week 6 Follow up session in case of the patients who were treated with 0.3mJ/mm2

None of the studies in the literature had ever made a comparison on the effects of two different intensities of Shockwave therapy however literature supports the usage of shockwave therapy in cases of chronic Tennis elbow. Shockwave therapy has always helped in short term pain relief[16], this was the reason why we assessed the patients at 3rd and 6th month post-treatment to know if they had recurrence of pain or not. But our findings did not support this fact, rather all the patients of both groups had pain relief on a longer term.[17-19]

The Maximum grip strength was also assessed by the Dynamometer that helped us a lot knowing the significance of shockwaves at an intensity of 0.3Mj/mm2. The patients of group A had a long term maximal grip strength as compared to those of group A. A study showed better effects of shockwave therapy than ultrasound on hand strength.[20] Another study similar results of shockwave therapy showing its efficacy in lateral epicondylitis.[21]

The upper Extremity functional index was found to be significantly improved soon after the treatment i.e. after 3 weeks but no significant changes were observed at the follow up treatment sessions. Similar results were shown by other studies. Shockwave therapy has improved upper limb functioning in most of the studies.[22,23]

CONCLUSION

It was concluded that shockwave at 0.3mJ/mm2 was found to be more effective in improving pain and maximal Grip strength at the post-treatment level while both 0.3mJ/mm2 and 0.2mJ/mm2 were found equally

effective on Upper Extremity Functional Index. However, the patients who were treated with 0.3mJ/mm2 intensity of shockwave had better outcomes of Maximal Grip strength at 6th Month**.**

Recommendations: The study should have been conducted at a greater number of patients and at acute state of tennis elbow to know the effectiveness of Shockwave in acute tennis elbow. A combination of therapies was also applied, rather we should have applied Shockwave therapy.

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Original Article

Prevalence of Hydrocephalous in the Patients, Presenting with Tuberculous Meningitis, in a Medical Institute Karachi, Pakistan

Hydrocephalous with TB Meningitis

Kanwal Melwani[1], Sanjay Kumar[2], Sunil Kumar Dodani[2], Sarmad Jamal Siddiqui[3], Vijia Kumar Gemnani[3] and Sonia Jetwani[4]

ABSTRACT

Objective: To evaluate the frequency of hydrocephalus among patients presenting with tuberculosis bacterial meningitis.

Study Design: Cross sectional study

Place and Duration of Study: This study was conducted at the Medicine and Neurology Department, Jinnah Postgraduate Medical Center (JPMC), Karachi during the period of Oct. 2019 to June 2020.

Materials and Methods: According to the selection criteria, a total of 137 patients were selected through the non-probability consecutive sampling method. A brief history, as well as demographic records, was reported into the performa. SPSS software was applied for the data analysis.

Results: In the study total of 137 patients presenting with TBM were included. The mean age and duration of symptoms in our study were 48.22±7.56 years and 8±3.47 days, respectively. 82 (59.9%) were male and 55 (40.1%) were female. Out of the 137 patients, 22 (16.1%) and 115 (83.9%) had TBM and did not have hydrocephalus.

Conclusion: Tuberculosis Bacterial meningitis is a frequently reported problem in our region of the world. Hydrocephalus is a common complication with other sequelae. Hydrocephalus may completely resolve in the early stages of tuberculous meningitis.

Key Words: Tuberculous Bacterial Meningitis and Hydrocephalus

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INTRODUCTION

Globally, an estimated 10 million people fell ill with tuberculosis (TB) and a total of 1.4 million people died from TB in 2019. Tuberculosis is numbered as the 10th topmost cause of death[1]while the central nervous system (CNS) tuberculosis is the third most common manifestation of extra-pulmonary tuberculosis and has a very excessive rate of morbidity and mortality.[2-3]

Main complaints present in TBM eg; fever, weight loss, photophobia, headache, vomiting, cranial nerve palsies, and altered level of attention that can be classified on the basis of British Medical Research Council (BMRC) contemporary diagnostic criteria into three stages.[4]

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Most cases are late to the hospital because symptoms are non-specific in early stage 1 TBM.[5] Despite the improvement of promising molecular diagnostic strategies, the prognosis of TBM is predicated in large part on microbiological methods that encompass Acid Fast Bacilli (AFB) smear on cerebrospinal fluid (CSF) or CSF culture for AFB, each of which might be tremendously insensitive, and pose a diagnostic assignment. That is a reason, why TBM is diagnosed late results in serious complications.[6]

Hydrocephalus is the most common complication of tuberculous meningitis (TBM), which is more severe, seemed in children than in adults, and the frequency of hydrocephalus among tuberculous bacterial meningitis patients is considered to be 65.5%.[7,8]

Hydrocephalus can be broadly defined as a disturbance of the formation, flow, or absorption of cerebrospinal fluid (CSF) resulting in an increase in the volume occupied by this fluid within the CNS,[9] It may lead to practical, behavioral, and psychological consequences.[10] In the early diagnosis of CNS tuberculosis, a CT scan (modern neuroimaging) is playing a key role.[11] when hydrocephalus is the presenting feature, immediate neurosurgical decompression may be required.[12]

The emergence of drug-resistant strains has enhanced in many regions globally, resultant disease presents a therapeutic challenge.[13,14] Almost 100% fatality rate

seemed in untreated TBM cases and late treatment can lead to permanent neurological damage.[15] Treatment for TBM should be begun as soon as clinical doubt is supported by preliminary CSF studies.[16]

As a minimum four first-line drugs, preferably isoniazid, rifampin, pyrazinamide, and streptomycin or ethambutol, as well as steroids should be included in empirical treatment to reduce mortality with TBM.[8]

Rationale: The frequency of hydrocephalus among tuberculosis bacterial meningitis show variable prevalence varies from 12% to 77%.[17] Such as, Chan et al and Mumtaz et al found the prevalence to be 29% and 48%.[18,19] and TusharRaut et al study showed the prevalence of 65%.[20] There is a need for a study to ascertain the prevalence as delays in diagnosis and initiation of treatment can contribute to high mortality and morbidity, especially in resource-limited regions. Study data will provide the base to estimate the magnitude of this problem in our population in respect to better management protocols catering to the needs of our setup can be implemented. Ultimately this will result in improved patient outcomes and quality of life of the patients.

MATERIALS AND METHODS

Tuberculosis Bacterial Meningitis: Patients represent with any 02 or more of the following clinical characteristics in one week along with any one of the positive laboratory data were applied to label TBM.

Clinical Features: • Fever ≥ 99^0F (occurring at least 6 hours/day for more than one week)

• Headache dull in nature persisting VAS ≥ 6 (occurring at least 3 hours/day per day for more than one week)

• Vomiting (occurring at least 3 times per day for 3 consecutive days)

• History of contact with TB patient in the family (living in the same house or outside in last 2 years)

Laboratory Data: AFB (+ve) smear on CSF (This was marked positive while culturing any Acid Fast Bacilli (AFB) on fluorescence staining of the CSF)

• Positive AFB culture on CSF (termed positive when Mycobacterium tuberculosis isolates and assessed at 4–6 weeks after their growth on the Bactek media used for culture.

• Typical CSF showed lymphocyticpleocytosis (range 20 – 500 lymphocytse per cubic mm) along increased CSF protein ≥100 mg/dl and decreased CSF glucose level ≤ 60percentage of relating plasma level analysed simultaneously as CSF inspected.

Hydrocephalus: Hydrocephalus was labeled as present on CT scan brain showing any ventricle (third, fourth, or lateral ventricle) dilated to ≥ 25 percentage of their normal value.

Hypertension: Known hypertension (> 02 years)

1- Patients taking medications (daily regularly)

2- SBP < 140 mmHg and <90 mmHg (more than six months).

Diabetes Mellitus Type II: Known diabetes mellitus,

1- Patients taking daily medications

2- HbA1C >7percentage

Smoker: Smoke 05 cigerates / day (at least one year)

Study Design: Cross-sectional examination.

Study Setting: The study was carried out at the Neurology and Medicine wards, Jinnah Postgraduate Medical Center (JPMC), Karachi.

Sample Size: The required example size calculated to be 137 patients By taking the frequency of hydrocephalus in tuberculosis bacterial meningitis patients at 65.5%,[13] margin of error 5% and certainty level 95%. WHO software was used for sample size calculation.

Sampling Technique: Consecutive sampling (Non-probability)

Inclusion Criteria: Patients presenting with tuberculosis bacterial meningitis in one week as per operational definition were included.

- BMRC stage ≥ 1.
- Either gender.
- Age 30-60 years.

Exclusion Criteria: Pregnant patients proven by dating scan. Patients with a history of congestive cardiac failure, COPD, CRF, stroke and malignancy. Patients with a history of administration of radioactive contrast agents. Patients with bacterial (other than tuberculosis bacterial meningitis) or viral meningoencephalitis.

- Patients with a history of head trauma.

Data Collection Procedure: In the study, according to selection criteria all the consented participation was enrolled from the Medicine and Neurological wards, Jinnah Postgraduate Medical Center (JPMC), Karachi. Institutional ethical review committee permission was taken prier to conduction of study. Written consent was taken from all patients/attendants and assured them for the confidence.

A brief history regarding socio demographic and the duration of illness was taken at the time of admission from the patient or the attendant. All the confirmed tuberculosis bacterial meningitis patients according to criteria, they all were going through a brain CT scan with contrast within 02 days of admission.

All scans had been concentrating with the guide of the radiologist of the health department with more than 10 years of experience who looked for the presence or absence of hydrocephalus as per operational definition.

The out coming of quantitative factors like age and duration of symptoms and qualitative variables like sex, BMRC stages, hypertension, diabetes mellitus type II, and smoking had been entered in questionnaire proforma attached as annexure –I. Data was analyzed on SPSS Version 16.

RESULTS

A total of 137 patients presenting with TBM, regarding selection criteria were included in this study. Out of 137 patients presenting with TBM, the mean age of the patient was 48.22±7.56 years and range between 20 to 60 years while the duration of symptoms in our study was 8±3.47 days respectively. Gender wise 82 (59.9%) were male and 55 (40.1%) were female. Table 1

In study age-wise, frequency distribution among TBM patients showed that 34 (24.8%), 40 (29.2%), 18 (13.1%), and 45 (32.8%) patients were in the age group 20-30 years, 31-40 years, 41-50 years and 51-60 years respectively. In study the duration of symptom among TBM patients, < 1 week 67 (48.9%) and > 1 week 70 (51.1%) respectively. Table 1

Frequency distribution of BMRC stage among TBM patients showed that out of 137 patients with TBM, 24 (17.5%), 91 (66.4%), and 22 (16.1%) patients were in BMRC stage I, II, and III respectively. While the frequency of DM, HTN, and among smokers was observed 31 (22.6%), 40 (29.2%), and 23 (16.8%) respectively. Table 1

Frequency of hydrocephalus among TBM showed 22 (16.1%), while according to age wise more seemed in 20-30 years age group 11(50%), and thereafter in 30-40 age groups 08 (36.4%)(p=0.00), and gender-wise seemed more in male group 13(59.1%) as compared to female group 09(40.9%) (p=0.55).Table 2

In the study, duration of symptoms < 1 week observed in hydrocephalus patients observed 15 (68.2%) while symptoms observed above 1 week in 07 (31.8%) (p=0.04), while in study BMRC in relation to hydrocephalous, stage I, 02(9.1%), stage II, 17 (77.3%), stage III 03 (13.6%). P-value was 0.44. As seemed in Table 02.In study, the known diabetes mellitus type II and hypertensive patients with respect to hydrocephalus seemed in **05** (22.7%) and 07 (31.8%) (p=0.59,p=0.47) respectively. Table 02 Stratification for smoking status with respect to hydrocephalus observed that patients who smoked, 03 (13.6%), p= 0.10, showed in table 2.

Table No.1: Frequencies of demographic and other variable of tuberclosis meningitis

Tuberculosis Meningitis demographic and other variables		
Variales		**(%)**
Gender	Male	82 (59.9%)
	Female	55 (40.1%)
Age	20-30 years	34 (24.8%)
	31-40 years	40(29.2%)
	41-50 years	18(13.1%)
	51-60 years	45(32.8%)
BMRC Stage in TBM	Stage I	24 (17.5%)
	Stage II	91 (66.4%)
	Stage III	22 (16.1%)
Symptom Duration	< 1 week	67(48.9%)
	>1 week	70(51.1%)
D.M Elittus	YES	31 (22.6%)
	NO	106 (77.4%)
Hypertension	YES	40 (29.2%)
	NO	97 (70.8%)
Smoking	YES	23 (16.8%)
	NO	114 (83.2%)

Table No.2: Analysis of Hydrocephalous in Tuberclosis Meningitis Patients

Hydrocephalous In Tuberclosis Meningitis Patients					
VARIALES		**HYDROCEPHALOUS**			**p-value**
		YES(%)	**NO(%)**	**TOTAL**	
GENDER	Male	13 (59.1%)	69 (60%)	82(59.9%)	0.55
	Female	09 (40.9%)	46 (40%)	55(40.1%)	
AGE	20-30 years	11 (50%)	23 (20%)	34(24.8%)	0.00
	31-40 years	08 (36.4%)	32 (27.8%)	40(29.2%)	
	41-50 years	00 (00%)	18 (15.7%)	18(13.1%)	
	51-60 years	03 (13.6%)	42(36.5%)	45(32.8%)	
BMRC stage	STAGE I	02 (9.1%)	22 (19.1%)	24(28.2%)	0.44
	STAGE II	17 (77.3%)	74 (64.3%)	91(66.4%)	
	STAGE III	03(13.6%)	19 (16.5%)	22(16.1%)	
SYMPTOM DURATION	< 1 week	15 (68.2%)	52 (45.2%)	67(48.1%)	0.04
	>1 week	07 (31.8%)	63 (54.8%)	70(51.1%)	
D.M ELITTUS	YES	05 (22.7%)	26 (22.6%)	22(100%)	0.59
	NO	17.7(77.2%)	89 (77.4%)	115(100%)	
HYPERTENSION	YES	07 (31.8%)	15 (68.2%)	40 (29.2%)	0.47
	NO	15 (68.2%)	82 (71.3%)	97(70.8%)	
SMOKING	YES	03 (13.6%)	20 (17.4%)	23(16.8%)	0.47
	NO	19 (86.4%)	95 (82.6%)	114(83.2%)	

DISCUSSION

Our study included a total of 137 patients presenting with TBM. The mean age and duration of symptoms in our study were 48.22±7.56 years and 8±3.47 days respectively. 82 (59.9%) were male and 55 (40.1%) were female. Out of 137 patients with TBM, 22 (16.1%) and 115 (83.9%) had and did not have hydrocephalus.

Another study at included 80 patents with tuberculous meningitis, during presentation among them 52(65%) had observed hydrocephalus and than other new 08 patients developed hydrocephalus during follow up. Factors related to hydrocephalus included advanced stage of illness, extreme disability, duration of illness more than 02 months, diplopia, seizures, visible impairment, papilledema, cranial nerve palsy, hemiparesis, CSF total cell count more than100cubic/ millimeter, CSF protein more than 2.5 gram/liter. CT scan neuroimaging feature that were significantly associated with hydrocephalus included basal exudates, tuberculoma, and infarcts. Multivariate analysis significantly associated with visual impairment, cranial nerve palsy, and the presence of basal exudates as predictors of hydrocephalus. Complete resolution of hydrocephalus, with early tuberculosis meningitis was seen in 13 patients. Hydrocephalus was significantly related with mortality and poor outcome.

Another study included 100 patients of TBM, among them 60 (60percentage) males and 40 (40 percentage) females (mean age of 47.23±10.39 years). The case seemed more in BMRC stage II 65(65%) and 29 (29%) and 6(6%) in stage III and I of the TBM. In study 48(48%) showed hydrocephalus patients. There become no significant association in gender and age variables s with p values of 0.67 and 0.58 respectively. The outcomes were significantly better in those who had stage III of TBM where it become observed in 19(65.52%) out of 29 patients in comparison to 27 (41.54%) cases in stage II and 2 (33.33%) in stage I respectively with a p-0.02. Hydrocephalus is observed almost in 50% of the cases with TBM and it is notably excessive in cases that had stage III of TBM.[21]

Another study, a total 116 identified cases of tuberculous meningitis participating during the course of study. In study 55.2%were female and 44.8% were male cases, age range was 15-73 years with means age of 45±17.8 years. Complaint during presentation, were fever in 92.2% females and 88.5% male patients, headache was show in 96.8% female and 92.3% male patients, while meningism 79.7% female and 71.2% male and in coma was observed 18.7% female and 9.6% male cases respectively. Presenting complaints were fever in 92.2% females and 88.5% male cases, the headache was present in 96.8% female and 92.3% male cases, signs of meningism were present in 79.7% female and 71.2% male cases and 18.7% female and 9.6% male cases presented in a coma. CT scan findings were 67.2% of hydrocephalous cases, edema in 36.2%, and infarction in 11.2% of cases. While on MRI brain, hydrocephalous was seen in 81(69.8%) cases, tuberculomas in 86(74%), and infarcts in 14(12.1%).[22]

CONCLUSION

This study showed that hydrocephalus is present in a great proportion of patients with tuberculous bacterial meningitis. Physicians needed to comprehend the significance of this association for well timed recognition and management of these events. Strategies aimed at preventing hydrocephalous cases among high risk residents want to be optimized.

Meningitis is the mostly lethal form of TB, specifically. Early diagnosis and remedy can dramatically lessen the high mortality associated with this disease. Complications of TBM are because of the development of hydrocephalus, arteritis, and organization of exudates at the base of the brain resulting cranial nerve palsies, leading to disability and epilepsy. At present, it is accepted, anti tuberculosis drug therapy (12 to 18 months) is essential to obtain a cure. Selective use of steroid and carefully use of high dose of predinisolone should be considered in TBM treatment therapy. The study signified that the increase age of patients, late diagnosis and treatment, increase the stage of disease and the development of hydrocephalous specify the morbidity in TBM.

Thus, it is critical to recognition on a comprehensive manner of management of TBM cases and their co morbidities relatively than initially treating the neurological signs and symptoms.

Author's Contribution:

Concept & Design of Study:	Kanwal Melwani
Drafting:	Sanjay Kumar, Sunil Kumar Dodani
Data Analysis:	Sarmad Jamal Siddiqui, Vijia Kumar Gemnani, Sonia Jetwani
Revisiting Critically:	Kanwal Melwani, Sunil Kumar Dodani
Final Approval of version:	Kanwal Melwani

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Comparative Analysis of Metformin and its Combination with Dapagliflozin in Type 2 Diabetes: Randomized Control Trial

Muhammad Kamran Yousuf[1], Mehar Fatima[1], Sadaf Haris[3], Hina Azfar[4], Faryal Gul[2] and Shahid Mustafa Memon[5]

ABSTRACT

Objective: The current clinical trial compared the effects of metformin monotherapy and dapagliflozin plus metformin combination in diabetic patients. The secondary objectives included estimating the effects of these regimens on safety and tolerability.

Study Design: Randomized clinical trial study

Place and Duration of Study: This study was conducted at the National Medical Center, Karachi, Pakistan from January – June 2020.

Materials and Methods: A total of 200 patients were recruited, had baseline FPG ≥ 126 mg/dL, and glycated hemoglobin A1c (HbA1c) ≥ 7.5- ≤10%. All the participants were divided into two groups: metformin (group A) and dapagliflozin plus metformin combination (group B). The study's primary endpoint was FBG and HbA(1c), and secondary included change in lipid profile, liver function test, renal function test, and urinalysis.

Results: The primary endpoints for combination therapy led to significantly greater reductions in FBG and HbA(1c) than metformin monotherapy. The change in FPG levels at week 12 in groups A and B were 184.05±14.82 vs. 101.40±16.85; $p < 0.0001$. The HbA(1c) change at week 12 in groups A and B was 7.83±0.54 vs. 6.91±0.74; $p < 0.0001$. Insignificant findings were observed for lipid profile, liver function test, renal function test, and urinalysis among both groups at the entire study.

Conclusion: This is the first randomized clinical trial in diabetic patients of Pakistan treated with and dapagliflozin-metformin combination. Combination therapy was generally well-tolerated and effective in reducing HbA(1c) and FPG relatively metformin monotherapy after initiation of therapy.

Key Words: β cell dysfunction, Dapagliflozin, hemoglobin A1c, Metformin, Type 2 diabetes mellitus

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INTRODUCTION

Pakistan is still listed as the top 10th country in the world for having high prevalence of people, i.e., 19.4 million with type 2 diabetes mellitus as per the estimates of the international diabetic federation[1] and this has been gradually increasing at an alarming level.

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Hence, this emerged as the focus of Pakistani researchers' attention in identifying effective therapeutic agents to control uncontrolled glycemia in diabetes. European Association for The Study of Diabetes and American Diabetes Association is deemed to use metformin as the cornerstone in native diabetic patients due to its clinical superiorities[2]. Nevertheless, many studies have revealed its limited response due to its gastrointestinal side effects in the Pakistani population[3].

The failure in the therapeutic intervention of metformin to maintain long-term glycaemic control in diabetic patients of Pakistan increases the need to identify the benefits and risk factors of different antidiabetic agents as monotherapy and combination therapy. Study of Harrower AD and team has shown an effective response by adding sulphonylureas in the regimen[4]. However, these regimens vary mechanistically. They employ an insulin-dependent intracellular cascade; subsequently, the reduction in effectiveness is observed due to b-cell dysfunction and insulin resistance, thus elevated disease progression. Moreover, the step-wise modification of strategy is inadequate for late-

diagnosed patients or experiencing severe hyperglycaemic events. For them, combination therapy with differing mechanisms has great importance as it produces a benefit to increase therapeutic response in the management of T2D.

One of the potential combination strategies involves metformin and sodium-glucose cotransporter-2 inhibitors (SGLT-2), in which one of them employs an insulin-dependent cascade while the other does not[5]. One potentially advantageous SGLT-2 regimen, dapagliflozin, was effective as add-on therapy to metformin in real-life clinical settings of the different genetical populations[6,7]. In Pakistan, it was first licensed to use in 2017[8]. The Pakistani population is genetically, demographically, and culturally diverse, and their lifestyle interventions are changed compared to the Western population[9-12], and with these changes, clinical response of the dapagliflozin-metformin combination is unknown. Therefore, the present clinical randomized trial aims to compare the efficacy of metformin and its combination with dapagliflozin to control diabetes in Pakistani patients. Moreover, the safety of these regimens was evaluated to prevent drug-induced complications.

MATERIALS AND METHODS

Clinical study design: The current randomized clinical trial was 12-week, conducted at the National medical center, Karachi, Pakistan. A total of 200 diabetic patients were recruited in the study who had uncontrolled glycemia with metformin; 190 were successfully completed. They were divided into two groups based on their treatment regimens. In the group A, patients was taken metformin 1500 mg, whereas the group B patients were given dapagliflozin 10 mg plus metformin 500 mg. The clinical trial was conducted after approval by the Ethical Research Committee (ERC) of Bahria University, Karachi, Pakistan. All diabetic patients provided informed consent.

Patients: All the diabetic patients were aged 45–55 years, had fasting plasma glucose (FPG) ≥ 126 mg/dL, hemoglobin A1c [HbA(1c)] >7-10%, and uncontrolled diabetes by restricted diet, regular exercise, and metformin monotherapy 1500 mg. Patients were excluded if their serum creatinine > 123.76 lmol ⁄ l; urine albumin to creatinine ratio (ACR) > 1800 mg ⁄ g; creatine kinase > 3 x ULN; glomerular filtration rate (GFR) < 45 ml/min/1.73 m^2; serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 x upper limit of normal (ULN); left ventricular ejection fraction (LEVF) < 40%; history of recurrent genitourinary tract infections, diabetes insipidus; cardiovascular event; and suffering with other than diabetes.

Endpoints and assessments: The sample size calculation of the diabetic population was estimated using OpenEpi, Version 3. The primary efficacy endpoint, i.e., FBG and glycated hemoglobin (hemoglobin A1c) levels, were estimated at different intervals (FPG: baseline, week 6, and week 12; HbA(1c): baseline, and week 12). The study's key secondary endpoints were lipid profile, liver function test, renal function test, and urinalysis. The change in lipid profile levels, i.e., high-density lipoprotein, cholesterol, triglyceride, and low-density lipoprotein, were estimated at baseline and week 12. Whereas, liver function test (serum glutamic pyruvic transaminase, serum glutamic-oxaloacetic transaminase, alkaline phosphatase, and bilirubin), renal function test, and (urea, creatinine) urinalysis (pyuria, white blood cell count, bacteria, ketonuria, leukocyte, and glucosuria) were quantified at baseline, week 6, and week 12. Moreover, the BMI and blood pressure difference with both treatment regimens were also observed for statistical significance.

All continuous variables were represented in mean ± SDev (standard deviation). The significant difference among the group was identified by applying student t-test and paired t-test. The analysis was carried out by using IBM statistical package of social sciences (SPSS) version 25 and taking P-values < 0.05 as significant.

RESULTS

The current randomized clinical trial enrolled 190 diabetic patients from Karachi, Pakistan. Of these patients, 50 % were men, and 50 % were women between the age of 45-55 years. At baseline, their mean BMI was 31±2.15 kg/m^2. All the patients had mean FBS level > 126 mg/dL and mean HbA(1c) level was ≥ 7 - ≤ 10 %. All the patients were initially being treated with metformin monotherapy. Table 1 depicts baseline and changes in mean characteristics of patients.

The primary objective of this study was to identify the efficacy of metformin vs. dapagliflozin-metformin combination in diabetic patients of Karachi. Followed by given respective treatment regimens, FBS and HbA(1c) levels were estimated. The results revealed that group A significantly increased concentrations of FBG at 1st follow-up (6th week) than group B (group A: FPG 144.23±12.54; group B: FPG 137.02±12.30 mg/dL; p<0.001). Consistently, significantly less control in FBG and HbA(1c) level was observed in group A relatively group B at 12th week (group A: FPG 122.89±9.22, HbA(1c) 7.51±0.49; group B: FPG 101.40±16.85 mg/dL, HbA(1c) 7.83±0.54 %; p<0.001). (Table 1).

The safety and tolerability were identified by measuring lipid profile, RFT, LFT, and urinalysis. Statistically insignificant changes in lipid profile were found between groups at the end of the study (12-week) by showing p-value >0.05, as represented in figure 1. Furthermore, no clinically significant levels of LFT and RFT and urinalysis were observed at 6th week and 12th week between both groups, as shown in Figures 1, 2, and 3. Furthermore, BMI, systolic blood pressure, and diastolic blood pressure were found similar in both groups and follow-ups. The mean change in characteristics at 1st and 2nd follow-up is presented in Table 1.

Table No.1: Mean changes in body mass index, systolic and diastolic blood pressure, glycemic profile, and glycosuria at 0-, 6- and 12-week followed by given metformin monotherapy and metformin-dapagliflozin combination therapy.

		Dapagliflozin-Metformin	Mean Difference	P-Value
Body mass index (BMI; kg/m^2, Mean±SDev)				
At Week 0	31±2.15	31±2.15		0.071
At Week 6	30±1.82	30±1.82		0.052
At Week 12	30±6.12	30±6.12		0.08
Systolic blood pressure (SBP; mm/Hg; Mean±SDev)				
At Week 0	130±9.04	134±14.82		0.052
At Week 6	123±11.34	137±12.30		0.064
At Week 12	134±8.12	131±16.85		0.073
Diastolic blood pressure (DBP; mm/Hg; Mean±SDev)				
At Week 0	95±0.22	95±0.25		0.075
At Week 6	93±0.24	93 ±0.73		0.062
At Week 12	97±0.57	92±0.89		0.082
Fasting plasma glucose (FPG; mg/dL; Mean±SDev)				
At Week 0	188. ±9.04	184. ±14.82		>0.05
At Week 6	144. ±12.54	137.±12.30		0.000^S
At Week 12	122. ±9.22	101. ±16.85		0.000 ^{S}
Glycated haemoglobin (HbA1c: %;Mean±SDev)				
At Week 0	7.91±0.45	7.83±0.54		>0.05
At Week 12	7.51±0.49	6.91±0.74		0.000 ^{S}
Glycosuria (n)				
At Week 0 Mild Moderate Severe	 98 2 0	 97 3 0		 <0.05
At Week 6 Mild Moderate Severe	 97 2 1	 12 86 6		 <0.01
At Week 12 Mild Moderate Severe	 98 2 0	 2 9 89		 <0.001

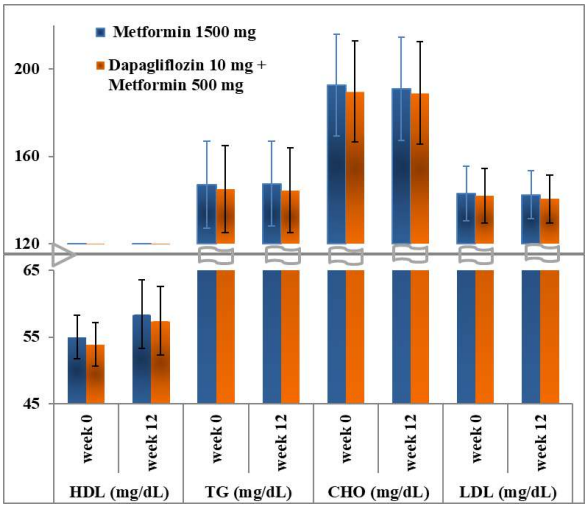

Figure No.1: Mean change in levels of lipid profile followed by given metformin monotherapy and metformin-dapagliflozin combination therapy.

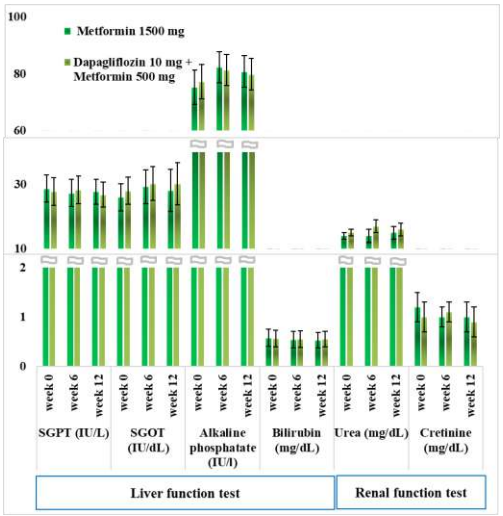

Figure No.2: Mean change in liver and renal function test in group A and B.

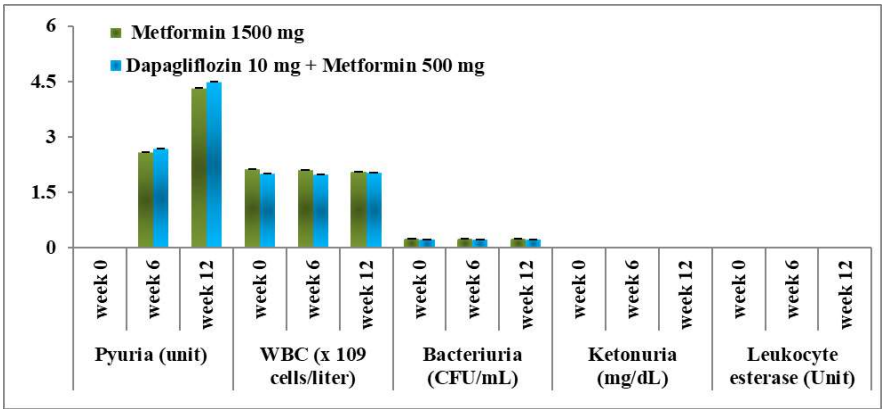

Figure No.3: Urinalysis followed by given treatment regimens.

DISCUSSION

The alarmingly increase incidence of diabetes needed the prompt identification of effective treatment. In general, as per the recommendation of the European Association for The Study of Diabetes and American Diabetes Association, the physicians of Pakistan routinely prescribed metformin monotherapy as pharmacotherapy of T2D[2]. However, a number of studies have been mentioned its decrease effectiveness of controlling glycemia in native patients. This elevates hyperglycemia which leads to various pathological impairments. The combination therapy is recommended by the American Association of Clinical Endocrinologists (AACE) in patients with HbA(1c) >8.5%. But, successful management of T2D in the population is a challenge. In Pakistan, the novel SGLT-2 inhibitor, dapagliflozin, was first licensed to use in 2017[8]. Previously several studies have been published on its potency and safety. But the focus on its effect in the patients of Pakistan was needed. Many studies have been found the diversity in the genetics, demography, culture, and lifestyle intervention of Pakistan's population compared to the Western population[9-12]. The alarmingly increase in the incidence and the diversity of population characteristics emerge the necessity of identifying the efficacy and safety of dapagliflozin-metformin and its comparison with first-line therapy, metformin. Therefore, a total of 200 patients were enrolled in the study and randomly assigned to receive metformin (group A) or dapagliflozin (10 mg) plus metformin (group B). As far as our knowledge, this is the first study which address the dapagliflozin combination in the population of Pakistan.

Our study revealed that both of these interventions effectively decrease levels of HbA(1c) and FBG in the Pakistani diabetic population. But comparatively, the proportion of achieving a greater decrease in FBG and HbA(1c) was significantly more in combination therapy than metformin monotherapy. Our findings are in line with the phase III trial conducted for 24-week in the population of northern Europe (Sweden)[13]. Another phase III trial covers the diabetic population of many north and south American areas and found −0.67%, −0.70%, and −0.84% mean changes in HbA(1c) by receiving 2.5, 5, and 10 mg monotherapy of dapagliflozin[14]. In the present study, we found a greater % change in HbA(1c) level, as this may due to the addition of metformin which may boost glycemic control. Furthermore, the age criteria recruited in our study was limited with may produce more potential outcomes as compared to their study, which was 18-77 years.

Besides the control effect of the combination, another most important challenge is to control or prevent the onset of comorbidity or drug-induced toxicity. Older age T2D patients are vulnerable to liver impairment, cardiovascular disease, and renal dysfunction. Drug-induced injury to the liver can mimic acute or chronic liver ailment triggered by cytochrome P450 action. This activation breaks drugs into reactive metabolites to bind with the protein moiety of unsaturated fatty acids, induce lipid peroxidation and subsequently impair calcium homeostasis. These events lead to death. Therefore, in the present study, the effect of both interventions on liver function tests was identified. As far as our knowledge, this is the first study that analysis the liver function in diabetic patients without co-morbidities. The results revealed similar findings between groups.

Besides, the safety of interventions was estimated at the different intervals of the study in both Pakistani diabetic patients. In South East Asian region of Pakistan, hypertension and obesity are prevalent comorbidities with T2DM, and SGLT-2 inhibitors, including dapagliflozin, are suggested as advantageous agents to prevent them potentially in multifold[15-18]. But in the present study, the reduction in BMI, systolic blood pressure, diastolic blood pressure were not found in any group during the entire study. The possible reason is that these studies are based on long-term, and thus, they found significant control of glycemia and maintained blood pressure and weight.

Identifying its effect on kidney function is vital before its use, as many previous studies suggested discontinuing it if the level of estimated glomerular filtration rate (eGFR) remains persistently less than 60 mL/min/ 1.73 m2. Other studies have shown genital or urinary tract infections, nasopharyngitis, diarrhea, back pain, and constipation as the most common adverse reactions of dapagliflozin. Urogenital infections were reported more frequently in diabetic patients of Europe, North America, South America, and Southern Africa followed by receiving dapagliflozin- metformin combination. But in the present study, urea and creatinine levels were observed normal, and no side effects were reported respected to the urogenital area. This may due to the short time duration of the study. Thus, this can be suggested that both of these interventions were not toxicants and retain the mechanism of kidney-specific detoxification, excretion, and homeostasis of body and are unable to produce a modification in tubular cell toxicity, crystal nephropathy, glomerular hemodynamics, inflammation, thrombotic microangiopathy and rhabdomyolysis in the population of Pakistan.

Next, the drug-mediated toxicity of heart is one of the major adverse effects. Therefore, the lipid profile was identified, followed by the intervention, and found similar HDL levels, LDL, CHO, and triglycerides among diabetic groups. Whereas, clinically significant findings of plasma lipids was observed by using dapagliflozin in LDL (4.8–0.9%), and triglycerides (−8.0% to 2.9%) levels as compared to placebo group[19]. The short duration of the current study may prevent significant findings.

Moreover, the hypoglycemic or hyperglycemic events were not observed during the entire study. Similarly, previous studies have found a similar observation in diabetic population of Europe (UK) and America receiving dapagliflozin monotherapy. Overall, the SGLT- 2 inhibitors have been shown to lower susceptibility of hypoglycemia than other oral antidiabetic drugs and insulin because of their insulin-independent mechanism of action. But, it is recommended to monitor the diabetic patients for the risk of hypoglycemia and make adjustments in doses of SGLT-2 inhibitors, including dapagliflozin. The religious and cultural practices of prolonged fasting (e.g., Ramadan) in Pakistan may elevate the risk of hypoglycemia in population.

Next, the lipid profile was identified, and found similar HDL levels, LDL, CHO, and triglycerides among diabetic groups. Whereas, clinically significant findings of plasma lipids were observed by using dapagliflozin in LDL (4.8–0.9%) and triglycerides (−8.0% to 2.9%) levels as compared to placebo group[19].

A key strength of this study is the comparison of first-line medication, metformin, with dapagliflozin-metformin combination for the treatment of glycemia in diabetic patients of Pakistan. Best of our knowledge, this is the first study that compares these two frequently prescribed medicines in the population of Pakistan. The efficacy of both therapeutic interventions for FBS and HbA(1c) were performed at intervals 0 and 12^{th} weeks of the study. The safety profile in both groups to liver functions, renal functions, cardiovascular dynamics, urinary and genital tract, and monitored closely. The possible limitations of the present study are the failure to observe the long-term potential and tolerability level on liver, kidney, and heart physiology, and the population size of the study is limited.

CONCLUSION

Metformin monotherapy and its combination with dapagliflozin improve glycaemic control, and both are well-tolerated pharmacotherapy for the treatment of type 2 diabetes. The dapagliflozin- metformin therapy inferior to reduced greater HbA(1c) and FBG levels compared to metformin monotherapy in diabetic patients of Pakistan. None of the interventions elevates the incidence of cardiovascular disorder, liver toxicity, renal impairment, and urinary tract and genital infections. Dapagliflozin-metformin therapy can be an alternative selection to reduce the obtain optimal glycemia without producing major side effects in the diabetic population of Pakistan.

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Author's Contribution:

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Drafting:	Mehar Fatima, Sadaf Haris
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Iron Deficiency Anemia and Intestinal Parasitic Infection in Children

Correlation Between Iron Deficiency Anemia and Intestinal Parasitic Infection in School-Age Children in Peshawar

Aysha Sarwar Khan[1], Shaista Alam[2], Iftikhar Hussain[4], Hafsa Sarwar Khan[4] and Ambreen Ali[3]

ABSTRACT

Objective: The aim of this study was to investigate whether iron deficiency anemia and intestinal parasitic infections in school aged children are correlated or not.

Study Design: Cross-Sectional Study

Place and Duration of Study: This study was conducted at Peshawar Institute of Medical Sciences, from March 2019 to March 2020.

Materials and Methods: The total of 130 samples were included in this study by using consecutive sampling technique. The samples were collected from the middle school children aged from 8 to 12. The children who were willing were included in this study after taking permission from their parents. Another criteria for the sampling of this study was that the children should not have taken any antiparasitic medication for at least past six months. The blood and stool samples were taken to analyze peripheral blood smear, serum ferritin and intestinal parasites. The data was analyzed using univariate and bivariate analysis method (ANOVA test). The occurrence of anemia due to different species of intestinal parasite was also figured out. The Chi-Square test was performed to find out the correlation between iron deficiency anemia and some variables like mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and serum ferritin.

Results: The results showed that the occurrence of iron deficiency anemia was almost 28 percent. The percentage of intestinal parasitic infections was 26.7. Seven types of parasites were identified in infected participants. Entamoeba histolytica was the most prevalent parasite while Hymenolepis nana was the least prevalent. The blood results of almost 37 percent of the participants with intestinal infections showed either lowered red blood cell count or lowered hemoglobin concentration. The participants infected with Escherichia coli had the highest percentage of anemia; almost 48.7 percent. Participants with Hymenolepis nana showed the least number of anemic patients, 21 percent. The Chi-Square test showed significant correlation of MCV, MCH and serum ferritin with anemia.

Conclusion: According to the results of this study, there is positive correlation between iron deficiency anemia and intestinal parasitic infections. 37 percent of the participants which were infected by intestinal parasite had anemia. This proves that intestinal parasitic infections do cause anemia. Escherichia coli caused the highest percentage of anemia in participants. Also, the occurrence of intestinal parasitic infections was high in children generally. Entamoeba histolytica is one of the most common intestinal parasite. This needs to be taken care of as parasitic infections can affect the life of children in a number of ways other than just causing anemia and can pave the way for other diseases too. Preventive and hygienic measures should be promoted among children by the collective effort of parents and teachers to stop the development and spread of such infections.

Key Words: Iron Deficiency Anemia, Intestinal Parasitic Infections, Children, Serum Ferritin, MCV, MCH.

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INTRODUCTION

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The percentage of school aged children having anemia is almost 34.3 percent in developing countries[1]. Anemia is a blood disorder having reduced hemoglobin, packed cell volume and red blood cell count[2]. There are many types of anemia depending on etiology but the most common type of anemia is iron deficiency anemia[2]. The causes of iron deficiency anemia can be less iron in diet, loss of blood, irregular food intake and parasitic infections.

Due to iron deficiency, the body cannot produce enough hemoglobin. Hemoglobin performs very important function of carrying oxygen in our body. Deficiency of hemoglobin can cause anemia, fatigue, dizziness, dyspnea, pale mucosa and skin, weakness and many other complications.[2]

The most common infections are intestinal parasitic infections. These infections effect nearly 3.6 billion individuals. Such infections also cause almost 455 million health issues yearly.[3] According to WHO, these infections are one of the 17 tropical neglected disease and also have high ability to spread from person to person[4]. The most common intestinal parasites are Giardia Intestinalis, Hookworm, Cryptosporidium and Strongyloides Stercoralis among others [5, 6].

The helminthes are a variety of parasitic worms that usually cause intestinal infections. Hookworm is one of the example of helminthes. These parasites cause infections in almost 2.1 billion people globally. It is one of the top disease causing parasite in the world especially affecting children.[7] These parasite suck blood directly from intestine and cause anemia in their host. They also reduce iron absorption from the intestine leading to iron deficiency anemia. By reducing iron absorption from the intestine, this parasite interferes with the iron metabolism in the body. [5]

Intestinal parasites can also damage intestinal mucosa lining, this damaged lining is then unable to absorb nutrients leading to nutritional deficiencies. In case of iron, it can cause iron deficiency anemia. Nutritional deficiencies can also weaken the immune system that can pave the way for other diseases to develop. This condition is particularly dangerous for children of development age.[5]

Intestinal parasites like Ancylostoma duodenale can also cause intestinal wall bleeding. This can also lead to iron deficiency and anemia.[8]

Intestinal parasitic infections are more common in developing countries as compared to other developed countries. The reason for it can be poor sanitary conditions in such countries, which makes the development and spread of such disease very easy. The socioeconomic conditions of these countries is also poor that can contribute to higher prevalence of disease.

In this study, we investigated the correlation between the two conditions described above; iron deficiency anemia and intestinal parasitic infections.

MATERIALS AND METHODS

This study was conducted in Peshawar, from March 2019 to march 2020. The total of 130 samples were included in this cross-sectional study by using consecutive sampling technique. The samples were collected from the middle school children aged from 8 to 12. The children who were willing were included in this study after taking permission from their parents. Another criteria for the sampling of this study was that the children should not have taken any antiparasitic medication for at least past six months. These children should also not have conditions like atopic eczema, asthma, immunological disorders, rheumatic disorders and cancer [5].

The blood and stool samples were taken to analyze peripheral blood smear, serum ferritin and intestinal parasites. Damaged samples were excluded from the study. The aim of the study was explained to the parents of participants and proper consent was taken from them. After that, history of disease and medication consumption of participants was taken.

Stool containers were provided to the participants for the collection of stool samples. After collection of samples, they were preserved in 10 percent formalin for transportation to the laboratory for examination. Kato technique was used to examine the stool sample. Parasite present in the stool at any stage of its life cycle i.e. cysts or trophozoites, or eggs of helminthes confirmed the diagnosis of intestinal infection. [5]

After the collection of stool sample, blood samples were collected for peripheral blood smear test and ferritin test. Peripheral smear test tells us about the morphology of red blood cells and establish the diagnosis for anemia. Blood samples were collected by phlebotomy and kept in heparin containing tube. Heparin act as anticoagulant for blood samples. All the samples were stored in cold box and then transported to the laboratory where they were analyzed in less than 15 hours of collection. SYSMEX T-2000i analyzer was used to study the mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV) and hemoglobin level of the samples. COBAS 6000 c501 was used to measure the ferritin, total iron binding capacity, and serum iron.

Predictive Analytics Software (PASW) was used to analyze all of the collected data. Then for the bivariate analysis, Chi-Square test was performed. This was done to find whether the correlation between iron deficiency anemia and intestinal parasitic infections existed or not. Then, ANOVA test was used to analyze the data variables like ferritin, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), serum iron and total iron binding capacity (TIBC).

RESULTS

Total 130 samples were collected from children aged 10 to 12 years from --- (name of place). 55 percent samples were collected from boys while 45 percent were collected from girls.

Table 1 shows descriptive analysis i.e. univariate data analysis which show the percentage of intestinal parasitic infections was 26.7. 28 percent of the participants had anemia. The blood results of almost 37 percent of the participants with intestinal infections showed either lowered red blood cell count or lowered hemoglobin concentration, which meant anemia. This shows the influence of parasitic infections on anemia. Seven types of parasites were identified in infected participants. Entamoeba histolytica was the most prevalent parasite while Hymenolepis nana was the least prevalent.

Table No.1: General characteristics of samples

Characteristics	Percentage
Gender	
Girls	45 %
Boys	55 %
Intestinal parasitic infection	
Yes	26.7 %
No	73.3 %
Anemia	
Yes	28 %
No	72 %
Anemia in infected participants	
Yes	37 %
No	63 %
Type of parasite	
Trichuris trichura	5.4 %
Giardia lamblia	23.6 %
Ascaris lumbricoides	3.9 %
Entamoeba histolytica	29.1 %
Hymenolepis nana	2.5 %
Ancylostoma dudenale	8.5 %
Escherichia coli	27 %
Serum ferritin (Low < 12 µg/mL)	
Normal	75 %
Low	25 %
Serum iron (low < 50 µg/mL)	
Normal	74 %
Low	26 %
MCV (78-98 fL)	
Normocytic	55 %
Macrocytic	0 %
Microcytic	45 %
MCH (25-33 pg)	
Normochromic	71 %
Hypochromic	29 %
TIBC (High TIBC > 346 ìg/dL	
Normal	61 %
High	39 %

25 percent of the population showed low serum ferritin value and 26 percent showed low serum iron. 45 percent of the population had microcytic red blood cells and 29 percent had hypochromic. Lastly, TIBC value was higher than normal in almost 39 percent of the participants. All of these values deviating from the normal indicates iron deficiency anemia in the participants.

Table No.2: ANOVA p-value

Variable	Anemia	Parasitic infection
Serum ferritin	.000	.345
Serum iron	.275	.654
MCV	.000	.356
MCH	.000	.246
TIBC	.368	.010

In the Table 2, we can see the bivariate analysis of anemia with serum ferritin, serum iron, MCV, MCH and TIBC; and bivariate analysis of parasitic infected participants with serum ferritin, serum iron, MCV, MCH and TIBC. The results show that the serum ferritin, MCV and MCH had a positive correlation with anemia. Other variables i.e. TIBC and serum iron did not show such correlation. The results also show that the serum ferritin, MCV, MCH, serum iron and TIBC had no correlation with parasitic infections. This show a positive correlation between MCV, MCH and serum ferritin with iron deficiency anemia.

Table No.3: Occurrence of anemia according to species of intestinal parasite

Parasitic specie	**Percentage of anemia**
Trichuris trichura	38 %
Giardia lamblia	31.4 %
Ascaris lumbricoides	34 %
Entamoeba histolytica	40 %
Hymenolepis nana	21 %
Ancylostoma dudenale	45.3 %
Escherichia coli	48.7 %

The Table 3 show the occurrence of anemia due to different species of intestinal parasite. According to the results, Hymenolepis nana infected participants show the least percentage of anemia while Escherichia coli infected participants show highest percentage of anemia. This show positive correlation between iron deficiency anemia and intestinal parasitic infestation, especially E coli.

DISCUSSION

Anemia affect the people globally. People of every age, gender and socioeconomic condition get affected by anemia. According to WHO, almost 800 million women and kids suffer from anemia worldwide[9]. Our study show anemia in nearly 28 percent of the participants.

The most common infections are intestinal parasitic infections. These infections effect nearly 3.6 billion individuals[3]. These infections are classified as neglected tropical disease according to WHO. In this study, 26.7 percent of the children were infected by some kind of intestinal parasite. The most common route of these infections is contaminated food, water and poor hygienic conditions. Entamoeba histolytica was the most common infectious parasite according to the results of this study, which is similar to the Al-Niaeemi, Khazal & Dawood's study. In a different study, the most common parasite was A. lumbricoides[10].

There are many types of anemia depending on etiology but the most common type of anemia is iron deficiency anemia[2]. The causes of iron deficiency anemia can be less iron in diet, loss of blood, irregular food intake and parasitic infections. Anemia is more prevalent in

developing countries, especially in school aged children[11].

Parasites can also be the cause of anemia. Like anemia, intestinal parasitic infections are also more common in developing countries due to a number of reasons i.e. poor hygienic conditions, poor socioeconomic conditions. These infections can also cause anemia. Maybe this is the reason of higher anemia rate in developing countries.[11]

The rupturing of blood vessels of the intestine is one of the many ways an intestinal parasite cause anemia in their host. Hookworms work through this mechanism. To further increase the blood loss, these worms secrete anti-coagulant substances to hinder the mechanism of clot formation to stop the bleeding. Trichuris trichura causes bleeding in the large intestine and causes anemia. Along with blood loss, these parasites absorb the nutrients from the gut wall of the host and cause malnutrition. This can lead to other disorders like anorexia.[5]

Ascaris lumbricoides also absorbs nutrient like iron from the small intestine and cause iron deficiency anemia. Some parasites can cause atrophy, inflammation and hypertrophy in the intestines. These processes hinder the nutrient absorption from the intestines and cause decreased amount of essential nutrients i.e. iron, folic acid and vitamins, in the body. [5] Such conditions are very harmful for children at development age.

According to this study, participants with intestinal parasitic infections had the higher percentage of iron deficiency anemia and it positively correlated in numerical analysis. Some other studies also showed similar results. One of these study was Gopalakrishnan, Eashwar, Muthulakshmi & Geetha's study conducted in India[11]. Mahmoud, Abdul Fattah, Zaher, Abdel-Rahmanm & Mosaad's study in Egypt also showed significant correlation between iron deficiency anemia and intestinal parasitic infections [12].

The MCV, MCH and serum ferritin showed positive correlation with anemia in our study. These variables did not show any significant correlation with intestinal parasitic infections in ANOVA test done for this study. These results were similar to the results of Darlan, Ananda, Sari, Arrasyid & Sari's study conducted in Medan.

This study shows significant link between intestinal parasitic infections and anemia. This also indicates lack of awareness about the association of such infections with hygiene and unclean food and water consumption. Also people need to be educated about the importance of iron supplements to overcome such huge number of anemia patients.

CONCLUSION

According to the results of this study, there is positive correlation between iron deficiency anemia and intestinal parasitic infections. 37 percent of the participants which were infected by intestinal parasite had anemia. This proves that intestinal parasitic infections do cause anemia. Escherichia coli caused the highest percentage of anemia in participants. Also, the occurrence of intestinal parasitic infections was high in children generally. Entamoeba histolytica is one of the most common intestinal parasite. This needs to be taken care of as parasitic infections can affect the life of children in a number of ways other than just causing anemia and can pave the way for other diseases too. Preventive and hygienic measures should be promoted among children by the collective effort of parents and teachers to stop the development and spread of such infections.

Author's Contribution:

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Original Article

Impact of Digoxin on Over All Mortality in Patients with Heart Failure and Atrial Fibrillation

Khawar Abbas, Kashif Ali Hashmi, Raheel Iqbal, Muhammad Amir Shahzad, Muhammad Zohaib Zahoor and Hafiz Muhammad Rizwan Amjad

ABSTRACT

Objective: The practice of digoxin in patients having a trial fibrillation (AF) with heart failure and deprived of heart failure has not been discussed. The purpose of this analysis was to investigate the effect of digoxin therapy on frequency of mortality stratified by heart failure.

Study Design: prospective / observational study

Place and Duration of Study: This study was conducted at the Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Pakistan. Patients included from January 2020 to January 2021 and were enrolled for a year.

Materials and Methods: This study encompassed 610 patients of atrial fibrillation. The analyzes were achieved using multivariate and univariate statistics.

Results: The study included 610 patients. 46 + 11 years was the patients mean age. At discharge from hospital, 34% (n = 214) of patients were prescribed digoxin and among 48% (n = 103) have heart failure. Discharged 75 (12.3%) patients died after 1year of follow-up. Patients with heart failure had higher mortality at one month (4.2% vs 2.0% without HF; p <0.001), at 6 months (12.1% vs 4.3 without HF%; p <0.001) and at 12 months (23.4% vs 6.9 without HF%; p <0.001).When stratified digoxin therapy showed significantly higher mortality at one-year in patients with heart failure (at 12-month (24.1% vs 11.1% without HF and at 6-months 11.1% vs 7.9% without HF).

Conclusion: In heart failure and atrial fibrillation patients, survival did not improve by digoxin. Though, in subjects deprived of heart failure, treatment with digoxin was related with significantly long-standing mortality.

Key Words: digoxin, atrial fibrillation, heart failure and mortality

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INTRODUCTION

With the development of approved drugs and more operative intervention procedures for the treatment of heart failure and a trial fibrillation (AF), the digoxin usage has decreased for the past two eras[1-2]. In the American Heart Association /Heart Rhythm Society/ American College of Cardiology (AHA /HRS/ ACC) strategies for controlling the incidence of a trial fibrillation, digoxin, though cited in the treatment but does not provide class recommendations, otherwise recommends digoxin for HF pre-excitation, heart rhythm (class IB) and digoxin is operative in controlling the inactive rate of heart in subjects with reduced EF having HF (class IC)[3-4]. In addition, combinations of digoxin and B blockers (or in patients with heart failure fixed by a non-dihydropyridine calcium channel blocker) make sense in the monitoring and use of patients with AF (Class IIA)[5-6]. European Society of a trial Fibrillation (ESC) guidelines recommend the use of digoxin after beta-blockers and calcium channel blockers as a third option in patients with idiopathic or associated a trial fibrillation (class IB) and heart failure, guidelines of ESC indorse IV class IB digoxin) and for frequency control in long-lasting conditions, digoxin in heart failure are recommended in subjects with sedentary lifestyle and left ventricular (LV) dysfunction[7-8]. Though, in practice, digoxin has remained to be overused or misused in AF patients, particularly in the aged populace and causes noxiousness[9]. Recent reports of the use of digoxin have raised controversy regarding the mortality and morbidity of patients with or without heart failure[10-11]. Due to the safety concerns of digoxin and recent reports, more evidence is needed before the digoxin policy can be changed. The purpose of this analysis was to investigate the effect of digoxin therapy on frequency of mortality graded by heart failure.

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MATERIALS AND METHODS

This is a prospective, and observational study which encompassed 610 patients of a trial fibrillation. Patients included from January 2020 to January 2021 and were enrolled for a year held in the Cardiology Department of Chaudhary Pervaiz Elahi Institute of Cardiology, Multan, Pakistan. All the particulars of the definitions and methods of data variables are available already. In summary, when patients were above 18 years of age, if they were entitled to have AF either on a 12-lead ECG electrocardiogram for 30 seconds time or having rhythm strip were included and received written permission. The treatment choices are according to the doctor of medicine. The research was approved by the ethical committee. The data was documented in a standard case description form and uploaded online. Data gathered comprised selectees' demographics; surgical and medical history; AF History, including AF-type; in emergency outcomes and management given at before, at discharge and during stay in hospital. Medications include diuretics, converting enzyme (ACEI) inhibitors, angiotensin, angiotensin receptor blockers, B blockers, statins, clopidogrel, warfarin and aspirin. Data complies with the AHA/ ACC guidelines for AF. Variables necessary for Hypertension, congestive heart failure, Age above 75 years; DM; the transient ischemic attack/ stroke was also calculated. HF was definite rendering to the criteria of Framingham listed in the AHA/ ACC variables data. LV systolic dysfunction was definite after EF less than 40% determined by ECHO.

The characteristics of patient were concise using categorical variables and mean rates, standard deviations and percentages between cases of continuous variables were measured and applied. The comparisons of groups of categorical variables were made using the Pearson's w2 test, followed by the Wilcoxon-man-Whitney test or Student's t-test, respectively. The effect of treatment by digoxin on overall mortality (30 days, 180 days and one year) was assessed by multivariate logistic regression using a step-by-step elimination approach. The mortality variables were as follows (Table 1) ($p < 0.1$). Changes include gender, age, LV systolic dysfunction, body mass index (BMI), diabetes, hypertension, chronic obstructive pulmonary disease (BPK), coronary artery disease (CAD),previous history of stroke / TIA, serum creatinine and peripheral vascular disease (PVD) were documented. The drugs prescribed in discharge include (diuretic, statin, beta-blocker, aspirin, warfarin, clopidogrel), type of AF and CHADS risk assessment were also recorded. The adaptive advantage of the logistics model was analyzed using Leme showand Hosmer statistical adapters. The discriminant potential of the logistic model was evaluated in the areas below the receiver efficiency curve, also called the C index. P value less than 0.05 was taken significant. Statistical analysis was achieved by means of STATA version 13.1.

RESULTS

The study included 610 patients. The clinical characteristics and demographic of the patients are presented in Table 1. 46±11 years was the patients mean age.

At discharge from hospital, 34% (n = 214) of patients were prescribed digoxin and among48% (n = 103) have heart failure. Discharge 75 (12.3%) patients died after 1year of follow-up.

Patients with heart failure had higher mortality at one month (4.2% vs 2.0% without HF; $p < 0.001$), at 6 months (12.1% vs 4.3 without HF%; $p < 0.001$) and at 12 months (23.4% vs 6.9 without HF%; $p < 0.001$).When stratified digoxin therapy showed significantly higher mortality at one-year in patients with heart failure (at 12-month (24.1% vs 11.1% without HF and at 6-months 11.1% vs 7.9% without HF).

Table No.1: Clinical characteristics and demographic of the patients

Characteristic	All (N =610)	Digoxin Therapy at Discharge		P
		No (n=396; 65%)	Yes (n=214; 35%)	
Demographic				
Age, mean ±SD, years	46 ±11	47 ±10	46 ±12	0.638
Male gender, n (%)	321 (52.6%)	225 (56.8%)	96 (44.9%)	<.001
Medical history, n (%)				
LV systolic dysfunction	109 (17.9%)	42 (10.6%)	67 (31.3%)	<.001
Heart failure	168 (27.5%)	65 (16.4%)	103 (48.1%)	<.001
Coronary artery disease	178 (29.2%)	105 (26.5%)	73 (34.1%)	0.001
Diabetes mellitus	184 (30.2%)	125 (31.6%)	59 (27.6%)	0.051
Rheumatic heart disease	98 (16.1%)	28 (7.1%)	70 (32.7%)	<.001
Hypertension	316 (51.8%)	209 (52.8%)	107 (50.0%)	0.052
COPD	34 (5.6%)	18 (4.5%)	16 (7.5%)	0.035
Stroke/TIA	75 (12.3%)	47 (11.9%)	28 (13.1%)	0.016

Peripheral vascular disease	13 (2.1%)	6 (1.5%)	7 (3.38%)	0.001
Creatinine, median (interquartile range), mmol/L	82 (68-100)	70 (59-101)	76 (62-103)	<.001
BMI, mean + SD, kg/m^2	23 + 4	24 + 4	22 + 4	<.001
Smoking status	131 (21.5%)	82 (20.7%)	49 (22.9%)	0.54
CHADS score category, n (%)				
0	172 (28.2%)	121 (30.6%)	51 (23.8%)	<.001
1	164 (26.9%)	107 (27.0%)	57 (26.6%)	0.642
2-6	274 (44.9%)	168 (42.4%)	106 (49.5%)	<.001
AF type, n (%)				
Don't know	21 (3.4%)	14 (3.5%)	7 (3.3%)	0.778
Paroxysmal	114 (18.7%)	94 (23.7%)	20 (9.3%)	<.001
First attack ever	221 (36.2%)	169 (42.7%)	52 (24.3%)	<.001
Persistent	56 (9.2%)	35 (8.8%)	21 (9.8%)	0.52
Permanent	198 (32.5%)	84 (21.2%)	114 (53.3%)	<.001
Medications at discharge, n (%)				
ACEI	238 (39.0%)	144 (36.4%)	94 (43.9%)	0.002
Diuretic	333 (54.6%)	158 (39.9%)	175 (81.8%)	<.001
b-Blocker	346 (56.7%)	245 (61.9%)	101 (47.2%)	<.001
ARB	80 (13.1%)	56 (14.1%)	24 (11.2%)	0.083
Aspirin	323 (53.0%)	224 (56.6%)	99 (46.3%)	0.001
Statin	287 (47.0%)	206 (52.0%)	81 (37.9%)	<.001
Warfarin	351 (57.5%)	189 (47.7%)	162 (75.7%)	<.001
Amiodarone	57 (9.3%)	46 (11.6%)	11 (5.1%)	<.001
Clopidogrel	68 (11.1%)	51 (12.9%)	17 (7.9%)	0.037
Mortality, n (%)				
1 month	17 (2.8%)	9 (2.3%)	8 (3.7%)	0.084
6 months	50 (8.2%)	22 (5.6%)	28 (13.1%)	<.001
12 months	75 (12.3%)	35 (8.8%)	40 (18.7%)	<.001

Table No.2: Comparison of Mortality among the patients at various interval

Mortality Stratified by CHF Status	All	Pearson χ2 Test		P	Multivariate Logistic Regression			
		No Digoxin	Digoxin		OR (95% CI)	Adjusted P	HL	ROC
1 month								
Without HF	19 (2.0%)	10 (2.1%)	9 (2.9%)	0.561	1.15 (0.22-4.75)	0.742	0.101	0.67
With HF	16 (4.2%)	7 (3.9%)	11 (4.9%)	0.796	2.52 (0.61-9.57)	0.138	0.724	0.72
6 months								
Without HF	58 (4.3%)	27 (3.1%)	21 (7.9%)	<.001	4.97 (2.25-10.0)	<.001	0.895	0.73
With HF	77 (12.1%)	17 (13.5%)	50 (11.1%)	0.246	1.52 (0.70-3.19)	0.167	0.84	0.59
12 months								
Without HF	93 (6.9%)	50 (5.7%)	33 (11.1%)	<.001	4.12 (2.13-7.89)	<.001	0.061	0.71
With HF	112 (23.4%)	31 (21.5%)	71 (24.1%)	0.443	1.27 (0.73-2.43)	0.307	0.806	0.57

DISCUSSION

The main finding of this study was that in patients without HF and with AF, digoxin treatment was related with suggestively advanced long-term mortality equated to patients who did not receive digoxin treatment[10-11]. Moreover, in cases with HF and AF, digoxin did not show an endurance benefit. In a recent huge analysis of 132005 freshly detected AF patients with a mean age of 72.2 years, 22.9% had given digoxin[12-13]. In contrast, the mean age of patients with AF in this study was 46 ± 11%. In the analysis of stroke prevention with an oral thrombin inhibitor in a trial fibrillation [SPORTIF] III and V show promising effects, in patients with AF receiving digoxin, the mortality was 4.22% per patient-year compared with 2.66% per patient-years in those receiving digoxin were not observed with an adjusted hazard ratio (HR) of 1.53[14]. Similar HRe of 1.42 and 1.41 were observed in patients treated with digoxin in the Swedish Intensive Care Admission Information and Knowledge Registry (RIKS-HIA) observed in the AF Follow-up AFFIRM study. The causes of the increased death rate from digoxin in patients with HF and AF are unknown[15-16].

Digoxin has been associated with malignant tumors, prothrombotic status, markers of endothelial activation, stroke, increased mortality in patients with renal failure and digoxin-induced arrhythmiaswithoutHF[17-18]. Therefore, relatively healthy young patients who do not have AF have a high risk of death after one year after stopping digoxin treatment[19-20]. Inform health authorities about use of digoxin in AF patients in the Middle East. The main limitation of these studies is the observational design, which limits the ability to assess causation. The study could not confirm whether patients who are controlling or switching to other medications are taking digoxin. In addition, no digoxin doses and serum digoxin levels were available, making it difficult to determine whether digoxin levels may in any way contribute to mortality.

CONCLUSION

This is the initial study in the Pakistan. In subjects with a trial fibrillation deprived of heart failure, treatment with digoxin had a suggestively longer life span equated to those who did not receive treatment with digoxin. Moreover, in HF and AF patients, digoxin did not show endurance benefit. These conclusions must be taken seriously as the A trial fibrillation in the younger age. These results suggest that doctors must consider more medications before administering other medications to control the HR before prescribing digoxin in subjects with atrial fibrillation deprived of heart failure.

Author's Contribution:

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Original Article

Expression of Vimentin in Breast Carcinoma & its Correlation with Histopathological Parameters

Humaira Khan[1], Mohibullah Khan[1], Shaista Alam[1], Sadaf Sabah[2], Shabir Ahmed Orakzai[3] and Mehwish Syed[2]

ABSTRACT

Objective: To explore vimentin expression in different forms of breast cancer 2) to establish whether vimentin expression has a relationship to prognostic markers such as tumor size, grades, and status of the lymph node.

Study Design: Observational study

Place and Duration of Study: This study was conducted at the Department of Pathology Hayatabad Medical Complex Peshawar from March 2019 to March 2020.

Materials and Methods: 50 Specimens of radical modified mastectomy have been received by the Department of Pathology Hayatabad Medical Complex Peshawar. After history has been collected, specs of hematoxylin and eosin and immunehistochemically stained sections were checked and fixed to 10 percent forms of formalin.

Results: In this research, the number of patients was 40-60 years of age. (It's about 51 years old on average.) In 23/50 (46%) of cases, Vimentin expression has been identified. It has demonstrated that its expression is highly linked to progressive malignancies (P-value 0,05) and that tumor cells transition from the epithelial to the mesenchymal. The bulk (48 percent) were classified as Invasive Carcinoma NST in Grade 2 and histopathologically identified. No link was found between the expression and status of the lymph node and the tumor size (P-value 0.05).

Conclusion: Vimentin is more typically seen in advanced cancers. Its expression is unrelated to tumor size or nodal metastasis, implying that it may assist patients to obtain early treatment and live longer lives regardless of other prognostic variables.

Key Words: Vimentin, Breast Carcinoma, Correlation, Histopathological Parameters

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INTRODUCTION

Cancer is a disorder group in which the cells of the body uncontrolled change and spread. The incidence of cancer and mortality are growing alarmingly on a global scale. The mammalian gland is a highly dynamic organ that is submitted to branching, morphogenesis in adolescence, alterations during the menstrual cycle, and goes in the course of pregnancy, lactation, and involution.

Breast neoplasm is the most frequent cancer in women all over the world.[1-2]

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Cervical cancer has previously been the most common disease in Indian women, but breast cancer has now outweighed cervical cancer as one of the principal reasons for mortality, however cervical cancer remains the most common cancer in rural India.[3]

Breast cancer has become more common as a result of changes in risk factors. According to GLOBOCAN 2018, 2 million new cancer cases were diagnosed in women, accounting for 25% of all new cancer cases. Breast cancer is a complex disease in which a variety of factors have a role in its development. Many investigations and experiments have shown that carcinomatous cells take on the characteristics of mesenchymal cells and express mesenchymal markers. That is, high-grade epithelial tumors lose their epithelial form and develop mesenchymal features, a process known as epithelial-mesenchymal transition (EMT), which is linked to tumor invasiveness and metastatic potential. EMT causes epithelial markers like vimentin and fibronectin to be downregulated while mesenchymal markers like vimentin and fibronectin are upregulated.[4-5]

In normal mesenchymal cells, vimentin, a class 3 intermediate filament, is widely expressed. It is well known for maintaining cellular integrity and providing stress tolerance. Vimentin is either laterally or

terminally connected to the nucleus, endoplasmic reticulum, and mitochondria. Vimentin is a multifunctional protein that can interact with a wide range of proteins, making it a possible controller of a variety of physiological activities. Expression of Vimentin is higher in a variety of epithelial malignancies, including prostate cancer.[6]

According to much research, the expression of Vimentin in breast cancer is a major prognostic predictor. High-grade tumors, increased tumor proliferation6, low-PR, low-AR, invasive membrane basement, and therapeutic resistances are connected to Vimentin positive cells.[7]

As a result, we used immunohistochemistry to examine the expression of Vimentin in breast cancer in our study. We also looked at how this marker's expression correlated with grade related to histopathologically, size of the tumor, & metastasis of lymph node.

MATERIALS AND METHODS

Lumpectomy specimens delivered to the pathology laboratoryof Hayatabad Medical Complex provided the data for this investigation. Age, sex, presentation style (side of a lump or nipple discharge), technique, gross tumor size, and axillary nodal status are all things to think about. Our college's ethics committee permitted us to do just that.

The sections of Haematoxylin& Eosin (H&E) for the histological type, grade, and status of lymph node were obtained and analyzed. The grades were calculated with the grading system of Nottingham. All portions for IHC have been selected after testing for representative tumor paraffin blocks (Immunohistochemistry).

The slide was covered and incubated overnight at 58 degrees Celsius, 4 micron neoplastic tissue blocks were sliced. Sections of xylene, purified alcohol, 90 percent, and 70 percent were de-affining and dehydration. The antigen recovery resulted in the microwave and subsequent coverage of the slides with three-sodium citrate buffer solutions by a peroxide block to suppress endogenous peroxidase. The areas were stained for an hour with main antimicrobials. After secondary stains with peroxidase anti-peroxidase, the antigen body complex was colored with DAB.

RESULTS

Brown color development was regarded as positive, as well as the method outlined below was employed to score it. Immunohistochemical staining was evaluated.

For scoring immunostaining patterns, the most typical tumor regions were chosen. Light microscopy was used to score the samples. Vimentin staining of the cytoplasmic granules was regarded as a good result. Positive was defined as the absence of positivity in 10% of tumor cells. (Table 1).

Table No.1: Score with vimentin expression

Score	Vimentin expression
0	Negative with on staining of tumor cells
1+	Weak staining of more than 10% of tumor cells
2+	Moderate staining of more than 10% of tumor cells
3+	Strong staining of more than 10% of tumor cells

In this study, the majority of instances were in the under 40-year-old age group, while the least number of instances were in the over 70-year-old age group. The patients ranged in age from 28 to 90 years old. In our investigation, the average age of the cases was 51.0 years. The average age of patients with vimentin-positive tumors was 29 years old for the younger patients and 75 years old for the older patients.

Breast cancer that has spread across the body NST was found in practically every instance of breast carcinoma in the study, except two cases of carcinoma with medullary features such as mucinous carcinoma and only one case of either invasive papillary carcinoma, lobular carcinoma, as well as mixed type invasive & lobular carcinoma. The WHO's 2012 recommendations were used to grade the students. (By adapting Bloom and Richardson's method to suit Elston's needs). There were 18 cases of Grade 1/well-differentiated carcinoma, 24 cases of Grade 2/ moderately differentiated carcinoma, and 8 cases of Grade 3/ badly differentiated carcinoma in the 50 cases studied. As a result, grade 2 carcinomas with considerable differentiation accounted for the vast majority of cases. The invasive tumors ranged in size from 2cm - 9cm in diameter, with a mean of 5cm. Only one case had a tumor size of 4, 14 cases had metastatic deposits in 1-3 lymph nodes, & 10 cases had none. The bulk of the patients, 36 (72%) out of 50, had tumor sizes ranging from 2 to 5 cm, with 13 instances (26%) having tumor sizes more than 5 cm.

Vimentin expression was found to be significant in 23/50 (46%) of the patients in our investigation. When cancer cells had a pronounced brown cytoplasmic staining, the tumor was declared positive. Fibroblasts, endothelial cells, lymphocytes, and macrophages were labeled positively, while non-neoplastic tubule epithelial cells were stained negatively. All 50 cases were subjected to immunohistochemical staining, vimentin expression analysis, and scoring to determine the intensity of expression. When noticeable brown granular cytoplasmic expression was detected, vimentin expression was considered to be positive. There were 27 cases with a negative/score 0 expression, 1 case with a score 1+ expression, 21 cases with a score of 2+ expression, and 1 case with a score of 3+ expression out of 50. (Table 2)

Table No.2: Vimentin score with number of cases

Sr.No.	Vimentin Score	No. of cases (total 50)	% of cases
1	Score 0 / Negative	27	54
2	Score 1+	1	2
3	Score 2+	21	42
4	Score 3+	1	2

Vimentin is preferably expressed in invasive NST breast carcinomas (49%) and medullary-like carcinomas (100%) but not in invasive papillary carcinomas, lobular carcinomas, invasive and lobster-like mixed carcinomas.

Vimentin positivity was found in 6/8 cases of grade 3/poorly differentiated tumors, 15/24 cases of grade 2/moderately differentiated tumors, and only 2/18 cases of grade 2/moderately differentiated tumors. The expression of vimentin was correlated with the tumor grade. Score 0 expression was prominent in grade 1 carcinoma. Grade 2 and 3 carcinomas, on the other hand, revealed a lot of score 2+ expression. With a P-value of 0.05, there was a significant link between carcinoma's grade & expression of and vimentin in breast carcinoma.

With a P-value of 0.05, there was no statistically significant relationship between vimentin expression as well as the size of the carcinoma. The total number of lymph nodes affected was correlated with vimentin expression. In the current investigation, there was no statistically significant link between expression of vimentin & involvement of lymph node. (P-value > 0.05).

DISCUSSION

Breast cancer manifests itself in a variety of ways. Clinical behaviors including the time to tumor growth and metastasis cannot be predicted with accuracy, despite histologic similarity at the time of sickness diagnosis. Breast cancer is a multi-faceted molecular disorder. Breast cancer. Hormone receptor ER and PR as well as human EGFR-2 over-expression (HER-2) is crucial in the treatment judgment process for patients with breast cancer. These characteristics may determine the chance of illness relapse in addition to predicting response to therapy. Negative triple breast cancer has a poor prognosis due to lack of ER, PR, and HER-2 expression and lack of targeted therapy. Hormone-positive receptors have good outcomes, while negative triple breast cancer has a poor prognosis due to lack of ER, PR, and HER-2 expression and lack of targeted therapy. As a result, doctors and researchers are increasingly paying attention to this aggressive TNBC. Consequently, identification of aggressive phenotypes, such as the presence of EMT (epithelial-mesenchymal tumor) cells, is important for predicting cancer cell behavior. Interactions between multiple secretory soluble molecules, growth factors, their effects, and many extracellular signals, including multiple transcription factors such as PDGF, Notch, and NF-KB, trigger EMT.[8] Since the Trans positive value of this EMT score is unknown, in this study we investigated the EMT marker vimentin in breast cancer patients.

Wendy A Raymond et al. were the first to describe vimentin expression in breast cancer in 1989.[8] In the development of breast cancer in the young, the patient's age is a crucial predictor. The patients were between the ages of 28 and 90. The mean age of the cases in our research was 51.0 years, which is marginally greater than WHO estimates of the Indian population's peak age of 45-50 years. The average age of the 6 patients with well moderately, & poorly differentiated tumors was 55.2, 49.2, and 45.5 years. Expression of Vimentin was shown to be significant in 23 of 50 instances (46 percent). Our results were lower than those of Thomas et al[9], who detected vimentin expression in 25/53 patients (47.1%) and observed a strong link between vimentin expression and high histological grade 3 tumors, as well as ki67 and EGFR expression. Vimentin expression in tumor cells has been found to vary between 18 and 22.7 percent, 17.4 percent, and 18 percent in other investigations. A cutoff of positive in 10% tumor cells was regarded as substantial positivity in the majority of the studies mentioned above. In our research, we used a cut off value of positive in more than 10% of tumor cells.

Vimentin expression was also discovered in invasive carcinoma breast NST and mucinous carcinoma by Rakshith et al., whereas vimentin negative was identified in lobular carcinoma breast. The shape and behavior of cells are used to grade cancer and determine its aggressiveness. In the current study, grade 1 and grade 2 tumors were found to be the most common, indicating that the patients had low-grade carcinoma. According to a study conducted, vimentin expression was substantial with grade 3 malignancies, by Hemalath et al, Rakshith et al., Korsching et al.[9]

The findings backed up the EMT theory, which claims that because E-cadherin and other proteins are present in low-grade cancer cells, they preserve their adhesion properties. Cells transition to mesenchymal cells as they progress in grade, losing their adhesiveness & producing more vimentin.[10] An elevation in vimentin expression is linked to epithelial keratin loss, which is a sign of breast cancer progression. Furthermore Vora et al[11] in their study that in In terms of illness state, those who experienced recurrence or metastatic outgrowth gained more vimentin as compared to those who did not.

The size of invasive tumors in our samples consisted of 3 to 9 centimeters, with a mean of 5 centimeters. Vimentin positive was observed in one case with a tumor that was less than 2 cm in size, however, the majority of vimentin positivity was found in tumors that

were 2-5 cm in size. The expression of vimentin and the size of the tumor had no obvious relationship. Domagala and colleagues. This unfavorable relationship has also been described by Hemalat and Rakshith V et al. Vimentin expression was found to be unaffected by the destructive size of a tumor, which would be linked to patient survival.

The existence of axillary lymph nodes is by far the most commonly utilized prognostic indication in breast carcinomas. While a positive lymph node does not rule out severe illness or distant metastases, a negative lymph node does not rule out serious illnesses or distant metastases.[12] In our investigation,[13] (34%) of the 23 vimentin-positive cases in the initial tumor had lymph node metastases, and except for a few studies by Vora et al., who showed that patients with lymph node-positive status had greater vimentin expression, we found no statistically significant association with nodal metastasis, which was consistent with many previous investigations.

Clinical Significance of EMT: Although EMT-prone cells can spread, they may only account for a small portion of the overall population of tumor cells. The presence of a single cancer cell or a tiny cluster of cancer cells at the invasive front of tumor tissues is known as tumor budding. Cancer cells in tumor buds have already been demonstrated to downregulate E cadherin expression & enhance vimentin expression, as well as having cancer stem cell characteristics.[14,15] It has been established that cells undergoing EMT have evolved the potential to infiltrate and gain resistance to most anticancer treatments as a result of numerous stressors such as radiation and hypoxia.[16] Targeted therapies are being developed and used to treat a wide range of malignancies, with improved survival rates & clinical outcomes.[17,18] EMT, on the other hand, was said to provide resistance to certain specific compounds. As a result, it has been demonstrated that EMT causes medication resistance and allows tumor development to be rapid. Clarifying the relationship between EMT and drug resistance may aid clinicians in selecting the best anticancer medication treatment as well as the mode of invasion for high-risk situations.

CONCLUSION

When taken as a whole, the idea of EMT provides a useful framework for understanding the morphologic and molecular alterations that occur during tumor cell invasion and metastasis. In malignancy, there is a well-established link between EMT-like cellular phenotype as seen by changes in marker protein expression and tumor aggressiveness. As a result, high-grade tumors expressed vimentin preferentially in our investigation, with no link to tumor size or nodal metastasis. Further research is necessary to investigate major cancer activities in vimentin to detect the future utility of vimentin as a biomarker for clinically relevant malignancy. Vimentin expression in cancer is expected based on existing evidence to become a popular and promising therapeutic objective with great potential to develop new predictions and diagnostics. Furthermore, the usage in conjunction with existing anti-cancer therapies of vimentin-specific pharmacologic inhibitors and new therapeutic drugs should be supported.

Author's Contribution:

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Original Article

Outcome of Depressed Skull Fracture Among Patients Admitted in Teaching Hospital

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ABSTRACT

Objective: To assess the outcome and associated factors of surgically managed depressed skull fractures in patients.
Study Design: Cross sectional analytical study
Place and Duration of Study: This study was conducted at the department of neurosurgery, DG khan Medical College, Dera Ghazi Khan from January 2020 to December 2020.
Materials and Methods: The calculated sample size for study at 95% level of confidence, 5% margin of error and 17%[7] anticipated population proportion was 215. All the clinically and radiologically diagnosed patients of depressed skull fracture (DSF) in age group of 15-65 years operated for elevation were included by non-probability consecutive sampling. Data was collected by using predesigned questionnaire. SPSS version 22.0, was used to enter and analyze the data. Chi-square test was used to determine whether there is statistically significant difference between the groups and p value less than 0.05 was considered as significant.
Results: A total of 215 patients of depressed skull fracture which underwent surgical elevation of bone were included the study. The mean age of the patients was 28±10.6 years. Highest proportion of patients i.e. 57 (26.5%) with depressed skull fracture was in the age group of 10-20 years. The most frequent cause of depressed skull fracture among patients was road traffic accident 143(66.5%) followed by assault 45 (20.9%). The cause of depressed skull fracture and GCS at admission time was found to be associated significantly with outcome among patients with depressed skull fracture ($p<0.001$).
Conclusion: Road traffic accident is the most common cause and outcome among patients with depressed skull fracture was significantly associated with causes and GCS at the time of admission.

Key Words: Outcome, Skull fracture, Assault

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INTRODUCTION

Traumatic head injuries are major cause of morbidity, disability and mortality worldwide. Annually about 5.48 million people suffer from traumatic brain injuries globally. Any break in the cranial bones is referred as skull fracture.[1,2] The skull fractures are mostly accompanied with brain injures either directly or indirectly through extrdural or subdual hematoma but this not always the case.[3] The skull fracture is labelled as depressed fracture when skull bone in dentate or extends to brain cavity.

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The frequency of depressed skull fracture among patients with traumatic brain injuries is increasing day by day.[4] The management of head injuries including depressed skull fracture required trained human resource, well equipped trauma centers and medicines to reduce long term disability and mortality rate. The patients of head trauma with depressed skull fracture are frequently victims of high energy collision such as motorbike or car accidents and assaults. The advanced trauma life support training workshops in post-graduation training programs and for already practicing surgeons in trauma centers has played important role in better management of head injury patients and reduction in long term disabilities and mortality among these patients.[5]

Study conducted by Ahmed S et al. in Punjab Pakistan revealed that majority of patients admitted with depressed skull fractures male. About one third of the patients were below thirty years of age. The frontal region was most frequent site of fracture and overall mortality was 5.5%.[6] The study conducted by Parkash A et al. at Rajendra Institute of Medical Sciences, Ranchi found that frequency of depressed skull fracture was highest among adolescents and male cases predominate in hospital. Assault was found to be the

most common cause and frequently involved bone was parietal bone. About two third cases admitted with depressed skull fracture were with GCS 13-15. The fatality rate in patients of depressed skull fracture was almost 17%.[7]

In developing countries like Pakistan the mortality rate among patients with depressed skull fractures is high. Along with the improvement in management strategies for patients with head injuries at hospital level it is also needed that awareness and strategies must have developed for an individual and community level to reduce and ultimately eliminate such incidents. Construction of roads as per international standards, implementation of traffic rules and improvement in case management at trauma centers has significant impact on reduction of mortality. Adolescent age is the period of life in which there is urge of thrill and risk taking behavior is predominant. Majority of the cases with head injuries including depressed skull fractures are from adolescent age group.[8,9,10] This study specifically determined the outcome of depressed skull fracture in surgically managed cases and various factors which are associate with the outcome at neurosurgery ward of teaching hospital Dera Ghazi Khan.

MATERIALS AND METHODS

This cross sectional analytical study was conducted from January 2020 to December 2020 at department of neurosurgery, DG khan Medical College, Dera Ghazi Khan after taking ethical approval from institutional ethical review committee. With 95% level of confidence, 5% margin of error and 17%[7] anticipated population proportion the sample size determined for study was 215. All the clinically and radiologically diagnosed patients of depressed skull fracture (DSF) irrespective of gender between the age group of 15-65 years which were operated for elevation were included in the study by non-probability consecutive sampling method after taking informed consent. Patients with penetrating head injuries, skull fractures other than DSF and with minimal depression who were operated for intracranial traumatic lesions other than depressed skull fracture were excluded.

A predesigned, structured questionnaire was used for data collection. Data regarding patient age, gender, GCS at the time of admission, fracture site, and per-operative findings was collected. Outcome was assessed according to Glasgow outcome score. The outcome of the patients after traumatic brain injury is divided into five categorize by the Glasgow Outcome Scale (GOS) i.e. death, persistent vegetative state (minimal responsiveness), severe disability (conscious but disabled; dependent on others for daily support), moderate disability (disabled but independent; can work in sheltered setting) and good recovery (resumption of normal life despite minor deficits) labelled as group 1, 2, 3, 4 and 5 respectively. Unfavorable outcome comprised of group 1, 2 and 3 on Glasgow outcome score (GOS) and group 4 and 5 on GOS comprised of favorable outcome.

Statistical Package for Social Sciences (SPSS version 22.0) was used to enter and analyze data. For quantitative variables like age and GCS at admission time we calculated the mean and standard deviation and for categorical variables like gender and presence or absence of dural tear frequencies and percentages were calculated. Stratification of the outcome was done according to age, gender, causes of injury and presence or absence of dural tear. Post-stratification chi-square test was used to determine whether there is statistically significant difference between the groups and p value less than 0.05 was considered as significant.

RESULTS

A total of 215 patients of depressed skull fracture which underwent surgical elevation of the bone were included the study. The mean age of the patients was 28±10.6 years. Age distribution of the participants showed that highest proportion of patients i.e. 57 (26.5%) with depressed skull fracture was in the age group of 10-20 years. Total 198 (92.1%) male patients were admitted with depressed skull fracture (Table I).

Table No.1: Age and gender distribution of the respondents (n=215)

Variable	Frequency	Percentage
Age		
10-20 years	57	26.5%
21-30 years	38	17.7%
31-40 years	46	21.4%
41-50 years	41	19.1%
≥ 51 years	33	15.3%
Gender		
Male	198	92.1%
Female	17	07.9%

The most frequent cause of depressed skull fracture among patients was road traffic accident 143(66.5%) followed by assault 45 (20.9%) and fall from tree or roof 16 (07.4%).

Table No.2: Causes of depressed skull fracture among patients

Causes of depressed skull fracture	Frequency	Percentage
Road traffic accident	143	66.5%
Assault	045	20.9%
Fall from tree or roof	016	07.4%
Others (Falling object or Sports injury)	011	05.2%
Total	215	100%

Association of the outcome in relation to the age distribution of the respondents showed that 10 (17.5%) patients in the age group of 10-20 years had unfavorable outcome and outcome among patients with depressed skull fracture was not significantly associated with the age. The cause and GCS at admission time was significantly associated with the outcome among patients with depressed skull fracture (Table 3).

Table No.3: Association of depressed skull fracture outcome with age, gender, causes of injury and GCS at admission time

Variable	Outcome		p-value
	Favorable	Unfavorable	
Age			
10-20 years	47 (82.5%)	10 (17.5%)	
21-30 years	32 (84.2%)	06 (15.8%)	
31-40 years	41 (89.1%)	05 (10.9%)	**0.786**
41-50 years	37 (90.2%)	04 (09.8%)	
≥ 51 years	28 (84.9%)	05 (15.1%)	
Gender			
Male	172(86.9%)	26 (13.1%)	**0.235**
Female	013(76.5%)	04 (23.5%)	
Causes of fracture			
Road traffic accident	129 (90.2%)	14 (09.8%)	**<0.001**
Assault	40(88.9%)	05 (11.1%)	
Fall from tree or roof	09 (56.2%)	07 (43.8%)	
Others (Falling object or Sports injury)	07 (63.6%)	04 (36.4%)	
Dural tear			
Yes	109(92.4%)	09 (07.6%)	**0.680**
No	091(93.8%)	06 (06.2%)	
GCS at admission time			
3-8	15 (57.7%)	11 (42.3%)	**<0.001**
9-12	24 (80.0%)	06 (20.0%)	
13-15	157(98.7%)	02 (01.3%)	

DISCUSSION

In both developing and affluent countries trauma especially the head injury is the major contributor of morbidity and mortality. In Pakistan head injuries are increasing day by day which ultimately require large amount of resources to establish trauma centers for better management of these patients and improve outcome. Majority of the patients with depressed skull fracture present with history of road traffic accident. The treatment of patients who have had a depressed skull fracture is either conservative or surgical depending upon the neurological sign and symptoms. In this study we particularly assessed the outcome among patients with depressed skull fracture who were managed surgically for elevation of the bone and association of the outcome with various demographic variables.

The mean age of the patients was 26.48±12.7 years and more than one fourth of study participants were between 10-20 years of age. These findings are consistent with observations revealed in study by Ahemd S et al. in which mean age of patients with depressed skull fracture was 27.58±11.329 years.[6] The higher proportion of patients in younger age group may be attributed to the fact that implementation of traffic laws is very poor in our region especially in rural areas and bad conditions of the road. Adolescent age period is of crucial importance in the life of human being. It is period when behavior of an individual is shaped. The adolescents are more daring and fond of taking risks. Due to risk taking tendency they usually don't wear protective gauges like helmet and seat belts while driving which lead to severe injury in case of road traffic accidents.

In our study in more than two third of patients the reason of depressed skull fracture was road traffic trauma which is similar to the findings of Vala H et al. in which most frequent reasons were traffic accidents and assault.[11] Cross tabulation of the outcome among patients of depressed skull fracture with age, gender, cause of injury and GCS at admission time revealed that outcome among patients of depressed skull fracture is associated with the cause of injury ($p<0.001$) and GCS at time of admission ($p<0.001$). This may be attributed to the fact that most common reason of depressed skull among patients included in the study was road traffic accident and it is fact that low GCS score at admission time indicate that injury to the brain is severe. Urbanization and high speed traffic accompanied by the bad conditions of the roads along with poor implementation of traffic rules and regulation has contributed to rapid increase in cases of head injuries in general and in particular depressed fracture in developing countries including Pakistan. This rapid increase in head injury cases require trained human resource, fully equipped trauma centers to limit disabilities and save life of the patients.[12,13]

The bone of skull vault is folded downward into the brain parenchyma in depressed skull fracture. The common cause of depressed fracture is high energy impact to the skull and frequent site of the fracture is frontoparietal region. Depressed skull fracture usually occurs along with other injuries to brain parenchyma including pneumocephalus, leakage of cerebrospinal fluid through nose or ear, contusions, extradural and subdural hematoma. Prompt identification and treatment of these cases is helpful to limit disabilities among survivors and help to reduce mortality rate in head injury patients. But unfortunately due to non-availability of skilled human resource for management of these cases and lack of basic diagnostic facilities like computerized tomography scan at primary and

secondary healthcare level, the patients of head injury are referred to teaching hospitals and this delay in management of cases results in poor outcome.[14-16] Findings of our study suggest that avoidance of handing over vehicles to adolescent can reduce the head injury cases. Early approach to hospital when GCS of the patient is between 13-15 may further contribute to increase survival among patients with depressed skull fractures.

CONCLUSION

Road traffic accident is most common reason of depressed skull fracture and outcome among patients of depressed skull fracture is significantly associated with cause and GCS at the time of admission.

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Original Article

Frequency of Acute Kidney Injury Among Septic Children, Admitted at a Tertiary Care Hospital

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ABSTRACT

Objective: The objective of our study was to determine the frequency of acute kidney injury (AKI) among septic patients admitted at a tertiary care hospital.

Study Design: Descriptive / observational study

Place and Duration of Study: This study was conducted at a Tertiary Care Hospital of Karachi from 1st July 2015 to 31st December 2015.

Materials and Methods: Total 237 patients who were diagnosed as having sepsis with age 1 to 144 months were included in the study. These patients were monitored till the development of acute kidney injury (AKI).

The frequency and percentages were calculated for qualitative variables i.e. gender, and age group, while mean and standard deviation was calculated for quantitative variables i.e., age, baseline serum creatinine, maximum serum creatinine and hospital stay. P-value ≤0.05 was considered as significant.

Results: Total 237 patients were included in study with age 1 to 144 months 61.93(±33.510). Out of 237 patients 62 i.e. (26.2%) developed Acute Kidney Injury (AKI). A significant association of acute kidney injury was observed with hospital stay (p<0.001) and male gender (p=0.045). No significant association of acute kidney injury was observed with age (p=0.737) and baseline serum creatinine (p=0.104).

Conclusion: Development of Acute kidney injury is common in septic children and is significantly associated with increased hospital stay. This study provides statistics of sepsis induced AKI in the local population. In addition, the results emphasize on early identification of AKI among septic children to prevent further morbidity and mortality.

Key Words: Acute Kidney Injury, Risk factors of Acute Kidney Injury, Pediatric sepsis, Sepsis induced Acute Kidney Injury.

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INTRODUCTION

Acute kidney injury (AKI) is a pathological term which is described as reversible and abrupt loss of renal function associated with decreased urine output or increased serum creatinine and urea level. It is characterized by a decline in renal function, decreased excretion of waste products, and dysregulated fluid homeostasis[1,2]. Multiple studies have shown that there is a higher incidence of AKI among hospitalized children which ranges from 35% to 85%[3,4,5]. Many predisposing factors have been reported that lead to AKI among which sepsis is an important risk factor[6].

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There is limited local data on etiological profile of Pediatric AKI. One study from Karachi found sepsis to be the most common cause of pre renal AKI in children[7]. Another study conducted in Multan states sepsis as one of the common risk factors of AKI in neonates, however most of the studies are still concentrated in developed countries and data on pediatric AKI in developing countries remain scarce[8].

Sepsis is a syndrome of pathologic, physiologic and biochemical abnormalities triggered by infection. Development of AKI during sepsis is one of the most feared complications and is associated with an increased duration of stay which ultimately leads to poor outcome. [3,9,10,]. AKI occurs in around 19% of patients who have moderate sepsis while its frequency increases with increase in severity of sepsis, approximately 50% of patients who have septic shock develop AKI[11.]

The keystone of prevention and management of AKI in sepsis is the early restoration of adequate renal perfusion and timely commencement of antimicrobial therapy [12,13].

Considering the increasing frequency of AKI in hospitalized children, and limited studies on pediatric AKI in our country, we have conducted this study to

identify the frequency of AKI among septic children, so that early identification can be done, protective and preventive strategies can be made timely and optimal renal support can be started if the renal function declines.

MATERIALS AND METHODS

Descriptive observational study was conducted for six months from 1st July 2015 to 31st December 2015 at Department of Pediatrics, of a tertiary care hospital of Karachi. The approval letter was issued by Research Evaluation Unit, CPSP with reference number CPSP/REU/PED-2012-183-2278. WHO software for sample size calculation was used, considering p=19%of AKI, d=5%, and 95% confidence interval, the calculated sample size was 237 study subjects. Non-probability consecutive sampling was used. All children aged 01 month to 12 years diagnosed as having sepsis, with hospital stay of at least 48 hrs and with baseline serum creatinine level ≤ 1 mg/dl at the time of admission were included in study. Children with chronic kidney disease stage 5 or those who have congenital renal anomalies were excluded from study.

Total 237 patients who were admitted in the Pediatrics ward diagnosed as having sepsis and fulfilling the inclusion criteria were included in the study. Children were diagnosed with sepsis as defined by International Pediatric Sepsis Consensus 2005[14]. Patients were said to have SIRS (Systemic Inflammatory Response Syndrome) if they have the presence of either core body temperature of more than 38.5°C or less than 36°C or leukocyte count or heart rate or respiratory rate elevated for age (any two of the above mentioned). Infection was suspected in patients if they have any evidence of infection based on clinical examination, radiological imaging or laboratory parameters consistent with infection[14]. Infection was said to be proven in the presence of positive blood or body fluids cultures. Children were diagnosed with sepsis if they have clinical characteristics of SIRS in presence of either suspected or proven infection. After explaining the purpose and procedure of the study a written informed consent was taken from parents/guardians of the patients. Patient's clinical history was taken by the principal investigator on a predesigned proforma. Serum level of creatinine was done at admission and thereafter every 48hrs in all patients till their total hospital stay. The patients were carefully evaluated to ascertain the development of AKI. AKI was defined as an increase in serum creatinine levels by 0.3 mg/dl within 48 hours or a 50% increase in serum creatinine from the patient's baseline serum creatinine levels, as defined by the Acute Kidney Injury Network (AKIN)[2.] Confounding variables and biases were controlled by strictly following inclusion and exclusion criteria.

Data compilation and analysis was done using Statistical Program for Social Sciences (SPSS) version 21. Results were expressed as mean ± SD for all quantitative variables i.e. age, hospital stay and serum creatinine level (mg/dl). The frequency and percentages were calculated for qualitative variables i.e. gender, and age group, while mean and standard deviation was were calculated for quantitative variables i.e. age, baseline serum creatinine, maximum serum creatinine and hospital stay, p-value ≤0.05 was considered as significant. The p-value was calculated for qualitative variables using chi square test and for quantitative variables using independent t-test.

RESULTS

Total 237 patients of either gender with age 1 to 144 months, diagnosed as having sepsis with baseline serum creatinine less than or equal to 1 mg/dl and with hospital stay of at least 48 hours were evaluated to determine the frequency of Acute Kidney Injury (AKI). The results showed that there were 131(55.3%) male and 106(44.7%) female patients. The mean age of the patients was 61.93±33.5 months.(Tabel-1). Mean baseline serum creatinine was 0.44±0.15 mg/dl while mean maximum serum creatinine was 0.827±0.63 mg/dl. The mean hospital stay was 131.44±51.1 hrs. (Table-1).

Table No.1: Showing basic Characteristics of Study participants (n=237)

Qualitative Variables	Frequency (N)	Percentage (%)
Sex		
Male	131	(55.3)
Female	106	(44.7)
Age category		
≤ 60 months	141	(59.5)
> 60 months	96	(40.5)
Quantitative Variables	Mean	±SD
Age(months)	61.93	±33.510
Baseline Serum Creatinine (mg/dl)	0.44	±0.148
Maximum Serum Creatinine (mg/dl)	0.827	±0.633
Hospital Stay (hrs)	131.44	±51.103

Table No.2: Showing association of Acute Kidney Injury with baseline characteristics (n=237)

Characteristics	Frequency (n)	Acute Kidney Injury		*P* value
		Yes (n=62)	No (n=175)	
SEX				
Male	131	41(31.3)	90(68.7)	0.045 *
Female	106	21(19.8)	85(80.2)	
AGE				
≤ 60 months	141	38(27.0)	103(73.0)	0.737
> 60months	96	24(25.0)	72(75.0)	

*****Chi square test was applied; p-value ≤0.05 considered as significant

Table No.3: Showing comparison of Mean between AKI and Non AKI patients (n=237)

Variable	Acute Kidney Injury(AKI)		P-value
	Yes (n=62)	No (n=175)	
Baseline Serum Creatinine Mean(SD)	0.468 (.1212)	0.432 (.1565)	0.104
Hospital stay (Hours) Mean(SD)	152.53(56.91)	123.97 (46.81)	<0.001*

Student t- test was applied; p-value ≤0.05 considered as significant

Most common cause of infection in our study was Community Acquired Pneumonia in 58 patients (24.5%), followed by typhoid fever in 36 patients (15%), meningitis in 28 patients (12%), urinary tract infections in 27 patient (11.5%) encephalitis in 21 patients (9%), dengue fever in 18 patients (7.5%), pulmonary tuberculosis in 17 patients (7%) and malaria in 15 (6%) and skin infections in 11 patients(4.5%). In addition there are also cases of sepsis with more than one focus of infection, which is found in 28 patients (12%)

Table 2 shows the main outcome i.e. Acute kidney Injury was observed in 62(26.2%) patients. We observed that 41(31.3%) of the male patients developed AKI as compared to 21 (19.8%) of female patients and a significant association of development of AKI was observed in male patients (p=0.045). Moreover 27% of the patients who were ≤ 60 months had AKI as compared to 25% of patients who were > 60months, thus no significant association of AKI was observed with the age of patients(p=0.74).

Independent test was applied to observe the association of AKI with baseline serum creatinine and hospital stay. There was a significant association of AKI with increased hospital stay (p<0.001). However, no significant association of acute kidney injury with baseline serum creatinine (p=0.104). (Table 3)

DISCUSSION

Sepsis-induced AKI is has a unique identity of its own and sepsis has been found to be a major contributing factor leading to acute kidney injury in critical illness[15]. In our study, out of 237 patients who were diagnosed as sepsis, AKI was found in 62 patients which comprised 26.2% of patients. This data was consistent with a study of Fitzgerald et al who found that 21% of the patients with sepsis had severe AKI and was associated with poor outcomes[1]. Ganda et al found that 40% of the patients diagnosed with sepsis developed AKI[15]. In another large pediatric cohort, infection was found to be a major risk factor[16]. Likewise, infection was identified as an independent predictor of AKI in a cohort conducted in South Nigeria[17]. Similar studies have been conducted showing sepsis as one of the important risk factors of AKI however, data vary widely[11,12,18,19]. Additionally, a notable percentage of the patients who survive after kidney disease ended up in early end-stage kidney disease leading to death[20]. In a recent study by Riyuzo et al, a mortality rate of 33.7% was found in patients with sepsis-associated acute kidney injury[10].

Total duration of hospital stay was significantly higher in patients with AKI with sepsis, compared to non-AKI septic patients (p=0.007). In a study of adult population Alobaidi et al also concluded that length of stay was longer in patients with sepsis associated Acute Kidney Injury as compared to sepsis alone.[12] Fitzgerald et al had also found a significant association between longer hospital stay and development of acute kidney injury[1]. Another large cohort study also reported an increased duration of hospital stay in patients with sepsis-associated acute kidney injury when compared with non-septic AKI or sepsis alone[21].

Moreover, in our study we found a significant association of acute kidney injury with male gender, this finding was consistent with a meta analysis of an adult population done by Grams et al[22]. However, most pediatric studies did not find any association of AKI with gender[6,15]. There was no significant association of development of acute kidney injury with baseline serum creatinine.

We didn't find any association of age with the development of AKI, however Mehta et al had reported that young age was one of the risk factors for the development of AKI[2]. McGregor et al had also found that patients with younger age were more likely to develop acute kidney injury[23]. Unfortunately there is no single agreement to define which parameter is better for early identification of acute kidney injury. Although serum creatinine test is cost effective, some limitations exist. After renal parenchymal injury there is a compensation mechanism which can lead to a delay in the creatinine rise. Fortunately, with the newer emerging biomarkers early identification of AKI is possible[24].

Our study has few limitations, the data used for this study was derived from a single tertiary care hospital and our single center survey was conducted with small sample size and in an urban environment therefore, the results might not be generalizable to larger populations. Our AKI definition was based on the AKIN criteria for changes in serum creatinine but did not include urine output or an estimation of glomerular filtration rate. Furthermore, our data cannot determine mortality due to sepsis-associated acute kidney injury, however our results suggest that acute kidney injury should be suspected early in septic patients. Increasing awareness of acute kidney injury among health care providers

would definitely increase their concern. This could lead to more cautious use of nephrotoxic drugs, renal dosing of medications, avoidance of contrast exposure and other insults in suspected or confirmed cases of AKI, thus avoiding further renal injury[9].

Given the global and ubiquitous impact of AKI and sepsis, an understanding of SA-AKI is now essential for the clinicians for appropriate plan recognition, treatment and follow-up strategies. Furthermore, studies also suggest that it is important to have increased vigilance on patients who survive for the sequelae of chronic renal damage[20].

CONCLUSION

Acute Kidney Injury is a common complication in septic children and it is associated with increased hospital stay. This study provides statistics of sepsis induced AKI in the local population. In addition the results also emphasize on early identification of AKI among septic children so that measures would be taken early to prevent further morbidity and mortality.

Author's Contribution:

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Original Article

Evaluation of Clinico-Pathological Features of Bladder Tumors

Muhammad Haroon Ghous, Sikander Afzal, Shahid Mahmud Malik and Mahwish Arooj

ABSTRACT

Objective: The main objective of the study is to find clinico pathological features of bladder tumors in local population of Pakistan.

Study Design: Descriptive, Cross Sectional Study

Place and Duration of Study: This study was conducted at the Department of Urology, University College of Medicine, University of Lahore from 2019 to 2020.

Materials and Methods: The data was collected from the OPD of the hospital. After permission from hospital ethical committee, total 120 patients meeting the inclusion and exclusion criteria will be enrolled in the study from Medical Emergency. Detailed history and physical examination will be done to meet the inclusion and exclusion criteria. Informed consent will be obtained.

Results: The data was collected from 120 patients. At the point when the complete populace of 180 patients under age 40 is thought of, the dissemination of bladder cancer inside age classes is as per the following: patients under 30 years of age, 4 percent patients; patients between the age of 30 to 39 years, 26 percent patients; patients between the age of 40 to 49 years, 70 percent patients.

Conclusion: It is concluded that pathologic discoveries after conclusive extremist cystectomy for urothelial malignancy of the bladder doesn't frequently connect with preoperative arranging. Thusly, the greater part of patients going through cystectomy will be surpassed on their usable pathology.

Key Words: Clinico-Pathological Features, Bladder Tumors, Population of Pakistan

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INTRODUCTION

Urinary systems most common malignancy is bladder cancer. Urothelial carcinoma is transcendent type in the United States of America and Europe, where it represents 90% of the bladder tumors. Non-urothelial carcinomas are more common in other parts of the world. Significantly not usually, urothelial tumors can emerge from different locales in the urinary system, including urethra, renal pelvis or ureter[1].

After prostate disease, bladder malignant growth is the most widely recognized urologic and the fifth most basic generally speaking danger. In 2005, roughly 63 thousand new instances of bladder malignant growth analyzed and more than 13,000 infection related passing in the United States of America[2].

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Most of new tumors related to bladder are shallow (65 - 70%) and out of those, almost 20% can be relied upon to advance to muscle obtrusive infection. All things considered, a critical amount of muscle-intrusive tumors are analyzed at the beginning show in patients with no earlier account of TCC[3].

The utmost well-known helpful methodology for obtrusive bladder malignancy is extremist cystectomy. Late upgrades in careful strategy and perioperative administration have diminished complexity rates and usable mortality for this methodology. Notwithstanding the upgrades in careful bleakness, up to half of patients going through cystectomy will encounter nearby or removed repeat. Lamentably, the majority of the patients, which are bound to repeat are not effortlessly recognized by pre-employable assessment[4]. Discoveries like these feature the huge medical under-arranging that happens in patients with bladder disease going through cystectomy. Our powerlessness to tentatively distinguish non-organ-restricted sickness or fundamental micro metastases stays a weakness of current preoperative assessment. Subsequently, numerous patients are surpassed at the hour of careful investigation and extirpation[5].

Dependable tests accessible for distinguishing bladder malignant growth are none; subsequently the analysis is normally dependent on the clinical indications and signs. Effortless hematuria – tiny or net is the best well-known sign and a hematuria investigation in a generally

asymptomatic patient recognizes bladder neoplasm in generally 25% of gross and 4% of infinitesimal cases[6]. Irritativeexcretion (recurrence, earnestness, as well as dysuria) is generally attributed to considerate urinary parcel issues however has been related with carcinoma in situ. Different side effects are regularly a sign of further developed illness, for example, flank torment brought about by ureteral block or pelvic torment from extra vesical attack of encompassing designs[7].

MATERIALS AND METHODS

This descriptive / cross sectional study was conducted from 2019 to 2020 in the Department of Urology, University College of Medicine, University of Lahore.

Study Technique: Non-probability consecutive sampling technique.

Data Collection: The data was collected from the OPD of the hospital during 2019 to 2020. After permission from hospital ethical committee, total 120 patients meeting the inclusion and exclusion criteria will be enrolled in the study from Medical Emergency. Detailed history and physical examination will be done to meet the inclusion and exclusion criteria. Informed consent will be obtained. The major problems told at first visit, demographic data, cystoscopic results, clinical follow up information and pathology findings were analysed. The pathological type, clinical group, site of the tumor, staging and size of the tumor were analysed in the cases of rhabdomyosarcoma.

Statistical Analysis: SPSS system for the Windows was used to analyse the data. Mean ± SD was expressed as continuous variable and frequencies and percentages were expressed as categorical variables.

RESULTS

The data was collected from 120 patients. At the point when the complete populace of 180 patients under age 40 is thought of, the dissemination of bladder cancer inside age classes is as per the following: patients under 30 years of age, 4 percent patients; patients between the age of 30 to 39 years, 26 percent patients; patients between the age of 40 to 49 years, 70 percent patients. 30 percent of the patients were younger than 40 years. 94 percent of the patients revealed indications on introduction.

The middle time among analysis and cystectomy was essentially unique between the Primary RCx bunch (2 months; 0-6 months) versus the Secondary RCx bunch (22 months; 5 - 149 months). Though maximum of the patients in the Primary RCx bunch were clinical T2 or higher (87%), those patients going through Secondary RCx were less frequently clinical T2 or more prominent (58%). This distinction additionally was heaps of neurotic organizing also.

Table No.1: Patients' showing signs and symptoms of bladder tumor

Clinical presentation	Patients
Rectal bleeding	99 (57)
Anemia	19 (11)
Abdominal pain	54 (31)
Bladder pain	7 (4)
Change in bowel habits	37 (21)
Weight loss	20 (11)
Bowel obstruction	16 (9)
Perforation	5 (3)
Perforated diverticulitis	1 (0.6)
Screening	5 (3)
Unknown	7 (4)

Table No.2: Stages of patients undergoing cystectomy

Stage	Primary RCx	Secondary RCx	All
<T1	33%	31%	24%
T2	52%	64%	48%
T3	15%	5%	28%

DISCUSSION

For the people of age 20 years and younger, urinary bladder tumor is very rare. Furthermore, it is hard to analyze such patients as there are numerous restrictions in analytic assessment, for example, tomography imaging or cystoscopy. Consequently, distinguishing the clinical qualities of urinary bladder tumors analyzed at this age is urgent data for the arrangement of patient administration[7]. Various investigations of urinary bladder tumors in patients matured under 40 years have been conducted, however the greater part of these patients were more seasoned than 20 years old[8]. Since all of these investigations showed that there were many differences in the tumor qualities, even in some patients somewhere in the range of twenty and thirty years of age, it is hard to comprehend the attributes of the urinary bladder tumors for the patients under the age of 20 years, in view of such past investigations.

For the patients in this examination, urothelial tumors were for the most part a solitary sore, stalks and papillary shape included. The most well-known indication was the gross hematuria, yet many of the cases were related to an accidental mass. By and large, finding was regularly postponed in light of the fact that it is hard to analyze bladder tumors[9]. Notwithstanding these highlights, bladder tumors are once in a while analyzed as high-grade or obtrusive urothelial carcinoma, in any event, when analyzed in a late stage to give net hematuria; this has prompted the act of not seeking after forceful findings, since these tumors infrequently progress[10].

At present, the TNM organizing framework, which depends on tumor histological subtype, obsessive tumor stage, lymph hub status and lymph hub status grade, is

the most commonly used preoperative model. It is used to anticipate CSS in bladder cancer patients[11]. The tumor markers that can precisely anticipate the cancer results in bladder cancer patients when used with other neurotic boundaries are fundamental for clinical dynamic. Some distributed investigations on atomic biomarkers, like basal and luminal subtypes, the quality changes atomic framework protein number 22, and the bladder tumor antigen (BTA) detail test[12].

CONCLUSION

It is concluded that pathologic discoveries after conclusive extremist cystectomy for urothelial malignancy of the urinary bladder doesn't frequently connect with preoperative arranging. Thusly, the greater part of patients going through cystectomy will be totally upstaged on their functional pathology. An ameliorated comprehension of the general reoccurrence of upstaging in cystectomy patients possibly have significant ramifications for adjuvant and non-adjuvant treatments for these hazardous populaces.

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Original Article

Frequency of Coronary Artery Disease in Adult Patients Based Upon their Sleep Duration

Mahboob Ur Rehman[1], Amjad Abrar[2], Abida Habib[1], Madeeha Butt[1], Muhammad Rafique[1] and Amjad Ali Shah[1]

ABSTRACT

Objective: The study's main aim is to look at the occurrence of the coronary artery disease in adults based upon their sleep duration.

Study Design: Cross-Sectional Study

Place and Duration of Study: This study was conducted at the Wah Medical College located at Wah Cantt, also Gomal Medical College in D.I. Khan January, 2018, to December, 2018.

Materials and Methods: The research included about 400 of the patients with coronary artery disease who were 18 to 65 years old and of either sexual orientation. The patients' average age was 48.96 12.5 years, with a range of 18 to 65 years. 277 (69.25 percent) of the 400 patients were men, while 123 (30.75 percent) were women.

Results: The average BMI of the people in the study was 29.27 4.42 kg/m2. 45.75 percent of patients had a BMI of less than 27.5 kg/m2, while 54.25 percent had a BMI of more than 27.5 kg/m2. 234 (58.5%) of the people in the study had diabetes, 189 (46.23%) have high blood pressure (hypertension), 229 (56.24%) smoke, 243 (60.70%) have dyslipidemia and about 238 of the people (59.5%) are diagnose with coronary artery disease family background. This study supposed that the recurrence of CAD in adults who slept for less than six hours and over eight hours was more prevalent.

Conclusion: Research suggests that coronary artery disease recurrence is more common for adults who have slept for less than six hours and 8 hours. We therefore propose coordination at the community level of educational programmes to teach individuals how to sleep (6-eight hours), in order to lower the danger of coronary artery conditions.

Key Words: coronary artery, short sleep, adult, CAD

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INTRODUCTION

Myocardial infarction, stable angina, shaky angina & sudden death are all symptoms of Coronary artery disease.1 Retrosternal chest pain radiating to the bear, arm, jaw, or back is a common symptom that arises in response to increased metabolic activity, such as exercise or vigorous strain, and improves with rest .[2]

One of the prime etiology of heinousness and mortality in today's world is computer-aided programming. In 20212, Cardiovascular diseases (CVD) took the lives of 17.5 million people worldwide, accounting for 31% of all deaths. An expected 7.4 million of these deaths were attributed to CAD.[3] In Pakistan, one out of every four patients over the age of 40 suffers from the symptoms of fundamental CAD.[4]

The potential of numerous new or evolving threat variables to affect the advancement of CAD has been demonstrated in ongoing studies, opening up new avenues for avoidance. A sleeping disorder, a lack of sleep, and a fluctuating rest time have become prevalent in recent years. Rotating rest designs have a detrimental effect on wellbeing, growing mortality rates, [5] types 2 diabetes[6] hypertension, and obesity.[7] Less rest radically breaks down metabolic framework, endocrine[8,] and resistant pathways.[9]

Increased appetite, high-calorie consumption, and a sedentary lifestyle contribute to obesity and low glycemic control, which raises cardiovascular risk. According to a pooled study, those who's sleeping duration is disburbed or they sleep for less than 7–8 hours on daily basis may have the higher threat of coronary artery disease. Short periods of rest increase the risk of coronary artery disease by causing inflammation.[10] Excessive tiredness is linked to depression, low financial status, unemployment, and reduced physical activity, as well as puzzling causes

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such as long periods of rest and dreariness, as well as mortality from coronary artery disease (CAD). [11, 12]

Our research is designed to determine whether or not CADs are recurring after admission to a tertiary care hospital. Since the correlation for both CAD and rest time does not occur locally, the aim of the research is to assess the patient CAD frequency by repository time. The results can produce close data and preventive steps to reinforce the result and the board can be taken.

MATERIALS AND METHODS

From January 1 to December 31, 2018, researchers at the Pakistan Institute of Medical Sciences in Islamabad, & in D.I. Khan conducted a cross-sectional analysis at their cardiology departments. A total of 400 patients between the ages of 18 and 65 with coronary artery disease of either sexual orientation were included in the study. Anxiolytic or entrancing medications were not permitted, as were patients with Body Mass Index of in excess of 30 kg/m2. The test was ordered with the blessing and approval of the Shaheed Zulfiqar Ali Bhutto Medical University's morals council in Islamabad. Following informed consent, patients presenting in the outpatient and crisis divisions were evaluated with a detailed history of symptoms, electrocardiography, and cardiovascular indicators, as well as other risk factors such as family history, smoking, the high sugar level in the blood, and dyslipidemias, as well as previous heart problems. The rest period was also measured based on the average number of sleep' hours per day over the previous year, such as 0-6 hours, 06-08 hours, and > 08 hours. The proforma was filled out for every discovery.

Data Analysis: SPSS 14.0 was used to carry out the research. Sexual identity, BMI, diabetes, hypertension, smoking, dyslipidemia, CAD family history, and patients with CAD as a percentage of the total population were all studied. For quantitative factors such as age, mean SDs were calculated. Age, gender, BMI, diabetes, hypertension, dyslipidemia, smoking, and family ancestry were all identified, and impact modifiers were excluded using the chi-square test. The value of P' significance of less than 0.06 was considered enormous.

RESULTS

The mean patient age was 48.96 ± 12.5 years, ranging from 18 to 65 years. Of the 400 patients, 277 (69.25%) were male and 123 (30.75%) female. In our study, the ratio of men to women is 2.3:1, as shown in Figure 1.

The research population's average BMI was 29.27 4.42 kg/m2. 45.75 percent of patients had a BMI of less than 27.5 kilograms per square meter, while 54.25 percent had a BMI of more than 27.5 kilograms per square meter. 234 (58.5%) of those examined had diabetes mellitus, 189 (47.25%) suffered from high blood pressure, 229 (57.25%) had cigarettes, 243 (60.70%) have dyslipidemia and about 238 of the people (59.5%) are diagnose with coronary artery disease family history of heart diseases. As shown in Table 1, the CAD recurrence was 158 (39.5%), 110 (27.5%) and 132 (33%) respectively, among 0-6, 06-08 and > 08-hour patients.

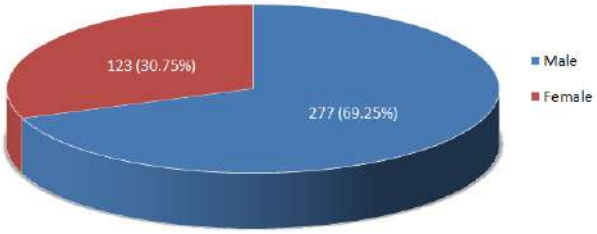

Figure No.1: Patients % age according to their gender (n=400)

Table No.1: CAD frequency in sleep-based patients

	CAD Frequency (%)	
Duration of Sleep	Yes	No
Less than 6 hours	156 (38.50%)	243 (60.50%)
6 to 8 hours	111 (27.50%)	291 (70.50%)
Greater than 8 hours	133 (33%)	269 (67%)

Gender-wise hierarchy of CAD's frequency based upon the sleep durations shown in Table 2.

Table No.2: Sleep duration was used to stratify the incidence of CAD by sexuality

Duration of Sleep	Man (n=277)	Women (n=123)	P-value
Less than 6 hours	109 (39.33%)	48 (39.2%)	0.950
6-8 hours	74 (26.30%)	37 (30.8%)	0.442
Greater than 8 hours	95 (34.2%)	38 (30.88%)	0.505

DISCUSSION

Not only are the mainstream trends affected by the quantity and essence of rest, but also trends in the general public that require more work, greater accountability and non-stop office use. This increases fatigue, slowdown and daily indications of the language.[13]

Sleep deficiency has detrimental consequences for the frameworks of our bodies, including metabolism, endocrine, and immune systems.[14] The U-formed linkage between rest and vascular events shows that many instruments play a role in intermechanics.[15]

Temporary sleep deprivation in healthy individuals led to physiological changes such as glucose bigotry, increased insulin obstruction, improved tone, and increased blood pressure, according to studies.[16] Elevated concentrations of C-receptive protein, directly related to CAD, were also related to sleep deprivation.[17]

The drawn out cardiovascular outcomes of lack of sleep are unsatisfactory. More limited or longer rest periods

than 7 hours have been linked to increased BMI in epidemiological studies.[18]

The age ranged from 18 to 65 in our study, with a mean time of 48.96 12.45 years. 277 (69.25 percent) of the 400 patients were men, while 123 (30.75 percent) were women. The ratio between men and women was about 2.3:1. Coronary artery disease repetition was 159 (39,05%), 111 (27,05%) or 132 between the individuals who slept for 6 hours, 6-8 hours or above 8 hours (33 percent). The CAD prevalence was 29.2%, 17.43%, and 18.5%, so according Sabanayagam C et al., among Americans who slept less than 5, 6, 6 or 8 hours and 9 hours.[19].

Aggarwal et al's study found that the prevalence of CAD was 6.9%, 5.8%, and 10.1% respectively among sleepers under 6 hours, 6-8 hours, and over 8 hours. They also discovered a strong connection between the amount of time spent resting and the risk of heart failure, heart attack, and stroke.[20]

Long and short durations of sleep were independently linked to CAD mortality, regardless of smoking, alcohol consumption, or BMI, according to Shankar et al. Compared to a 7-hour rest period, the risk of death was 1.57 for a 5-hour rest period and 1.79 for a 9-hour rest period. These results indicated that rest time may be a significant indicator of coronary artery disease. Qureshi et al. used National Health and Nutrition Survey (NHANES I) data to show persons sleeping for more than eight hours had a greater danger of stroke (relative danger: 1.5 96 percent). CI: 1.1 to 2.1).[21]

Our study's findings, such as the U-shaped rest period bends and the incidence of numerous events of CV, are consistent with earlier reports that found U-shaped connections between the rest period and the risk of mortality.[22,23]

Cappuccio FP et al. found that both long (9 hours) and brief (5 hours) rest periods raised the risk of a coronary event (RR=1.38, 95 percent CI 1.05–1.84; RR=1.36, 95 percent CI 1.2–1.85).[24] Chien and colleagues observed a higher risk of CVD in those who had a sleeping disorder and a long rest time (>9 hours) relative to people who slept 7–8 hours (HR=2.7, 95 percent CI 1.11-3.86). The WHI associate's measured impact was similar to Chien et al's study among a moderately aged Chinese population.[25]

Our findings also show a connection between a longer rest period and sleep deprivation, which increases the risk of coronary artery disease by twofold. These findings apply to postmenopausal women.

CONCLUSION

Research suggests that coronary artery disease recurrence is more common for adults who have slept for less than six hours and 8 hours. We therefore propose coordination at the community level of educational programmes to teach individuals how to sleep (6-eight hours), in order to lower the danger of coronary artery conditions.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Mutational Analysis of Sr-B1 Gene in Relation with Dyslipidemia in Diabetic Patients

Tayyaba Batool[1], Farooq Ahmad Malik[2], Muhammad Roh ul Amin[3], Sabir Hussain[3], Irfan Ahmad Buzdar[3] and Mujahid Iqbal[3]

ABSTRACT

Objective: To find the mutation in scarb1 gene that may be the cause of dyslipidemia in type 2 diabetes mellitus (T2DM).

Study Design: A cross-sectional comparative study

Place and Duration of Study: This study was conducted at the department of Biochemistry, Quaid e Azam Medical College, Bahawalpur from October 2020 to April 2021.

Materials and Methods: A total 50 individuals (20 having T2DM and dyslipidemia, 20 with T2DM without dyslipidemia and 10 healthy individuals) were enrolled for this study. Informed consent from the study participants was taken. Nuclear DNA was extracted from the blood. Quality and quantity of DNA was checked by 1% agarose gel electrophoresis. Primers of exon 8 were designed by using primer 3 software. Sequencing PCR was performed. On the purified product of sequencing PCR mutational analysis was conducted.

Results: In genotyping analysis no mutation was found but the single nucleotide polymorphism was detected in all groups. The detected polymorphism was rs5888 at c.1050 position. Group I patients were diabetic with the deranged lipid profile.18 patients of this group diagnosed with SNP. Group II individuals were diabetics with normal lipid profile and three patients from this group were diagnosed with SNP. The third group was of healthy individuals and two patients from this group were also detected with SNP. Exon-8 was used for study. This SNP was not lethal. The transition from T to C did not change the amino acid which is coded. In both the cases coded amino acid is Alanine.

Conclusion: The SNP rs5888 was found in all the 3 groups of study. This alteration in nucleotide sequence is non-deleterious as the amino acid which is formed is alanine. This indicates that this polymorphism has no role in causing dyslipidemia in the diabetic individuals.

Key Words: Dyslipidemia, type-2 diabetes mellitus, amino acid.

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INTRODUCTION

Diabetes is a metabolic disease which occurs due to insufficient production of insulin by pancreas or by the inappropriate use of insulin by cell while there was 5% increase in death rate from 2000 to 2016 worldwide among patients having diabetes.[1] In uncontrolled diabetic patients there are episodes of hypoglycemia and hyperglycemia, both of these conditions are related with adverse effects on patient health. These may include myocardial infarction, cerebrovascular accident, retinopathy, nephropathy, neuropathy and death. Hence immediate and vigilant care of diabetic patient is mandatory.[2] Patients of diabetes have 2-4 times greater risk of death due to cardiac issue as well as the cerebrovascular disease like CVA. Dyslipidemia is the major contributor in these diseases.[3] Many consider diabetes as equivalent to the coronary heart disease. More than 65% diabetic patients have high LDL.[4] Insulin resistance leads to increased production of VLDL-C by liver and chylomicron by the intestine. These are rich in triglyceride contents. Moreover, impaired insulin secretion impairs the activity of lipoprotein lipase which decreases the metabolism of VLDL-C and chylomicrons. Hence there is subsequent hypertriglyceridemia which enhances the transfer of triglyceride from VLDL-C and chylomicron to LDL-C and HDL-C respectively.[5] Triglyceride rich HDL-C comparatively has less half-life.[6]

Class B-type 1 of scavenger receptor (SR-B1) is a receptor for multiple ligands and it has high affinity for HDL-C. It is present on hepatocytes and play a pivotal role in reverse cholesterol transport.[7] SR-B1 receptor is encoded by SCARB1 gene. This gene is present on

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12q24.31.polymorphism in SCARB1 gene leads to dyslipidemia.[8] Relationship between the different variants of sr-b1 gene and dyslipidemia was observed among the several communities.[9] A single nucleotide polymorphism rs5888 was found by Acton.[10] At position 1050 of cDNA there was substitution of " C" to" T" in exon 8 whereas rs5888 SNP T allele was associated with the decreased HDL-C and increased LDL-C, TG and apo B level in Guangxi population.[11,12] The present study was aimed to find the mutation in scarb1 gene that may be the cause of dyslipidemia in type 2 diabetes mellitus (T2DM).

MATERIALS AND METHODS

This was a cross-sectional comparative study conducted at the department of Biochemistry, Quaid e Azam Medical College, Bahawalpur from October 2020 to April 2021. A total 50 individuals (20 having T2DM and dyslipidemia, 20 with T2DM without dyslipidemia and 10 healthy individuals) were enrolled for this study. Informed consent from the study participants was taken. Approval from Institutional Ethical Committee was Sough.

Exctraction of genomic DNA from blood was done as described by Sambrook and Russell 2001.[13] The quality and quantity of extracted DNA was checked on 0.8% agarose gel through horizontal electrophoresis. Primer 3 software was used to design the primers of *SR-B1* gene and also of exon 8 (Table 1).

Primer 3 software calculated the annealing(Tm) and reconfirmed by the formula:

Tm= 4(G+C) + 2(A+T)

The following are the steps of PCR. These stages were optimized by parameters through chain of reaction;

1. Denaturation
2. Annealing
3. Extension
4. Final Elongation

By PCR all the samples were amplified. The 1% agarose gel was used to check the results and these were visualized on Gel documentation (Bio-Rad). PCR purification kit (Genomed GmbH Inc) was used to purify the PCR product by following the instructions. The quality and quantity of product was checked on 1% agarose gel. On both strands of DNA with forward and reverse primer the sequencing PCR was performed as it had 30 repeats. The mutational analysis was carried out by CEQ8000 automated sequencer genetic analyzer.

RESULTS

In genotyping analysis no mutation was found but the single nucleotide polymorphism was detected in all groups. The detected polymorphism is rs5888 at c.1050 position. Group I patients were diabetic with the deranged lipid profile.18 patients of this group diagnosed with SNP. Group II individuals were diabetics with normal lipid profile and three patients from this group were diagnosed with SNP. The third group was of healthy individuals and two patients from this group were also detected with SNP. Exon-8 was used for study. This SNP was not lethal. The transition from T to C did not change the amino acid which is coded. In both the cases coded amino acid is Alanine. Figure 1 is showing DNA sequencing of SR-B1 gene as SNP rs5888 was detected in exon8.

Table No.1: SR-B1 gene and exon 8 primer sequence

Exon	Upstream primer	Exon	Downstrem primer	Size
Sr-8-f	Ggttatcttg tcatcgccac	Sr-8-r	Gtgctccaaccaggaatc	291

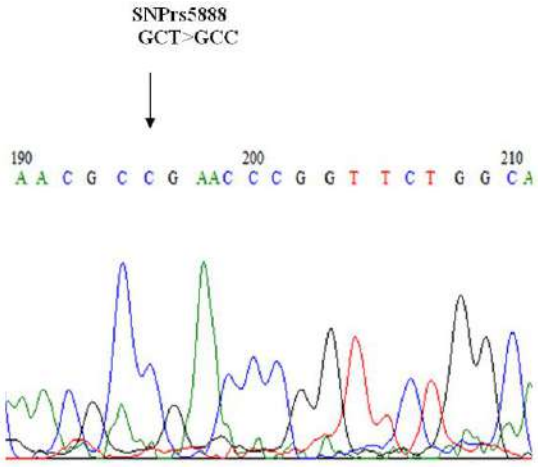

Figure No.1: DNA sequencing of *SR-B1* gene as SNP rs5888 was detected in exon8

DISCUSSION

"Diabetic dyslipidemia" is known to be a mixture of plasma lipid as well as lipoprotein disorder which are metabolically interconnected to each other. Dyslipidemia is known to be linked with insulin resistance, visceral obesity and liver fat contents.[14] Researchers are putting efforts in discovery of definite regulation steps that can help controlling the complications related to dyslipidemia among patients with DM. Genetic contribution to natural course of DM is well established.[15] Researchers have confirmed the enhanced production of apoB in T2DM which is known to be an important constituent of VLDL and LDL because of up-regulation of intestinal SR-B1 receptor.[16] Variant of HDL receptor gene SR-B1 may be a key influential factor of dyslipidemia in females which leads to the coronary artery disease.[17] In a study done by Acton S et al, five genetic variants of SR-B1 gene were found while two were found in the introns 3 and 5 while three were found in exons 1, 8 and 11 whereas exon 8 variant was associated with low LDL-C.[10] SR-B1 polymorphism is related to the coronary artery disease and atherosclerosis. Age and gender plays an important role in this regard.[18] In our study SNP rs5888 was found at the exon 8. This SNP is found in all the individuals including diseased one and the healthy one. As the sr-b1 gene has 13 exons there is the possibility

that there may be any other mutation or polymorphism which may cause the dyslipidemia in the diabetic patients but it needs further investigation.[19] The inconsistent results of variants of sr-b1 regarding the metabolism of lipids and coronary artery disease indicates that there may be an involvement of another pathway in this regard.[20].

CONCLUSION

The SNP rs5888 was found in all the 3 groups of study. This alteration in nucleotide sequence is non-deleterious as the amino acid which is formed is alanine. This indicates that this polymorphism has no role in causing dyslipidemia in the diabetic individuals.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Postnatal Oral Glucose Tolerance Test in Normoglycemic Women Delivering Macrosomic Babies

Hadia Aziz[1], Jaweria Faisal[2], Zeb un Nisa[2], Zeba Munzar[3], Ayesha Basharat[2] and Sadia Kanwal[4]

ABSTRACT

Objective: To determine the frequency of diabetes by oral glucose tolerance test (OGTT) among normoglycemic women delivering macrosomic babies.

Study Design: Observation study.

Place and Duration of Study: This study was conducted at the MCH Unit II, Pakistan Institute of Medical Sciences, Islamabad from May 2015 to April 2017.

Materials and Methods: 100 normoglycemic woman with BMI of 19-25 Kg/m^2 and singleton pregnancy at 37-40 weeks of gestation who delivered macrosomic babies >4kg were included. Patients with twin pregnancy, type II diabetes, gestational diabetes and medical diseases were excluded. All OGTTs were performed after 24 hours of delivery and then six weeks postpartum in the morning after an overnight fast. Blood plasma glucose levels above 5.6mmol/l, fasting and 7.8 mmol/L (140 mg/dl) at 2 hours were categorized as diabetes.

Results: The mean age of total 100 women was 29.9 years and the mean gestational age was found 38. 6 weeks. The mean of birth weight was 4.48 (n=100). After 24 hours, diabetes was diagnosed by OGTT in 40 (40.0%) woman but there was no diabetes in 60 (60.0%) patients (total n=100). At 6 weeks diabetes was found in 27 (27.0%) woman who delivered macrosomic babies, whereas there was no diabetes in 73 (73.0%) patients.

Conclusion: Frequency of diabetes diagnosed by oral glucose tolerance test (OGTT) among normoglycemic women delivering macrosomic babies is high.

Key Words: Macrosomia, Gestational Diabetes Mellitus, Glucose Intolerance, OGTT, Growth Curve, Large for Gestational Age

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INTRODUCTION

Macrosomia is a term, used to describe a newborn whose birth weight is greater than 4–4.5kg.[1] This condition affects 3–15% of all pregnancies worldwide. The Center for Disease Control and Prevention has classified macrosomia as one of the major risk factors for Type II diabetes[2]**.** Macrosomia is known to be associated with various grave complications as operative delivery, postpartum hemorrhage, obstetric anal sphincter injury, shoulder dystocia, brachial plexus injury and birth fractures.[3,4]

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Pregnancy is universally recognized as a state of physiological insulin resistance[5,6]. It is expected that women who had a macrosomic infant are more likely to have elevated plasma glucose levels during pregnancy than those without. These women might have an underlying β-cell dysfunction and be likely to develop diabetes later in life**.** Along with diabetes other risk factors for macrosomia are maternal obesity, post term gestation, maternal birth weight > 3.7 kg and increased weight gain during pregnancy.[7-11]**.** To diagnosis GDM, the World Health Organization (WHO) has proposed using a 2-h 75g OGTT, with a threshold plasma glucose concentration of greater than 7.8 mmol/L at 120 min.[5] OGTT is performed at 24-28 weeks usually in pregnancy to diagnose GDM.[12] In woman in which antenatal OGTT has been missed due to late booking and who have given birth to macrosomic baby despite normal glycemic levels, postpartum abnormal glucose tolerance can be diagnosed by BSF, HbA1c and OGTT. The American Congress of Obstetricians and Gynecologists recommends a 2-hour, 75-g oral glucose tolerance test (OGTT) performed at 4–12 weeks' postpartum to screen for disorders of glucose metabolism, including DM in all women with a GDM-affected pregnancy.[13] GDM occurs more often in women from certain ethnic groups and is also

associated with macrosomia.[14] Rates of Type II DM diagnosed post-partum range from 2 to 12.5% within one year. Women with GDM are seven times more likely to develop Type II DM than women without GDM.[15,16] In a study, it was noted the rate of macrosomia neonates increased significantly from 8.5% in women with normal blood glucose values to 29.5% in women with higher values than normal.[17] Maternal insulin is known to be the primary hormone responsible for intrauterine fetal growth. During pregnancy, irregularity of maternal postprandial blood glucose levels and excessive insulin secretion, especially in the second- and third-trimester can cause fetal macrosomia.[18] Macrosomia and diabetes are vice and versa, the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study identified a continuous relationship between maternal glucose and increasing birth weight.[19] However, approximately 60% of macrosomic fetuses are born to mothers without identifiable risk factors.[20] In our country, most women lack antenatal health care facilities and presents in late pregnancy when the time for OGTT has already passed so it is missed. For woman with gestational diabetes, it is known that fasting sugars should be checked at 13 weeks to exclude diabetes but for normoglycemic mothers with macrosomic infants there is no guideline available. We decided to determine the frequency of diabetes by oral glucose tolerance test among normoglycemic women who deliver macrosomic babies. This study will add in existing knowledge and will contribute some information for drawing conclusions for betterment of such mothers.

MATERIALS AND METHODS

The study was conducted at MCH unit-II, PIMS Islamabad from 1st May 2015 to 30th April 2017. One hundred postnatal normoglycemic women either non booked or late booked patient in which antenatal OGTT was missed, with BMI 19-25Kg/m2 and singleton pregnancy at 37-40 completed weeks delivering macrosomic babies (birth weight > 4 kg) were included in this study taking expected prevalence of diabetes in macrosomic delivery in non-GDM as 15.2%[1] using non-probability, purposive sampling. Women with gestational diabetes, Twin pregnancies, history of type II diabetes (overt diabetes)/cardiac/respiratory/hepatic and other medical disease, anomalous babies and preterm deliveries were excluded from the study. Woman blood sugar random were cheeked before recruiting them for study. After obtaining the informed consent, 75 g OGTTs were performed after 24 hours of delivery and then six weeks postpartum in the morning after an overnight fast. The plasma glucose was estimated in the central laboratory by the glucose oxidase peroxidase (GOD-POD) method. Blood plasma glucose levels above 5.6mmol/l at fasting and 7.8 mmol/l (140 mg/dl) at 2 hours were categorized as diabetes.

Data Analysis: The data was entered on the pre-formed pro forma for the analysis. Collected data was analysed through computer software SPSS 16. Mean and standard deviation were calculated for quantitative variables i.e. age, gestational age, parity and birth weight. Frequency and percentage were calculated for qualitative variables i.e. education, ethnicity and booking. Effect modifiers like booking status and education were controlled through stratifications and post-stratification chi-square was applied to see their effect on outcome. P-value ≤0.05 was taken as significant.

RESULTS

The mean age of total 100 women was 29.9 years, and the mean gestational age was found 38. 6 weeks. The mean of birth weight was 4.48 (n=100). Table I. Diabetes, by oral glucose tolerance test after 24 hours of delivery was found in 40 (40.0%) woman, whereas there was no diabetes in 60 (60.0%) patients (total n=100). Figure I. At 6 weeks diabetes was found in 27 (27.0%) woman who delivered Macrosomic babies by oral glucose tolerance test, whereas there was no diabetes in 73 (73.0%) patients as shown in Figure 2. The distribution of diabetes among different confounding variables is shown in the Table 2 which indicates that high frequency of diabetes was found in uneducated women. The stratification of diabetes with respect to the educational status described that the educational status factor did not contribute to any statistical difference in our study populace p = .157.

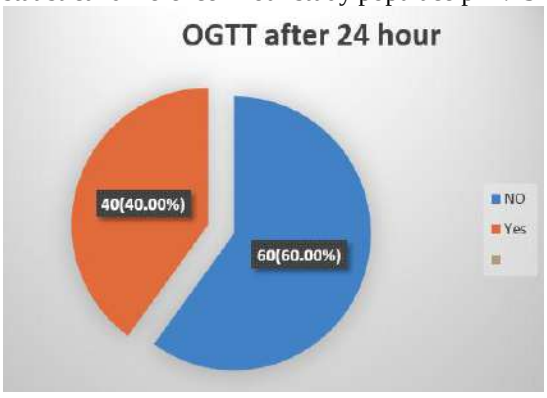

Figure No.1: Frequency of diabetes among women delivering macrosomic babies at 24 hours (n=100)

The women with non-booked status (n=64) reported high frequency of diabetes (18 +ve diabetes) than the women with booked status (n=36) reported (9 +ve diabetes). The stratification of diabetes based on booking status which showed no significant difference between booked and non-booked patients p=.735 (Table 2). The p-values of educational status and booking status (.157 and .735) which are more than alpha value (α= .05) show that there is no significant

association between educational status, booking status and diabetes.

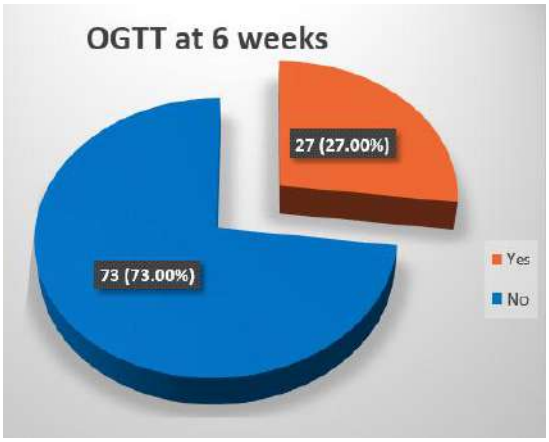

Figure No.2: Frequency of diabetes among women delivering macrosomic babies at 6 weeks (n=100)

Table No.1: Demographic data

Descriptive variable	N	Mean	Std. Deviation
Age	100	29.9	4.60
Gestational age	100	38.600	1.19
Birth weight	100	4.4759	0.42

Table No.2: Stratification of Diabetes with respect to educational and booking status. n=100

Confounding variable	Diabetes		p-value
	Yes	No	
Educated (56)	12 (21.42%)	44 (78.58%)	
Un-educated (44)	15 (34%)	29 (66%)	**0.157**
Booked (36)	09 (25.0%)	27 (75.0%)	
Non-booked(64)	18 (28.13%)	46(71.87%)	**0.735**

DISCUSSION

Normoglycemic mothers who deliver macrosomic babies has significant risk for developing diabetes later on in their life. In our study, diabetes by oral glucose tolerance test among women delivering macrosomic babies was found in 27 (27.0%) patients, as similarly observed by Kew S and cols where prevalence of diabetes in macrosomic delivery in non-GDM was 15.2% and in GDM was 9.1%.[21] In a study by Savona-Ventura Cv, it was noted that the rate of macrosomia neonates increased significantly from 8.5% in women with normal blood glucose values to 29.5% in women with higher values than normal.[17] Black recently demonstrated that the risk of adverse pregnancy outcomes differs between women with impaired fasting plasma glucose values (FPG) and abnormal glucose levels during the OGTT, providing evidence that women with elevated FPG particularly suffer from delivering large for gestational age(LGA) infants[21,22.] Similarly, Retnakaran and cols. found that FPG best predicts LGA risk, whereas post load glucose levels from OGTT predict postpartum pre diabetes or diabetes risks [23].

Our study demonstrates the risk of postnatal diabetes among normoglycemic women delivering macrosomic babies. In this quest we were able to identify 27 % of women with diabetes at six weeks postnatal, which is alarming considering the fact that our study included non-GDM cases as well. Our research highlights the need for having regular antenatal screening of all the women with an OGTT. This study also resonates with the previous NICE guidelines regarding diabetes in pregnancy which clearly stated that OGTT should be used as a screening test for diabetes in pregnancy in Asian ethnic population. The confounding factors featuring in this article including the booking status and education do not show any statistical significance although the non-booked women did have higher frequency of deranged OGTT. The much-feared shortcoming of this inquest was that we were not able to isolate the results pertaining to the number of women having diabetes with previous history of GDM. This process can be further improved by performing OGTT of women at their booking visits and then following them up to their delivery to assess the macrosomia. Further OGTT can be performed in non-diabetic women postnatal to assess the degree of glucose intolerance. Therefore, we think that by identifying the glucose tolerance of patients a better screening of the mother can be done in our subset of population and complications associated with glucose intolerance and macrosomia can be avoided in the next pregnancy.

CONCLUSION

Frequency of diabetes diagnosed by oral glucose tolerance test (OGTT) among normoglycemic women delivering macrosomic babies is high.

Author's Contribution:

Concept & Design of Study:	Hadia Aziz
Drafting:	Jaweria Faisal, Zeb un Nisa, Zeba Munzar
Data Analysis:	Ayesha Basharat, Sadia Kanwal
Revisiting Critically:	Hadia Aziz, Jaweria Faisal
Final Approval of version:	Hadia Aziz

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Assessment of Vitamin D Status in Pregnant Women and Non-Pregnant Women

Beenish Samreen Hamid[1], Noor Nasir Khattak[1], Fauzia Qadir[2], Rana Tauqir Ullah Khan[3] and Zahoor Ahmed[4]

ABSTRACT

Objective: The objective of this study to evaluate Vitamin D deficiency in pregnant women as compare to non – pregnant women.

Study Design: Cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Obstetrics and Gynecology KMU-IMS Kohat and Biochemistry of Northwest School of Medicine Peshawar from February, 2018 to August, 2019.

Materials and Methods: We include 200 women in this study in which 100 pregnant women and 100 non-pregnant women as control. Blood samples were collected both groups women and centrifuged at 3000 RPM for 10 min for serum. 25(OH) D was estimated from blood serum of the both groups by automatic chemical Analyzer and for estimation used Merk kits.

Results: Result of both groups pregnant women and non-pregnant women showed that blood serum 25(OH)D of pregnant women is lower as compare to non-pregnant women. In pregnant women we found 16.1 ng/mL serum vitamin as compare to non-pregnant women in which vitamin D value was 20 ng/mL.

Conclusion: The present study demonstrated that in pregnant women high risk of vitamin D deficiency present as compare to non-pregnant women. It is essential that to evaluate vitamin D deficiency in pregnancy and provide vitamin D supplement at early stage.

Key Words: Vitamin D, Pregnant, Non- Pregnant

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INTRODUCTION

Vitamin D is a fat-soluble vitamin approved for its uses in continuing bone condition. Vitamin D levels have also been connected with higher occurrences of various types of cancers.[1-3] Vitamin D happens certainly in an inadequate number of foods but is primarily synthesized by UVB light exposure in the skin.[4] In some countries, which are located in 35°North (and South), Vitamin D is not synthesized in sufficient amount and caused deficiency of Vitamin D.[5]

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Various studies showed that maternal health and fetal development had closely relation with Vitamin D status and it is also said that it has adverse effects on pregnant women and baby it is necessary that vitamin D should be monitor in pregnant women.[6] Insufficient maternal vitamin D statuses has certainly been associated with pregnancy problems such as preeclampsia and it is also caused infants born small for gestational age and also premature birth. [7–10] Vitamin D deficiency also caused other type of complication among children such as respiratory tract infections these complications are overcome with vitamin D supplement.[11] In different countries studies were conducted to determine the incidence of vitamin D deficiency in pregnant women such as Switzerland. The reasons of deficiency of Vitamin D is unknown.[12] The Objective of the present study to evaluate vitamin D in pregnant women.

MATERIALS AND METHODS

The study was conducted in Department of Obstetrics and Gynecology KMU-IMS Kohat and Biochemistry of Northwest School of Medicine Peshawar. We include 200 women in this study in which 100 pregnant women and 100 non-pregnant women as control. Blood samples were collected both groups women and centrifuged at 3000 RPM for 10 min for serum. 25(OH)D was estimated from blood serum of the both

groups by automatic chemical Analyzer and for estimation used Merk kits. Other biochemical tests were performed for both groups' women such as sugar, lipid profile, Serum creatinine (Cr), blood urea nitrogen (BUN) and uric acid (UA). Statistically analysis by SPSS version 20 software.

RESULTS

In this study, we were selected 200 women for vitamin D estimation in which 100 pregnant women and 100 non-pregnant. Result of both groups pregnant women and non-pregnant women showed that blood serum 25(OH)D of pregnant women is lower as compare to non –pregnant women. In pregnant women we found 16.1 ng/mL serum vitamins as compare to non-pregnant women in which vitamin D value was 20 ng/mL. It was showed that lipid profile is higher in pregnant women as compare to non-pregnant women. The result indicates that all the lipid profile (LDL, Triglyceride) is higher except HDL in women with as compare to normal control women. Total cholesterol (251.5 ± 12.8) mg/dl, LDL (128.8 ± 21.5) mg/dl, and Triglyceride (198.2 ± 32.5) mg/dl.

Table No.1: Participant characteristics

	Pregnant Women (n=100)	Non-Pregnant Women (n=100
Age (years)	41.53 ± 10.48	40.55 ± 10.38
Education		
Basic	B-50%, S-25%, U-25%	B-50%,S- 31% U-19%
Secondary		
University		
Body Weight(kg)	69.3 ± 11.4	71.4 ± 11.5
BMI (Kg/m2)	25.4 ± 2.6	25.3 ± 2.7

Table No.2: Assessment of Vitamin D in Pregnant women and non- pregnant women

Pregnant women (n=100)	Non- Pregnant women (n=100)
25(OH)D ng/mL	
16.1 ± 2.1	20.2 ± 2.3

Table No.3: Biochemical profile of pregnant women and non- pregnant women

Pregnant women (n=100)	**Non- women (n=100)**
Fasting Blood Glucose(mg/dl)	
97.7 ± 4.3	98.4 ± 4.6
Total Cholesterol (mg/dl)	
251.5 ± 12.8	191.6 ± 31.5
LDL (mg\dl)	
128.8 ± 21.5	113.5± 18.3
HDL (mg\dl)	
40.71± 8.5	57.3 ± 9.1
Triglycerides (mg\dl)	
198.2 ± 32.5	133.3 ± 31.2

DISCUSSION

Result of the different studies showed that there have been various problems and complication is attached with vitamin D deficiency. In present study, we study the Vitamin D deficiency in pregnant women and non-pregnant women. Vitamin D is a fat-soluble vitamin approved for its uses in continuing bone condition. Vitamin D levels have also been connected with higher occurrences of various types of cancers. Vitamin D happens certainly in an inadequate number of foods but is primarily synthesized by UVB light exposure in the skin. In some countries, which are located in 35°North (and South), Vitamin D is not synthesized in sufficient amount and caused deficiency of Vitamin D.[5]Various studies showed that maternal health and fetal development had closely relation with Vitamin D status and it is also said that it has adverse effects on pregnant women and baby it is necessary that vitamin D should be monitor in pregnant women. [6] Insufficient maternal vitamin D statuses has certainly been associated with pregnancy problems such as preeclampsia and it is also caused infants born small for gestational age and also premature birth. Vitamin D deficiency also caused other type of complication among children such as respiratory tract infections these complications are overcome with vitamin D supplement. In different countries studies were conducted to determine the incidence of vitamin D deficiency in pregnant women such as Switzerland. The reasons of deficiency of Vitamin D are unknown. In European and American studies showed that low level of 25(OH)D concentration has been found in pregnant women.[13-17] In present study we still found low level of 25(OH)D in pregnant women as compare to control women. Result of both groups pregnant women and non-pregnant women showed that blood serum 25(OH)D of pregnant women is lower as compare to non –pregnant women. In pregnant women we found 16.1 ng/mL serum vitamins as compare to non-pregnant women in which vitamin D value was 20 ng/mL. It was showed that lipid profile is higher in pregnant women as compare to non-pregnant women. The result indicates that all the lipid profile (LDL, Triglyceride) is higher except HDL in women with as compare to normal control women. Total cholesterol (251.5 ± 12.8) mg/dl, LDL (128.8 ± 21.5) mg/dl, and Triglyceride (198.2 ± 32.5) mg/dl.It is believed that vitamin D deposition has been occurred in fat tissue at higher level which caused deficiency vitamin in circulation in blood.[18] In one of study, smoking has enhanced vitamin D deficiency risk in pregnant women. In another study result showed that smoking pregnant women have vitamin D deficiency as compare non-pregnant women[19].

CONCLUSION

The present study demonstrated that in pregnant women high risk of vitamin D deficiency as compare to non-pregnant women. It is essential that to evaluate vitamin

D deficiency in pregnancy and provide vitamin d supplement at early stage.

Author's Contribution:

Concept & Design of Study:	Beenish Samreen Hamid
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Comparison of Virtual Reality and Conventional Balance Training to Improve Balance and Walking in Parkinson's Disease Patients

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ABSTRACT

Objective: This study is done to compare home based virtual reality training and conventional balance training in Parkinson's disease patients to improve balance and walking.

Study Design: A quasi experimental study

Place and Duration of Study: This study was conducted at the Kanaan Physiotherapy & Spine clinic from July 2020 till December 2020.

Materials and Methods: A convenient sample 24 patients were recruited with diagnosis of Parkinson's' disease. Patients were divided in to 2 groups of 12 patients in ach group. Virtual Reality Group (n=12) received 45 minutes training session, 3 days a week for 4 weeks and Conventional Physical therapy group (n=12) received balance training. The outcome measure was Berg balance scale (BBS) and timed up and go test. Data was analysed through SPSS 24.

Results: The data was found to be normally distributed. Virtual reality training group shows better effects as compared to conventional balance training group in terms of BBS ($p<0.001$) and TUG-test ($p<0.001$).

Conclusion: It was concluded that virtual reality balance training group showed more significant effect on balance and walking than conventional balance training group. Conventional balance training was also effective but Virtual reality training group showed better effects.

Key Words: Virtual reality, Rehabilitation, Stroke, Physiotherapy

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INTRODUCTION

Patients who suffer from Parkinson's disease present with balance dysfunction and difficulty in walking.[1,2] These patients are more instable while in standing posture and as there is reduced postural correction response from the body systems.[3] Parkinson's patients walk with small steps and increased stride to stride variation.[4] This increase the chances of patients fall and therefore, deteriorating impact on patient's quality of life.[5]

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Recently, virtual reality has proven to be an important therapeutic tool for patients with neurological dysfunctions. It involves multiple sensory channels in the simulated environment to increase patients interaction.[6,7] There are multiple ways of applying VR training. A number of devices are available in the market e.g., Nintendo Wii with balance board. Esculier et al used Wii Fit with a balance board for balance training of Parkinson patients. VR can be very beneficial in improving static as well as dynamic balance and thus overall walking experience of patients suffering from neurological disorders.[8,9] Another study compared the effect of Nintendo Wii-based motor cognitive training versus balance exercise therapy in patients with PD via a randomized controlled trial. Both the interventional groups showed remarked improvement on balance and the effects were maintained at follow-up too. Well, this is still not clear how beneficial Nintendo Wii based VR balance training in comparison with conventional balance training.[10]

Hsieh et al[11] cleared that Parkinson's patients showed more impairment in internal cues skills rather than external cues skills. So if external visual feedback is given to such patient then it will make compensation of impaired kinaesthetic feedback. This way internal cuing

can be bypassed.[12-14] It was cleared that VR could improve cognitive and visual cues and ultimately motor learning of a patient with more retention of memory.[14] So, the objective of the present study was to compare the Virtual reality balance training and conventional balance training.

MATERIALS AND METHODS

It was a quasi-experimental study design. The 24 patients of Parkinson's disease were included in the study from Kanaan Physiotherapy & spine clinic. The study was completed in six months from July 2020 to December 2020. The inclusion criteria were (1) age 45–65 years; (2) the score on mini mental state examination should be > 24(15) (3) Hoehn–Yahr Stages II–III; (4) bot under any kind of therapy in last 2 to 3 months; (5) some medical conditions like osteo-arthritis that directly affects walking and balance function. The exclusion criteria were anxiety or depression or having any underlying visual or auditory disturbances. An informed consent was signed by all participants before inclusion in to the study. All patients received twelve 45-minute training, 3 times in a week for 4 weeks. The trainings were conducted by 2 trained physical therapists. All patients were assessed before and after the 4 weeks of intervention by an assessor who was blinded about the group allocation. There were total 12 sessions for each patient.

VR balance training system: Nintendo Wii gaming device was used for virtual reality training group patients. Wii has a console, 2 hand held wireless sensors, 1 infrared bar, remote and adapter. Patients stands at 6-meter distance and plays different balance games under the supervision of a physical therapist. Balance board was used for balance games. The games used for these patients were Wii sports and balance board games. The warm up session was conducted with each patient before the start of intervention.[16,17]

Conventional Balance Training Group: In this group, training was done under the supervision of a trained therapist. Participants were asked to maintain static posture for 10 minutes and dynamic posture maintaining for 20 minutes. Patients were provided with verbal instructions by therapist throughout the session. Different balance exercises were performed in addition to static and dynamic balance control.[18,19]

Outcome measures

The main outcome measure in the study was berg balance scale[20]. The other outcome used was 3 meter Timed up & go test.[21]

Data analysis: Data was found to be normally distributed. Between group analysis was done by independent t-test and within group comparison was done by paired t-test. Significance was set with $p < 0.05$. All statistical tests were done by using SPSS.

RESULTS

Twenty-eight patients were physically screened between July 2021 and august 2021. Two patients were excluded for not fulfilling the criteria. Twenty-four patients were enrolled and randomized into the Virtual reality training group ($n = 13$) or Conventional training ($n = 13$) group. One patient from each group left the study due to personal reasons.

Participants in VR group were presented with mean age of 55.0±6.84years and in Conventional Balance Training group with 52.25±6.77 years. Participants in Virtual Reality Group were presented with mean height of 1.68± 0.13centimeters and in Conventional training group with 1.67± 0.16 centimeters. Participants in the Virtual Reality Group were presented with mean weight of 89.41±12.70kg and in Conventional Balance Training category with 90.16± 17.33 kg. Participants in Virtual Reality Group were presented with mean BMI of 31.94± 5.93 kg/m2 and in Routine Physical Therapy group with 32.88±8.04 kg/m2 as shown in Table 1.

The comparison of pre and post treatment BBSS values in two groups was done using independent sample t test. Analysis revealed that there was significant difference ($p<0.001$) in both groups. Virtual Reality Training group showed greater improvement in BBSS as compared to Conventional balance training group as shown in table 2. The pre and post treatment 3 meter Timed up and Go test values between two groups was done using independent sample t test. Analysis revealed that there was statistically significant difference in both groups with p value < 0.001. Virtual Reality Training Group showed greater improvement in TUG test as shown in Table 2.

Table No.I: Demographic data

Study Group		N	Mean± Std. Deviation
Virtual Reality	Age of Participants	12	55.0±6.84
	Height in m	12	1.68± 0.13
	Weight in kg	12	89.41±12.70
	Body Mass Index of Participants	12	31.94± 5.93
	Valid N (list wise)	12	
Routine Physical Therapy	Age of Participants	12	52.25±6.77
	Height in cm	12	1.67± 0.16
	Weight in kg	12	90.16± 17.33
	Body Mass Index of Participants	12	32.88±8.04
	Valid N (list wise)	12	

Table No.2: Independent t-test Between Group Analysis

Scale		Treatment group		P value
		Virtual reality Balance Training	Conventional Balance Training Group	
BBSS	Pre-treatment (Mean±SD)	19.92 ± 4.48	19.91±3.99	0.97
	Post-treatment (Mean±SD)	38.17±8.01	23.0±3.76	<0.001
TUG	Pre-treatment (Mean±SD)	13.92±1.40	13.97±1.68	0.94
	Post-treatment (Mean±SD)	8.81±1.08	11.05±1.36	<0.001

Table No.3: Paired t-test within Group Analysis

Paired Sample t test		Treatment group		p-value
		Virtual reality Balance Training (Mean difference ±SD)	Conventional Balance Training Group (Mean difference ±SD)	
BBSS	Pre-treatment - Post-treatment (Mean±SD)	18.25 ±6.15	3.08±3.42	<0.001
TUG test	Pre-treatment - Post-treatment (Mean±SD)	5.12±1.52	2.92±1.27	<0.001

Paired sample t-test was used to compare the values of BBSS score and TUG test within each treatment group. Results declared significant difference ($p<0.001$) in both the groups but greater improvement was seen in Virtual Reality balance training Group as shown in Table 3.

DISCUSSION

Many of the studies related to VR showed better effects of VR in terms of time, velocity, balance, control of posture and function of upper and lower extremity as compared to other treatment options.[19,22] The focus of this study is to compare VR training and conventional balance training in Parkinson's disease patients to improve balance and walking.

The results of our study showed significant effect on berg balance scale score. The berg balance scale score showed more improvement in VR training group ($p<0.001$) as compared to conventional training group. Results of current study are supported by another study and similar results were found.[23,24]

It was hypothesized that VR training is superior than conventional balance training in improving walking and balance of patients effected by Parkinson's disease. The results were similar to our hypothesis. Both treatments were effective but VR is more effective as proven by results. The possible explanation for this could be the neuroplasticity effect of VR training. Patients were found to be more interested in VR training group games.[25]

This hypothesis was further supported by Baltaci et al[25]

Other explanations of improvements can be following: VR training tasks mimics the daily tasks and activities; difficulty of tasks can be increased as required and VR training does not require any preparation in advance. Patient remains calm and focus on his treatment plan.

VR training relies on visual feedback and patient tries to achieve the required movement as early as possible. Patient learns the skills on priority as that skill is required to play the games perfectly.[26]

In current study, patients in VR training group showed more improvement in 3 meter timed up and go test as compared to conventional training group ($p<0.001$). Similar results were found in other studies with early improvement in walking function and balance.[27] The possible explanation of this walking improvement in VR group can be due to neuroplasticity effect of VR training. VR training focus on motor learning of patients are the movements performed are real time movements as done by patient in routine life.[28] Patient has the knowledge of performance as well as the knowledge of results and tries to improve the results and thus more productive in VR training. Conventional balance training is a bit more hectic for patient and loses confidence.

There is degeneration of basal ganglia circuits in Parkinson's disease patients and that's why patients have difficulty in implicit learning.[29] So auditory pacing, visual feedback and visual targets and knowledge of performance and results are important clinical ways to improve motor learning in patients with Parkinson's disease.[26] Thus VR training would be so helpful.

CONCLUSION

It was concluded that virtual reality balance training group showed more significant effect on balance and walking than conventional balance training group.

Conventional balance training was also effective but Virtual reality training group showed better effects.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Burden of Infections Caused by Multidrug Resistant Organisms and Antibiotics Stewardship Program in Poor Country

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ABSTRACT

Objective: To assess the burden of resistant infections and need for Antibiotic Stewardship Program at hospital of resource limited country.

Study Design: Prospective cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Pulmonology, Fatima Jinnah Chest Institute affiliated with Bolan Medical College Quetta from January 2017 to December 2019.

Materials and Methods: Two hundred and two patients aged 14 years and above with pneumonia or sepsis, admitted to intensive care unit, high dependency unit and ward were enrolled. Demographics, physical examination findings, duration of illness and use of antimicrobials (along with group) during last three months were documented. Blood, respiratory secretions, pleural fluid/pus, and urine samples are sent for microbiological studies at time of admission.

Results: One hundred and sixty (79.2%) showed positive bacterial growth while 42 (20.8%) exhibited no growth. Out of 160 positive samples, 66 (41.2%) grew multi-drug resistant Pseudomonas 28 (17.5%) samples grew extended spectrum beta lactamases producing Gram negatives and 17 (10.7%) showed growth of Methicillin resistant Staphylococcus aureus. One hundred and thirteen (70.6%) of patients were required care in critical areas like intensive care unit and high dependency unit.

Conclusion: Infections caused by multi-drug resistant organisms are very high in our country. Patients infected with resistant organisms generally require admission to critical care areas that might have significant financial implications on patients and hospital budgets.

Key Words: Multi-drug resistant organism, Antibiotic Stewardship Program, Burden

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INTRODUCTION

The MDRO is a microbe that resists three or more kinds of antimicrobial drugs. The MDROs are primarily bacteria.[1] These include Staphylococcus aureus (MRSA) resistant methicillin (SMR), Enterococci (VRE) species resistant to vancomycin, Enterobacteriaceae generating carbapenemase and Gram negatives that produces large spectrum beta-lactamases (ESBLs). These two last kinds of diseases produce compounds that resist the effect of some antimicrobials and this adaptability between various species is easily transferred.[2] Antimicrobial resistance is one of the largest challenges to human, animal and ecological health in the world at present.[3-4]The emergence and spreads of AMR continue to pose severe concerns by the abuse and misuse of antibiotics in human beings and animals, although this is a natural evolutionary phenomena.[5] Resistance to antimicrobials impacts on financial sustainability, global health, food and safety, environment and socioeconomic development. [6] Antimicrobial resistance has had a negative impact such as severe illnesses, longer hospital stays, increased healthcare expenses, a heavier public health system, higher second-line medicines costs, failure to treat and even greater levels of death.[7] Antimicrobial stewardship has been defined as the appropriate treatment selection, dosage and duration of antimicrobial therapy resulting in the best clinical outcome for infection treatment or prevention, with

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minimum patient toxicity and low consequences for the resistance to infection.[8] Includes the unjustified use of broad spectrum antibiotics as well as poor prevention and management of infections and antibiotic stewardship policies, which are the key causes which increase Pakistan MDR rates.[9-11]

As a result, throughout the past years, an AMR spike has been seen, making drug therapy challenging for infectious conditions such as typhoid, tuberculosis, etc.[12,13] In 2016, the Pakistan Society for Medical Microbiology & Infectious Diseases approved the Guidelines for combating antibiotic (ASP) Resistance laid down by the World Health Organization (WHO) Global Plan of action (GAP).[14,15] We conducted present study that aimed to determine the burden of multi-drug resistant infections and need for Antibiotic Stewardship Program at hospital of resource limited country.

MATERIALS AND METHODS

This prospective cross-sectional study was conducted at Department of Pulmonology, Fatima Jinnah Chest Institute affiliated with Bolan Medical College Quetta from January 2017 to 31st December 2019 and comprised of 202 patients. Patients below 14 years of age and those did not give any written consent were excluded. Patients aged 14 years and above with pneumonia or sepsis, admitted to intensive care unit (ICU), high dependency unit (HDU) and ward were enrolled. Demographics, physical examination findings, duration of illness and use of antimicrobials (along with group) during last three months were documented. Blood, respiratory secretions, pleural fluid/pus, and urine samples are sent for microbiological studies at time of admission. Complete data was analyzed by SPSS 22.

RESULTS

There were 110 (54.45%) male patients and 92 (45.54%) were female patients. Mean age of the patients was 32.54±8.36 years. One hundred and twenty (59.40%) were from urban area, 115 (56.9%) were literate and 108 (53.46%) were from high socioeconomic status (Table 1). One hundred and sixty (79.2%) showed positive bacterial growth while 42 (20.8%) exhibited no growth. Out of 160 positive samples, 66 (41.2%) grew multi-drug resistant (MDR). Pseudomonas 28 (17.5%) samples grew extended spectrum beta lactamases producing Gram negative and 17 (10.7%) showed growth of Methicillin Resistant Staphylococcus aureus (Table 2). One hundred and thirteen (70.6%) of patients were required care in critical areas like ICU and HDU among 160 cases of positive growth (Table 3).

Table No.1: Baseline details demographics of enrolled cases (202)

Variable	No.	%
Mean age (years)	32.54±8.36	
Gender		
Male	110	54.45
Female	92	45.54
Educational status		
Illiterate	115	56.9
Literate	87	43.06
Locality		
Rural	120	59.40
Urban	82	40.6
Socioeconomic status		
High	108	53.46
Low	94	46.54

Table No.2: Outcomes after culture and sensitivity reports (n=202)

Variable	No.	%
Bacterial growth		
No	42	20.8
Yes	160	79.2
Positive bacterial growth (n=160)		
MDR Pseudomonas	66	41.2
ESBL	28	17.5
MRSA	17	10.7
Others	49	30.6

Table No.3: Treatment and admission of affected cases in ICU and HDU (n=160)

ICU/HDU Admission	No.	%
No	113	70.6
Yes	47	29.3

DISCUSSION

There is little or no such monitoring in most developed countries to ensure appropriate monitoring of antibiotic resistance development. In 2014, the WHO released its first antimicrobial resistance report, in which the World Health Organization collected country data on nine bacterial infections/antimicrobial combinations that are the most serious health concerns.[16] In this prospective cross-sectional study 202 patients with ages >14years were presented. Mean age of the patients was 32.54±8.36 years. Majority 110 (54.45%) cases were males and the rest were 92 (45.54%) female patients. Our findings were comparable to the previous study.[17]

In the current study mostly infected patients were non-educated 56.9% and from rural areas 59.40%. Majority of the patients 53.46% had high socioeconomic status.

There are a shortage of qualified doctors and health workers certified for diagnosing and treating illnesses in many developing countries and particularly rural areas. As a consequence, many unqualified, low-training medical workers as well as traditional healers treat and prescribe antibiotics.[18] A study of pediatric diarrhea and pneumonia carried out in rural India indicated that out of 340 doctors, 80 of them did not have formal schooling.[19,20] The study also found that unskilled professionals are more likely to prescribe dangerous treatments.[20] The repercussions of unrestricted antibiotic usage are often little or nothing understood by unqualified health personnel and healers.[21]

We found in our study that, one hundred and sixty (78.4%) showed positive bacterial growth while 44 (21.6%) exhibited no growth. Out of 160 positive samples, 66 (41.2%) grew multi-drug resistant (MDR). Pseudomonas 28 (17.5%) samples grew extended spectrum beta lactamases producing gram negatives, and 17 (10.7%) showed growth of Methicillin Resistant Staphylococcus aureus. These results were comparable to the previous findings in which use of medications without prescriptions had adverse effects.[21,22] While antibiotics have been prohibited in Europe since 2006 as growth boosters, this practice remains standard in numerous nations, including the United States.[23]

In the current study 70.6% patients were required care in critical areas like ICU and HDU among 160 cases of positive growth. Previous study presented same results.[24] The hospitals have an important role in preventing the appearance and transmission of antimicrobial resistant micro-organisms and ensuring that the available antimicrobials are effective. Infection and antimicrobial stewardship programs are run by multi-disciplinary expert teams such as infectious diseases doctors, clinical pharmacists, clinical microbiologists.[25,26].

CONCLUSION

Infections caused by multi-drug resistant organisms are very high in our resource limited, developing country settings. Patients infected with resistant organisms generally require admission to critical care areas that might have significant financial implications on patients and hospital budgets. This might also be a contributing factor to global threat of antibiotics resistance. Implementation of Antibiotic Stewardship Program could be the only evidence based solution to this problem.

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Original Article

Compare the Outcome of Endoscopic Endonasal versus Transcranial Approach for Cerebrospinal Fluid Leak Repair

Hameed Ullah Khan[1], Abdul Rauf[2] and Mubarak Hussain[2]

ABSTRACT

Objective: To determine the outcome of endoscopic endonasal versus transcranial approach for cerebrospinal fluid leak repair.

Study Design: Comparative study

Place and Duration of Study: This study was conducted at the Department of Neurosurgery, Indus Medical College Tando Muhamad Khan from January 2019 to December 2019.

Materials and Methods: Sixty patients of both genders and aged between 20-65 years were enrolled. Patient's details demographics age, sex and body mass were recorded. Patients had cerebrospinal fluid leaks and the history of cerebrospinal fluid leak was presented. Patients were equally divided into two groups, I and II. Group I treated by endonasal technique and group II treated by transcranial approach. All the patients were undergone for magnetic resonance imaging and computerized tomography scan. Complete follow up among both groups were taken in the duration of 10 months for the assessment of efficacy.

Results: Mean age of the patients in group I was 30.08±17.09 years with mean BMI 26.14±8.16 kg/m^2 and in group II, mean age was 29.74±6.48 years with mean body mass index 26.54±7.22 kg/m^2. Thirty six (60%) patients were males (18 in each group) and 24 (40%) patients were females (12 in each group). In group I recurrence rate was found in 4(13.3%) cases and in group II recurrence rate was (6.7%). 2 (6.7%) patients in group II developed infection but no any infection rate was found in endoscopic endonasal group. Satisfaction among patients in endonasal group was greater than that of transcranial group. Overall efficacy rate among both groups was 54 (90%).

Conclusion: For repair of cerebrospinal fluid leak both endoscopic endonasal and transcranial approach was effective and safe method. Minimum rate of recurrence and high rate of recovery was fund in this study.

Key Words: Cerebrospinal fluid, Endoscopic endonasal, Transcranial approach, Complications, Recurrence

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INTRODUCTION

Cerebrospinal fluid (CSF) leaks are classified as traumatic (accidental and iatrogenic trauma) and spontaneous (idiopathic) leaks based on etiology. Patients with a CSF leak may present with a variety of symptoms ranging from clear nasal discharge and headaches to mental status changes, meningitis, or brain abscesses, or they may be asymptomatic.[1]

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Clinically a CSF leak can be diagnosed by asking the patient to lean forward (reservoir test) to check for wet rhinorrhea from the nose. A fluid sample can be sent to a lab for Beta-2 transferrin or Beta-2 trace protein testing.[2] Cerebrospinal fluids can enter the nose via deficiencies in the anterior cranial fossa such as the cribriform plate, frontal sinus, ethmoid sinus, and sphenoid sinus, or via a defect in the middle cranial fossa via the sphenoid sinus.[1]

Traumatic CSF leaking commonly happens after basilar skull fractures, however it can also occur as an iatrogenic side effect of surgical treatments.[3-6] Spontaneous leakage can occur with or without high intracranial pressure. On the other hand, spontaneous CSF leaks will always necessitate surgical intervention.[6] In the last 30 years, the advancement of CSF fistula repair has been tremendous, from craniotomy, which had a greater failure rate and severe morbidity, to endoscopic repair.[7]

Conservative treatment, particularly for post-accidental CSF leaks, consists of bed rest, elevation of the head, avoidance of straining activities, fluid restriction, and

diuretics. The majority of acute post-accidental CSF leaks recover with conservative treatment.[8]

The surgical technique chosen is determined by various criteria, including the extent and consistency of the tumor, the approach utilized in the original operation, and the surgeon's experience and preference.[9,10] Endoscopic trans sphenoidal techniques, transcranial approaches, and combinations of both have been documented for the management of these difficult cases with varying outcomes.

An extra cranial extradural approach is used for endoscopic CSF fistula repair. Because of its excellent visualization, precise graft placement, minimal damage to surrounding tissue, preservation of olfactory function in case of fistula leak through the cribriform plate, shortened operating time, and faster recovery time, it has been accepted worldwide as the method of choice.[11,12] We conducted present study with aimed to compare the outcomes of endoscopic endonasal versus transcranial approach for the management of cerebrospinal fluid leak.

MATERIALS AND METHODS

This comparative experimental study was conducted at Department of Neurosurgery, Indus Medical College Tando Muhamad Khan from 1st January 2019 to 31st December 2019 and comprised of 60 patients of cerebrospinal fluid leaks. Patient's details demographics were recorded after taking informed written consent. Patients had chronic renal failure, chronic liver disease, patients had wound infection and meningitis were excluded from this study. Patients were aged between 20-65 years. Patient's details demographics age, sex and body mass were recorded after taking written consent. Patients had CSF leaks and the history of CSF leak was presented. Patients were equally divided into two groups, I and II. Group I received endonasal technique and group II received transcranial approach. All the patients were undergone for MRI and CT scan. Complete follow up among both groups were taken in the duration of 10months for the assessment of efficacy. Standard deviation and mean was used for numerical values. Categorical variables were assessed by percentages and variables. Complete data was analyzed by SPSS-22.

RESULTS

Mean age of the patients in group I was 30.08±17.09 years with mean body mass index 26.14±8.16 kg/m^2 and in group II mean age was 29.74±6.48 years with mean BMI 26.54±7.22 kg/m^2. Total 36 (60%) patients were males (18 in each group) and 24 (40%) patients were females (12 in each group) [Table 1].

In group I, recurrence rate was found in 4(13.3%) cases and in group II, recurrence rate was 2 (6.7%) [Table 2]. Two (6.7%) patients in group II developed infection but no any infection rate was found in endoscopic endonasal group (Table 3).

Overall efficacy rate among both groups was 54 (90%). Satisfaction among patients in endonasal group was greater than that of transcranial group (Table 4).

Table No.1: Baseline details demographics of enrolled cases (n=60)

Variable	Group I	Group II
Mean age (years)	30.08±17.09	29.74±6.48
Mean BMI (kg/m^2)	26.14±8.16	26.54±7.22
Gender		
Male	18 (30%)	18 (30%)
Female	12 (20%)	12 (20%)

Table No.2: Comparison of recurrence rate among both groups (n=60)

Recurrence rate	Group I	Group II
Yes	4 (13.3%)	2 (6.7%)
No	26 (86.7%)	28 (93.3%)

Table No.3: Prevalence of infection among both groups

Infection	Group I	Group II
Yes	0	2 (6.7%)
No	30 (100%)	28 (93.3%)

Table No.4: Comparison of satisfaction among both groups

Variable	Group I	Group II
Success rate		
Yes	26 (43.3%)	28 (46.7%)
No	4 (6.7%)	2 (3.3%)
Satisfaction		
Yes	29 (48.3%)	27 (45%)
No	1 (1.75)	3 (5%)

DISCUSSION

Cerebrospinal fluid rhinorrhea is a life-threatening problem. It results from a rupture of the dura and fractures at the base of the skull and can lead to severe consequences such meningitis and abcess of the brain.[13] Cerebrospinal fluid rhinorrhea management is contentious but can be categorized into conservative or operative therapy. For the first 1–2 months, the conservative treatment is indicated and surgery should start if it does not. The operation is classified into intracranial or extracranial treatments. A craniotomy was historically the first procedure utilized to treat anterior cranial fossa leaks in the intracranial approach. Extracranial techniques became more prevalent afterwards. More recently, a new approach for closure of CSF leaks has been offered with the introduction of endoscopic sinus surgery.[13]

In present study majority of the patients, 36 (60%) were males and 24 (40%) were females. Average mean age of the patients was 30.48±18.90 years with mean BMI

26.84±7.44 kg/m^2. Our findings were comparable to the previous studies.[9,14]

In our study recurrence rate was 13.3% in endonasal group and (6.7%) in transcranial group. A study conducted by Simair et al [9] reported that 10% patients and 5% patients had recurrence whom were treated with endonasal and transcranial approaches for CSF leak repair. Overall efficacy rate among both groups was 54 (90%). Our study showed a significantly lower hospitalization time in the endonasal group and the duration of the surgical operation. A study by Mansour et al[15] reported that the success rate of endoscopic approach was 90% at first attempt and after second attempt the success rate was 97.5%.

Nyquist et al[16] have investigated 28 individuals and reported an overall success rate of 93.8% endonasal closure (30 of 32 procedures). Lee and Colleagues[17] have examined a sample similar in size to Nyquist et al[16] reported a success percentage in the first attempt (86%) and in the second effort (93%). The overall success rate for Virk et al[18] following the second operation was of 93 percent and 100 percent. Lee and Colleagues[17] believe it depends mostly on the direct visualization of the lesion to succeed in endoscopic endonasal repair. Seth and Colleagues[19] stress fluorescein use, it was greater to locate the leaks when fluorescein-colored CSF was observed, 100% faults were detected compared to 81.3% without fluorescein and provided that the proper intrathecal solution of fluorescein is utilized, no adverse effects will occur at the right dose.[20,21]

Two (6.7%) patients in group II developed infection but no infection rate was found in endoscopic endonasal group. Satisfaction among patients in endonasal group was greater than that of transcranial group in our study and this was comparable to the previous study.[22].

CONCLUSION

For repair of cerebrospinal fluid leak both endoscopic endonasal and transcranial approach was effective and safe method. Minimum rate of recurrence and high rate of recovery was recorded.

Author's Contribution:

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Original Article

Comparison of Depressive Disorders in Working and Non-Working Adolescent

Haresh Kumar[1], Sarika Bai[2], Om Parkash[3], Pirbho Mal[4], Rakesh Kumar[5] and Anny Dhanwani[6]

ABSTRACT

Objective: To determine the prevalence of depressive disorders in working and non-working adolescent and their comparison among them.

Study Design: Cross-sectional descriptive study

Place and Duration of Study: This study was conducted at the Fellows Clinic Sukkur from January 2017 to June 2017.

Materials and Methods: One hundred and sixty patients of both genders and age from 10 to 19 years were enrolled. Patient's socio demographics such as age, sex, body mass index, education status, socio-economic status and locality were recorded after taking written consent. Patients were divided into two groups I and II, group I had 80 working adolescents and group II with 80 non-working adolescents.

Results: Mean age of the patients in group I was 15.5±2.1 years with mean BMI 22±4.3 kg/m^2 and in group II mean age was 14.9±2.5 years with mean BMI 22.3±3.7 kg/m^2. In group I 30 (37.5%) cases were literate, 28 (35%) were from high socio economic status and 45 (56.25%) were from urban area while in group II 28 (35%) were literate, 32 (40%) had high socio-economic status and 42 (52.5%) had urban residency. 30 (37.5%) patients had depression, 32 (40%) had anxiety and 35 (43.75%) cases had stress in group I as compared to this 23 (28.75%) patients had depression, anxiety found in 27 (33.75%) cases and stress found in 25 (31.25%) patients.

Conclusion: The frequency of depressive disorders among children workers was significantly higher than that of non-workers and there is need to diagnose this earlier to overcome and reduce its severity.

Key Words: Adolescent, Workers, Non-workers, Depression, Anxiety, Stress

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INTRODUCTION

Unipolar depressive illness is a widespread problem with mental health in teenagers throughout the world1 and is approximately[1] year old in mid- to late adolescence of 4–5%.[2,3] The second-to-third largest reason for death in this age group[4] is depression in teenagers and more than half of the adolescent victims reported depression in deaths, which is the key risk factor for suicide.[5] Depression also results in severe social and educational deficiencies[6,7] as well as increased smoking, substance misuse, and obesity.[8,9] It is so crucial to recognize and treat this disease.

Depression is described as a cluster of unique impairment symptoms. In adolescents and adults, the clinical and diagnostic characteristics are largely similar (panel).[10,11] Depression is defined in the two principal classification systems (international classification of disease-10 [ICD-10] and the American Mental Disorders-IV Diagnostics and Statistics Manual (DSM-IV)), although DSM-IV is a single-except for children and adolescents, allowing for the core diagnostic symptoms to be irritable instead of depressed.[12] Depression in teenagers is more common than in adults, however probably due to the presence of irritability, mood responsiveness and adolescent changing symptoms.[13] Depression can also be neglected if the major difficulties exhibited are unexplained health complaints, food disorder, anxiety, school refusal, decreasing academic performance, abuse of posture or problems of behavior.

Depression in young people might in some ways be seen as the early-coming substitute of the adult

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equivalence, due of its significant connections in later life with recurrence.[14] The disease has comparable neurological clinical characteristics and patterns as adults and is linked to the family history of the disease.[11] However, there are major disparities in treatment response between the two illnesses, with highly separate viewpoints on the best therapy approaches.[10] Prepubertal child depression in adolescents or adults is less common than adolescent depression, and several of its causal, epidemiological and prognostic traits seem to be different from these diseases.[15,16]

We concentrate on adolescent unipolar depression. When there is proof, we concentrate rather than on symptoms of depressive disorder. In some cases, however, the only evidence available studies are which report depressive symptoms. These situations are observed despite the research findings for depression and depressive disorder often have considerable commonalities.

MATERIALS AND METHODS

This cross-sectional study was conducted at Fellows Clinic Sukkur over a period of six months from 1st January to 30th June 2017and comprised of 160 adolescents. Patients' baseline details were recorded after taking informed consent. Patients of age from 10-19 years and those did not give any written consent were excluded. Patient's details demographics age, sex, body mass index, education status, socio-economic status and residency were recorded after taking written consent. Patients were divided into two groups I and II, group I had 80 working adolescents and group II with 80 non-working adolescents. Frequency of depression, anxiety and stress were calculated among both groups. Complete data was analyzed by SPSS 24.

RESULTS

Mean age of the patients in group I was 15.5±2.1years with mean BMI 22±4.3kg/m^2 and in group II mean age was 14.9±2.5years with mean BMI 22.3±3.7kg/m^2. In group I 30 (37.5%) cases were literate, 28 (35%) were from high socio economic status and 45 (56.25%) were from urban area while in group II 28 (35%) were literate, 32 (40%) had high socio-economic status and 42 (52.5%) had urban residency (Table 1).

Around thirty-eight percent (37.5%) patients had depression, 32 (40%) had anxiety and 35 (43.75%) cases had stress in group I as compared to this 23 (28.75%) patients had depression, anxiety found in 27 (33.75%) cases and stress found in 25 (31.25%) patients of group II. Significantly, depressive disorders were greater in working adolescents as compared to non-working adolescents (Table 2).

Table No.1: Socio demographic characteristics of adolescents who attended fellow clinic (n=160)

Variable	Group I	Group II
Mean age	**15.5±2.1**	**14.9±2.5**
Mean BMI	**22±4.3**	**22.3±3.7**
Gender		
Male	50 (62.5%)	50 (62.5%)
Female	30 (37.5%)	30 (37.5%)
Education		
Literate	30 (37.5%)	28 (35%)
Illiterate	50 (62.5%)	52 (65%)
Socio-economic status		
High	28 (35%)	32 (40%)
Low	52 (65%)	48 (60%)
Locality		
Urban	45 (56.25%)	42 (52.5%)
Rural	35 (43.75%)	38 (47.5%)

Table No.2: Comparison of depressive disorders among both groups (n=160)

Disorders	Group I	Group II
Depression		
Yes	30 (37.5%)	23 (28.75%)
No	50 (62.5%)	47 (71.25%)
Anxiety		
Yes	32 (40%)	27 (33.75%)
No	48 (60%)	53 (66.25%)
Stress		
Yes	35 (43.75%)	25 (31.25%)
No	45 (56.25%)	55 (68.75%)

DISCUSSION

In the factories, workshops, restaurants, cafes, etc., children and adolescents are at risk for working conditions. The 21 physical, social, emotional, mental and spiritual health are damaging to it.[17] Child labour, which has numerous dimensions of childhood's lifetime development that impair the child's ability to achieve proper educational chances, potential and dignity, and to deny them their infancy and innocence is becoming endemic and menacing for society in general. The topic of child labor is pervasive and has shifted from regional to 22 international fora.[18]

In this study, majority were males 62.5% with mean age 15.5±2.1years with mean BMI **22±4.3**kg/m^2. Our findings were comparable to the previous study.[19] Eighty cases were working adolescents and the same were non-working. Among these 30 (37.5%) cases were literate, 28 (35%) were from high socio economic status and 45 (56.25%) were from urban area in working group while in group II 28 (35%) were literate, 32 (40%) had high socio-economic status and 42 (52.5%) had urban residency.[20]

A WHO special panel report highlighted the need of treating mental health issues in low-income and middle-income countries with inadequate resources, with depression as a particular concern for teenagers.[21,22] The treatment of children exposed to traumatic IPT incidents by trained local community workers is one potential technique. The IPT among local community staff significantly enhanced depressive symptoms in adolescent girls.[23]

Stress was more common among working teens, the conclusions of current research showed. A careful analysis of the findings showed that 37.5% of the work force was depressed, 40% were anxieties and 43.75% was stressful. This discovery was validated by earlier studies. Their natural psycho-social health was not developed by children engaged in varied workplace work; almost 40% of kid workers suffered from 23 aberrant psychological growths.[24] In another study, working youngsters showed lower levels of adaptive ability, lower physical health and undesired social behaviour, use of scoundrels and excessive use of cigarettes. They committed themselves, destroyed their social and emotional well-being, leading to depression and suicide. They also committed themselves. There have also been 24 reports of violence and antisocial behavior.[25]

As far as difference in the presentation of symptoms of depression, stress and anxiety is concerned, the only statistically significant difference was discovered in stress and anxiety among working and non-working adolescents. It is also indicated by the research investigations that environmental factors played a crucial part in generating stress reactions in adolescents exposed to hazardous working situations. But if a closer focus is paid to the processes of sadness and anxiety, it pointed several diverse causes ranging from hereditary sensitivity to environmental and personality factors in both working and non-working groups. Therefore, it is proposed that preventative efforts should be implemented for both working and school going adolescent 25 addressing their individual requirements and concerns.[26].

CONCLUSION

The frequency of depressive disorders among adolescent workers was significantly higher than that of non-workers and there is need to diagnose this earlier to overcome and reduce its severity.

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Original Article

Surgical Outcome of Anterior Cervical Disectomy and Fusion Using Peek Cage for Cervical Disc Herniation in Terms of Pain Relief

Outcome of anterior cervical discectomy and fusion (ACDF) using a PEEK Cage

Naeem ul Haq[1], Musawer Khan[1], Adnan Ahmed[1] and Aziz ul Haq[2]

ABSTRACT

Objective: The purpose of this study was to evaluate the outcome of anterior cervical discectomy and fusion (ACDF) using a PEEK cage.

Study Design: Prospective study

Place and Duration of Study: This study was conducted at the Neurosurgery Department, Bacha Khan Medical College, Mardan Medical Complex, Peshawar from December 2017 until December 2020.

Materials and Methods: The study excluded patients who required multiple level ACDF or corpectomy with plating and redo instances. A proforma was completed that covered the patient's age, gender, address, level of prolapsed disc, signs and symptoms, pain score, and MRI findings. All patients were evaluated on the day of discharge and during a one-month follow-up visit. SPSS version 22 was used to analyze the data.

Results: A total of 53 patients were included, including 62.26% males and 37.73% females. Patients ranged in age from 27 to 64 years, with a mean of 50.4 years. (61%) patients had radicular pain on the right side. Radiculomyelopathy was present in patients with 5.26 percent. C5–C6 was the most often operated level (35 patients). Using Odom's criteria, excellent results were obtained in 81 percent individuals and adequate results in the remaining patients. At six months, 92 percent of patients had a fusion of the bones.

Conclusion: ACDF with PEEK cage fixation is a safe and beneficial treatment for cervical prolapse disc disease at one level.

Key Words: Surgical Outcome, Anterior Cervical Disectomy, Fusion Using Peek Cage, Cervical Disc Herniation

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INTRODUCTION

Cervical radiculopathy is a prevalent disorder with a frequency of 3.5 per 1,000 and an annual incidence of 83 per 100,000. Radiculopathy is a disorder that can be caused by a variety of clinical conditions, including prolapsed intervertebral discs, stenosis, and trauma, as well as malignancies and even spinal instability[1]. Cervical spondylosis, on the other hand, is the most common cause, followed by disc herniation.

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Prolapsed discs are more prevalent in the 30- to 50-year-old population. The most frequently impacted level of disc herniation is C5-C6. The majority of prolapsed cervical discs can be treated conservatively. However, certain circumstances necessitate surgery, which can be accomplished in a variety of methods from anteriorly and posteriorly[2].

Anywhere along the spine, from the neck (cervical) to the low back, a discectomy can be performed (lumbar). The surgeon accesses the injured disc through the throat area from the front (anterior) of the spine. The disc and bone vertebrae are exposed by repositioning the neck muscles, trachea, and oesophagus. Frontal neck surgery is more accessible than posterior neck surgery because the disc can be reached without disrupting the spinal cord, spinal nerves, or the powerful neck muscles. Depending on the severity of your symptoms, one or more discs (single-level) or multiple discs (multi-level) may be removed[3].

The gap between the bony vertebrae is left empty after the disc is removed. Previously the bone graft was put into the disc space and fixation was applied with plating. But then it was then transformed with PEEK cage between the two vertebral bodies to accommodate the space and zero profile screws are applied in the

vertebrae above and below. The PEEK cage acts as a connector between the two vertebrae, resulting in spinal fusion. Following surgery, the body's natural healing process begins, with the formation of new bone cells around the graft. After three to six months, the PEEK cage and zero profile screws were followed for fusion. Instrumentation and fusion function in concert, just like reinforced concrete does[4].

We present our investigation and illustrate the surgical outcomes of anterior cervical disectomy and PEEK cage fixation and the patients with cervical disc herniation[5].

MATERIALS AND METHODS

Cervical disc herniation (CDH) was indicated surgically when the following criteria were met: progressive myelopathy; persistence or worsening of radiculopathy despite 12 weeks of medical treatment; and motor impairment or intractable pain. Our inclusion criteria were single CDH and post-operative follow-up of greater than 12 months. Cases were excluded if they had coexisting spine diseases, a history of previous spine surgery, or a postoperative follow-up of less than 12 months[6].

This series includes 53 CDH cases that were handled with ACDF using PEEK cage. The result instruments were as per the following: an investigation planned survey that evaluated remaining and additionally new objections, just as abstract fulfillment with the activity; a new (multi week before the meeting) postoperative VAS for neck and furthest point radicular torment; Evaluation Questionnaire; and follow-up visits[7].

The senior author entered preoperative medical information at the time of surgery, including preoperative symptoms, duration of pain (from commencement to surgery), physical examination, and pain severity as measured by the Visual Analogue Scale (VAS). Intraoperative problems were reviewed in the surgery notes. The postoperative course was read from the follow-up notes. Our study population was contacted via phone to educate them about the research and to invite them to a follow-up visit. The follow-up visits were conducted by a physician who specializes in spine research[8].

This prospective study was undertaken at the Hospital's Department of Neurosurgery from December 2017 until December 2020. All patients provided written consent prior to enrollment in the trial, which was approved by the hospital's ethical review committee[9].

Criteria for Inclusion	Criteria for Exclusion
Only individuals with a single level of prolapsed intervertebral cervical discs who had failed conservative therapy were enrolled in the trial.	Multiple levels of involvement, trauma, fracture, and previously operated patients with any cervical disease were excluded.

Before surgery, each patient's full pre-operative history, clinical examination findings, X-ray cervical spine, and MRI cervical spine were performed and documented in the database[10]. To optimize fusion in all patients, PEEK cage was placed in the disc space and zero profile screws were applied. All patients underwent surgery supine and under general anesthetic. An image intensifier was used to check the surgical level. The cervical collar was worn postoperatively. According to Odom's criteria, various outcome questionnaires were completed preoperatively and at postoperative intervals. Additionally, outcomes were analyzed and quantified utilizing a neck and arm pain visual analogue scale. Fusion was determined using dynamic cervical x-rays, and at the third month follow-up visit, 1mm movement at the necessary spot was declared fused[11].

Statistical Analysis: SPSS version 16.0 was used to analyse the data (SPSS, Inc., Chicago, IL, USA). The level of statistical significance was fixed at 0.05. The central and dispersion trends were calculated for descriptive statistics. The nonparametric test (chi-square) was used to compare qualitative variables. The nonparametric test was used to compare qualitative and quantitative data (Mann-Whitney test)[12].

RESULTS

The gender distribution among ACDF patients using PEEK cage is shown below:

Table No.1: Gender distribution

Gender	No. of patients	%
Males	33	62.26%
Females	20	37.73%
total	53	100%

C5–C6 was the most frequently fused site, whereas C6–C7, C3–C4, and C4–C5 were the least frequently fused sites, as illustrated:

Table No.2: Disc involvement.

Disc Involvement	No. of Patients	%
C3-C4	5	9.43%
C4-C5	3	5.66%
C5-C6	35	66.03%
C6-C7	9	16.98%
C7-C11	1	1.88%

The procedure's outcome was determined using Odom's criteria. 81 percent of individuals had excellent scores.

Table No.3: Procedural Outcome

Outcome	No. of patients	%
Excellent	43	81.13%
Good	7	13.2%
Fair	2	3.77%
Poor	1	1.88%

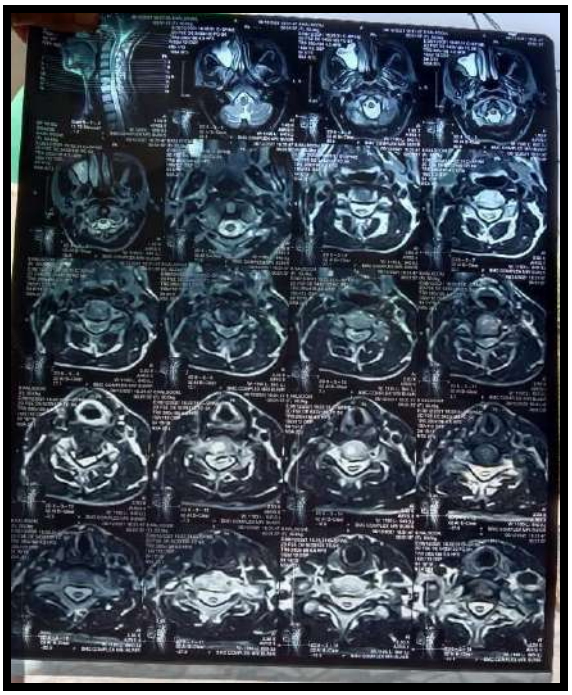

Figure No.1:

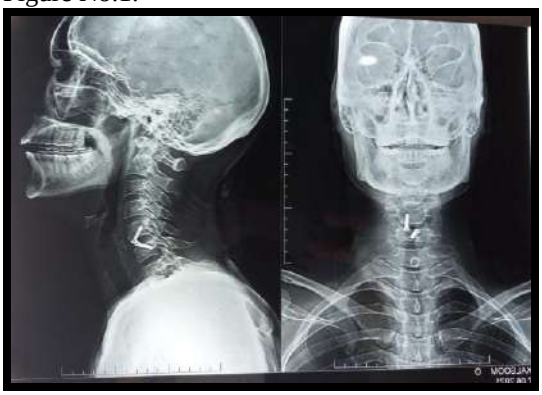

Figure No.2:

Figure No.3:

DISCUSSION

The purpose of inserting PEEK cage into the disc gap is to fill the space and maintain the cervical alignment. The use of a cage reduces the requirement for external orthosis and facilitating early mobilization[13]. Only single level ACDF was performed using Peek cage and discussed in this study. Wanget al conducted a study on ACDF with multiple levels. They achieved 91.7 percent fusion rates inpatients without plating and 95.5 percent with plating. Additionally, they demonstrated in his study that results were outstanding in 91 percent of cases with caging, compared to 88 percent of cases without caging[14]. Kaiser et al compared the results of 157 cases of single level anterior cervical discectomy and fusion with a cohort of 242 non-plated individuals in another investigation. He discovered a fusion rate of 90% in non-instrumented individuals and 96% in plated patients. Khan et al. reported a fusion rate of 96.93 percent for one level anterior cervical discectomy and fusion in a local trial. The fusion rate of 96.38 percent observed in this study is consistent with Wang et al work's and other local and international studies[15]. Thus, the above results demonstrate that the use of micro plates during one level cervical discectomy improves fusion rates. The results of the current research indicate that 82 percent of patients had great outcomes, while 12.05 percent had satisfactory outcomes. Khan et al findings are similar, implying that ACDF is the preferred treatment for radicular discomfort. Numerous studies demonstrate that complication rates vary significantly around the globe[16]. Infection is a rather common problem in our region. This study demonstrates a 3.61 percent infection rate. However, comparable results were also observed in the Khan et al study, indicating that this is a perfectly acceptable range. After examining the research populations, overall outcome in terms of clinical outcome and complication rate. We feel that ACDF with titanium miniplates is the most appropriate treatment choice due to its high efficacy and minimal surgical time prolongation. However, our study is limited by a lack of long-term follow-up. Proving these findings will require larger prospective RCT studies[13].

The prevalence of subsidence in our investigation was 19%, which is greater than the 14.3 percent reported by Cabraja et al. in their series of PEEK cage sinking at a mean follow-up of 28.4 months. Galhom reported three incidences of subsidence (7.5 percent) during a two-year follow-up period. Ha et al. identified a rate of PEEK cage associated subsidence of 8.1 percent at a mean follow-up time of 18.9 months. Furthermore, Park et al. observed that 22.6 percent of their subjects exhibited subsidence after an average follow-up of 12

months. Subsidence was reported at a rate of 32.3 percent in a research done by Song et al[14].

Kao et al. found a solid relationship among subsidence and sexual orientation, the quantity of treatment levels, and treatment at C5–7. Age and sexual orientation had no impact on subsidence in Kast et al arrangement. There was no connection between age, sexual orientation, the quantity of treatment levels, and subsidence; nonetheless, the greater part (75%) of cases related to subsidence had gotten single-level ACDF (C5-C6, C6-C7)[15].

At a half year, Kulkarni et al. discovered a combination pace of 93.33 percent for PEEK confines. At a mean development of ten months, Cho et al. noticed a 100% combination rate. Kulkarni et al study populace combination was kept up following a normal of year and a half of follow-up. Cabraja et al. announced a 88.1 percent combination rate for PEEK confines after a mean development of 28.4 months. Liu et al. noticed a 72 percent combination rate after a mean development of 25.6 months. Tune et al. detailed a combination pace of 78.9 percent. Niu et al. tracked down that the PEEK confine bunch had a 100% combination rate at year follow-up. Ha et al. accomplished 94.5 percent combination after a normal subsequent length of 18.9 months. At a mean development of almost 53 months, we acquired a 100% combination rate[16].

Another study conducted by Akramullah in Pakistan, excellent results were obtained in 75 patients (79 percent) using Odom's criteria, while adequate results were obtained in the other patients. At six months, 92 percent of patients had a fusion of the bones. While the current study shows 81 percent excellent results and adequate results in the remaining patients[18].

CONCLUSION

Cervical disc disease management has evolved over time. Even now, several surgical procedures and bone fusion materials are used. Anterior cervical discectomy with PEEK cage fixation is a successful and safe therapeutic option for single level cervical disc disease with a favourable outcome in terms of pain and neurological function[17].

Author's Contribution:

Concept & Design of Study:	Naeem ul Haq
Drafting:	Musawer Khan
Data Analysis:	Adnan Ahmed, Aziz ul Haq
Revisiting Critically:	Naeem ul Haq, Musawer Khan
Final Approval of version:	Naeem ul Haq

Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Six Week Melatonin Therapy Improves the Triglyceride to HDLc Ratio and Prevents Atherogenic Tendency

Aftab Abbasi[1], Hina Mawani[3], Abdul Majid[2], Asim Mehmood[4], Rasheed Ahmed Soomro[5] and Samreen Pandhiani[6]

ABSTRACT

Objective: To observe the effects of six weeks melatonin oral therapy on TAGs/HDLc ratio and atherogenic tendency in alloxan induced diabetic rat model.

Study Design: Experimental study

Place and Duration of Study: This study was conducted at the Department of Anatomy, Pharmacology, and Pathology, SRMC, Tando Adam from May 2019 to December 2020.

Materials and Methods: A sample of one hundred male Wistar albino rats was divided equally into five groups. Group A (negative control) and B (positive diabetic control) were untreated. While Experimental groups D, E and F were treated with melatonin 5, 10 and 15 mg/Kg bwt daily orally for six weeks. Alloxan (120 mg/Kg body weight) was injected (i.p) to induce diabetes mellitus. Blood samples were analyzed for biochemical testing. Log TAG/HDLc ratio was defined as atherogenic index of plasma (AIP). Data variables were analyzed statistically (SPPSS ver. 21.0) at 95% CI ($p \leq 0.05$).

Results: Six weeks melatonin therapy significantly ameliorated the glycemic control (glucose, A1C, fasting insulin and C – peptide), blood lipids (Cholesterol, TAGs, LDLc and HDLc) of experimental diabetic rats (P=0.0001). TAGs/HDLc ratio (atherogenic index of plasma (AIP) was significantly improved after six weeks melatonin therapy (P=0.0001).

Conclusion: We report six week melatonin therapy improves triglyceride to HDLc ratio thus preventing the atherogenic tendency.

Key Words: Melatonin, Lipid profile, TAG/HDLc ratio, Atherogenicity

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INTRODUCTION

Melatonin is an amine hormone of pineal gland released at night time. Melatonin produces multiple biological effects.[1,2] Melatonin functions through its receptors on target cells. Melatonin receptors (MT) are two types - MT1 receptor is linked with brain functions while the MT2 receptor modulates the body's circadian rhythms.[2] Melatonin exerts neuroprotective and cardioprotective effects.

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Melatonin plays role in female and male reproductive system, synchronizing circadian rhythms, sleep cycle, metabolism, ocular functions, etc. Melatonin interacts with cell through its membrane receptors and intracellular mechanisms altering broad spectrum of physiological functioning vital for organism survival including cell metabolism, apoptosis, biological rhythms, etc.[3-5] Melatonin is also produced in other tissues such as the gonads, gut, bone marrow, retina, skin, astrocytes and lymphocytes, etc.[6] Synthesis of melatonin is reportedly controlled by postganglionic sympathetic nerves. Thus the melatonin is ubiquitously acting hormone.[7] Immunomodulatory, anti – inflammatory and anti – oxidative effects of melatonin are noticeable. Most vital physiological function is in the sleep wake cycle. It regulates the biological clock, immune response, and control of seasonal reproduction in lower animals.[3,8] Melatonin is reported regulate the body weight and energy balance.[3] Several metabolites of melatonin are effective scavengers thus making it an effective anti – inflammatory and anti – oxidant agent. Various food stuffs contain melatonin such as the herbs, olive oil, fruits, and vegetables. FDA classified melatonin as food supplement free from any serious adverse effects and toxicity.[1,3] Currently, the DM is

increasing in the country[9] with associated risk of metabolic derangements such as the dyslipidemia and atherogenicity. Altered blood lipids increase the tendency of vascular events due to atherosclerosis including the coronary vascular disease, peripheral arterial disease, coronary artery disease and cerebrovascular injuries, etc.[3,9] The present experimental study investigated the effects of melatonin therapy on TAGs/HDLc ratio and atherogenic tendency (AIP) in Alloxan induced diabetes mellitus in male Wistar albino rat model.

MATERIALS AND METHODS

The present experimental study, analyzing the therapeutic efficacy of melatonin, was approved by the Ethical Review Committee (ERC) of Suleman Roshan Medical College. Experiment covered duration from May 2019 to December 2020 and conducted at the Department of Anatomy, Pharmacology, and Pathology, SRMC, Tando Adam from May 2019 to December 2020. We purchased one hundred adult male albino rats (Wistar strain) form animal house according to inclusion and exclusion criteria. Inclusion criteria were declared as; male rat, body weight 150 – 200 gram, Albino Wistar strain. Animal feeding well and moving around the cages, looking healthy and active were as per inclusion criteria. While lazy male rats, sick, not feeding well, not moving actively and female sex were decided for exclusion from study protocol. Equipped animal house was ensured for all necessary requirement and animals housing was in according to the NIH Guidelines (Animal Research). 12/12 hour dark/light cycle was maintained strictly. Rats were examined on daily basis. Proper ventilation was ensured. Rats were given chow feeding twice daily. Control group A (n=20) were tagged as negative control – as DM was not inducted and was given 9.0% N/Saline as placebo therapy. Group B (n=20) was tagged as positive control – DM was inducted with Alloxan but therapy was not given. This group was used for comparison of research variable results of experimental diabetic melatonin treated groups (Groups C, D and E). Alloxan was purchased from Sigma Aldrich (USA). Alloxan dose of 120 mg/Kg[9] body weight was administered into the peritoneal cavity in fasting rats for DM induction. A rat attained random blood glucose level ≥250 mg/dl[9] was termed as diabetic rat. Rats showing successful DM induction were divided into Positive control B and Experimental groups D, E and F. Diabetic experimental groups D, E and F received melatonin 5, 10 and 15 mg/Kg bwt therapy. Melatonin was administered orally mixed diet daily orally for six weeks. After six weeks melatonin therapy, the rats were kept on fasting for six hours. Rats were anesthetized with ethylene ether in plastic containers. Comatose rats were pricked with capillary tube in the retro-orbital space to collect blood samples. Blood was centrifuged (x3000 rpm for fifteen minutes). Squeezed sera were preserved at – 20 ^{0}C. Sera were used for the biochemical analysis of study research variable of glycemic control – glucose, glycated hemoglobin (A1C), fasting insulin and C – peptide using standard clinical laboratory methods. Lipids profile was estimated on Cobas chemistry analyzer. TAG/HDLc ratio (AIP) was calculated as; Log TAG/HDLc ratio (AIP) determined by manually using scientific calculator. Scaling of TAG/HDLc ratio (AIP) used was; low risk 0.3 – 0.1, medium risk 0.1 – 0.24 and high risk >0.24 of atherogenic tendency.[10] Biochemical parameters of research interest were analyzed on SPSS ver. 21.0 using appropriate statistical tests (one – way analysis of variance and LSD Fischer`s post- Hoc test). Level of significance among group differences was taken at 95% CI ($p \leq 0.05$). Graphs were plotted on Microsoft Excel sheet.

RESULTS

Six weeks melatonin therapy significantly ameliorated the glycemic control (glucose, A1C, fasting insulin and C – peptide), blood lipids (Cholesterol, TAGs, LDLc and HDLc) of experimental diabetic rats (P=0.0001) (Table –1) (Graph – 1). TAGs/HDLc ratio (atherogenic index of plasma (AIP) was significantly improved after six weeks melatonin therapy in experimental diabetic rats (P=0.0001) (Graph – 2).

Table No.1: Biochemical findings and TAG/HDLc ratio (n=100)

	Group-A	Group-B	Group-C	Group-D	Group-E	P
Body weight (g)	158.3±25.3	131.3±34.1	135.3±13.1	141.3±12.3	151.4±11.5	0.95
Glucose (R) (mg/dl)	114.6± 6.9	352.4±40.3	285.1± 48.2	261.6±49.0	207.6±29.4	0.003
A1C (%)	4.08±1.1	8.6±0.7	7.3±1.5	6.65±1.1	6.0±0.58	0.016
Insulin (F) (µU/L)	6.2±0.5	2.6±1.2	4.5±1.1	4.7±1.0	5.3±0.4	0.018
C- peptide (mg/dl)	2.1±0.7	0.5±0.3	1.2±0.36	1.32±0.2	1.58±0.3	0.018
Cholesterol (mg/dl)	108.1±5.2	223.0±58.2	196.9±35.8	176.7±54.2	121.6±15.5	0.018
TAGs (mg/d)	109.4±6.0	176.6±33.0	191.0±31.7	156.8±25.3	139.4±22.3	0.015
LDLc (mg/d)	91.2±11.0	139.3±36.0	123.1±20.1	123.0±21.0	111.8±5.7	0.001
HDLc (mg/d)	39.0±3.6	21.9±3.3	25.0±2.3	30.5±3.0	32.7±4.3	0.001
TAG/HDLc ratio (AIP)	0.03±0.01	1.11±0.1	0.74±0.21	0.59±0.23	0.39±0.10	0.0001

AIP- Atherogenic Index of Plasma

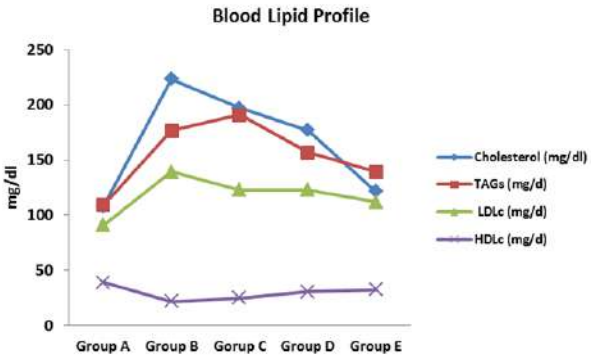

Figure No.1: Graph showing the blood lipid profile levels

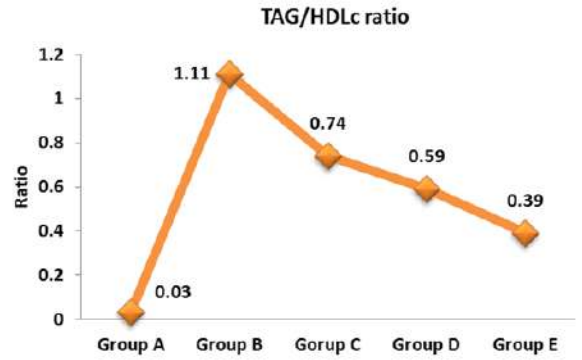

Figure No.2: Graph showing the TAG/HDLc ratio (AIP)

DISCUSSION

Melatonin is the chief hormone of the pineal gland that interacts with a variety of different cells.[1] In humans, melatonin receptors has been detected in the retina, brain, suprachiasmatic nucleus, central and peripheral arteries, kidneys, pancreas, adipocytes and immune cells.[12,13] It is known that melatonin exerts antioxidant, anti-inflammatory, anti-hyperlipidemic and antihy-pertensive actions and also modulates insulin secretion and action.[14,15] There are reports showing that melatonin–insulin interactions and relationship between melatonin–insulin ratio and lipid profile may exist in patients with metabolic syndrome[16] and that melatonin therapy improves blood pressure, lipid profile and parameters of oxidative stress in patients with metabolic syndrome.[17] The present study has demonstrated that melatonin treatment of obese rats was associated with a reduction in body weight without affecting food intake. We observed six weeks melatonin therapy significantly improved the glycemic control (glucose, A1C, fasting insulin and C – peptide), blood lipids (Cholesterol, TAGs, LDLc and HDLc) and TAGs/HDLc ratio (atherogenic index of plasma (AIP) in the experimental diabetic rats (P=0.0001). Log TAG/HDLc was taken as atherogenic tendency.[9] The findings of present study are in agreement with previous reports.[1-3] A previous study[18] observed the melatonin decreased blood cholesterol levels in genetically mutated hypercholesterolemia rats with improvement of fatty liver. Another previous study[19] analyzed the fructose fed rats with melatonin therapy and found dyslipidemia was attenuated in experimental rats. A previous animal study[20] conducted on rats, observed the melatonin therapy attenuated the lipid peroxidation. Serum Cholesterol, TAGs, FFA and phospholipids were decreased to normal in the brain and liver rat. A previous study[21] conducted on normal rats found melatonin intake improved total plasma lipids and hepatic phospholipids and increase in n-6 polyunsaturated fatty acids (PUFA) was observed. A recent review by Danilenko et al[1] (2019) has critically proved lipid lowering potential of melatonin. A previous study[22] administered 10 mg melatonin to 14 patient's diagnosed idiopathic hypercholesterolemia. They found improvement of blood lipid concentration with significant rise in serum HDLc similar to present study (table 1). However, findings of previous studies[23,24] conducted in post menopause women with two weeks melatonin therapy (6 mg) found deterioration of TAGs and VLDL levels. The findings are inconsistent to present and previous studies.[20-22] Another clinical study[24] analyzed 14 elderly women with melatonin therapy for six months, and reported no change in the blood lipids compared to baseline. Inconsistent findigns of above studies[23-25] are most probably due to the small sample of study subjects with altered milieu of hormone in post menopause hence findigns are incomparable. A previous study[26] investigated the effects of melatonin therapy in obese rats and found TAGs and LDLc were decreased, HDLc was increased but observed no changed in total cholesterol. The forming finings of TAGs, LDLc and HDLc are concordant to our present study; however insignificant cholesterol change is discordant to present and other previous studies.[22-22] Evidence based findgins of melatonin therapy in induced diabetic rats of present experimental study are highly significant that may be exploited for treating the hyperlipidemia and dyslipidemia of diabetes mellitus patients and atherogenic tendency may be prevented, however this needs further experimental and clinical trials in indigenous populations to validate the findings for making melatonin available using in clinical practice.

CONCLUSION

We report six week melatonin therapy improves triglyceride to HDLc ratio thus preventing the atherogenic tendency Melatonin improves the blood lipids, glycemic control and atherogenic index of plasma (AIP) in alloxan induced diabetes in male Wistar albino rat model. Further experimental studies and clinical trials are warranted for in – depth studies to reach to proper benefits of melatonin therapy making

this natural remedy available for clinical use for preventing the atherosclerosis.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Potential Protective Effect of Pumpkin Seed Oil against Carbon Tetrachloride Induced Hepatotoxicity in Albino Rats

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ABSTRACT

Objective: To determine the potential protective effect of pumpkin seed oil (PSO) against Carbon tetrachloride Induced Hepatotoxicity in Albino Rats.

Study Design: Experimental study

Place and Duration of Study: This study was conducted at the Department of Anatomy, Pharmacology and Pathology, SRMC, T. Adam from March 2019 to January 2020.

Materials and Methods: 100 rats were divided equally into five groups. Group A negative control and Group B (positive control) (CCl_4 (0.2 mL/kg), Group C – CCl_4 (0.2 mL/kg) + PSO (1 mL/Kg bwt), Group D –CCl_4 (0.2 mL/kg+ PSO (2 mL/Kg) and Group E– CCl_4 (0.2 mL/kg)+(PSO (3 mL/Kg). Carbon tetrachloride was administered intraperitoneal at a dose of 0.2 mL/kg twice a week and PSO for 8 weeks. Blood samples were collected from the retro – orbital capillary plexus after anesthesia. Sera were used for the biochemical analysis; liver function tests (spectrophotometric), superoxide dismutase, glutathione peroxidase and catalase were detected by ELISA assay. Data was analyzed on statistical SPSS package (ver. 21.0) at 95% Confidence interval.

Results: We observed carbon tetrachloride (CCl_4) induced hepatotoxicity was improved significantly after 8 weeks pumpkin seed oil (PSO). Serum bilirubin, PT, ALT, AST and GGT were mitigated significantly ($P\leq 0.0005$). Pumpkin seed oil (PSO) augmented the superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT) activity after 8 weeks therapy ($P\leq 0.0005$).

Conclusion: The present study reports hepatoprotective potential of pumpkin seed oil against carbon tetrachloride induced hepatotoxicity in male Wistar albino rats.

Key Words: Pumpkin Seed Oil, Carbon tetrachloride, Hepatotoxicity, Rats

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INTRODUCTION

Liver is largest gland of body that detoxifies the digested food particles and portal vein blood. Detoxification is major function of liver besides others. Disturbance in the liver functions manifests clinically as derangement of physiological functions throughout the body. Liver injury also occurs as its detoxification function declines resulting in fatty liver, chronic hepatitis, fibrosis, etc.[1] Organisms are taking thousands of xenobiotic in food as contaminants that, if not detoxified by liver produced adverse toxic effects. Liver dysfunction caused by xenobiotics is known as hepatotoxicity. Xenobiotics that selectively damage liver are called the hepatotoxin.[2,3] One of the hepatotoxin, the carbon tetrachloride (CCl_4) is used for experimental injury in animal models to observe the hepatoprotective effects of herbs and drugs.[4] Carbon tetrachloride (CCl_4) is used for scientific experimental studies in laboratory animals producing chemical liver injury.[4,5] Carbon tetrachloride (CCl_4) is biotransformed into free radicals, the trichloromethyl and proxy chloromethyl by the liver microsomal CYP P450 system. Trichloromethyl and proxy chloromethyl react with various cell components such as the amino acids, nucleic acids, phospholipids, proteins, fatty acids, etc.[3,5-7] Nowadays, many natural herbs have gained

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attention for the chemical induced liver injury. One such herbal compound is the pumpkin seed oil (PSO), this has been used by previous studies.[8] PSO contains minerals, proteins, poly unsaturated fatty acids (PUFA) and phyto – sterols. Investigators have reported anti – bacterial, anti – fungal, anti – nematocidial, anti – carcinogenic, anti – helminthic and anti – oxidant, and hepatoprotective potential of PSO. Investigators have observed the PSO ameliorates tissue architecture in liver toxicity animal models.[9,10] However, limited literature is available on the effects of PSO on biochemical markers of chemical induced hepatotoxicity.[11-13] We planned an experimental rat study to analyze the effects of PSO on biochemical markers of chemical induced hepatotoxicity. The present rat model experimental study was conducted to determine the potential protective effect of pumpkin seed oil (PSO) against Carbon tetrachloride -Induced Hepatotoxicity in Albino Rats.

MATERIALS AND METHODS

The present rat animal experimental study was conducted at the Department of Anatomy, Pharmacology and Pathology, SRMC, T. Adam. Approval for conducting experimental study was taken in writing in collaboration with Animal house, Sindh Agriculture University. Animals were housed at the animal house of Sindh Agriculture University; Tando Jam. Experimental study duration was from March 2019 to January 2020.

Animal Housing: One hundred male Wistar albino rats were purchased from the animal house SAUTA. Inclusion criteria were male gender, body weight 180 – 200 grams, moving and feeding actively. Female rats were excluded. Animals were housed in accordance to the Guidelines of Animal Experimentation of Institute. Animal house is equipped with all facilities. Five rats were put per cage under appropriate conditions. Room temperature was maintained at (21 ± 2°C), ventilation (12 rpm), 12 – 12 hours light/dark cycle and humidity (50 ± 5%). Feeding and water were available ad – libitum.

Dose calculation of CCl_4 and PSO: CCl_4 was administered at dose of 0.2 mL/kg as 1:1 mixture in corn oil, twice a week for 8 weeks as cited.[3] This dose is well documented to cause hepatotoxicity in rats.[3] PSO dose was given 1, 2 and 3 mL/kg/bwt as cited[14] given for total 8 weeks duration.

Experimental Grouping: One hundred rats were divided into five groups. Group A (negative control) – received 0.9% NaCl orally as placebo therapy. Group B (negative control) – received CCl_4 (0.2 mL/kg as 1:1 mixture in corn oil, twice a week for 8 weeks). It was left untreated. Group C – received CCl_4 (0.2 mL/kg as 1:1 mixture in corn oil, twice a week for 8 weeks) + treated with PSO (1 mL/Kg bwt orally for 8 weeks). Group D – received CCl_4 (0.2 mL/kg as 1:1 mixture in corn oil, twice a week for 8 weeks) + treated with PSO (2 mL/Kg bwt orally for 8 weeks), and Group E– received CCl_4 (0.2 mL/kg as 1:1 mixture in corn oil, twice a week for 8 weeks) + treated with PSO (3 mL/Kg bwt orally for 8 weeks). Carbon tetrachloride was administered intraperitoneal at a dose of 0.2 mL/kg as 1:1 mixture with corn oil, twice a week for 8 weeks.

Blood sampling: After the experiment duration was over, the rats were anesthetized by ketamine (50 mg/kg intramuscularly) and xylazine (10 mg/kg intramuscularly) injection. Blood samples were collected from the retro – orbital capillary plexus by putting a capillary tube below and behind the eyeball.[15] Blood samples were centrifuged (x1300g rpm) for 15 minutes. Sera were separated and stored at temperature -20°C in refrigerator for biochemical analysis later on.

Biochemical analysis: Sera were used for the biochemical analysis. Liver function tests (7 parameters) were analyzed and estimated (spectrophotometric).

Superoxide dismutase (SOD), Glutathione peroxidase (GPX) and Catalase (CAT) were detected by ELISA assay kit (Fortress Diagnostics) on Roche Cobas Biochemistry Analyzer

Statistical Analysis: Research variable results were saved in Microsoft Excel Sheet. Values were copied and pasted on SPSS package (ver. 21.0, IBM, incorporation, USA) for data analysis. One – way analysis variance (1- ANOVA) post – Hoc Benforinni test analyzed the results of different groups with descriptive analysis. Level of statistical significance was taken at Confidence interval 95% ($p \leq 0.05$).

RESULTS

We observed carbon tetrachloride (CCl_4) induced hepatotoxicity was improved significantly after 8 weeks pumpkin seed oil (PSO) in experimental groups C-E.

Table No.1. Liver function tests after 8 weeks therapy

	Group A	Group B	Group C	Group D	Group E	P
Bilirubin	0.57±0.03	2.7±0.32	1.5±0.64	1.1±0.27	1.01±0.07	0.0001
PT (sec)	7.1±1.54	13.6±1.7	11.5±3.15	9.1±2.43	9.1±1.12	0.0003
ALT	32.7±6.39	69.8±13.19	57.5±8.21	53.1±7.63	52.1±7.1	0.0001
AST	31.6±6.51	42.9±19.2	36.5±10.71	35.5±8.3	33.1±3.1	0.0004
ALP	79.5±17.3	139.5±32.3	115.3±41.5	97.3±31.1	91.3±31.2	0.0001
LDH	109.1±16.5	161.3±31.1	139.5±31.1	130.1±19.1	119.3±10.3	0.0005
GGT	35.1±4.8	71.1±17.3	57.3±18.7	47.3±19.1	41.1±11.0	0.0001

Table No.2: SOD, GPX and CAT after 8 weeks therapy

	Group A	Group B	Group C	Group D	Group E	P
SOD **(U/ml)**	136.0±33.8	75.3±15.3	112.7±19.2	121.5±13.2	131.1±11.31	0.0001
GPX **(nM/mL)**	137.1±31.2	87.1±21.3	117.1±15.7	121.3±11.0	129.5±13.1	0.0005
CAT**(nM/mL)**	307.3±30.3	133.6±52.3	201.3±71.1	276.1±61.3	187.7±77.6	0.0001

SOD- superoxide dismutase, GPX- glutathione peroxidase, CAT- catalase

Differences in serum bilirubin, PT, ALT, AST and GGT were found statistically significant among groups as shown in table –1 (P≤ 0.0005). Pumpkin seed oil (PSO) therapy shows rise in the natural anti – oxidant enzymes the; superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT) after 8 weeks therapy as shown in table – 2 (P≤ 0.0005).

DISCUSSION

During the modern era, the human beings are constantly exposed to chemical toxins in form of pollutants, agriculture pesticides, drugs, etc. Most of the chemical toxins are seriously injurious to the liver producing acute chronic liver toxicity. Various agents have been experimented against the chemical induced liver injuries.[10-12] Present report is the first experimental research conducted to observe the PSO against the CCl_4 induced hepatotoxicity rat model. We report the PSO shows excellent anti – toxic and hepatoprotective effects against CCl_4 induced hepatotoxicity. Liver is major site of biotransformation of drugs, toxins and chemical pollutants. Hepatocyte enzymes leak out of cell as the cell injury occurs and are best biomarkers of hepatotoxicity.[2,16] Serum ALT, AST, ALP, LDH and GGT are best predictors of liver toxicity in experimental rat models. ALT is the first to rise and identified by standard laboratory investigations.[2] Raised serum ALT is an indicator of disruption of functional integrity of hepatocyte cell membrane and its waning levels indicates healing of liver.[16,17] Hepatotoxicity causes leakage of liver enzymes into the circulating blood.[17] In present study, it was observed carbon tetrachloride (CCl_4) induced hepatotoxicity was improved significantly after 8 weeks pumpkin seed oil (PSO) in experimental groups C-E. Differences in serum bilirubin, PT, ALT, AST and GGT were found statistically significant among groups as shown in table –1 (P≤ 0.0005). The findigns of present study are in agreement with previous studies.[10,12,16,17] Pumpkin seed oil (PSO) increased the natural anti – oxidant enzymes status in present study that is in agreement with previous studies.[16,17] In present study, the superoxide dismutase (SOD), glutathione peroxidase (GPX) and catalase (CAT) were found increased in experimental groups C to E after 8 weeks therapy (table – 2) (P≤ 0.0005). It has been reported the serum ALT raises at the earliest indicating most vital parameter of liver function test,[4,18,19] that has been confirmed in the present study. In present study, the liver functions derangement was too much in positive control B that was ameliorated by eight weeks PSO therapy in experimental groups C to E. The findigns are in keeping line with previous studies.[2,17,20] In present study, the CCl_4 at dose of 0.2 mL/kg as 1:1 mixture in corn oil for 8 weeks was sufficient to produce hepatotoxicity rat model. This is in agreement with previous studies.[3,17] In present study the dose of PSO used was in range of 1-3 mL/kg that proved of therapeutic effects ameliorating the liver function tests and anti – oxidant enzyme status of experimental rat groups. Finding is supported by a previous study.[14,17] A previous study[21] reported the PSO augments Islet β- cell functions of pancreas, resulted in increased insulin secretion sufficient to normalize the blood glucose levels. Evidence based of present study proves the biological potential of PSO against the CCl_4 induced hepatotoxicity in rats. Hepatoprotective effects of PSO may be attributed to its rich polyphenol and polyunsaturated fatty acids contents. Hence PSO may be used as hepatoprotective agents for human beings however; this needs clinical trials in patients with hepatic affections.

CONCLUSION

The present study reports potential protective effect of pumpkin seed oil (PSO) against carbon tetrachloride (CCl_4) induced hepatotoxicity in male Wistar albino rats. PSO in doses of 1, 2 and 3 ml/Kg body weight was significantly improved and mitigated the carbon tetrachloride induced liver injury. PSO improved the liver functioning enzymes, ALT, AST, ALP, LDH and GGT along with boosting of superoxide dismutase, glutathione peroxidase and catalase. Future animal studies are recommended and clinical trials too to make this remedy available for liver affections in clinical practice to better patient management with cost effective herbal therapy.

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Relationship Between Non–High-Density Lipoprotein Cholesterol and Coronary Heart Disease

Javed Khurshed Shaikh, Shahbaz Ali Shaikh, Muhammad Hassan Butt, Muhammad Rafique Kanher, Muhammad Hashim Kalwar and Sarfraz Hussain Sahito

ABSTRACT

Objective: To study the association between lipoprotein cholesterol not of high density and stenosis of the coronary artery demonstrated by the coronary angiography**.**

Study Design: Prospective and cross-sectional study

Place and Duration of Study: This study was conducted at the National Institute of Cardiovascular Diseases Karachi from December 2019 to November 2020.

Materials and Methods: In three subsets, we compared the non-high-density cholesterol level and coronary heart disease. Spearman's correlation has been applied to analyze the correlated non-high-density cholesterol lipoprotein and coronary heart disease.

Results: The cholesterol -lipoprotein-high-density rate was higher in the group of coronary artery disorders compared with the group of the non-coronary artery ($P < 0.01$). The analytical correlation of Spearman demonstrated that a strong association between non-high-density lipoprotein and SYNTAX score ($r=0.071$, $P<0.001$; $r=0.316$, $P<0.001$) was observed. In multivariate logistic regression analysis, the indigenous predictor of coronary artery condition was non–high density lipoprotein cholesterol high density lipoprotein cholesterol ratio, (Odds ratio: = 3,645; = 2.096; 95% confidence interval; = 1.438–3.054).

Conclusions: The ratio of non–high-density lipoprotein cholesterol was associated with the severity of coronary artery disease, suggesting that it might be utilized as a biomarker.

Key Words: Non–High-Density, Cholesterol, Coronary Heart Disease

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INTRODUCTION

CAD is a major disease that endangers human health, impacts the quality of life and long-term prognosis of patients. Coronary artery disease (CAD) The occurrence and progression of CAD are supported by many variables. The main cause of heart disease is atherosclerosis. The major mechanisms of atherosclerosis include inflammation, oxidative stress, and endothelial dysfunction. And in the entire atherosclerosis process, inflammation plays a significant role[1]. Non-HDL-C is the sum of all serum atherogenic cholesterol, as stated in the third national cholesterol educational report, the second objective of the antiatherosclerosis process is to reduce non-HDL-C.[2] Nonstandard cholesterol (non-HDL-C) is antiatherogenic cholesterol. Earlier investigations have demonstrated that the risk of coronary heart disease is related to non-HDL-C[3,4].

The protein compound of HDL-C is 70 percent of the anti-inflammatory and antioxidant apolipoprotein A-I (apoA-II)[5], with a protective impact on the endothermal vascular cell, nitric oxide production, inflammatory mediator expressions, and the endothelium proliferation of cells[6,7]. In the formation of atherosclerosis, monocytes and macrophages are the principal pro-inflammatory cells and could be used to secret inflammatory substances in atherosclerosis production[8]. Research into inflammatory atherosclerosis biomarkers has been a popular issue in recent years based on the function of non-HDL-C, HDL-C, and monocytes in atherosclerosis. The non-HDL-C and highly dense were more convinced to predict the severity of coronary heart diseases, which are being given great attention by clinicians. The purpose of the study was to evaluate the connection of non-HDL-C with CAD gravity.

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MATERIALS AND METHODS

There were a total of 1460 patients registered and prospectively analyzed at the National Institute of

Cardiovascular Diseases Karachi from 1st December 2019 to 30th November 2020. CAD was identified. The control group was selected for 300 patients hospitalized for non-coronary artery disease and the three SYNTAX- subgroups were classed of 500 patients who were diagnosed with coronary arterial disease.

Exclusion criteria are various infectious diseases, blood therapy, severe anemia, operation and severe trauma within three months, autoimmune or immunosuppression, malignant tumor, hepatic and kidney disorder, preliminary myocardial infarction, previous coronary artery or coronary bypass grafting, cardiomyopathy and decompensated heart failure were not included.

Coronary angiography: Two competent cardiologists in our hospital conducted coronary angiography and analyzed the angiographical results. Coronary angiography was carried out by radial or femoral approach following the Judkin procedure. The degree of coronary artery stenosis, anterior down arteries, circumflex arteries, and the right coronary arteries were assessed.

SYNTAX score and group: The degree of CAD was measured using a SYNTAX grading method based on coronary angiography results. A novel tool to measure coronary artery diseases complexity is the SYNTAX Score. The SYNTAX score has been calculated with the website of the SYNTAX score. The results were sorted into three categories according to the scoring therapies: a moderate (<8), a moderate (8-15), and a serious (>15) group.

Laboratory measurements: In the morning, blood samples from the antecubitus have been gathered in our hospital (fasting for more than 10 hours). The blood cell counts, HDL-c, and other biochemical markers were measured using the biochemical analyzer. The ratio between the serum non-HDL-C level and the serum level was determined by non-HDL-C cholesterol minus HDL-C, and the MHR by the separation of the monocyte count by the monocyte count with HDL-C.

Statistical analysis: Statistical analysis was carried out with the Software SPSS Version 23.0. The continuous variables are reported as mean ± SD. The percentages for categorical variables were reported. The categorical variables between groups were compared with the μ2 trial. Univariate and multivariate logistical regression tests have been conducted to determine the independent CAD predictors. The results were assessed within a trust interval of 95 percent with a P-value of less than 0.05.

RESULTS

Table 1 indicated a reduced proportion of diabetes, high bloody blood pressure, males, and smokers in the control group. The CAD group was greater than the CAD groups, such as fast blood glucose, serum creatinine, triglycerides, hypersensitive C-reactive protein, white blood cell counting, monocyte counts, non-HDL-C.

The SYNTAX tertiary score groupings for coronary heart disease were separated into three groups. There are three groups compared non-HDL-C and MHR levels. The results indicated the greater non-HDL-C levels compared to the mild group ($P < 0.05$), while the smaller group, modest and severe groups had no important differences. The levels of MHR for the severe group were greater than in the mild and moderate groups, whereas the levels of MHR for the moderate group and the moderate group were not significantly differing ($p<0.05$).

Non-HDL-C and MHR with SYNTAX scores were analyzed with Spearman correlation. The results have indicated a favourable correlation between Non-HDL-C and SYNTAX (($r=0.071$, $P<0.001$; $r=0.316$, $P<0.001$).

We did multivariable logistic regression analysis with factors that exhibit statistically significant relationships in the univariate regression study to discover independent CAD predictors. The results showed that the C-reactive protein, non-HDL-C, age, smoking, diabetes, hypertension, and hypersensitivity might be considered as independent risk factors for CAD.

Table No.1: Basic clinical characteristics of the study participants (n = 800)

Variables	Control group n = 300	CAD group n = 500	P value
Age	57.18 ± 10.70	64.13 ± 11.53	0.679
Gender [man (%)]	209 (69.66%)	417 (83.4%)	0.000*
Smoking	94 (21.7%)	594 (40.1%)	0.014**
Diabetes	48 (12.5%)	151(30.2%)	0.000*
Hypertension	290 (96.6%)	343 (68.5%)	0.000*
FBG (mmol/l)	4.36 ± 1.20	5.36 ± 17.60	0.013**
Cr (mmol/l)	72.06 ±18.40	78.58 ± 32.34	0.001*
UA (mmol/l)	323.61 ± 96.65	363.01 ± 101.42	0.597
TC (mmol/l)	4.40 ± 1.00	4.25 ± 1.33	0.198
TG (mmol/l)	1.61 ± 1.13	1.56 ± 1.72	0.007*
HDL (mmol/l)	1.18 ± 0.29	1.07 ± 0.27	0.170
LDL (mmol/l)	2.68 ± 0.88	2.51 ± 0.94	0.599
ApoA-I (mmol/l)	1.20 ± 0.24	1.06 ± 0.25	0.677
Non-HDL-C (mmol/l)	3.21 ± 0.99	2.52 ± 0.88	0.317
hs-CRP (mg/l)	3.11 ± 7.52	8.20 ± 21.20	0.000*
WBC (10^9/l)	5.34 ± 1.98	6.50 ± 3.14	0.000*
MONO(10^9/l)	0.45 ± 0.15	0.53 ± 0.23	0.000*
LYMP (10^9/l)	2.65 ± 0.67	1.56 ± 0.6	0.000*
MHR	0.40 ± 0.20	0.53 ± 0.30	0.000*
Non-HDL-C	2.52 ± 0.88	2.71 ± 1.17	0.043**

Table No.2: Multivariable logistic regression analysis of independent factors for coronary artery disease (n = 800)

Variables	B	Wald	P value	OR	95% CI
Age	0.043	45.600	<0.01	1.044	1.039–1.071
Smoking	0.510	11.461	<0.01	1.741	1.272–2.664
Diabetes	0.671	16.363	<0.01	2.263	1.471–3.181
Hypertension	0.508	8.238	0.007	1.404	1.117–2.026
hs-CRP	0.034	4.081	0.024	1.024	1.003–1.046
MHR	1.183	6.755	0.016	3.545	1.267–10.486
Non-HDL-C	0.830	13.828	<0.01	2.086	1.438–3.054

DISCUSSION

The effect on the quality of life of the person is the high incidence and mortality of CAD. The process involves numerous mechanisms including oxidative stress, hypoxia, inflammation, vascular endothelial damage, pl atelet aggregation, etc. Atherosclerosis is a pathologic process. In the process of forming, developing, and breaking up the atherosclerotic plaque, activation of inflammatory cells and releasing of inflammatory factors play a major role. Monocyte activation is an essential step in atherosclerosis development[9]. During atherosclerosis, vascular endothelium damage, circulating monocytes stick to vascular endothelium and penetrate the wall of the blood vessel into macrophages which are transformed into foam cells by phagocytosis by oxidizing the LDL via scavenger receptors (LDL)[10].

Foam cells release proinflammatory cytokines, which can lead to the proliferation, migration, and development of plaques of vascular smooth muscle cells. Various cytokines act on hematological tissue during the formation and occurrence of atheroma and encourage the compensation for the proliferation of monocytes, and cause the increase of mononuclear peripheral cells of the blood. Peripheral blood monocytes are employed therefore as the source of tissue macrophages, and the quantity of foam cells represents plaque progression and can be used to prevent atherosclerosis from progressing[11]. The main risk factor of CAD is dyslipidemia. HDL-C plays its part in antioxidants by eliminating cholesterol from macrophages and preventing thrombosis[12]. In addition, the endothelial function and low viscosity of the blood of HDL-C are antiatherosclerotic[13]. Apo A-I is the principal component of HDL and is primarily involved in cholesterol transportation and has a key function in inflammatory and immunological regulatory action[14,15]. Duong pointed out that upon-I predominantly mediates the transport of intercellular cholesterol via ABCA1 on the cell membrane[16]. Furthermore, ApoA-I promotes acyltransferase of lecithin cholesterol, resulting in HDL particles maturing[17]. Studies have demonstrated that apoA-I may suppress cell and platelet death to carry out antitherosclerosis[18]. Therefore, studies have indicated the ability to ameliorate atherosclerosis and lower the risk of cardiovascular events by certain increasing serum HDL-C levels[19]. Non-HDL-C is the total of HDL-C excluding serum lipids. Many investigations have indicated that atherosclerotic cardiovascular disease has a major effect on the occurrence of incidents. A study reveals that asymptomatic cerebral artery stenosis is closely linked to non-HDL-C[20].

The study showed that the link between non-HDL-C levels and cardiovascular predicts and the risk of major cardiovascular events has increased in comparison to LDL-C objectives, with the increase in non-HDL-C levels following acute myocardial infarction[21]. It is therefore found that the amount of non-HDL-C for atherosclerotic cardiovascular disease is a major risk factor[22]. MHR is a significant indication and predictor for CAD and cardiovascular events based on the processes and function of monocytes and HDL-C in atherosclerosis.[23] Increasing MHR is connected with cardiovascular adverse events and is an automatic predictor of chronic renal illness and significant cardiovascular events, as proven by Kanbay and others. In Karataş et al.[24], the MHR has been connected with major cardiovascular adverse events and mortality, with 2.81 times the main cardiovascular adverse events, and the risk of death increases to 19.15 times in the higher group of MHRs, amongst the ST segments. Akboga et al[25] have demonstrated that MHR is linked to coronary atherosclerosis scale and SYNTAX scale in individuals with stable angina.

The higher the MHR, the better the score of SYNTAX is. Canpolat has confirmed that high levels of MHR could represent increased inflammation and oxidative stress and that MHR is closely linked to sluggish coronary flow[26]. MHR additionally has been identified as an independent predictor of recurrence following the removal of atrial fibrillation from radiofrequency[27]. The SYNTAX score for measuring the amount of CAD and severity of arterial stenosis is an anatomic integrated system based on coronal angiography. There are now fewer MHR and CAD gravity investigations and they are smaller sample studies with a single center. The results demonstrated a positive association between scores of MHR and SYNTAX. The greater the MHR, the higher the score for SYNTAX, and the more severe the coronary stenosis were discovered.

Multivariate logistic regression study has shown MHR to be an autonomous CAD risk factor. In our investigation, the CAD scale also was added to the non-HDL-C. Our findings have shown that the increase in

the score of SYNTAX is greater with the increase of non-HDL-C levels. The logistic regression study of the multivariate system has shown that non-HDL-C was also an independent coronary heart disease risk factor. The use of non-HDL-C and MHR to measure the severity of the easy, quick, economic, and less inflammatory effect of other inflammation markers, like White Blood Cells and C-Reactive Protein, in clinical practice. To conclude, the biomarker of inflammatory response that is close to the severity of CAD and artery stenosis can easily be obtained from non- HDL-CI and MHR, which can be an independent risk factor for CAD. It should be stressed in clinical practices the importance of non-HDL-C and MHR. The diagnosis and prognosis of CAD patients might be enhanced by early detection.

CONCLUSION

This study showed that non-HDL-C and CAD are significant to SYNTAX scores and that the potential for the detection of the severity of coronary atherosclerosis is easily measured, and is inexpensive. The identification of patients with CAD may be part of a cardiovascular assessment. However, large-scale and forward-looking trials remain necessary for the predictive utility of non-HDL-C and MHR, particularly in CAD patients.

Author's Contribution:

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Conflict of Interest: The study has no conflict of interest to declare by any author.

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Original Article

Etiology and Outcomes of Post-Partum Acute Kidney Injury: A Hospital Based Cross Sectional Study

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ABSTRACT

Objective: This study is designed to determine various risk factors, causes and outcome of Post-Partum Acute Kidney Injury in a tertiary care hospital of Pakistan.

Study Design: Cross sectional / descriptive study

Place and Duration of Study: This study was conducted at the Nephrology Department and MCH Center of PIMS Islamabad from January 1, 2018 to December 31, 2019.

Materials and Methods: 60 patients were included in this study who were previously healthy and developed acute kidney injury in Post-Partum period. A rise of $\geq$ 0.3mg/dl in serum creatinine or urine output $\leq$ 0.5ml/kg/h for 6 hours is defined as Acute Kidney Injury. Detail history was taken though a predesigned form to explore risk factors and causes. Cause of AKI was established though history, through examination and laboratory investigations as required. Course of disease and management was also reviewed. Patients were followed up for 3 months to see disease outcomes. Return to normal renal function was labelled as complete recovery while impaired renal function beyond 3 months during follow up was labelled as CKD.

Results: In our study Puerperal sepsis was the leading cause of post-partum AKI in 35 (58.3%) patients. Second leading cause of PPAKI was pre-eclampsia /eclampsia in 8 (13.4%) patients followed by DIC in 7 (11%) patients and Ante-partum/Post-Partum hemorrhage in 6 (10%) patients. Patients with HELLP were 3 (5%) and HUS 1 (1.6%). Out of 60 patients 12 (20%) patients responded to conservative management while 48 (80%) patients required hemodialysis. During follow up 41 (68.3%) patients achieved complete recovery of renal functions, 15 (25%) patients had partial recovery of renal function and labelled as chronic kidney disease (CKD) while 3 (5%) became dialysis dependent and labelled as ESRD. 1 (1.6%) patient expired during hospital stay due to sepsis.

Conclusion: In our study puerperal Sepsis is the most common cause of Post-Partum Acute Kidney Injury.

Key Words: Acute kidney injury (AKI), Pregnancy, puerperal sepsis

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INTRODUCTION

Pregnancy related acute kidney injury (PRAKI) is a major challenge in healthcare system worldwide and is a burden in tertiary care centers carrying high mortality and morbidity[1]. Post-partum acute renal injury (PPAKI) is a major contributor of pregnancy related acute kidney injury which accounts 26-70 percent of total cases of obstetric related AKI[2].

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The incidence of this entity has decreased in developed countries due to good maternity care, health facilities and patient education[3]. In developing countries it is common due to lack of adequate healthcare facilities, poverty and low literacy rate[4]. The main causes of post-partum acute renal failure includes pre-eclampsia/eclampsia, HELLP syndrome, ante-partum hemorrhage, post-partum hemorrhage, puerperal sepsis, disseminated intravascular coagulation (DIC)[5].

Spectrum of etiology of post-partum acute kidney injury is different in developing and developed countries. In developing countries puerperal sepsis is most common cause due to septic abortions, poor maternity care and home deliveries by untrained dies while in developed counties thrombotic microangiopathies (TMAs) are common[6,7].

Acute kidney injury during pregnancy and presentation of previously undiagnosed chronic kidney disease in form of acute kidney injury is also common in clinical setting. Progression of CKD is also accelerated during pregnancy by various pathophysiological mechanism[8]. Pre-existing comorbidities especially hypertension and

diabetes are considerable risk factors for developing AKI during pregnancy[9,10]

Diagnosis of postpartum AKI can be made clinically and by biochemical laboratory results according to KDIGO Guidelines; ≥ 0.3mg/dl increase in serum creatinine from baseline value or ≤ 0.5ml/kg/h urine output for 6 hours. While renal biopsy may be required in selected undiagnosed cases[11].

Post-partum AKI requires aggressive management by multidisciplinary team. Patients may require intensive care unit (ICU) admission and hemodialysis. PPAKI is mostly reversible if treated properly. But unfortunately may lead to chronic kidney disease and Renal Replacement Therapy (RRT) dependency. She H et al reported 37 patients of PPAKI from China. Out of 37 patients 26(70.3%) required ICU and 20 patients required dialysis during hospital stay. 30(81.1%) patients gained normal renal functionss, 1(2.7%) patient gained partial recovery while 1(2.7%) patient became dialysis dependent. 5 patients lost follow up[12].

Identifying the cause of PPAKI and appropriate management is key to achieve good outcomes. Causes of PPAKI are different in different countries. Its causes may also vary in different communities and areas of a same country. Spectrum is also in process of continuous change with improvement of healthcare facilities and literacy rate. So local and recent data is important to manage this clinical challenge.

This study is designed to determine various risk factors, causes and outcome of PPAKI in a tertiary care hospital of Pakistan.

MATERIALS AND METHODS

This cross sectional descriptive study was done after approval of Ethical Review Board of Shaheed Zulfiqar Ali Bhutto Medical University/PIMS Islamabad.

Patients were selected according following criteria;

Inclusion criteria: previously healthy patients who developed AKI in postpartum period.

Exclusion criteria: Patients with known history of renal impairment, diabetes, hypertension, glomerular disease, connective tissue disease, stone disease or previous history of AKI were excluded.

After taking written consent detailed history (age, education and financial status, parity, obstetrical history, history of bleeding, shock, time of stop of urine output) was taken from patients through a predesigned form. They were thoroughly examined and laboratory investigation (complete blood count with peripheral film, Renal and liver functions, serum electrolytes, urine analysis, urine, blood, vaginal and cesarean wound swab culture, bleeding profile, FDP, D Dimer, ultrasound abdomen) were performed to establish a diagnosis.

AKI was defined according to KDIGO (Kidney Disease Improving Global Outcomes) guidelines; a rise of ≥ 0.3mg/dl in serum creatinine or urine output ≤ 0.5ml/kg/h for 6 hours.

Disease course and management (Number of days of hospital stay, requirement of dialysis, need of ICU) was also reviewed. Patients were followed up for 3 months to see disease outcomes. Return to normal renal function was labelled as complete recovery while impaired renal function beyond 3 months during follow was labelled as CKD or partial recovery. Permanent dialysis dependency was labeled as End Stage Renal Disease (ESRD).

RESULTS

Total 60 patients with postpartum AKI were included according to selection criteria. Majority of patients 34 (56.6%) were within age limit 21-30 years. 42 patients (70%) had parity of 3. Of the patients 43 (71.6%) were non-booked and 17(28.3%) were booked. Patients belonged to rural areas were 39 (65%) whereas 21 (35%) were from urban areas. Patients with no formal education were 28 (46.6%), primary education were 12 (20%), middle 10 were (16.6%) and matric or above were 10 (16.6%). Patients belonged to poor socioeconomic status were 48 (80%) having less than 20,000 Rupees income per month. There demographic characteristics are shown in table No. I.

Out of 60 patients, 43 (71%) required cesarean section delivery, 10 (16%) had vaginal delivery and 7 (11%) required evacuation of retained products of conception (ERPC) secondary to incomplete miscarriage

Puerperal sepsis was found to be most common cause of Acute kidney injury in 35 (58.3%) patients, among these 35 patients 27 had cesarean section, 6 had vaginal delivery and 2 had ERPC. Second leading cause of PPAKI was Pre-eclampsia/eclampsia in 8 (13.4%) patients followed by DIC in 7 (11%) patients and Ante-partum/Postpartum hemorrhage in 6 (10%) patients. HELLP was diagnosed in 3 (5%) patients and HUS was found in 1(1.6%).

Table No.1: Demographic detail of patients

Demographic detail		**No of women**	**%age**
Age	21-30 years	34	56.6%
	31-40 years	26	43.3%
area	Rural	39	65%
	Urban	21	35%
income	<20,000	48	80%
	>20,000	12	20%
Education	Uneducated	28	46.6%
	Primary	12	20%
	middle	10	16.6%
	Matric and above	10	16.6%

Patients who stayed more than 7 days at hospital were 49 (81%). Out of all the patients, 12 (20%) patients

responded to conservative management while 48 (80%) patients required hemodialysis. During follow 41 (68.5%) patients achieved complete recovery of renal functions, 15 (25%) patients had partial recovery of renal function and labelled as chronic kidney disease (CKD) while 3 (5%) became dialysis dependent and labelled ESRD. Unfortunately 1 patient (1.6%) expired due to sepsis during hospital stay.

DISCUSSION

The incidence of postpartum AKI in developing countries is very high, mainly due to lack of availability of antenatal care, Die handling and delayed referral of pregnancy related complications like obstructed labour, abruption, eclampsia, antepartum hemorrhage and postpartum hemorrhage.

Puerperal sepsis is the most coommon cause of post-partum AKI in our study which is 58% of total patients. Puerperal sepsis is mainly due to retained products of conception, handling by unskilled birth attendant/Dies in the rural areas, obstructed labour and infected cesarean section. Sepsis leads to AKI by various mechanisms. Sepsis causes generalized vasodilatation and renal hypoperfusion which leads to AKI.

Our results are compatible with results of studies conducted in other developing countries of Asia and Africa. Sepsis is found to be the most common cause of PPAKI in developing counties which is probably due to poor healthcare system. A similar study conducted in India reported sepsis as leading cause of PPAKI. Sepsis was found 70% causes of post-partum AKI, followed by DIC 55.5%, pre eclampsia/eclapmsia 40.7% and postpartum hemorrhage 40.7%[13]. Goplani et al noted puerperal sepsis as the most common etiology of postpartum AKI in 61% of women[14].

Unlike the developing counties, studies conducted in developed countries shows a quite different spectrum. TMAs, Pre-eclampsia/ eclampsia, HELLP and hemorrhage are more prevalent in these counties. Meibody F. et al conducted a similar study in France which explored pre-eclapmsia as the most common cause of AKI in 38% patients followed by Postpartum hemorrhage 31% and thrombotic microangiopathy in 13.3% patients[15]. A study conducted in Brazil reported causes of AKI as; pregnancy induced hypertension (PIH) in 41.8% , HELLP syndrome in 40%, Puerperal sepsis in (14.5%), placenta abruption in (9.1%) and HUS (9.1%)[16]. In a study conducted in China hemorrhagic shock (31%) and severe pre-eclampsia (18%) was found to be the most common cause of post-partum AKI[17].

Khattak et al studied pregnancy related renal failure in Pakistani population. He described causes of pregnancy related AKI, not specifically post-partum AKI. In this study, sepsis was the most common cause of pregnancy related AKI in Pakistani population (31.8%)[18].

In our study 80% patients required hemodialysis which was compatible to data from India. In an Indian study 92% patients of PPAKI required hemodialysis. In our study 68.5% patients achieved complete recovery of renal functions while in Indian study 40% of patients reached to complete recovery. In our study 5% of patients became Dialysis dependent while 7% patients in the respective study[13]. Mortality was found quite low (1.6%) in out setup comparing with Indian study where mortality was 18.5%.[13]

In our study, PPAKI is more common in low economical group (80%), in patients belonging to rural areas (65%) and uneducated group (46.6%), it is probably due to lack of health awareness in population lack affordability and accessibility to medical facilities. But these demographic characteristics are not studied in other similar studies to best of our knowledge.

CONCLUSION

Sepsis is the most common cause of post-partum AKI in our study which is due to poor maternal care. These facts emphasize to improve healthcare system in Pakistan.

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