Original Article

CKP are Diagnosing Renal Failure

Elevated Levels of Serum Creatine Phosphokinase as a Marker for Diagnosing Renal Failure and Rhabdomyolysis due to Para Phenylene-Diamine (PPD) Poisoning

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ABSTRACT

Objective: To determine the clinical lab diagnostic accuracy for renal failure and rhabdomyolysis due to paraphenylene-diamine (PPD).

Study Design: Non-experimental cross-sectional study

Place and Duration of Study: This study was conducted at the Department of Forensic Medicine, Foundation University Medical College, Islamabad from Jan-Dec 2018.

Materials and Methods: Data was analyzed on SPSS version 20. Chi-square test was applied for the analysis of qualitative variables. Two tail tests were applied for quantitative variables. Frequencies with percentages mean with standard deviation and median with inter-quartile range was given for quantitative data. P-value < 0.05 was considered significant. Exclusion criteria include patient with mixed disease history or having medical co-morbidities were excluded from this study

Results: In the present study, 658 cases of Kala Pathar poisoning were diagnosed and treated. M: F ratio is 5:20. There were 518 (78.8%) females and 139 (21.2%) males. Majority of the female patients were married 488 (78.0%). Most common clinical manifestations include marked facial edema; dysphagia and stridor. Post complications include Rhabdomyolysis and acute renal failure which develop after two to five days. Initial lab investigations within 6-8 hours after ingestion showed marked increase in TLC count, SGPT and Na^+ ions. There is decrease in K^+ & HCO_3 ions. There is marked elevation of serum creatinine kinese (CK) after 24 hours.

Conclusion: 'PPD poisoning is more common in females of younger age group belonging to rural areas. Early diagnosis and prompt supportive treatment can save many lives. There is no specific antidote available.

Key Words: Para Phenylene Diamine, acute renal failure.

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INTRODUCTION

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Serum Creatine Kinase (CK) or Creatine Phosphokinase (CPK) is an enzyme primarily found in muscle tissue. It catalyzes the conversion of creatine into phosphorcreatine and adenosine-triphosphate (ATP) into adenosine diphosphate (ADP).

This reaction is reversible and thus phosphocreatine serves as a rapidly available source of ATP when muscle is stressed or inflamed[1]. When the poison damages the muscle membrane (sarcoplasmic membrane), it becomes permeable and releases the myocytic enzymes like lactic dehydrogenase (LDH), creatine phosphokinase (CPK) and aspartate aminotransferase (AST) into the bloodstream[2]. Extraneous exercise, running or accidental injuries to the muscles damages the sarcoplasmic membrane that releases the muscular enzymes in to the blood results in high levels of creatine phosphokinase (CPK). Most of these patients are either sports man or victims of Road traffic accidents. These patients are usually referred to rheumatologists to evaluate any idiopathic

inflammatory myopathy (IIM) [3]. However, it was also found that in certain cases of poisoning the levels of CKP are also very high. Such poisons causes direct damage to the myocites. These include snake bite and ingestion of Hair dye (Paraphenylene-diamine) [4].

Paraphenylenediamine (PPD) poisoning is an emerging problem of developing African and South Asian countries[5]. It is a main ingredient of hair dye formulation marked with the name of 'Kaala Pathar' and easily available in market at a low cost. It is available in the form of powder or crystals. It is used as hair dye to enhance the color of hair when mixed with henna. Para phenyl Diamine (PPD) is brown or black color substance highly toxic, insoluble in water but easily soluble in hydrogen peroxide. PPD is a coal-tar derivative which on oxidation by cytochrome P450-peroxidase produces Brondrowski's base having allergenic, mutagenic and highly toxic properties. PPD avtivates type -4 hypersensitivity reaction, capillary leaking, anaphylactic reactions and cellular damage to nephrons and hepatocytes [6]. This poison produces highly toxic effect on respiratory, hepatic, renal and cardiac systems by inhibiting cellular oxidation and also effect on muscles. It causes rhabdomyolysis, laryngeal edema, severe metabolic acidosis and acute renal failure[7].

PPD is used in industry of making tattoo marks over body, fabrics, dark makeup and printing inks[8]. The incidence of suicide with household items is increasing every year. Most common incidences of suicide were reported in low socioeconomic countries[4-6].

The clinical manifestations include edema of the face, neck, pharynx, tongue and larynx initially within 6-8 hours of ingestion. Post symptoms include angioneurotic edema, rhabdomyolysis. It produces very devastating effects on different systems leading to acute renal failure, respiratory acidosis and hepatic failure. Its toxicity depends upon the quantity of dose ingested. When taken orally, death may occur within initial 6-24 hours due to angioneurotic edema[9].

MATERIALS AND METHODS

It was a non-experimental cross-sectional study. In this study we compared test's classification of a diagnosis with a normal non diseased population standard's classification of lab test and clinical manifestations in a population of two districts of KPK and Punjab. The study was conducted at District Head Quarter (DHQ) Hospitals of two districts of South Punjab Bakkhar, DG Khan and one from district of KPK i.e. DI Khan. Data collected from Jan-Dec 2018. A total of 658 cases of PPD (kala pathar) presented to emergency department over a period of 1 year. The ratio of male and female cases was 5:20 respectively and age range of both the genders was 15-30 years. Prior to the analysis, collected data was subjected to Kolmogrove Simonov normality test. The demographic statistics included gender, age, and socioeconomic status, mode of administration, intention and amount ingested. Information about treatment, discharge and mortality within first 48 hours was recorded. The clinical lab findings were correlated with clinical manifestations. Data was analyzed on statistical package for social sciences (SPSS) version 20. Chi-square test was applied for the analysis of qualitative variables. Two tail tests were applied for quantitative variables. Frequencies with percentages mean with standard deviation and median with inter-quartile range was given for quantitative data. P-value < 0.05 was considered significant. Exclusion criteria include patient with elevated levels of CPK due to acute and chronic myopathies, accidental crush injuries and Road traffic accidents were excluded from this study.

RESULTS

In the present study, 658 cases of Kala Pathar poisoning were diagnosed and treated. There were 518 (78.8%) females and 139 (21.2%) males. Their age range was from 5 - 59 years, in adults average age was 21 ± 6 for females and 35 ± 3 for males. 33 (5.0%) were children (5-12 years). In adults, median age was 21.0 (IQR 4) years. Among children, there were 22 (68.7 %) males and 11 (33.3%) females. The results were opposite to that found in adults. The majority female victims were adult i.e. 507 (81.1%), and 117 (18.7%) were males. (Table I).

The Poison was taken orally by all patients (n=658). Majority of the female patients were married 488 (78.0%) The socioeconomic status of all the presented cases was below average. The intention of suicide was determined. 499 (98.2%) females and 101 males use it either as exhibitional poison or with the intention of suicide.

Table No.1: Demographic characteristics of the patients

Gender	Poisoning due to Para Phenylene Damine (PPD)	
	Children (5 >12 years)	Adults
Male	22 (68.7%)	117 (18.7%)
Female	11 (33.3%)	507 (81.1%)

Clinical manifestations include marked edema of face; dysphagia and stridor are the early presenting complaints. Rhabdomyolysis, hepatic damage, neuropathy and acute renal failure were developing after two to five days. Urine examination showed albinuria and haemoglobinuria. Survival rate is subject to early performance of gastric levage, hemo-perfusion and symptomatic treatment. Out of 668 case 581 arrived within 2 hours of ingestion.

Initial lab results showed decrease in Hemoglobin <11.9 ± 2.2 gm/dl, increase white blood counts of >14000 ± 2000g/dl, platelet counts ±>

422,000; serum glutamate-pyruvate transaminase (SGPT)> ± 229 IU/L, increase Sodium 141 mmol/L, decrease Potassium 3.4 mmol/L, decrease Bicarbonate ± 24.2 mmol/L. Serum creatinine phosphokinase (CPK) ± 1200U/L after 24 hours. Arterial blood gas (ABGs) analysis showed partial pressure of oxygen 121 mmHg, carbon dioxide 33.90 mmHg and pH of 7.41 (Table -2) Chest X ray done was unremarkable.

Table No.2: Clinical Features and outcome of Kala Pathar poisoning

Clinical Features	N=658 (%)
Pain in Throat	416 (63.2%)
Oral Erythema	376 (57.1%)
Cervicofacial Edema	658 (100 %)
Dysphagia	317 (48.1%)
Dysphonia	416 (63.2%)
Difficulty in Opening of Mouth	311(47.6%)
Muscle Aches/Rigidity	100 (15.1%)
Dark urine	134 (20.3%)
Rhabdomyolysis	309 (46.9%)
Oliguria/Anuria	405 (61.5%)
Acute Renal Failure	406 (61.5%)
Hyperkalemia	303 (47.8%)
Hepatitis	314 (48.1%)
Hemodynamic shock	203 (30.8%)
Sinus bradycardia	103 15.6%)
Sinus tachycardia	213 (32.3%)
Outcome	N (%)
Tracheotomy	324 (49.2%)
Ventilator	212 (32.2%)
ICU stay (days)	6.43±3.61
Mortality	06 (37.5)

On examination of victims, arrived within 2 hour of ingestion have marked puffiness on face and neck. After 8 hours patient was vitally unstable, heart rate 150-160/min, gradual fall in blood pressure systolic 90-100 mmHg and diastolic 50-60 mmHg, hyperventilation rate 35-40/min, and slight raise in temperature 38.8°C.Neurological examination include Glasgow Comma Scale (GCS) 11 ±2 /15 and diminished muscle reflexes. There was an average loss of power 3/5 in upper limb whereas, 1/5 in lower limbs. Sensory system was intact.

Clinical lab diagnostic accuracy was determined after 6-8 hours showed marked hemolysis [Hb 8.5 ±1.6 gm/dL (12.1-15.1 gm/dL)], low levels of potassium (K) [2.2 ± 1.1 mEq/L (3.5-5.2 mEq/L)], raised creatinine (CPK) 1200±2U/L (22-198 U/L), raised WBC that is 15.6 ±1.7 (4.0-10.0×109/L), increased SGPT (Table-3).

289 (44%) cases respond to symptomatic treatment when given within initial 12 hours of ingestion. Common complaints include anxiety, generalized pain and marked facial swelling. Patients were managed with anxiolytics (bromazepam) to relief anxiety, transfusion of glucose and i/v electrolytes for correcting electrolyte imbalance and forced alkaline dieresis to avoid renal failure. These procedures were performed within 6 hours of admission. Fluid input and output chart was maintained. Anti histamines were given along with steroids for hypersensitivity as most patients present with cervico-facial edema.

Table No.3: Laboratory parameters

Laboratory parameters	Mean + SD	Normal Range
TLC (4.0-10.0×109/L)	15.6 ±1.7	4.0-10.0×109/L)
CPK (U/L)	1200 ± 200	22 – 198
AST (U/L)	1365.18 ± 1186.28	10-40
ALT (U/L)	851.19±1604	7-56
Serum creatinine (mg/dL)	1.98± 1.6	0.50-1.2

The patients were kept under observation for 2 days. If symptoms persist and lab investigations showed raised CPK level and urine color changes to brown turbid then it is a diagnostic for the parphenyl Diamine such patients then referred to tertiary care Hospitals for Hemodilaysis to avoid ARF. Catheterization in the emergency department reveals dark brown urine. There is no specific antidote for PPD.

The mortality rate is quiet high. On average survival rate is less than 20% (n=119). The median for duration of stay in the hospital was 7± 2 days (inter-quartile range=6.45). Out of 518 female patients with 26 (5.0%) had a pregnancy. 44 (8.6%) had left the hospital against medical advice.

DISCUSSION

The levels of many muscle enzymes such as serum lactic dehydrogenase (LDH), creatine phosphokinase (CPK), and aspartate transaminase (AST) increases in the main blood stream after myocardial infarction. Their elevated levels can help in diagnosis and quantification of infarct size[10]. Similarly elevated CPK levels and marked cervico-facial edema can also help in early diagnosis of PPD poisoning 658(100%) [11]. The primary differential diagnosis for the elevated CPK levels is the snake bite poisoning 234(34%), paraphenylene-diamine (PPD) poisoning (23%) and muscular diseases of unknown origin known as idiopathic inflammatory myopathies (IIMs) 445(52%)[12,13,14].

During the last decade, there has been a remarkable increase in the misuse of PPD[15]. Most of the cases reported from low socioeconomic rural areas located in southern districts of Punjab and KPK[4-6]. Almost in all cases of the adult, victim uses it with suicidal intention[16]. The poison is cheap and easily available. It has salty taste in contrast to most of the poisons with bitter taste that is why it has become third most popular

suicidal poisons among young females [17]. In current study 517 victims were females and out of them 488 (78%) females were married; this indicate that the problem was more linked with family disputes and low socioeconomic status. The chemical composition of kala-pathar is Para-phenylen-diamine, Sodium ethylene, Diamine tetra acetic acid and Propylene glycol. These compounds are harmful for kidneys and liver. The metabolites cause renal tubular necrosis leading to hyper kalemia and raised SGPT[11]. The toxicity of Para-phenylene-diamine is dose dependent with estimated lethal dose of oral 0.5g- 0.8g/kg or 7–10 grams/daily[18].

In 241(37.5%) cases PPD causes unconsciousness leading to coma; in another two studies done in 2011 and 2014 percentage was 20 and 26.3%[6-13]. Hemolysis, acute septicemia and myocarditis might be the underlying cause. Hyperkalemia in 12.5% patients was observed[14]. Hyperkalemia was noted to be 20% and 26.3% patients in another study [13-14]. Rhabdomyolysis and Acute Renal Failure (ARF) may be cause of hyperkalemia. Skeletal muscle fatigue was evident in 62.4% patients in our study due to rhabdomyolysis. ARF occurred in 37.5% of patients whereas in study done on the same population in 2011 and 2014 indicates 47.4% and 40 %.[6, 13]. We also found that the ALT a markers of hepatitis was significantly higher in our patients. Acute renal failure (ARF) develops as a consequence of tubular necrosis. ARF developed only in patients who ingested more than 100ml of kala-pathar. Cervico-facial edema was not dose dependent it was present in all victims[19]. CPK levels were 642, 410, and 271 above baseline on days 4, 7, and 10 after the exercise due to muscle break down[20]. These levels were much lower than found in our study. In another study CPK level was 1200 ±2.2 in 324 (39.2%) patients. These patients ingested with suicide intention and underwent tracheotomy to clear airway obstruction. Angioedema, Dysphagia, Rhabdomyolysis was observed in more than 60% of the patients[18-20]. We believe that elevated levels of CPK is a good a reliable indicator for diagnosing PPD poisoning in for young patients admitted with ARF and marked Cervico-facial edema.

CONCLUSION

High index diagnostic indicators such as Hyperkelemia, increase ALT and CPK are the diagnostic indicators in cases presented with clinical features such as dysphagia, angioedema, rhabdomyolysis and acute renal failure. There is no specific antidote for PPD and treatment is supportive. Supportive treatment may be helpful such as tracheotomy and alkaline dieresis for preventing choking and renal failure. It is recommended that more such findings should be published in peer reviewed journals, so they could influence the authorities. It is suggested that sale of Kala Pathar should be legally restricted by government.

Author's Contribution:

Concept & Design of Study:	Yasmin Aamir
Drafting:	Anwaar Ahmed, Farooq Ahmed Abro
Data Analysis:	Rizwan Zafar Ansari, Muhammad Arslan Javed, Javed Iqbal Khokhar
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Conflict of Interest: The study has no conflict of interest to declare by any author.

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