Original Article

Effectiveness of Oral Zinc Sulphate in Reducing the Serum Bilirubin Level in Neonates Having Unconjugated Hyperbilirubinemia

Muhammad Sarfraz Alam, Ubaid Ullah Khan, Mimpal Singh and Hamid Raza

ABSTRACT

Objective: To determine the effectiveness of oral zinc sulphate in reducing the serum bilirubin level in neonates having unconjugated hyperbilirubinemia.

Study Design: Randomized Control Trial study.

Place and Duration of Study: This study was conducted at the in Neonatal Unit Paediatric Medicine Unit II Mayo hospital Lahore in one year from January 2019 to December 2019.

Materials and Methods: Total 100 neonates (50 patients in each group) were enrolled by non-probability, consecutive sampling. Study population was divided in to two groups. Baseline serum bilirubin level was measured of each neonate included in study. Group A was given oral zinc 10 mg / day in once daily dose orally in suspension form. Total serum bilirubin was measured after every 24 hours in both groups. Percentage reduction in total serum bilirubin level was measured on 3rd and 5th day with baseline serum bilirubin of each neonate and results were compared among both groups. The neonates having total serum bilirubin in phototherapy zone in both groups were given phototherapy. Duration of phototherapy was compared between groups. Data was entered SPSS-20. Comparison of two groups, placebo group and zinc sulphate apply independent sample t-test. P-value ≤ 0.05 was taken as significant.

Results: After 24 hours phototherapy, the mean indirect bilirubin of group A patients were 13.50±3.68 mg/dl whereas the mean indirect bilirubin of group B patients was 12.35±3.77 mg/dl. After 48 hours the mean indirect bilirubin of group A patients were 10.99±3.19 mg/dl whereas the indirect bilirubin of group B patients was 10.35±2.94 mg/dl. After 72 hours the mean indirect bilirubin of group A patients were 9.30±2.99 mg/dl whereas the mean indirect bilirubin of group B patients was 9.35±3.33 mg/dl. Similarly, after 96 hours the mean indirect bilirubin of group A patients were 9.33±2.58 mg/dl whereas the mean indirect bilirubin of group B patients was 9.60±0.75 mg/dl. Regarding indirect bilirubin at follow up, there was statistically insignificant difference between the study groups i.e. p-value>0.05. The median duration of treatment in group A was 3.00 days (range=2-4) while in group B was 2.50 days (range=2-4). The difference was insignificant (p>0.05).

Conclusion: Oral zinc sulphate has no effect in reducing the total serum bilirubin level in full term and near term neonates having unconjugated hyperbilirubinemia.

Key Words: Unconjugated Hyperbilirubinemia, Neonates, Serum Bilirubin, Zinc Sulphate

Citation of article: Alam MS, Khan U, Singh M, Raza H. Effectiveness of Oral Zinc Sulphate in Reducing the Serum Bilirubin Level in Neonates Having Unconjugated Hyperbilirubinemia. Med Forum 2021;32(5):40-43.

INTRODUCTION

Unconjugated hyperbilirubinemia can result from increased production, impaired conjugation, or impaired hepatic uptake of bilirubin, a yellow bile pigment produced from hemoglobin during erythrocyte destruction.

[1.] Department of Pediatrics Unit-II, King Edward Medical University, Lahore.

Correspondence: Dr. Mimpal Singh, Assistant Professor of Pediatrics Unit-II, King Edward Medical University, Lahore.
Contact No: 0333-4229251
Email: singh.ms1437@gmail.com

Received: November, 2020
Accepted: February, 2021
Printed: May, 2021

Nearly sixty percent of full term or near term newborn develop jaundice in 1st week of life.[1] The main purpose of treating jaundice in neonates is to prevent encephalopathy caused by bilirubin and its sequela. Neonatal jaundice has mainly been treated by phototherapy and exchange transfusion but both treatments have many complications. But the later poses more threats which may include graft versus host disease and even death. [2]

Many researchers have done different studies to establish a relationship between micronutrients and their role in reducing neonatal jaundice by decreasing the absorption of zinc through enterohepatic circulation, which showed different results[5]. Zinc is an essential micronutrient for growth of neonate. Different studies both on humans and animals have shown the role of zinc in reducing total serum bilirubin and duration of phototherapy in neonatal jaundice.[3] Zinc lowers the

bilirubin levels by inhibiting the normal enterohepatic circulation of unconjugated bilirubin by binding with it.[4] Mendez et al. proved the role of zinc in decreasing the serum bilirubin in hamsters with Gilbert syndrome.[4] Hashemian S et al. had reported that administration of oral zinc sulfate decreases the duration of phototherapy and total serum bilirubin in neonates having neonatal jaundice.[5] Mafinejat et al. from lran reported that administration of zinc sulfate neither affected hyperbilirubinemia nor delayed appearance of jaundice. However, fewer admissions and phototherapy duration was reported in the zinc group.[6] Ashok et al. studied the role of oral zinc in idiopathic neonatal jaundice and concluded that oral zinc is not effective in management of idiopathic neonatal jaundice[7]

The objective of this study was to determine the effectiveness of oral zinc sulphate in reducing the serum bilirubin level in neonates having unconjugated hyperbilirubinemia. We hypothesized that oral zinc sulphate has no role in reducing the total serum bilirubin level in full term and near term neonates having unconjugated hyperbilirubinemia.

MATERIALS AND METHODS

This randomized control trial was conducted in Neonatal unit Paediatric Medicine Unit II Mayo hospital Lahore in one year. Total 100 neonates (50 patients in each group) were enrolled [estimated by using 5 % level of significance and the power of test as 90% along with expected mean value of bilirubin 10.3+-2.09 with zinc sulphate and 11.9+- 1.74 with placebo group] by non-probability, consecutive sampling. Neonates with age 24 hours-28 days of both sexes, weight more than 2500 g, full term or late pre-term neonates with unconjugated hyperbilirubinemia within phototherapy zone, physiological jaundice without identifiable cause in phototherapy zone were included. Rh and ABO incompatibility, hypoxic ischemic encephalopathy grade III, and sepsis were excluded.

Based on inclusion criteria sample was taken from admitted patients of Neonatology unit of Paediatric Medicine Unit 2 of Mayo hospital Lahore. First of all, informed written consent was taken from the parents of the patients. Study population was divided in to two groups i.e group A and group B by computer generated random table number. Baseline serum bilirubin level was measured of each neonate included in study. Group A was given oral zinc 10 mg / day in once daily dose orally in suspension form. Total serum bilirubin was measured after every 24 hours in both groups. Unconjugated hyperbilirubinemia was defined as unconjugated serum bilirubin level more than 80% of total serum bilirubin. Percentage reduction in total serum bilirubin level was measured on 3rd and 5th day with baseline serum bilirubin of each neonate and results were compared among both groups. The neonates having total serum bilirubin in phototherapy zone in both groups were given phototherapy of a standard wavelength 460-490 nm and at a distance of 40 cm. Duration of phototherapy required for the baby to out of phototherapy zone was measured and comparison was made with placebo group.

Data was entered SPSS-20. Quantitative variables like age was presented as mean ± SD. Qualitative variables like gender was presented as frequency and percentages. Comparison of two groups, placebo group and zinc sulphate apply independent sample t-test. P-value ≤ 0.05 was taken as significant.

RESULTS

In this present study, total 100 neonates were enrolled. The mean age of the neonates was 6.85±4.32 days. Mean age of the neonates in group A was 6.64±4.402 days whereas the mean age of neonates of group B was 7.06±4.28 days. Mean value of gestational age of the neonates was 36.93±0.902. Mean value of gestational age of neonates in group A patients was 36.92±0.922 weeks whereas the mean value of gestational age of the mothers in group B patients was 36.94±0.890 weeks. Mean weight at admission of neonates was 3.284±2.53 kg with minimum and maximum weights of 2.5 & 4.0 kg respectively. Mean weight at admission of group A patients was 3.578±3.55 kg whereas the mean weight at admission in group B patients was 2.99±0.43 kg.

Test of normality was applied and normality of indirect bilirubin level was tested. P-value of Shapiro-Wilk test was insignificant showing that data is following normal distribution. So mean±SD was calculated for indirect bilirubin level and independent samples t-test was applied to check significant difference between groups. According to this study after 24 hours phototherapy, the mean indirect bilirubin of group A patients was 13.50±3.68 mg/dl whereas the mean indirect bilirubin of group B patients was 12.35±3.77 mg/dl. After 48 hours the mean indirect bilirubin of group A patients were 10.99±3.19 mg/dl whereas the indirect bilirubin of group B patients was 10.35±2.94 mg/dl. After 72 hours the mean indirect bilirubin of group A patients were 9.30±2.99 mg/dl whereas the mean indirect bilirubin of group B patients was 9.35±3.33 mg/dl. Similarly, after 96 hours the mean indirect bilirubin of group A patients were 9.33±2.58 mg/dl whereas the mean indirect bilirubin of group B patients was 9.60±0.75 mg/dl. Regarding indirect bilirubin at follow-up there was statistically insignificant difference between the study groups i.e. p-value>0.05. (Table 2)

Test of normality was applied and normality of duration of treatment was tested. P-value of Shapiro-Wilk test was significant showing that data is not following normal distribution. So median and range were calculated for duration of treatment and Mann-Whitney U test was applied to check significant difference between groups. The median duration of treatment in

group A was 3.00 days (range=2-4) while in group B was 2.50 days (range=2-4). The difference was insignificant (p>0.05). (Table 3).

Table No.1: Comparison of age, gestational age, weight on admission in both groups

		Study Groups		P-Value
		A	B	
Age on Admission (Days)	n	05	05	0.630
	Mean	6.64	7.06	
	SD	4.402	4.28	
Gestational age (Weeks)	n	05	05	0.912
	Mean	36.92	36.94	
	SD	0.922	0.890	
Weight on Admission (KG)	N	05	05	0.247
	Mean	3.578	2.99	
	SD	3.55	0.43	

Table No.2: Comparison of indirect bilirubin (mg/dl) at different time intervals in both groups

	Time (Hours) after phototherapy started	Study Groups		P-Value
		A	B	
Indirect bilirubi (mg/dl)	24	13.50± 3.68	12.35± 3.77	0.129
	48	10.99 ± 3.99	10.35± 2.94	0.302
	72	9.30± 2.99	9.35± 3.33	0.957
	96	9.33± 2.58	9.60± 0.75	0.872

(Note: Time in this table is duration of phototherapy, not the age of neonate)

Table No.3: Comparison of duration of treatment (days) in both groups

Duration	Study Groups	
	A	B
Median	3.00	2.50
Minimum	2	2
Maximum	4	4
Range	2	2

Mann-Whitney U test value = 1203.000
P-value = 0.716 (Insignificant)

DISCUSSION

Hyperbilirubinemia is a common disease and unconjugated hyperbilirubinemia has been seen mainly in neonates. In recent years, substantial researches have been carried out to predict neonates who are most likely to develop hyperbilirubinemia. Reliable predictions can reduce hospital stay for low-risk neonates resulting in their early discharge and identifying high-risk neonates facilitating their closer follow-up. Zinc is one of the essential elements in neonatal growth, protein synthesis and regulation of inhibitory and stimulatory synapses of the brain. Zinc lower the bilirubin levels by inhibition of the normal enterohepatic cycling of unconjugated bilirubin (UCB).[3,8]

This study results showed no significant effect of reducing the serum bilirubin level in neonates by administration of oral zinc sulphate. In our study total serum bilirubin, direct bilirubin, indirect bilirubin all showed statistically insignificant difference between groups after 24, 48, 72 and 96 hours phototherapy follow up. Some of the studies are discussed below showing the results in favor of our study and few showed contrary results. One recent study by Mousa Ahmadpour-kacho et al [9] demonstrated in their study results that there is no significant effect of administration of oral zinc sulphate for decreasing serum bilirubin level. According to their study after intervention the mean difference of decrease of serum bilirubin level in both groups was 8.8 & 8.3. This difference was statistically insignificant i.e. p-value>0.05. The study by Rana et al. in New Delhi, India showed that early administration of zinc sulfate had not decreased the incidence of neonatal jaundice; however, it decreased the length of stay for phototherapy.[3]

The study by Nabavi Zadeh et al. in full-term neonates on the age 2-7 days with non-complicated hyperbilirubinemia, who were hospitalized in Imam Sajjad Hospital of Yasuj, Iran, showed that although oral zinc salts can reduce bilirubin levels through the inhibition of intestinal-hepatic circulation of bilirubin, but they are not effective in treating neonatal physiologic jaundice.[10]

Another study by by Mamouri et al in Mashhad, Iran (2013) on 151 neonates (35 weeks and over), administration of 10 mg oral zinc sulfate was shown that zinc administration had no significant difference with placebo in serum bilirubin level reduction. However, the need for phototherapy was less for neonates in the experiment group.[6] Patton et al. studied the effect of oral zinc on 60 neonates with hyperbilirubinemia. The neonates were divided into the study group receiving 5mg oral zinc twice daily for five days and the control group. They reported that bilirubin level measurement on day 5 of treatment have showed no significant difference in the duration of hyperbilirubinemia between the two groups.[11]

The recent meta-analysis by Mishra et al. (2015)[12] on 18 published studies, only the study, which was done by Rana et al got the criteria to enter to the meta-analysis. He showed that there was insufficient evidence on the effectiveness of zinc in reducing the serum bilirubin level.[12] On the other hand in a study by Vitek et al. in 2005,[13] the oral administration of zinc salts efficiently decreased serum bilirubin levels in hyperbilirubinemic rats, most probably due to the inhibition of enterohepatic circulation of bilirubin. They suggested that this approach might be useful in the treatment of severe unconjugated hyperbilirubinemia.[13] Mendez-Sanchez et al. proved the role of zinc in decreasing the serum bilirubin in patients with Gilbert syndrome.[4] Hashemian S et al. Conducted a study showing that administration of oral zinc sulfate

decreases the duration of phototherapy and total serum bilirubin in neonates having neonatal jaundice.[5]
Further studies are recommended to be conducted in future with a larger sample size, formulation of zinc and with more precise laboratory studies to confirm the findings of our study.

CONCLUSION

This study results concluded that the Oral zinc sulphate has no role in reducing the total serum bilirubin level in full term and near term neonates having unconjugated hyperbilirubinemia.

Author's Contribution:

Concept & Design of Study:	Muhammad Sarfraz Alam
Drafting:	Ubaid Ullah Khan, Mimpal Singh
Data Analysis:	Mimpal Singh, Hamid Raza
Revisiting Critically:	Muhammad Sarfraz Alam, Ubaid Ullah Khan
Final Approval of version:	Muhammad Sarfraz Alam

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

REFERENCES

1. Stoll RM. Jaundice and hyperbilirubinemia in the newborn. Nelson textbook of pediatrics 21st ed. Philadelphia: WB Saunders;2019.p.871-80.
2. Kaplan M, Wong R, Sibley E, Stevenson D. BJ, Kliegman Neonatal jaundice and liver disease. Neonatal-Perinatal Medicine Diseases of the Fetus and Infant. 9th ed. Cleveland, Ohaio: Mosby 2011;1443-96.
3. Rana N, Mishra S, Bhatnagar S, Paul V, Deorari AK, Agarwal R. Efficacy of zinc in reducing hyperbilirubinemia among at-risk neonates: a randomized, double-blind, placebo-controlled trial. Ind J Pediatr 2011;78(9):1073-8.
4. Méndez-Sánchez N, Roldán-Valadez E, Flores M, Cárdenas-Vázquez R, Uribe M. Zinc salts precipitate un-conjugated bilirubin in vitro and inhibit enterohepatic cycling of bilirubin in hamsters. Eur J Clin Investigation 2001; 31(9):773-80.
5. Hashemian S. Efficacy of zinc sulfate in reducing unconjugated hyperbilirubinemia in neonates. Reviews Clin Med 2014;1(4):229-32.
6. Maamouri G, Boskabadi H, Mafinejad S, Bozorgnia Y, Khakshur A. Efficacy of oral zinc sulfate intake in prevention of neonatal jaundice. Iranian J Neonatol IJN 2014;4(4):11-6.
7. Ashok et Al. Zinc supplementation for neonatal hyperbilirubinemia: A randomised controlled trial. Ind J Pediatr 2014;51(8):0420-1.
8. Méndez-Sánchez N, Martínez M, González V, Roldán-Valadez E, Flores MA, Uribe M. Zinc sulfate inhibits the enterohepatic cycling of unconjugated bilirubin in subjects with Gilbert's syndrome. Annals Hepatol 2002;1(1):40-3.
9. Ahmadpour-kacho M, Zahed Pasha Y, Ranjbar B, Pouramir M, Hajian K, Pounasrollah M. The Effect of Oral Zinc Sulfate on Serum Bilirubine Level in Term Neonates with Jaundice. Int J Pediatr 2017;5(6):5053-60.
10. Nabavizadeh S, Keshavarz K, Sadati S, Abidi H, Poursamad A, Zoladl M. Impact of Oral Zinc Sulfate on Uncomplicated Neonatal Jaundice. Armaghane Danesh 2015;20(6):460-71.
11. Patton P, Rachmadi D, Sukadi A. Effect of oral zinc on hyperbilirubinemia in full term neonates. Paediatrica Indonesiana 2011;51(2):107-10.
12. Mishra S, Cheema A, Agarwal R, Deorari A, Paul V. Oral zinc for the prevention of hyperbilirubinaemia in neonates. Cochrane Database of Systematic Reviews 2015(7).
13. 13. Vitek L, Muchova L, Zelenka J, Zadinova M, Malina J. The effect of zinc salts on serum bilirubin levels in hyperbilirubinemic rats. J Pediatric Gastroenterol Nutr 2005;40(2):135-40.