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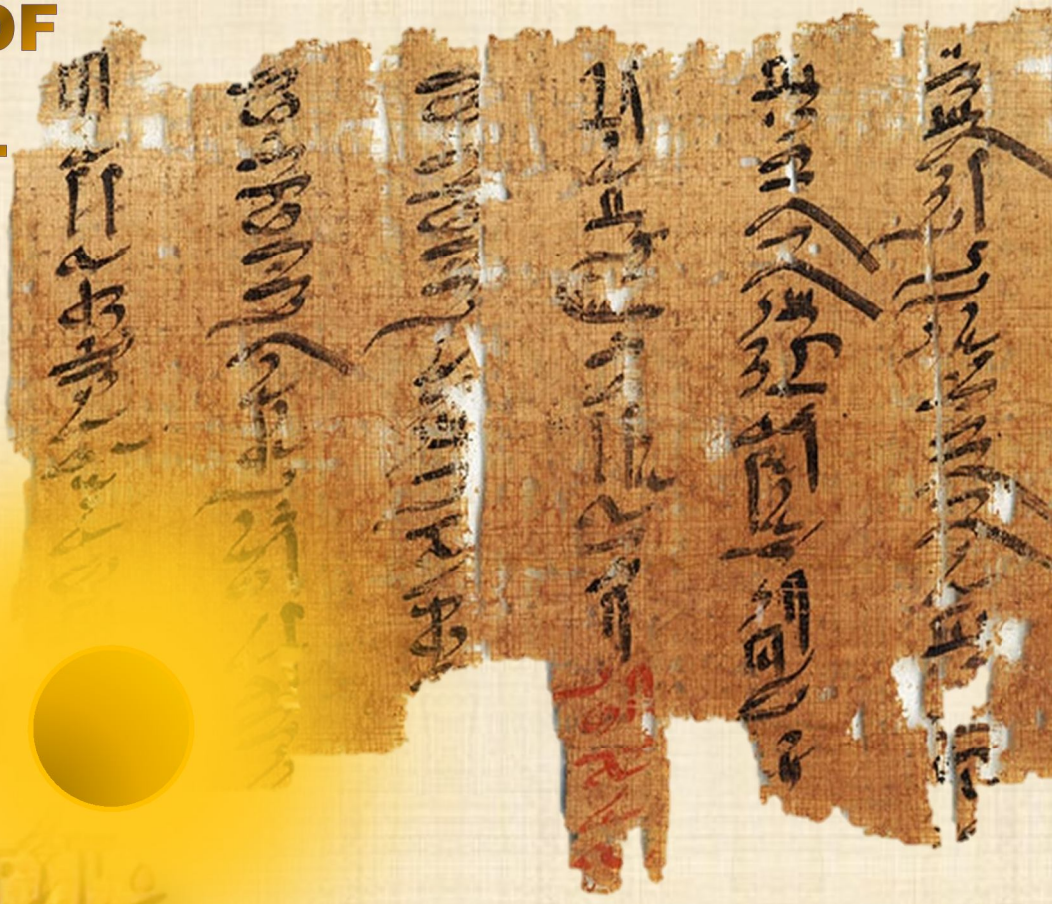

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Original article

Effect of Zinc Supplementation on Serum Bilirubin Level in Term Neonates Undergoing Phototherapy

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ABSTRACT

Background: Neonatal jaundice is considered a major health problem in neonates owing to bilirubin deposition. Recently, zinc demonstrated a high efficiency in reduction of low bilirubin level when administrated in association with phototherapy.

Aim of the work: To assess efficiency and safety of oral zinc as a therapy in treatment of indirect hyperbilirubinemia in term neonates during phototherapy.

Patients and Methods: A total of 100 term neonates with indirect hyperbilirubinemia were divided into two equal groups: Intervention Group (n=50) received oral zinc sulphate preparation, in a dose of 5 mg twice daily in combination with phototherapy. Control group (n=50) received phototherapy without oral zinc supplementation. In both groups, the total serum bilirubin levels were measured at admission, 12 hours, 24 hours and at discharge.

Results: Treatment of full-term neonates with hyperbilirubinemia by oral zinc sulfate at a dose of 5 mg given twice-daily induce a significant reduction of total serum bilirubin [TSB] after 12 hours, 24 hours and at discharge when compared to the control group. The duration of phototherapy in intervention group was markedly decreased with statistically significant difference in comparison to the control group. However, there was no significant differences between groups regarding adverse effects of phototherapy and zinc therapy.

Conclusion: Oral zinc could play a major role in the management of neonatal jaundice when administrated at dose of ten mg/day as it can decrease the neonatal TSB with subsequent reduction of phototherapy duration.

Keywords: Neonatal jaundice; Hyperbilirubinemia; Zinc; Phototherapy; Total serum bilirubin.

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* Main subject and any subcategories have been classified according to research topic.

INTRODUCTION

Neonatal jaundice means yellowish discoloration of the skin, sclera, and mucous membranes that is caused by tissue deposition of bilirubin. The newborn Jaundice becomes obvious when the total serum bilirubin (TSB) level reaches 5 mg/dL (86 µmol/l)[1]. Elevated levels of unconjugated bilirubin can lead to bilirubin encephalopathy resulting in kernicterus[2]. Several modalities exist for treatment of unconjugated neonatal hyperbilirubinemia. The most common form is phototherapy[3]. Zinc has a crucial role in a broad variety of biological activities involving the preservation of cell architecture and functions, protein synthesis and immune functions by serving as a co-factor for the development of more than 200 enzymes, including phosphatases, metallo-proteinases, oxido-reducatases, and transferases [4]. Zinc was recorded to inhibit heme enzyme oxygenase. Zinc (4µmol/kg) administration decreased the levels of carbon monoxide (CO) and bilirubin substantially one to six hours following management [5]. Zinc salts block the enzymes of hem-oxygenase with a subsequent prevention of jaundice development[6,7]. Zinc sulfate supplementation has been documented to be capable of reducing TSB, it appears possible that oral zinc salt may decrease the possibility of hyperbilirubinemia and the need for phototherapy and transfusion exchange in jaundiced neonates, thereby reducing the possibility of kernicterus[8].

AIM OF THE WORK

The current work designed to evaluate the effect of oral zinc as an adjuvant therapy for indirect hyperbilirubinemia during treatment with photo-therapy.

PATIENTS AND METHODS

The current study was a randomized clinical control trial conducted on all term neonates with indirect hyperbilirubinemia with no clinical or laboratory evidence of sepsis from February 2019 to February 2020 at the Neonatal Intensive Care Unit of Al-Azhar University Hospital in New Damietta. The current study was submitted for approval by Institutional Review Board (IRB) at Al-Azhar University in new Damietta. The research purpose was clarified to the parents and oral consent was obtained. A total of 100 term neonates aged 2-7 days with indirect hyperbilirubinemia were divided into two equal groups (50 neonates in each group). Intervention Group (n=50): received oral zinc sulphate preparation, in a dose of 5 mg twice daily in combination with phototherapy. Control group (n=50): received phototherapy without oral zinc supply. The drug and the medication were administered orally by the plastic syringe. Neonates with pathological jaundice, underlying gastro-intestinal issues preventing oral ingestion, sepsis, chromosomal aberrations, congenital anomalies and previous history of surgeries or the potential need for surgical interference were ruled out from the current study. Both groups had a comprehensive history of taking including demographic details, full maternal and perinatal history, family history of siblings who had jaundice, history of medications, feeding methods, manifestations of zinc deficiency as well as toxicity. Furthermore, all underwent diligent general examination including respiratory, abdominal examination, neurologic examination and manifestations of zinc deficiency. Both studied groups had Complete Blood Count (CBC), Coomb test and reticulocytic count for mother and neonate at admission. In both groups, measurement of serum zinc level before and after phototherapy was performed. In both studied groups, the TSB level was measured at admission, 12 hours, 24 hours and at discharge.

Statistics:

Sample size was calculated using G power program version 3.0.10 for windows using results published by Agrawal et al.[9] with the post-treatment TSB as the primary outcome. The post-treatment TSB with zinc was reported by Agrawal et al. [9] as 7.83 mg with standard deviation 3.36 while that for the control group was 9.47 ± 3.1 mg. The null hypothesis is assumed to be the absence of difference between both groups regarding the post-treatment TSB. A sample of 49 patients is needed to achieve 80% power (1-β or the probability of rejection of the null hypothesis when it is false) using one-sided independent samples unequal-variance t-test and a significance level of 0.05 (α or the probability of rejection of the null hypothesis when it is true). Statistical presentations and analysis were calculated using Statistical Package for Social Science (SPSS) version 20.0.

Independent sample T and Mann Whitney tests were utilized for inter-group (between subjects) comparison of parametric and non-parametric continuous data with no follow up readings respectively. For pair-wise comparison of data (within subjects), the follow-up values were compared to their corresponding basal value using paired samples T test, Wilcoxon matched pairs signed ranks test or related-samples Friedman's two-way analysis of variance by ranks with Bonferroni correction of p value for multiple comparisons. Fisher exact and Chi square tests were used for inter-group comparison of nominal data utilizing the crosstabs function. P is significant if <0.05.

RESULTS

At time of admission, there was no statistically significance variations in the mean ±SD of the TSB among both studied groups (P=0.069). Whereas, there were statistically significant variations among both studied groups after 12 hours (P=0.019), 24 hours (P<0.001) and at time of discharge (P=0.001). Furthermore, there were no significant variations in the mean difference of the TSB between the two studied groups (P=0.986) **[Table 1].** Before zinc administration, there was no statistically significant difference in zinc level among both groups, while after zinc administration there were highly statistically significant differences between both studied groups **[Table 2].** However, there were highly significant variations between both groups as regards duration of phototherapy, there were no statistically significant changes among both studied groups as regarding age of onset of phototherapy, source of phototherapy, previous siblings' need for phototherapy and side effects [rash] associated with phototherapy or associated with zinc supplementation (vomiting and diarrhea) (P=1). **[Table 3].**

Table [1]: Total serum bilirubin (TSB) in the study groups in relation to time of admission

TSB	Intervention group (N=50)	Control group (N=50)	t	P
At admission	16.98± 0.86	16.58± 1.31	0.837	0.069
At 12 hours	14.13± 0.93	14.96± 1.27	2.390	0.019*
At 24 hours)	11.88 ± 0.89	13.34± 1.28	6.633	<0.001*
At discharge)	9.16± 0.47	8.76± 0.67	3.450	0.001*
Difference	**7.82 ± 0.39**	**7.82 ± 0.64**	**0.015**	**0.986**
Paired comparison	P1= 0.064; P2= 0.001*; P3<0.001*; P4= 0.039*; P5= 0.001*; P6= 0.143	P1= 0.085; P2= 0.043*; P3<0.001*; P4= 0.437; P5 <0.001*; P6= 0.049*		

TSB: total serum bilirubin; *: statistically significant; P1: significance between value at admission and at 12 hours; P2: significance between value at admission and at 24 hours; P3: significance between value at admission and at discharge; P4: significance between value at 12 hours and at 24 hours; P5: significance between value at 12 hours and discharge; P6: significance between value at 24 hours and discharge

Table [2]: Zinc levels among studied groups before and after treatment

Zinc levels	Intervention group (N=50)	Control group (N=50)	t	P
Before treatment (µg/dl)	121.99 ± 11.56	121.14 ±9.72	0.398	0.692
After treatment (µg/dl)	133.35 ± 3.83	122.32 ± 10.6	6.92	< 0.001*
Mean Difference	11.37 ± 10.69	1.18 ± 2.07	6.61	< 0.001*
Serum zinc level (before treatment)				
Normal	13 (26%)	10 (20%)	χ^2=0.51	0.635
Deficient	37 (74%)	40 (80%)		
Serum zinc level (after treatment)				
Normal	47 (94%)	11 (22%)	χ^2 = 53.2	<0.001*
Deficient	3 (6%)	39 (78%)		

χ^2 = Chi-square test, statistically significant if P ≤0.05.

Table [4]: Phototherapy parameters in the studied groups

Variable	Intervention group (N=50)	Control group (N=50)	t	P
Age of onset of phototherapy (hrs)	84.6 ± 22.09	87.43 ± 24.35	t= -2.217	0.135
Duration of phototherapy (hrs)	37.62± 4.11	59.96± 3.78	t= -9.221	<0.001*
Source of phototherapy				
Single	50 (100%)	50 (100%)	χ2 = 0	1
Previous siblings' need for phototherapy				
One baby	8 (16%)	7 (14%)	χ2 =1.386	0.194
Two babies	2 (4%)	1 (2%)		
Side effects of phototherapy				
Rash	1 (2%)	3 (6%)	χ2 =1.432	0.162
Side effects of zinc therapy				
Vomiting	1 (2%)	1 (2%)	χ2 = 0	1
Diarrhea	0 (0%)	0 (0%)		

χ2 = Chi-square test, Statistically significant if P ≤0.05

DISCUSSION

The current study aimed to assess the role of oral zinc as an adjuvant therapy in the management of indirect hyperbilirubinemia in term neonates and its effect on TSB. The current study demonstrated that treatment with oral zinc sulfate solution in full-term neonatal at a dosage of 5 mg [twice-daily] lead to substantial reduction of TSB after 12 hours, 24 hours and at discharge as compared to the control group. Such action may be explained by that, oral zinc enhance action of phototherapy with a subsequent reduction of phototherapy duration. Support to this theory come form the fact that, zinc alone cannot manage the jaundice individually indicating that phototherapy is remaining the main line of treatment and oral zinc supplementation is considered as an adjuvant therapy. In addition, zinc supplementation showed no influence on phototherapy requirement but only induce reduction of phototherapy period. Another explanation of the role of zinc was that oral zinc salts has the ability to suppress the entero-hepatic circulation of bilirubin. In clinical practice, association of oral zinc together with phototherapy may have an important role in the reduction of the potential adverse effects of phototherapy which may be developed owing to the prolonged period of exposure to phototherapy.

Sharma et al.[10], in accordance with the present research, demonstrated that there was a significant variation in the TSB level at 12 hours and 24h between intervention and control groups. Moreover, **Hashemian et al.**[11] stated that the TSB decreased by oral zinc sulfate in neonatal jaundice. **Agrawal et al.**[9] showed that oral zinc supplementation in the form of zinc acetate suspension given at a dose of 10 mg/day in two divided doses significantly reduces the incidence of hyperbilirubinemia in the initial seven days of life and a reduction in the mean TSB level in day 7 in healthy near-term and full-term risk-neonates.

Rana et al. [12] on the contrary, showed no substantial difference in mean TSB levels at 72±12 hours of age (zinc 11.3 ± 3.3 vs control 11.5± 3.8 mg/dl. The discrepancy between the current study and Rana et al. may be due to the use of 10 ml of zinc gluconate which is known to be deficient in its elemental zinc (14.3%) in contrast to the current study (10 ml of zinc sulphate (25% elemental zinc)) which was a higher dose in relation to them. **Patton et al.** [13] found no effect of zinc on incidence and median duration of hyper-bilirubinemia. This might be owing to the fact that in their study they included term neonates with umbilical cord bilirubin [2mg/dl] and used zinc sulphate salt at a lower 5 mg/day, single dose. They also didn't calculate the amount of zinc before and after the intervention and included this in their limitation.

Current results agree with **Kumar et al.** [8] who showed no age changes in staring phototherapy recorded for both groups.

The current study revealed that the photo-therapy duration in the intervention group decreased significantly with comparison to control group. **Rana et al.**[12] **and Hashemian et al.** [11] found that zinc administration reduced the duration of phototherapy needed in treatment of neonatal hyperbilirubinemia. **Maamouri et al.** [14] also revealed significant changes in admission and phototherapy duration between intervention and control groups (p=0.043).

In contrary, **Agrawal et al.**[9] showed that the proportion of neonates needing phototherapy and the duration of phototherapy in those neonates was not significantly reduced in comparison with the control group.

In conclusion, oral zinc in a dose of 10 mg/day can reduces the mean TSB in neonates with hyper-bilirubinemia, reduces the duration of phototherapy in neonatal jaundice. Thus it could be considered as a cost effective modality. The main limitation of the present study was small sample size. The strength in the present study was the utilization of special type of zinc compound (zinc sulphate) as the majority of the preceding studied utilized different zinc forms.

Declaration of interest

The investigators have no related affiliations or financial participation with any organization or entity with a financial interest in or financial conflict with the subject matter or material discussed in the manuscript.

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