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Original Article

Concomitant Oral Zinc Sulfate and Phototherapy versus Phototherapy alone in Treatment of Neonatal Indirect Hyperbilirubinemia: A Randomized Clinical Trial Study

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Abstract

Objectives: To evaluate the role of oral zinc supplement with phototherapy on treatment of indirect hyperbilirubinemia. **Study design:** This was a randomized clinical trial study included 184 neonates with indirect neonatal jaundice who were randomly assigned into two groups; group (1): received oral zinc sulfate with phototherapy and group (2): received phototherapy alone. Neonates allocated according to gestational age into full-term and late-preterm neonates All cases underwent measurement of total serum bilirubin (TSB) level on admission and serially according to severity, then after 24 and 72 hours after stoppage of phototherapy. TSB reduction calculated as TSB on admission minus TSB on discontinuation of phototherapy. Level of serum zinc level on admission, side effects related to oral zinc and duration of phototherapy, where total hours of phototherapy calculated as 1 daily hour on double phototherapy equals 2 hours of phototherapy, were assessed in this study. **Results:** No statistically significant difference between the two groups regarding the decrease of initial TSB after 24 hours, the level of TSB reduction, re-increasing of TSB during NICU admission, daily hours of phototherapy, total hours of phototherapy during NICU admission, duration of NICU admission (p. value > 0.05 for all), in all neonates, full term and late preterm subgroups. **Conclusions**: Concomitant oral zinc sulfate and phototherapy had no additive value over phototherapy alone in lowering serum bilirubin levels in treatment of neonatal indirect hyperbilirubinemia.

Keywords: Indirect hyperbilirubinemia, Zinc sulfate, Full-term, Pre-term.

Introduction

Conventional treatment for neonatal indirect hyperbilirubinemia consists of phototherapy and/or exchange transfusion are depending on serum bilirubin levels. Although effective, both these modalities associated with undesirable consequences such as extended hospital admission with risk of infection, increase the cost of care, and are associated with other side effects [1]. Phototherapy usage may associate with watery diarrhea, low serum calcium, retinal damage, skin rash, dehydration, and DNA mutation [2]. Exchange transfusion can cause electrolyte imbalance, cardiac overload, air embolism, thrombophlebitis, thrombocytopenia, sepsis, necrotizing enterocolitis, transmission of blood-borne diseases, and portal vein thrombosis [3]. These harmful adverse effects indicate the need to develop alternative therapeutic pharmacological strategies which aim to decrease the plasma concentration of indirect bilirubin by inhibiting production, stimulating hepatic clearance, or interrupting the enterohepatic circulation (EHC) of bilirubin [4]. Various substances have been used to bind the bilirubin in intestinal lumen to prevent its absorption and disrupt enterohepatic circulation. These substances are such as oral agar, orlistat, active charcoal, cholestyramine, calcium phosphate or glucoronidase inhibitor like hydrolyzed casein; although the obtained results have been inconsistent [6].

Mendez-Sanchez et al., study was the first one which reported that zinc salts at physiological pH can be flocculated and almost completely adsorb indirect bilirubin from unsaturated micellar bile salt solutions [7].

Vitek et al. studied the effect of zinc salts ingestion in hyperbilirubinemic rats and reported that oral zinc salts can decrease serum bilirubin levels efficiently, due to the probable enterohepatic circulation inhibition of bilirubin [8]. Méndez-Sánchez et al., showed that administration of oral zinc sulphate can significantly decrease serum indirect bilirubin levels in

adult patients with Gilbert´s syndrome [9]. Therefore, the anticipated role of zinc supplementation in neonatal jaundice seems to be an attractive issue for research. This study aimed to determine the role of oral zinc with phototherapy on treatment of indirect hyperbilirubinemia in full-term and late-preterm neonates associated with risk factors.

Patients and Methods

Materials and Methods

Study population: This prospective randomized clinical trial was carried out on 184 neonates with indirect hyperbilirubinemia, admitted at neonatal intensive care unit (NICU) of Pediatric Hepatology, Gastroenterology and Nutrition Department, National Liver Institute, Menoufia University during the period from June 2018 to June 2019. Neonates in this study were classified according to gestational age `into full term neonates (≥ 37 weeks of gestation) and late preterm (≥ 34 to less than 37 weeks of gestation) [10]. The study has been approved by the Research Ethics Committee of National liver institute, Menoufia University (NLI IRB number 00136/2018). An informed consent was signed by parents of all neonates enrolled in this study. The study was also registered at classic.clinicaltrials.gov (Clinical trial ID: NCT06227624). The neonates enrolled in the study were randomly allocated into two groups by computer based randomization. Group (1) (zinc and phototherapy group) included 92 neonates receiving phototherapy and oral zinc sulfate with a dose of 5 mg every 12 hours using a calibrated dropper provided with the bottle, during the period of NICU admission on phototherapy (oral zinc supplementation continued as long as the neonates need NICU admission). Group (2) (phototherapy group) included 92 neonates receiving phototherapy alone. Both groups receiving phototherapy based on the guidelines of AAP for the treatment of neonatal indirect hyperbilirubinemia [11].

Neonates submitted to blood transfusion and/ or exchange transfusion, who were

early preterm and those associated with congenital anomalies, co-morbidities such as sepsis, pneumonia, respiratory distress cephalhematoma and/ or ABO blood and Rh-D grouping mismatching with their mothers were excluded from the study.

Full perinatal and maternal history including maternal age, parity, and presence of jaundice in previous sibling were collected for all neonates. Routine general and systemic examination, laboratory investigations including complete blood count, reticulocytic count, C-reactive protein, ABO blood grouping and Rh-D type for neonates and their mothers and neonatal serum zinc level on admission to NICU were done.

All cases underwent measurement of TSB and direct serum bilirubin (DSB) levels on admission and then TSB serially measured after 24 hours (hrs) of intervention and according to the severity and response to treatment, until discharge then after 24 and 72 hours after stoppage of phototherapy to detect rebound hyperbilirubinemia. TSB reduction calculated as TSB on admission minus TSB on discontinuation of phototherapy and duration of phototherapy, where total hours of phototherapy calculated as 1 daily hour on double phototherapy equal 2 hours of phototherapy, were assessed in this study. Any adverse effects in neonates related to ingestion of zinc sulphate like retching, vomiting, abdominal distension, diarrhea, skin rash, irritability/crying, change in neonate's behavior or physical signs were noted and recorded. All risk factors for neonatal jaundice reported in this study.

Measurement of Zn level on admission: Total serum zinc levels were measured on admission before initiation of phototherapy using the colorimetric method according to the manufacturer's instructions the where the normal range is 65- 137 μg/dl) [12].

Samples were mixed and incubated for 8 minutes at 25ºC or 5 minutes at 37ºC. The absorbance was measured at wavelength 560 nm, and the concentration of the zinc in serum was calculated using the

following equation, where, s is the sample, RBL is the reagent blank and STD is the standard [$^{\gamma}A_{(s)}$ = A $_{(sample)}$ - A $_{(RBL)}$; $^{\gamma}A_{(STD)}$ = A $_{(standard)}$ - S $_{(RBL)}$]. Calculation of results with standard [C= 200× ($^{\gamma}A_{(s)} \div {}^{\gamma}A_{(STD)}$) (µg/dl)].

Ethics approval and consent to participate: Informed and written consent was obtained from all parents of neonates included in the study. The research protocol of this study was approved and reviewed by the Research Ethics Committee of the NLI, Menoufia University, Egypt on April 2018 (NLI IRB number 00136/2018), and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study was also registered at classic.clinicaltrials.gov (Clinical trial ID: NCT06227624).

Statistical analysis

Descriptive data were expressed as (mean ± SD) and range; or frequency and percent. For quantitative data, significance between the two studied groups was tested by Student t-test or Mann–Whitney U-test. For qualitative and categorical data, significance was tested by Chi-square test or Fisher's exact test. Significance was set to $P< 0.05$. Statistical analysis was performed using statistical package for social science (SPSS) software version 22 (IBM Corp. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

Results

This randomized clinical trial involved 184 neonates. Male gender represented 94 (51.1 %) of cases. Neonates involved in group (1) were 92 neonates (46 males); and group (2) were 92 neonates (48 males), with mean age of all neonates in hours (99.48± 61.27, range 4- 360 hrs) (table 1). Mean gestational age of all neonates (37.34± 1.34, rang 34- 40), full term neonates were 153 (83.2); late

preterm were 31 (16..8) of neonates. Mean neonates' body weight (2.88± 0.49, range 1.78- 4.3). Majority of cases 156 (84.8) delivered by cesarean section and 28 (15.2%) of neonates delivered vaginally.

Neonatal and maternal risk factors for jaundice reported in this study. There were 59 (32.1) neonates reported without risk factors, and 125 (67.9) neonates had one or more risk factors with no statistically significant difference reported between the two studied groups. Maternal DM reported in 60 (32.6), maternal HTN in 12 (6.5), PROM in 7 (3.8), jaundice in other sibling in 45 (24.5), prematurity in 31 (16.8) and low birth weight in 14 (7.6) of all cases (data not shown). 135 (73.4) neonates were exclusively breast fed, while 22 (11.96) neonates were exclusively formula fed (table 1).

Pretreatment laboratory tests showed no statistically significant as regards levels of initial TSB, Hb and reticulocytic count while zinc level was higher in group (1) (P= 0.036) (table 1). Concerning post intervention assessment for all neonates, no statistically significant difference between the two groups regarding the decrease of first TSB after 24 hours from the intervention, the level of TSB reduction, single units phototherapy and double& single units usage, re-increasing of TSB during admission, daily hours of phototherapy and total hours of phototherapy during the admission and the discharge from NICU after 24, 48 and ≥ 72 hours (P> 0.05 for all) (table 2). No statistically significant difference between the two studied groups of intervention in both subgroups of GA, full term (tables 3) and late preterm neonates (tables 4). No adverse events related to enteral zinc supplementation noticed in all neonates ingested it during the study.

Table (1): Demographic, perinatal and pretreatment findings of studied groups

Item	Group 1 n (%)= 92	Group 2 n (%)= 92	P. value
Male gender	46 (50)	48 (52.17)	0.769
Gestational Age *(weeks)* Min- Max	37.33± 1.31 34- 40	37.31± 1.31 34- 40	0.941
Age *(hours)* Min- Max	101.62± 70.37 4- 360	87.59± 45.3 9- 230	0.101
Body Weight *(kg)* Min- Max	2.86± 0.52 1.78- 4.3	2.90± 0.46 1.81- 4.21	0.613
Initial TSB *(mg/dL)* Min-Max	16.24± 3.01 5.10- 22.7	16.16± 2.83 8.2- 23	0.396
Hb *(g/dl)* Min-Max	15.7± 2.16 10.3- 20.2	16.24± 2.57 10.3- 22.4	0.117
Reticulocytes *(%)* Min-Max	2.24± 0.54 1.2- 3.9	2.1± 0.60 1.2- 3.8	0.091
Zinc level *(µg/dL)* Min-Max	95.85± 13.74 69- 133	91.86± 13.69 75-128	**0.036** *
Onset of jaundice			0.617
Within 24 hrs	5 (5.43)	3 (3.26)	
From 24 up to 72 hrs	30 (32.61)	35 (38.04)	
After 72 hours	57 (61.96)	54 (58.7)	
Type of Feeding			0.361
Breast feeding	66 (71.74)	69 (75)	
Formula feeding	14 (15.26)	8 (8.7)	
Breast+ formula	12 (13.0)	15 (16.3)	

*TSB: total serum bilirubin; Hb: hemoglobin, *Significant p. value <0.05*

Table (2): Study the role of zinc sulfate on all jaundiced neonates in the study

Item	**Group 1** n= 92	**Group 2** n= 92	**P. value**
First TSB * *(mg/dL)*	12.13± 3.12	11.83± 2.84	0.498
Min-Max	4.8- 18.9	6.7- 21	
TSB Reduction **	5.69± 3.06	5.51± 2.75	0.927
Min-Max	0.0- 13.6	0.0- 12.1	
Reincreased TSB during admission			
Cases number	4 (4.3)	3 (3.2)	0.70
Phototherapy Number			0.392
Single	72 (78.3)	67 (72.8)	
Double& single	20 (21.7)	25 (27.2)	
Duration of NICU admission with phototherapy			
24 hours	59 (64.13)	68 (73.9)	0.262
48 hours	13 (14.13)	7 (7.6)	
≥ 72 hours	20 (21.74)	17 (18.5)	
Daily hours of phototherapy			
Hours number	39.16± 23.50	36.87 25.47	0.222
Min- max	24-144	24-168	
Total hours of phototherapy**			
Hours number	52.55± 39.81	51.96± 40.50	0.871
Min- max	24- 240	24- 240	

*TSB: total serum bilirubin; Hb: hemoglobin; * First TSB: after 24 hrs from the intervention; ** TSB reduction= (TSB on admission - TSB on discontinuation of phototherapy); *** Total hours of phototherapy calculated as 1 daily hour on double phototherapy= 2 hours of phototherapy.*

Table (3): Study the role of zinc sulfate on jaundiced full term neonates

Item	Group 1 n= 77	Group 2 n= 76	P. value
Initial TSB *(mg/dL)*	16.2± 3.15	16.22±2.79	0.531
Min-Max	5.1- 22.7	8.2- 23	
Hb *(g/dl)*	15.6±2.01	16.2± 2.53	0.106
Min-Max	10.3- 18.9	11- 22.4	
Reticulocytes *(%)*	2.25± 0.57	2.09± 0.6	0.092
Min-Max	1.2- 3.9	1.2- 3.98	
Zinc level *(µg/dL)*	94.95± 13.12	91.21± 13.29	0.082
Min-Max	69- 133	75- 128	
First TSB * ***(mg/dL)***	11.83± 3.13	11.63± 2.66	0.666
Min-Max	4.8- 18.1	6.7- 18.9	
TSB Reduction **	5.44± 2.93	5.32± 2.43	0.775
Min-Max	0- 13.6	0.3- 11.3	
Reincreased TSB during admission			
Cases number	3 (3.9)	2 (2.6)	1.00
Phototherapy Number			0.966
Single	60 (77.9)	59 (77.6)	
Double& single	17 (22.1)	17 (22.4)	
Duration of NICU admission with phototherapy			
24 hours	54 (70.1)	63 (82.9)	0.119
48 hours	11 (14.3)	5 (6.6)	
≥ 72 hours	12 (15.6)	8 (10.5)	
Daily hours of phototherapy			
Hours number	35.53±19.7	31.26±17.54	0.08
Min- max	24- 96	24- 96	
Total hours of phototherapy**			
Hours number	46.44± 32.88	43.26± 29.59	0.687
Min- max	24- 168	24- 168	

*TSB: total serum bilirubin; Hb: hemoglobin; * First TSB: after 24 hrs from the intervention; ** TSB reduction= (TSB on admission - TSB on discontinuation of phototherapy); *** Total hours of phototherapy calculated as 1 daily hour on double phototherapy= 2 hours of phototherapy*.

Table (4): Study the role of zinc sulfate on jaundiced late preterm neonates

Item	Group 1 n= 15	Group 2 n= 16	P. value
Initial TSB *(mg/dL)*	16.73± 2.32	16.54± 3.16	0.856
Min-Max	12.1- 19.8	10.3- 21.6	
Hb *(g/dl)*	16.13± 2.33	15.4± 2.64	0.418
Min-Max	11.8- 20.2	10.3- 21.2	
Retics *(%)*	1.95± 0.29	2.1± 0.65	1.00
Min-Max	1.5- 2.4	1.2- 3.3	
Zinc level *(µg/dL)*	96.73± 14.75	89.75±14.38	0.193
Min-Max	76- 133	75-123	
First TSB* ***(****mg/dL****)***	13.77± 2.8	12.93± 3.45	0.458
Min-Max	9.5- 18.9	8.1- 21	
TSB Reduction**	7.07± 3.65	5.94± 3.90	0.409
Min-Max	2.1- 12.8	0- 12.1	
Reincreased TSB during admission			0.484
Cases number	1 (6.7)	0 (0.0)	
Phototherapy Number			
Single	13 (86.7)	8 (50)	0.966
Double& single	2 (13.3)	8 (50)	
Duration of NICU admission with phototherapy			
24 hours	6 (40)	8 (50)	0.646
48 hours	1 (6.7)	2 (12.5)	
≥ 72 hours	8 (53.3)	6 (37.5)	
Daily hours of phototherapy			
Hours number	51.2± 23.77	48± 27.71	0.700
Min- max	24- 72	24- 96	
Total hours of phototherapy ***			
Hours number	73.6± 38.98	69± 45.43	0.715
Min- max	24- 120	24-144	

*TSB: total serum bilirubin; Hb: hemoglobin; * First TSB: after 24 hrs from the intervention; ** TSB reduction= (TSB on admission - TSB on discontinuation of phototherapy); *** Total hours of phototherapy calculated as 1 daily hour on double phototherapy= 2 hours of phototherapy.*

Discussion

Chronological age of neonates in hours, sex, weight, gestational age, and type of feeding were statistically insignificant between the two studied groups (table 1). Concomitant to our results, Kumar et al., revealed that there was no significant difference between zinc group and placebo group as regards age at starting phototherapy [1]. Rana et al., found statistical difference between the two groups regarding age but no regarding sex, weight, gestational age [13].

We did not find any statistically significant difference between the two groups regarding the neonatal and maternal risk factors for neonatal jaundice. In agreement of our results Rana et al., revealed that there is no significant difference between the two groups as regards hyperbilirubinemia in previous sibling [13].

No adverse events related to enteral zinc supplementation noticed in all neonates ingested it. Also Patton et al., did not find any significant side effects in their cases received oral zinc sulphate 10 mg divided in two doses daily for 5 days [14]. Faal et al., found only increased bowel motions with usage the zinc sulfate syrup in preterm infants with dose (1 cc/kg) [15]

Concerning the laboratory parameters of neonates involved in the study, no statistically significant difference reported between the studied groups as regard mean of TSB levels on admission, Hb level, reticulocyte count between the two groups (table 1). Our results were in agreement with Mohammadzadeh et al., who revealed that there was no statistically significant difference between the two groups as regards TSB on admission [16].

In this clinical trial, despite the serum zinc level before the intervention was statistically significant higher in group (1) who received oral zinc with phototherapy, we reported no statistically significant difference between the two groups as regards the effect of zinc sulfate on the first TSB follow up after 24 hours from

the intervention, the level of TSB reduction during NICU admission, phototherapy units' number, re-increasing TSB during NICU admission, duration of NICU admission with phototherapy, daily hours of phototherapy, and total hours of phototherapy (table 2). We agreed with Kumar et al., who revealed that after intervention, no difference in TSB levels was observed between the studied groups anytime during the study period and the duration of phototherapy did not reach statistical significance between the studied groups [1]. Ahmadpour-kacho et al., reported that no difference in the mean TSB between the experimental and control groups after intervention at the time of discharge, but reported a statistically significant difference regarding the mean phototherapy length (P=0. 01) between the experimental (86.4 ±36 hours) and control group (98.4± 43.2 hours) [17]. Beiranvand et al., reported that there was statistically significant difference between the two groups as regards the first TSB follow up after 24 hours from the intervention and level of TSB reduction [18]. Hamed et al., reported significantly shorter duration of hospital stay ($p < 0.01$) with significant TSB reduction in neonates who received oral zinc and phototherapy compared to those received phototherapy only after 24 and 48 hours ($p < 0.01$), with comparable levels of TSB levels after 72 and 84 hours [19]. Rana et al., which observed that duration of phototherapy was shorter in zinc group (22.8±19.4) versus (35.6±16.1) [13].

We categorized the eligible neonates according to gestational age into full-term and late pre-term neonates, to study the oral of zinc sulfate on reducing indirect hyperbilirubinemia in neonates having the same physiologic conditions. We could not found any statistically significant difference between the two groups of intervention in full-term neonates subgroup in table (3), and in late pre-term neonates subgroup in table (4), as regards HB, reticulocyte count, sex, weight, age, TSB on admission, zinc level on

admission, first TSB follow up after 24 hours from the intervention, and TSB reduction level, number of phototherapy units, reincreasing TSB during admission, daily hours of NICU admission on phototherapy, and total hours of phototherapy ($P > 0.05$ for all). We agreed with Beiranvand et al., who reported that there is no significant differences were observed between the experimental (oral zinc and phototherapy) and control (phototherapy only) groups in terms as regards age, gender, birth weight, Hb level, reticulocyte percentage and TSB at the beginning of the study [18]. Ahmadpour-kacho et al., revealed that neither TSB (on admission) nor its reduction at the time of discharge were significant between the two studied groups in full term neonates similar to our results, but disagreed with us regarding the mean duration of phototherapy, which was statistically significant lower in the intervention group than the control group ($P= 0.017$) [17]. In the other way, Mandlecha et al., found that Oral zinc sulfate ingestion with phototherapy significantly decrease levels of TSB and minimize the duration of phototherapy required for jaundiced full-term [20]. Elfarargy et al., reported that no significant difference in level of serum bilirubin observed on the second, fourth, and sixth days of admission, but serum bilirubin was decreased in neonates received zinc with phototherapy on the eighth, ninth, and tenth days of admission [21].

Indrio et al., reported that oral zinc salt couldn't be applicable for treatment of early jaundice in neonates in clinical practice for several causes for example; the most hazardous risks of neonatal jaundice occurs during the first week of life too early for the therapeutic effect of oral zinc which occurs after two weeks; the uncontrolled ingestion of zinc salts may alter the trace elements absorption like copper by the neonatal gut; the absorption capacity of zinc by neonatal gut may not be efficient as rat gut; and finally, it was recorded that neonates

suffering from elevated levels of indirect hyperbilirubinemia have altered intestinal permeability with impaired intestinal epithelial surface which suggested that supplementation of any oral substance is unlikely to have a therapeutic value [22]. Also we can recommend against the usage of oral zinc in the treatment of neonatal hyperbilirubinemia early in life, because the diversity and variability of the neonatal gut microbiota and zinc salts may need long duration to release to reach its active site in the terminal ileum which necessitate delayed onset of action, and the high risk of developing bilirubin neurotoxicity during the first week of life. The limitations in our study were the usage of oral zinc for short duration during the period of NICU admission on phototherapy and the lake of measurement of serum level of zinc on discharge from the hospital to assess the ability of the gut to absorb zinc in this age group. Oral zinc salts may be effective with long duration of ingestion, so further studies are recommended in older neonates with prolonged physiological jaundice not in risk of development of bilirubin neurotoxicity or rapid unexpected increase of bilirubin and during first week of life, using higher doses and long duration of ingestion to assess the safety and the possible long-term effect of zinc in reducing indirect bilirubin in neonates.

Conclusions

Addition of zinc to the neonates under phototherapy for treatment of neonatal indirect hyperbilirubinemia is safe but had no additive effect in lowering of serum bilirubin levels. Concomitant oral zinc sulfate and phototherapy had no additive value over phototherapy alone in lowering serum bilirubin levels in treatment of neonatal indirect hyperbilirubinemia.

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Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors HE, HS, HE*, MH and SA were involved in the study concept and design; HE, HS, MH and SA were involved in patients' recruitment, clinical management and follow up of the patients. HE* performed the biochemical analysis. SA was involved in statistical analysis, and interpretation. All the authors write, reviewed, and approved the final manuscript; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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