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Efficacy of Oral Zinc Acetate in Reducing Hyperbilirubinemia in Full-Term and Near-Term High Risk Neonates

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Abstract
Objective: *To determine the efficacy of oral zinc supplementation in reducing incidence of hyperbilirubinemia and level of serum total bilirubin (STB) during the first week of life in full-term and near-term high risk neonates in comparison with placebo.*
Method: *We conducted a randomized double-blind placebo-controlled trial on 100 neonates born at ≥35 weeks of gestation with STB ≥5 mg/dl at 24 ± 6 hours of age. They were administered either 10 mg zinc acetate syrup (zinc group) or placebo (control group) in twice daily doses till day 7 of life. Incidence of hyperbilirubinemia (STB ≥15 mg/dl) anytime between day 2 to 7 of life and mean STB levels on day 7 of age were compared between the two groups.*
Results: *Incidence of hyperbilirubinemia was significantly lower in the zinc group (8%) as compared to placebo group (26%); p= 0.033. Mean STB level on day 7 of life was significantly lower in the zinc group (7.828±3.36 mg/dl) as compared to placebo group (9.474±3.1mg/dl); p= 0.017. No significant adverse effects related to oral zinc administration were noted.*
Conclusion*: Oral zinc in a dose of 10 mg/day reduces the incidence of hyperbilirubinemia and mean STB levels in the first week of life in at-risk full-term and near-term neonates.*
Keywords: *Neonatal hyperbilirubinemia, Oral zinc, Serum total bilirubin.*

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I. Introduction

Neonatal hyperbilirubinemia is the most common condition that requires medical attention in newborns. Although upto 60% of term neonates become visibly jaundiced during the first week of life, in most of the cases it is benign and lies within the physiological range**.** Nearly 6-15% of neonates develop hyperbilirubinemic levels that require intervention to prevent bilirubin toxicity [1, 2]. Unconjugated bilirubin (UCB) can be toxic to the central nervous system, resulting in encephalopathy and neurological impairment [3].

Substantial research has been done to predict neonates who are most likely to develop hyperbilirubinemia. Bhutani and colleagues generated a percentile based bilirubin normogram using hour-specific pre-discharge STB levels from a racially diverse group of healthy near-term and term newborns. This normogram is divided into 4 zones. Based on their normogram, it has been found that the best prediction for subsequent hyperbilirubinemia is made when STB is measured after 18-24 hours of age. According to them, neonates with pre-discharge STB levels in the low risk zone (<40th percentile which corresponds to a level of <5 mg/dl at 24 hours of postnatal age) did not develop hyperbilirubinemia subsequently [4]. Seidman et al (1996) suggested a STB ≥5 mg/dl at 24 hours of life to predict the risk of significant hyperbilirubinemia with a high probability [5].

Currently the standard therapies for hyperbilirubinemia include phototherapy and exchange transfusion which are costly, time consuming and potentially risky. Several lines of evidence suggest the importance of intestinal metabolism of UCB and enterohepatic circulation (EHC) in the pathogenesis of neonatal jaundice [6-8]. Resorption of bilirubin from the gastrointestinal tract in the form of UCB and delivery back to the liver for reconjugation is called EHC. High levels of intestinal glucuronidase which converts conjugated bilirubin to UCB, absence of an intestinal flora for the reduction of conjugated bilirubin to urobilinoids which are not substrates for glucuronidase, decreased gut motility and limited nutrient intake thus prolonging intestinal transit time with poor evacuation of bilirubin laden meconium during neonatal life increases the EHC. Studies have suggested that in a neonate, EHC can be largely significant in the overall body economy of bilirubin. To block the process of enhanced EHC, various strategies have been used to bind the bilirubin in the intestinal lumen to

substances that resist its resorption. Products such as activated charcoal, oral agar and calcium phosphate have been used but with inconsistent results and adverse effects [7, 9].

Zinc has been reported to decrease STB levels in two animal models [10, 11] and in adults with Gilbert syndrome [12]. However, little is known about the role of oral zinc salts in jaundiced neonates, in whom two studies have been conducted, but with inconsistent results [13, 14].

As oral zinc presumably reduces the STB by precipitating UCB from unsaturated micellar solution of bile salts consequently inhibiting the EHC of bilirubin [10, 11], possibility of zinc as an agent in the treatment of severe unconjugated hyperbilirubinemia and also in the prevention of its development in at-risk neonates, appears to be an attractive low-cost, low-risk intervention.

II. 2. Materials And Method

This study was a double-blind, placebo-controlled, randomized control trial conducted in the Department of Pediatrics, MLB Medical College, Jhansi in active collaboration with Department of Obstetrics and Gynecology. The protocol was cleared by the institutional ethics committee.

All neonates born at ≥35 weeks of gestational age with STB ≥5 mg/dl at 24±6 hours of age were potentially eligible for enrolment in this study. Neonates with Rh incompatibility, major gross congenital anomaly, cephalhematoma, systemic sepsis requiring intravenous antibiotics, those who required exchange transfusion / phototherapy within 24 hours of age or neonatal intensive care for more than 24 hours within first 7 days of age were excluded.

All potentially eligible neonates were screened for STB at 24 ± 6 hours of age. Neonates with STB ≥5 mg/dl at 24 ± 6 hours were enrolled in the study after taking an informed consent from parents. The enrolled newborns were subdivided into either the study group who were administered oral zinc acetate syrup in a dose of 10 mg/day in two divided doses from day 2 to day 7 of life, or the control group who received placebo syrup in the form of sucrose solution in similar amounts in twice daily doses from day 2 to day 7 of life. Randomization was done using a random sequence generated by a table of random numbers with the use of GraphPad software. Zinc and placebo syrups were identical in color, taste and appearance and packaged in similar looking bottles. The code was kept blinded from the participants and the investigator till the end of the study.

The first dose of the medication was administered under the doctor's direct supervision after enrolment while the rest of the doses were given by mother. The enrolled neonates were assessed clinically for development of hyperbilirubinemia twice a day and STB was monitored anytime the neonate appeared clinically jaundiced till the day of discharge. The babies who were discharged earlier than day 7 were followed up on day 7 of life. Parents were asked to come earlier if the legs or sole of the neonate appeared yellow. In neonates developing hyperbilirubinemia, serum bilirubin was monitored every 12 hourly until it was <13 mg/dl. STB was recorded on day 7 of life in all neonates.

The primary outcome variable was the incidence of hyperbilirubinemia, taken as STB ≥15 mg/dl anytime between day 2 and 7 of life. The secondary outcome variables included the mean STB levels on day 7 of life and the incidence and duration of phototherapy requirement.

Statistical analysis was done using GraphPad and Medcalc softwares. Group characteristics were compared with Chi-square test and t-test for discrete and continuous variables respectively. For the primary and secondary outcome variables, Chi square test was used for discrete variables and't'-test for continuous variables. 'p' value of ≤0.05 was taken as statistically significant.

The 100 enrolled neonates were subdivided into two groups according to the therapeutic modalities received. The study group contained 50 neonates who received zinc therapy while the control group contained 50 neonates who received placebo therapy.

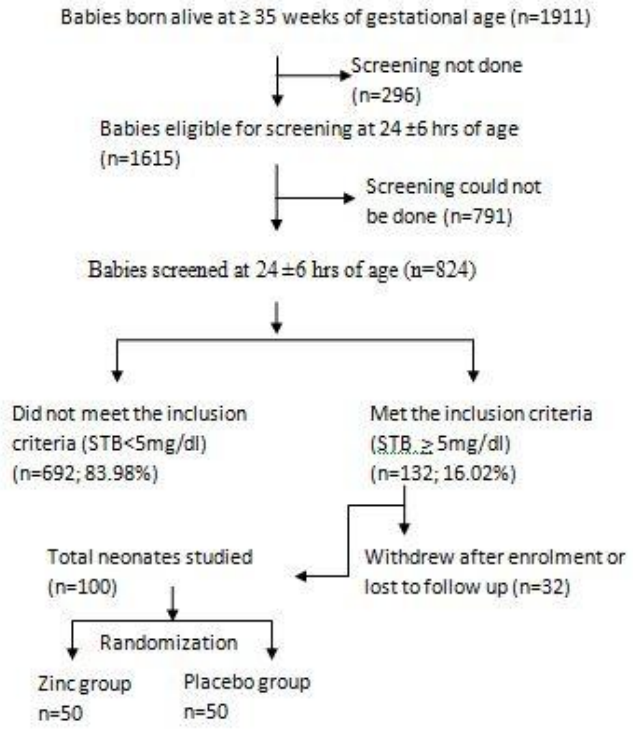

FIGURE 1 Flow Chart of the Study

III. 3. Results

All the baseline characteristics and risk factors for hyperbilirubinemia were comparable in both the groups. The incidence of hyperbilirubinemia was significantly lower in the zinc group as compared to the control group (8% in the zinc group versus 26% in the placebo group; p= 0.033). Mean STB level on day 7 was significantly lower in the neonates receiving zinc therapy (7.828 ± 3.36 mg/dl) as compared to those receiving placebo (9.474 ± 3.1mg/dl); (mean difference=1.646, CI: - 2.99 to 0.299, p= 0.017). The incidence of requirement of phototherapy was lower in the zinc group (8%) as compared to placebo group (24%), but the difference was not quite statistically significant (p=0.056). The mean duration of phototherapy in the zinc group (18 ± 6.93 hrs) was however, not significantly different from the control group (25 ± 11.95 hrs); (mean difference: 7hrs; 95% CI: - 20.7 to 6.7, p= 2.29) (Table 3p).

The incidence of adverse effects like vomiting, diarrhoea, rash, seizures and sepsis was not significantly higher in the zinc group as compared to placebo group.

TABLE 1 Comparison of Baseline Characteristics in Both Groups (Continuous variables)

Characteristics	Zinc group (n=50)	Placebo group (n=50)	p value
Mean gestational age ± SD (weeks)	38.6 ± 1.6	38.6 ± 1.2	0.94
Mean maternal age ± SD (years)	23.5 ± 2.5	23.2 ± 2.3	0.64
Mean STB at 24±6 hrs of age ± SD (mg/dl)	6.68 ± 1.38	6.39 ± 1.12	0.24
Mean birth weight ± SD (kg)	2.637±0.273	2.615±0.316	0.71

TABLE 2 Comparison of Baseline Characteristics in Both Groups (categorical variables)

Characteristics	Subgroups	Zinc group (n=50) Number (%)	Placebo group (n=50) Number (%)	p value
Gender	Male	26 (52)	28 (56)	0.84
	Female	24 (48)	22 (44)	
Birth weight Category	SGA	22 (44)	23 (46)	0.84
	AGA	28 (56)	27 (54)	
Gestational age Category	Near-tern (>35-37 wks)	6 (12)	3 (6)	0.48
	Full-term (>37-40 wks)	44 (88)	47 (94)	
Mode of delivery	Vaginal	17 (34)	23 (46)	0.30
	LSCS	33 (46)	27 (54)	
Type of feeding	EBF	37 (74)	41 (82)	0.47
	Mixed	13 (26)	9 (18)	
Oxytocin use		13 (26)	15 (30)	0.82
ABO setting		6 (12)	7 (14)	0.77
Meconium stained liquor		9 (18)	10 (20)	0.80

TABLE 3 Primary and Secondary Outcome Measures in Both Groups.

	Zinc group n=50	Placebo group n=50	p value
Incidence of hyperbilirubinemia (STB ≥ 15 mg/dl) n (%)	4 (8)	13 (26)	0.033
Mean STB on day 7 of life in mg/dl (mean ± SD)	7.83 ± 3.36	9.47 ± 3.1	0.017
Requirement of phototherapy n (%)	4 (8)	12 (24)	0.056
Duration of phototherapy in hours (mean ± SD)	18 ± 6.9	25 ± 11.9	0.290

IV. Discussion

Our study demonstrated that treatment with oral zinc acetate in a dose of 10 mg/day results in a significantly lower incidence of subsequent neonatal hyperbilirubinemia in near-term and full-term at-risk neonates during the first week of life. The highlight of the study was a significantly lower mean total serum bilirubin value on day 7 of age in the zinc administered group as compared to the placebo administered group.

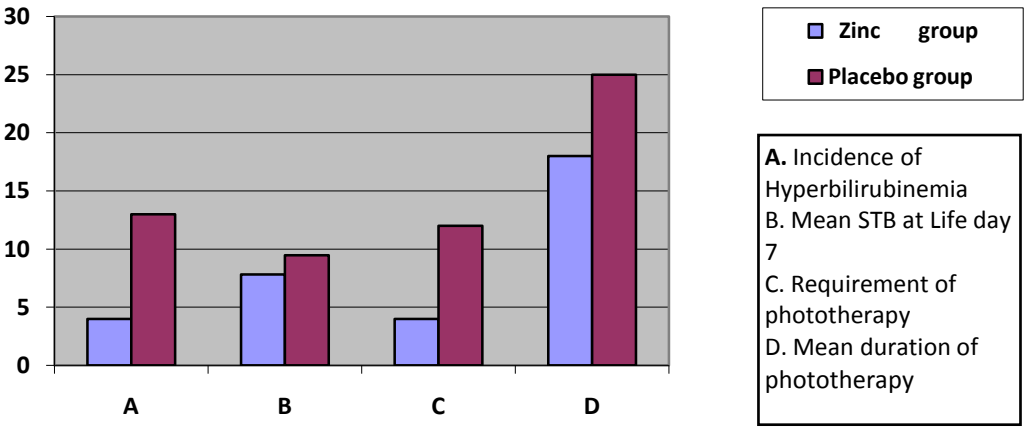

Figure 2 Comparison of primary and secondary outcome measures in both groups**.**

Jaundice is an important problem in the first week of life. The fundamental aim of detecting and treating severe neonatal jaundice is to prevent bilirubin encephalopathy and its chronic sequelae.

Prevention of EHC of bilirubin via enhancement of bilirubin sequestration or degradation in the intestinal lumen is an exciting approach for prevention of neonatal hyperbilirubinemia. Hence, the rationale of this study is the possible role of zinc in decreasing serum bilirubin by inhibiting its EHC. Its role in neonatal jaundice has been speculated but has not been proved consistently in the few studies conducted earlier.

The two animal studies in this regard are those by Mendez Sanchez et al in 2001 [10] and Vitek et al in 2005 [11]. They conducted both in-vivo and in-vitro studies and concluded that, at physiological pH(7-8), zinc salts adsorb and bind UCB almost completely from unsaturated micellar bile salt solutions forming precipitates as well as resulting in a significant reduction of serum bilirubin levels when administered orally in hyperbilirubinemic rats, possibly due to inhibition of EHC of bilirubin. The first human study on this issue is one by Mendez Sanchez et al in 2002 on adult patients of Gilbert syndrome which reported that oral administration of zinc sulphate significantly decreased serum UCB in these patients [12].

The only two studies on neonates with respect to the role of oral zinc in hyperbilirubinemia are those by Rana N et al (2011) and Patton et al (2011). Rana N et al found that zinc administration reduces the duration of phototherapy required for treatment of hyberbilirubinemic neonates; however, it did not decrease the incidence of hyperbilirubinemia and requirement of phototherapy in at-risk neonates in the first week of life [13]. Patton et al included term neonates with umbilical cord bilirubin ≥2 mg/dl in their study and used zinc sulphate salt in a lower dose of 5 mg/day. Their sample size was small including 30 neonates in each group. They could not find any effect of zinc on incidence and mean duration of hyperbilirubinemia [14]. Hence, the paucity of studies on neonates and a positive role of zinc being stressed upon by the previous studies on animals and adult patients was an impetus for our study to work further in order to evaluate the efficacy of oral zinc in neonatal hyperbilirubinemia.

In our study we used a different salt i.e. zinc acetate which contains the highest percentage of elemental zinc (30%) as compared to other salts and is associated with lower gastric irritation [15]. It was given in a dose of 10 mg/day in view of the safety of zinc in this dose which comes from several trials in treatment of large number of children with diarrhea, measles, pneumonia, common cold and malaria. [16, 17].

Our study also demonstrated that zinc administration significantly reduces the mean STB levels at day 7 of life. However, the proportion of neonates requiring phototherapy and the duration of phototherapy in such neonates was not significantly reduced. In our study, STB was monitored every 12 hourly once phototherapy was started until it was less than 13 mg/dl, at which phototherapy was stopped. One possible explanation of the lack of effect of zinc in reducing duration of phototherapy could be infrequent measurement of STB. Also, if STB was monitored on all 7 days of life, we could have detected a small number of neonates with transient elevation of bilirubin which may have been possibly missed. This was, however, not practically possible due to inability to keep all patients in the hospital for 7 days and lack of willingness of parents for frequent blood sampling. There were no significant adverse effects in the zinc group in our study. The incidence of vomiting, diarrhea, rash, seizures and sepsis were not higher in the zinc group as compared to placebo.

Strengths of the current study include a robust design, an adequate sample size, proper follow-up and monitoring, good parents' counselling and high compliance to therapy.

V. Conclusion

To conclude, our study demonstrated that oral zinc administration 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 first week of life as well as mean total serum bilirubin level on day 7 in healthy near-term and full-term at risk-neonates. The proportion of neonates requiring phototherapy and duration of phototherapy in these neonates was also found to be lower in the zinc administered group as compared to placebo, however, the difference was not found to be statistically significant.

Conflict of study: none

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