Original Research Paper

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Neonatology

ROLE OF ORAL ZINC IN PREVENTION OF HYPER BILIRUBINEMIA IN NEONATES AND IT'S IMPACT ON REDUCING NEONATAL INTENSIVE CARE UNIT(NICU) STAY FOR PHOTOTHERAPY- A RANDOMISED CONTROL TRIAL

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ABSTRACT **Introduction:** Neonatal hyperbilirubinemia is a major cause of concern in first week of life. Oral zinc has been studied to reduce enterohepatic circulation, decrease hyperbilirubinemia and reduce phototherapy duration.

Objectives:
1) To study the effect of oral zinc in reducing hyperbilirubinemia in neonates.
2) To study the impact of zinc in reducing NICU stay for phototherapy in neonates with hyperbilirubinemia

Methodology: This was double blind RCT where 100 neonates fulfilling inclusion criteria were recruited. Out of them, 50 were given oral zinc 10mg/day while the rest, placebo from day1 to day7. Serial monitoring of icterus was ensured clinically twice a day. Mean levels of total bilirubin (TB) monitoring done on day3, day5, day7 of life and in icteric neonates. Duration of phototherapy administered was also considered. **Results:** The incidence of hyperbilirubinemia in both groups was comparable 50% in zinc and 58% in placebo group. Mean TB levels were found comparable on day 3 and day 7 but significantly lower in zinc group than placebo group on day 5. Mean initiation age of phototherapy was found later in zinc group than placebo group. There was no significant reduction in mean duration of phototherapy and NICU stay. **Conclusion:** Oral zinc did not reduce mean TB on day 3 and day 7 but decreased on day 5 of life compared to placebo group. Significant delay in the initiation of phototherapy in zinc group compared to placebo group.

KEYWORDS : Oral Zinc; Neonatal Hyperbilirubinemia; Phototherapy; Serum Total Bilirubin

INTRODUCTION

Neonatal hyperbilirubinemia is a very common condition occurring in 5-25% of neonates, requiring evaluation and management as it remains a frequent reason for hospital readmissions during the first week of postnatal life.[1] Hyperbilirubinemia commonly manifests as jaundice or yellowish discolouration of skin. Jaundice in neonates progress in cephalocaudal fashion with increasing hyperbilirubinemia as classically characterized by Kramer.[2] It reflects developmental RBCs, hepatic and gastrointestinal immaturities that results in an imbalance favouring bilirubin production over hepatic-enteric bilirubin clearance.[3] In adults bilirubin levels are considered to be normal if <1mg/dL, whereas in newborns it can be >1mg/dL and can still be considered as normal. Hyperbilirubinemia in newborns can be plotted in hour specific Bhutani normogram for reference based on percentile based serum bilirubin values.[4]

Marked hyperbilirubinemia can cause acute bilirubin encephalopathy (ABE) and evolve into chronic bilirubin encephalopathy (CBE); a devastating, permanently disabling neurologic disorder, synonymous with kernicterus.[5] CBE is classically characterised by dystonia, athetosis, auditory neuropathy spectrum disorders, paresis of vertical gaze and dental enamel dysplasia.[6] Prevention of bilirubin encephalopathy and its chronic sequelae is the essential aim of detecting and treating neonatal hyperbilirubinemia earliest. Therapeutic options for unconjugated hyperbilirubinemia in neonates like phototherapy and blood exchange transfusions are costly, time consuming and potentially risky. One of the possible therapies for preventing bilirubin neurotoxicity is via reducing bilirubin levels by inhibition of enterohepatic circulation. Zinc salts have a potential to inhibit enterohepatic circulation of bilirubin probably by precipitating unconjugated bilirubin in the intestine.[7]

METHODOLOGY

This is a double blind randomised double blind control trial conducted at K.V.G Medical College &Hospital during the period from November 2018 to April 2020 in Paediatric ward and NICU.

Inclusion Criteria: Term neonates (≥ 37 completed weeks)

Exclusion Criteria:
1. Newborns with Rh incompatibilities, gross congenital anomalies , sepsis requiring intravenous antibiotic therapy
2. Newborns with pathological jaundice.
3. Newborns requiring intensive care for more than 24 hours for other reasons.
4. Newborns whose parents who didnot give consent.

After informed consent, detailed data on birth history, maternal history, antenatal history, post natal history were recorded. Gestational age assessment was done based on first trimester ultrasound of mother or based on LMP and confirmed by New Ballard score. Neonates were examined thoroughly, anthropometry and head to toe examination was done.

Randomization was done using computer generated random numbers. Similar color and size bottles were used, thus both investigator and patient were blinded about the contents of the bottle. Osteocalcium was used as placebo. Neonates received oral zinc as zinc sulphate 10 mg/day, in 2 divided doses from Day 1 to Day 7. They were assessed clinically twice a day and serially with transcutaneous bilirubinometer. Serum bilirubin levels were done using dimethylsulphoxide method at day3, day 5, day 7 and when neonates were icteric. If icteric, phototherapy was initiated in NICU and repeat blood TB was done.

Statistical Analyses-
Collected data was entered in Microsoft Office Excel. Significance was tested using Chisquare test and t-test for analysis of the data. P value <0.05 is taken to be significant.

Ethical clearance and permission to conduct study was obtained from the ethical committee of K.V.G. Medical College and Hospital.

RESULTS

Out of 50 subjects in zinc group, 26 (52%) were males and rest 24 (48%) were females. The gender difference between two groups was not significant. Children who were born appropriate for gestational age were -43(86%) in zinc group and 44(88%) in placebo group; while SGA neonates were 3(6%) in zinc group and 2(4%) in placebo; whereas LGA neonates were 4(8%) in zinc and placebo group. Number of neonates delivered via normal delivery were 36(72%) in placebo group were 38(76%) in zinc group; whereas neonates delivered via LSCS were 14(28%) in zinc and 12(24%) in placebo. The mean time at initiation of breast feeding in zinc group is 1.3±0.46 while those in the placebo group were 1.32±0.55 Number of neonates with ABO incompatibility was 16(32%) in zinc group and was 12(24%) in placebo group. Neonates who had hyperbilirubinemia were less in number compared to those whose siblings had hyperbilirubinemia. Zinc group had 8%; while placebo group had 11%

. Baseline characteristics of Zinc and placebo group have been summarised in Table 1.

Table 1: Summarises Baseline Characteristics Of Zinc Group And Placebo Group.

Baseline characteristics	Categories	ZINC GROUP	PLACEBO GROUP	P value
Gender Number (percentage)	Male	26 (52 %)	27 (54%)	0.841
	Female	24 (48%)	23 (46%)	
Mean age of mothers (years)		24.24 ± 3.28	24.82 ± 3.36	0.3846
Parity	Primigravida	22 (44 %)	15 (30%)	0.197
	2nd child	22 (44 %)	31 (62 %)	
	3rd child	6 (12 %)	4 (8%)	
Gestational age No. (%)	Term	44(88 %)	44 (88%)	0.801
	Post dated	4 (8%)	5 (10%)	
	Post term	2(4%)	1(2%)	
Birth weight	Appropriate for gestational age	43 (86 %)	44 (88%)	0.900
	Small for gestational age	3 (6 %)	2 (4%)	
	Large for gestational age	4(8%)	4 (8%)	
Low birth weight	Present	11 (22%)	12 (24 %)	0.812
Mode of delivery	Normal vaginal delivery	36 (72%)	38 (76%)	0.648
	Lower segment caesarean section	14 (28%)	12 (24%)	
Mean time of initiation of breast feeding (hours)		1.3 ± 0.46	1.32 ± 0.55	0.8440
ABO incompatibility		16 (32%)	12 (24%)	0.373
Cephalhematoma	Present	3 (6%)	3 (6%)	1.00
H/o hyperbilirubinemia in sibling	Present	4 (8%)	11 (22%)	0.050

Incidence of neonates with hyperbilirubinemia was found to be 26(50%) in zinc group and 29(58%) neonates in placebo group. Mean bilirubin levels of zinc group vs placebo group on day 3 was 9.76 ± 2.25mg/dl vs 9.95 ± 2.89mg/dl, day 5 was 15.41 ± 4.71mg/dl vs 18.13 ± 3.02 ($p < 0.0009$) and on day7 was 7.19 ± 2.88mg/dl vs 6.85 ± 2.77 (Figure 1). Number of children receiving phototherapy was 26 (52%) in zinc group and 29 (58%) in placebo group. Mean age of initiation of phototherapy was found to be 76.88 ± 33.93hours in zinc group and 59.82± 34.50hours in placebo group ($p < 0.0143$). Mean total duration of phototherapy was found to be 36.46 ± 21.32 hours in zinc group and 38.06 ± 21.76 hours in placebo group. The side effects seen in zinc group were excessive cry 1(2%), rash 2(4%), vomiting 1(2%); whereas in placebo group - rash 1(2%), vomiting 1(2%) were noted. Comparison of observation findings and results between zinc and placebo group is summarised in Table 2.

Table 2: Summarises Observations And Results Of Zinc Group And Placebo Group.

Results	Categories	ZINC GROUP	PLACEBO GROUP	P Value
Children with hyperbilirubinemia		26 (50%)	29 (58%)	
Mean bilirubin levels	3rd day	9.76 ± 2.25	9.95 ± 2.89	0.7145
	5th day	15.41 ± 4.71	18.13 ± 3.02	0.0009*
	7th day	7.19 ± 2.88	6.85 ± 2.77	0.5488
Children receiving phototherapy		26 (52%)	29(58%)	
Mean age of initiation of phototherapy (hours)		76.88 ± 33.93	59.82 ± 34.50	0.0143*
Mean duration of phototherapy (hours)		36.46 ± 21.32	38.06 ± 21.76	0.7845
Weight loss between day3 and day 5	< 10 %	42 (84%)	42 (84%)	0.444
	> 10 %	8 (16%)	11 (22%)	
Adverse effects	Excessive cry	1 (2%)	0 (0%)	0.687
	Rash	2 (4%)	1 (2%)	
	Vomiting	1 (2%)	1 (2%)	

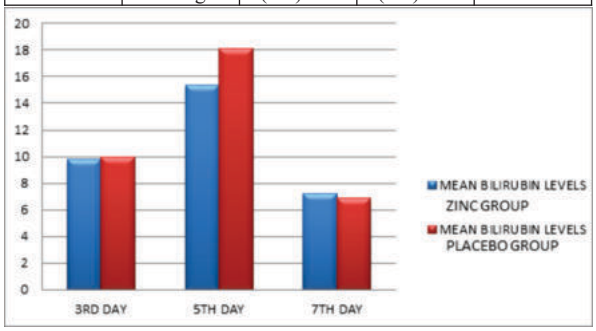

Figure 1: Differences In The Mean Bilirubin Levels Between Zinc And Placebo Groups

DISCUSSION

In neonates, jaundice has been one of the major problems especially in first week contributing to morbidity and mortality. The major aim is early detection of hyperbilirubinemia and preventing its severe consequences. Zinc has been studied for its role in prevention of enterohepatic circulation of bilirubin by increasing its sequestration or degradation in intestine.

In our study neonates who were AGA was 43(86%), SGA 3(6%) and LGA 4(8%) in zinc group while that in placebo group were 44(88%), 2(4%), 4(8%) in AGA, SGA and LGA respectively. It was similar to study by Agrawal R[8] et al ,SGA in zinc group was 22 (44%) and AGA were 28(56%); while in placebo group it was 23(46%) and 27 (54%). It was noted that low birth weight neonates in zinc and placebo group were 11% and 12%, which was in concordance to study conducted by Kumar A[9] et al which showed number of neonates who are low birth to be 14(35%) and 15(37.5%) . Incidence of neonates with hyperbilirubinemia was found to be 26(50%) in zinc group and 29(58%) neonates in placebo group. This was in concordance with Agrawal R[8] et al study which showed 4 (8%) had hyperbilirubinemia in zinc group whereas 13(26%) in placebo group which was of statistical significance.

We found that on day 5, mean total bilirubin levels were much decreased in zinc group when compared to placebo group with statistical significance. Similar results were reported by Babaei et al[10], significant reduction in transcutaneous bilirubin level from the third to fifth day in intervention arm ($p<0.05$). Maamouri et al[11] showed no significant difference in mean bilirubin values on 3rd (12.9±3 vs. 12.6±2 mg/dl, p=0.473) and 7th day (12.4±3 vs. 12.4±4, p=0.989) in infants who are very low birth weight. Kumar et al[9] documented no difference in mean TSB at day 2 (zinc 13.9± 2.5 vs. control 13.4 ± 1.9 mg/dL, p= 0.30), day 4 (zinc 13.1 ± 2.7 vs. control 12.8± 2.3, p= 0.708) and day 6 (zinc 8.0± 2.0 vs. control 8.6 ± 1.2 mg/dL, p=0.166).

Our study showed significant difference in mean age of initiation of phototherapy in both group (76.88 ± 33.93 hours - zinc group vs 59.82 ± 34.50 - placebo group) ($p<0.005$). The result showed that in placebo group the age of initiation of phototherapy was earlier than in zinc group. In study done by Kumar et al[9], mean age of initiation of phototherapy in zinc group was 87 hours whereas 92 hours in placebo

group. This study showed that the number of neonates receiving phototherapy, therefore who were admitted to neonatal intensive care unit and treated with phototherapy in zinc group was comparable to placebo group. Maamouri et al[11] reported that in placebo group, neonates needed more admission and treatment with phototherapy in comparison with intervention group (zinc 8.5% vs control 24%; p=0.043). Kumar et al[9] showed equal incidence of requirement of phototherapy in both the group with no statistical difference (zinc 52.0% vs control 45.0%, OR 0.736; 95CI: 0.282- 1.921; p= 0.629).

The total duration of phototherapy was found to be 36.4621.32 hours and 38.06 21.76 hours in zinc and placebo group respectively. Maamouri et al[11] showed that mean phototherapy duration was 18 hours in zinc group and 36 hours in control group. Kumar et al[9] reported reduction in the mean duration of phototherapy in the zinc group (zinc 61.9 ± 12.1 vs control 83.3 ± 17.6 hours) but the difference was not significant.

The adverse effects seen were excessive cry, rash and vomiting and were comparable in both groups with no statistical significance. Kumar et al[9] showed various adverse events like vomiting, skin rash, diarrhoea, excessive cry and were comparable between placebo and zinc groups.

CONCLUSION

To conclude, our study demonstrated that oral zinc reduced mean serum bilirubin levels on day 5 but on day 3 and day 7, levels were comparable in both groups. Mean age of initiation of phototherapy was more in zinc group than placebo, which indicates that zinc delays onset of hyperbilirubinemia.

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