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Original Research Article

EFFECTIVENESS OF ORAL ZINC SUPPLEMENTATION FOR TERM NEONATES WITH HYPERBILIRUBINEMIA RECEIVING PHOTOTHERAPY: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background: When it comes to neonatal hyperbilirubinemia, which is one of the most common reasons newborns are admitted to the hospital, phototherapy is the traditional treatment, but it has its drawbacks. A lengthy hospital stay, piling up healthcare costs, and a great deal of worry for parents. Well-known oral zinc supplementation, however, may be a solution to the problem. Zinc has been shown to slow down the enterohepatic circulation of bilirubin, and it's believed to be a way to strengthen the effectiveness of phototherapy. **Aim**: To study the effectiveness of oral zinc supplementation in term neonates with hyperbilirubinemia receiving phototherapy. **Materials and Methods**: This is a randomized control trial study which was done in the Department of Pediatrics, Aarupadai Veedu Medical College and Hospital, Puducherry. A total of 90 term neonates with unconjugated hyperbilirubinemia were enrolled and randomized into two groups: Group A (45) received zinc 5 mg/day with phototherapy and Group B (45) received phototherapy alone. Bilirubin levels were done at 0, 24, 48, and 72 hours. Hours of phototherapy and the duration of hospital stay were observed. **Results**: The drop in bilirubin levels was dramatic, when newborns received zinc supplementation. Coming out of the hospital just 24 hours later, the average bilirubin level in the zinc group was 13.42 mg/dL, whereas it was 14.65 mg/dl in the non-zinc group, and this difference was highly significant. The reduction in bilirubin levels in the zinc group continued to be more marked, at 48 and 72 hours. The time the babies spent in phototherapy and in the hospital was less in the zinc group. Side effects were rare and virtually the same in both groups. **Conclusion**: Oral zinc supplementation is a safe and affordable supplementary treatment that greatly improves the clearance of bilirubin and shortens the length of phototherapy and hospital stays for term neonates with hyperbilirubinemia.

INTRODUCTION

Neonatal jaundice, it's one of the most common reasons for hospital admission, when a newborn baby has neonatal hyperbilirubinemia. Coming on within the first week of life, this condition affects approximately 60% of term and 80% of preterm newborns, and in many cases, is a normal part of the baby's development.

However, high levels of bilirubin can cause a dangerous and permanent condition, kernicterus, and if severe, can lead to bilirubin-induced neurotoxicity and acute bilirubin encephalopathy. According to the World Health Organization, 25 million newborns worldwide develop significant jaundice, and over 100,000 deaths occur, mainly in sub-Saharan Africa and South Asia. In developing countries, including India, neonatal hyperbilirubinemia is a pressing

public health issue, with The National Neonatology Forum stating that 20-25% of neonatal admissions in tertiary hospitals are due to jaundice.

Phototherapy, usually the gold standard for neonatal hyperbilirubinemia treatment, has been known to turn bilirubin into a water-soluble form, enabling the baby to safely excrete it. However, extended periods of this treatment come with unpleasant side effects. Dehydration, diarrhea, irregular temperatures, and dangerous imbalances of potassium and sodium. Babies have to stay in the hospital longer, taking a toll on the family's lives, depleting medical supplies and putting a huge strain on parents. Exchange transfusions, that can be effective in clearing out bilirubin, are far from being perfect, aggressive, costly, and risky.

The discovery of zinc's therapeutic abilities presents an opportunity in fighting this neonatal hyperbilirubinemia. Oral zinc works in many ways: it can stop the normal return of bilirubin into the baby's bloodstream by mixing it into an insoluble form in the gut. And since zinc is basically free, easy to find, and doesn't usually cause any harm, there's no good reason not to consider its role as an inexpensive therapy for neonatal hyperbilirubinemia, though further research is required for Indian babies, in particular.

MATERIALS AND METHODS

Study Design

This was a prospective, randomized controlled trial conducted over an 18-month period from January 2024 to June 2025.

Study Setting

The study was conducted at the Department of Pediatrics, Neonatal Intensive Care Unit (NICU), Aarupadai Veedu Medical College and Hospital (AV.MCH), Puducherry, a tertiary care teaching hospital providing comprehensive neonatal services to both inborn and referred neonates.

Study Population

Inclusion Criteria: Term neonates (≥37 weeks gestation) aged 2-7 days with unconjugated hyperbilirubinemia requiring phototherapy as per National Neonatology Forum guidelines.

Exclusion Criteria: Preterm neonates (<37 weeks), pathological hyperbilirubinemia, systemic illness, severe respiratory disease, sepsis, or those requiring exchange transfusion at enrollment.

Sample size calculation: Based on anticipated 1.74 mg/dL difference in serum bilirubin reduction between groups with standard deviation of 2.53, 90% power, and 5% significance level, a sample size of 45 neonates per group (90 total) was calculated.

Randomization and Blinding

Eligible neonates were randomly allocated to two groups using computer-generated randomization sequence with sealed, numbered, opaque envelopes to prevent selection bias.

Intervention

Group A: Received oral zinc sulfate 5 mg/. day along with standard phototherapy.

Group B: Received standard phototherapy alone as control.

Both groups received identical phototherapy using standardized protocols. Serum total and indirect bilirubin levels were measured at baseline, 24, 48, and 72 hours, or until bilirubin levels dropped below the treatment threshold.

Outcome Measures

Primary outcome: Reduction in serum bilirubin levels at 24, 48, and 72 hours.

Secondary outcomes: Duration of phototherapy, duration of hospital stay, and adverse effects (vomiting, diarrhea, feeding intolerance).

Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 21. Continuous variables are expressed as mean ± standard deviation. Independent Student's t-test was used to compare means between groups. Categorical variables were compared using Chi-square test. Mann-Whitney U test was applied for non-normally distributed data. A p-value <0.05 was considered statistically significant.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of Aarupadai Veedu Medical College and Hospital.

Informed written consent was obtained from parents or legal guardians in English or Tamil after detailed explanation of study objectives, procedures, and risks. All participants received standard NICU care without alteration of clinical management.

RESULTS

The researchers randomly split them into two groups, 45 in the zinc group and 45 in the control, when studying the effects of zinc supplementation in 90 neonates with unconjugated hyperbilirubinemia. Well-known demographic characteristics such as gender, gestational age, birth weight, and the way they were born were virtually identical in both groups. Coming into the study, the starting levels of bilirubin in both groups were roughly the same, 16.82 mg/dL in the zinc group and 16.74 mg/dL in the control, and weren't significantly different.

Over the next 72 hours, the neonates in the zinc group saw a significantly sharper decline in bilirubin levels than the control group, dropping from 16.82 to 8.92 mg/dL, whereas the control group dropped from 16.74 to 11.24 mg/dL.

The zinc supplementation group had a shorter stay in the hospital (60.8 hours on average) compared to the control group (74.5 hours) and also required less phototherapy, which is the standard treatment for unconjugated hyperbilirubinemia, $p < 0.001$.

Only a handful of adverse effects were reported, and were split almost equally between the two groups, with 2 out of 45 neonates in the zinc group, and 3 out

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of 45 in the control, experiencing vomiting, and 3 in the zinc group, and 5 in the control experiencing diarrhea. No serious side effects that could be pinned to the zinc supplementation were noted.

Table 1: Demographic Characteristics of Study Groups

Characteristic	Zinc Group (n=45)	Control Group (n=45)	P-value
Gender (Male/Female)	27/18 (60%)	26/19 (57.8%)	0.56
Gestational Age (weeks)	38.6 ± 0.8	38.5 ± 0.9	0.71
Birth Weight (kg)	2.89 ± 0.35	2.86 ± 0.38	0.64
Mode of Delivery (NVD/LSCS)	32/13	34/11	0.42
Baseline Serum Bilirubin (mg/dL)	16.82 ± 2.14	16.74 ± 2.32	0.73

Table 2: Serum Bilirubin Levels at Different Time Points

Time point	Zinc group (mg/dl)	Control (mg/dl)group	P-value
Baseline	16.82 ± 2.14	16.74 ± 2.32	0.73
24 hours	13.42 ± 1.98	14.65 ± 2.07	<0.001
48 hours	11.18 ± 1.76	13.02 ± 1.89	<0.001
72 hours	8.92 ± 1.64	11.24 ± 1.95	<0.001

Table 3: Duration of Phototherapy and Hospital Stay

Outcome	Zinc group	Control group	P-value
Duration of Phototherapy (hours)	60.8 ± 9.6	74.5 ± 10.8	<0.001
Hospital Stay (hours)	60.8 ± 9.6	74.5 ± 10.8	<0.001

Table 4: Adverse Effects in Study Groups

Adverse effects	Zinc group	Control group	P-value
Vomiting	2 (4.4%)	3 (6.7%)	0.55
Diarrhea	3 (6.7%)	5 (11.1%)	0.31
Feeding Intolerance	1 (2.2%)	1 (2.2%)	1.00
Total Complications	6 (13.3%)	9 (20%)	0.46

DISCUSSION

This randomized controlled trial demonstrates that oral zinc supplementation is an
effective and safe adjunctive therapy for reducing bilirubin levels and shortening the duration of phototherapy and hospital stay in term neonates with unconjugated hyperbilirubinemia.

The mechanism by which zinc reduces bilirubin levels is multifaceted. Zinc salts bind to unconjugated bilirubin in the intestinal lumen, forming insoluble complexes that are excreted in feces rather than being reabsorbed via enterohepatic circulation. Additionally, zinc acts as a cofactor for uridine diphosphate-glucuronosyl transferase (UG.T1A1), the enzyme responsible for bilirubin conjugation, thereby enhancing hepatic bilirubin processing. Zinc also possesses antioxidant properties, protecting against oxidative stress induced by phototherapy. Our findings are consistent with previous studies demonstrating the efficacy of zinc supplementation in neonatal jaundice. Hashemian et al showed significant reduction in bilirubin levels at 24 and 48 hours with zinc administration.[15]

Patton et alsimilarly reported faster bilirubin decline and reduced phototherapy duration. The safety profile of oral zinc supplementation is excellent in our study, with minimal and comparable adverse effects between groups. Gastrointestinal side effects were uncommon, and no serious adverse events occurred. Zinc does not interfere with bilirubin measurements or phototherapy efficacy.[19]

A critical advantage of zinc supplementation lies in its cost-effectiveness and accessibility, particularly relevant in resource-limited settings. Unlike phototherapy equipment requiring expensive maintenance and skilled personnel, or exchange transfusions requiring specialized training and blood products, zinc supplementation requires minimal infrastructure. At approximately 1-2 USD per neonate per treatment course, zinc represents an economically sustainable intervention for developing countries.

Our study shows that oral zinc supplementation is very safe, with few and similar side effects between groups. Gastrointestinal side effects were rare, and there were no serious adverse events. Zinc does not affect bilirubin measurements or the effectiveness of phototherapy.[19] One of the best things about zinc supplementation is that it is cheap and easy to get, which is especially important in places with few resources. Unlike phototherapy equipment, which needs expensive maintenance and skilled staff, or exchange transfusions, which need specialized training and blood products, zinc supplementation needs very little infrastructure. At about 1-2 USD per neonate per treatment course, zinc is a cost-effective intervention for developing countries. Our study only included term neonates to avoid variables that could affect liver maturity and feeding practices. However, the results may apply to other term populations with similar starting points. The study was done in a tertiary care setting, and doing it again in primary and secondary care settings would make the results more generalizable. We didn't look at long-term neurodevelopmental outcomes, but we did confirm short.-term safety. These results are in line with recent systematic reviews and meta-analyses that say

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zinc is a good add.-on treatment. The ICMR Task Force Report 2021 says that India should look into low-cost treatments like oral zinc to cut down on hospital stays. Our study contributes evidence supporting this recommendation.

Future research should investigate zinc's efficacy in preterm neonates, those with hemolytic disease, and those with G6PD deficiency. Long.-term neurodevelopmental follow-up and assessment of rebound hyperbilirubinemia are warranted.

CONCLUSION

Oral zinc supplementation is a safe, cost-effective and very effective way to give them a boost, when neonates at term are receiving phototherapy to combat unconjugated hyperbilirubinemia. Coming dashing off the heels of starting phototherapy, it dramatically reduces bilirubin levels, cuts down the time neonates need to spend under the phototherapy lights and sends them home from hospital more quickly, all without any adverse effects.

Well-known for its favourable safety profile, affordability and simplicity, oral zinc supplementation is something that should be added to standard phototherapy protocols. Coming from anywhere in the world, it has the potential to seriously cut the toll of neonatal jaundice and even prevent brain damage caused by kernicterus in countries where medical resources are scarce.

Declaration by Authors

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