

Evaluation of Serum Zinc Levels in Hyperbilirubinemic Neonates Before and After Phototherapy

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Abstract

Background: The existing therapeutic methods for neonatal jaundice are costly, time-consuming and potentially risky. Zinc salts can reduce phototherapy duration by precipitating unconjugated bilirubin in the intestine (bilirubin and zinc can form a complex in physiologic pH); however, zinc toxicity is an issue that must be considered since theoretically bilirubin reduction by phototherapy may increase serum zinc levels, making additional zinc supplementation the potential cause of zinc toxicity.

Objectives: So, our purpose was evaluating the serum zinc level alterations before and after phototherapy, in hyperbilirubinemic newborns.

Materials and Methods: A prospective cohort study was performed at the children's medical center of Tehran University of Medical Sciences from 2012 to 2014. Healthy, full-term exclusively breast fed newborns with non-hemolytic jaundice were enrolled in the study. Participants were divided into two groups based on serum bilirubin levels (TSB < 18 mg/dL and TSB ≥ 18 mg/dL) at admission. Pre- and post-phototherapy total serum zinc level was measured before and 12 - 24 hours after termination of phototherapy.

Results: Phototherapy was associated with a significant increase in the serum zinc level in neonates with severe hyperbilirubinemia (TSB ≥ 18 mg/dL) but not in those with mild-moderate hyperbilirubinemia (TSB < 18 mg/dL). In addition, phototherapy caused a significant increase in the rate of zinc with potentially toxic levels (zinc > 200) in only neonates with severe hyperbilirubinemia.

Conclusions: Phototherapy increases serum zinc level by reducing bilirubin level so that additional supplementation of this element can lead potentially to zinc toxicity.

Keywords: Hyperbilirubinemia, Neonate, Zinc, Phototherapy

1. Background

Deposition of indirect bilirubin in the neuron membrane leads to permanent neuronal injury. Prevention of bilirubin encephalopathy and its chronic sequels is the essential aim of detecting and treating neonatal hyperbilirubinemia (1). Therapeutic options for unconjugated hyperbilirubinemia in neonates, like phototherapy and blood exchange transfusion are costly, time-consuming and potentially risky (2, 3). New therapeutic methods appear to be necessary to decrease elevated serum bilirubin. One of the possible therapies for preventing bilirubin neurotoxicity is via reducing the unconjugated bilirubin level by inhibition of enterohepatic circulation (4). Zinc salts have a potential to inhibit enterohepatic circulation of bilirubin probably by precipitating unconjugated bilirubin in the intestine (5). Accordingly, some clinical trials have evaluated the effects of zinc supplementation on hyperbiliru-

binemic neonates undergoing phototherapy (6-9).

The intracellular free zinc concentration is lower than its extracellular concentrations, so the electrochemical gradient causes zinc influx. An excessive load of intracellular zinc has toxic effects (10). Sobieszczanska et al. (11) hypothesized that reducing extracellular zinc by chelating agents in energetically insufficient cells, could prevent the influx of this element and its subsequent toxic effects. Therefore, "Zinc is potentially a 'Two-edged sword' which can both induce damage and protect neuronal cells from damage" (12).

The chemical structure of bilirubin has the potential to chelate metal ions, such as zinc (13). As a result, bilirubin reduction by phototherapy may cause an increase in serum zinc levels. In this situation, additional zinc supplementation may bring about zinc toxicity.

2. Objectives

This study evaluates serum zinc level alterations before and after phototherapy in hospitalized hyperbilirubinemic newborns undergoing phototherapy.

3. Materials and Methods

3.1. Subjects and Protocol

The present study was a prospective cohort study performed at the children's medical center of Tehran University of Medical Sciences (TUMS) from December 2012 to April 2014. Healthy, full-term, appropriate for gestational age and exclusively breast fed newborns that were admitted for evaluation and treatment of non-hemolytic jaundice were enrolled in the study. Newborns who had undergone exchange transfusion, had been formula fed, had any congenital malformation, inborn errors of metabolism, proven sepsis or infection, or jaundice in the first 24 hours of life, or whose mothers had a history of diabetes were excluded. Informed consent was obtained from the parents. This study was approved as a student thesis by the research and medical ethics committee of TUMS in accordance with the Helsinki declaration.

3.2. Measurements

Management of hyperbilirubinemia was performed largely based on American academy of pediatrics (AAP) guidelines (14) (adherence to AAP guidelines is not complete even in USA (15)); serum bilirubin was measured using the spectrophotometric method with the Selectra-2 autoanalyzer. The phototherapy was discontinued when the total serum bilirubin declined below 12 mg/dL.

The neonates with indication for phototherapy were divided into two groups based on their serum bilirubin levels on admission (TSB < 18 mg/dL: mild-moderate hyperbilirubinemia and TSB \geq 18 mg/dL: severe hyperbilirubinemia). Total serum zinc levels were measured before and 12 - 24 hours after termination of phototherapy using the atomic absorption spectrometry method [Ziest Chem Diagnostics kit, Iran (normal range: 50 - 150 μ g/dL)]. The time between blood sampling and separation of the serum by centrifuge was about 2 hours. Complete blood count, peripheral smear, blood group determination and Rh typing, Coombs test, thyroid function tests and a G6PD activity test were also performed in all cases in order to detect exclusion criteria.

3.3. Sample Size

With a significance level of 95% ($P < 0.05$) and power of 90% the accepted minimum sample size was calculated at 100 cases.

3.4. Statistical Analysis

Data were analyzed using SPSS 22 and the chi-square test, Fisher's exact test and paired t-tests were also used. Correlation analysis was performed by the Pearson test. A P value of < 0.05 was indicated as significant.

4. Results

This prospective cohort study was conducted on 128 full-term breastfed hyperbilirubinemic neonates who were admitted to the children's medical center hospital requiring phototherapy. At enrollment, the mean \pm standard deviation (SD) for gestational age at birth was 38.5 ± 0.6 weeks; birth weight 3163 ± 362 grams; neonatal age 5.7 ± 2.9 days; admission weight was 3002 ± 370 grams; admission bilirubin level was 18.5 ± 2.9 mg/dL; admission zinc level was 133.5 ± 54.4 μ g/dL; admission hemoglobin was 15.7 ± 1.7 mg/dL; and the duration of phototherapy was 2.4 ± 0.6 days and zinc level after phototherapy was 145.8 ± 52.1 μ g/dL. Of the neonates, 64 (50%) were male, 81 (63%) were born by Cesarean section (C/S), and 66 (51%) had admission bilirubin ≥ 18 mg/dL. There were no significant differences in the demographics among the neonates with bilirubin ≥ 18 mg/dL and those with bilirubin < 18 mg/dL.

4.1. In the Neonates With Bilirubin < 18 mg/dL

There was no linear correlation between the serum bilirubin and zinc levels before or after phototherapy ($P = 0.2$, $P = 0.12$, respectively). There was no statistically significant change in the zinc levels after phototherapy in these neonates (before phototherapy = 137 ± 60 , after phototherapy = 143 ± 55 , $P = 0.43$). There was no significant increase in the percentage of neonates with zinc levels > 200 mg/dL after phototherapy (before phototherapy 7 (11%) neonates, after phototherapy 9 (14%) neonates OR = 1.35, 95% CI = 0.47 - 3.89, $P = 0.59$).

4.2. In the Neonates With Bilirubin ≥ 18 mg/dL

There were significant adverse correlations between the serum bilirubin and zinc levels before phototherapy ($r = -0.31$, $P = 0.01$) and after phototherapy ($r = -0.4$, $P = 0.01$). There was a significant increase in the zinc levels after phototherapy in these neonates (before phototherapy = 129 ± 48 , after phototherapy = 148 ± 49 , $P = 0.01$). There was a significant increase in the percentage of neonates with zinc levels > 200 mg/dL after phototherapy (before phototherapy 3 (4%) neonates, after phototherapy 10 (15%) neonates, OR = 4.22, 95% CI = 1.11 - 15.93, $P = 0.04$).

5. Discussion

In this prospective cohort study, a significant inverse correlation was detected between zinc and bilirubin levels in neonates with severe hyperbilirubinemia. Phototherapy was associated with a significant increase in the serum zinc levels in neonates with severe hyperbilirubinemia but not in those with mild-moderate hyperbilirubinemia. In addition, phototherapy caused a significant increase in the rates of neonates with potentially toxic zinc levels (zinc > 200) among neonates with severe hyperbilirubinemia, while no significant change was observed among those with mild-moderate hyperbilirubinemia.

In our study an inverse correlation, which was statistically significant in cases with severe hyperbilirubinemia, was observed between zinc and bilirubin levels before and after phototherapy among all neonates with hyperbilirubinemia. The mechanism could underlie the observed relation between zinc and bilirubin levels investigated previously as in vitro studies (4, 11, 16) showing that zinc salts can precipitate unconjugated bilirubin at physiological pH, because the chemical structure of bilirubin has the potential to chelate with metal ions, such as zinc. In vivo studies showed that zinc salts can inhibit the enterohepatic circulation of unconjugated bilirubin by precipitating it in the intestine because prescription of zinc salts causes a decrease in serum unconjugated bilirubin but an increase in the fecal bilirubin excretion (5).

In this study phototherapy in neonates with severe hyperbilirubinemia was associated with a significant increase in the serum zinc levels and also in the rates of neonates with potentially toxic zinc levels. Although zinc has traditionally been known as a nontoxic element, nowadays it has been shown that free ionic zinc can potently kill neuronal cells (17). Recently some studies have proposed using zinc salts for lowering bilirubin levels in neonates with jaundice or preventing the incidence of neonatal jaundice (6, 7, 9, 10). The results of these studies should be considered when evaluating the effect of zinc therapy in hyperbilirubinemic neonates. Rana et al. (6), Kumar et al. (7), and also Maamouri et al. (8) found that the incidence of hyperbilirubinemia and requirement of phototherapy did not differ with zinc supplementation, except for a shorter duration of phototherapy. None of these studies reported any zinc toxicity in zinc supplemented neonates (the studies included all neonates, not only neonates with hyperbilirubinemia). As serum zinc level is higher in hyperbilirubinemic neonates (18), zinc supplementation in addition to phototherapy may cause an increase in the serum zinc level and zinc toxicity.

5.1. Limitations

In this study we did not ethically allow to get a control group with the same bilirubin level who were not treated with phototherapy.

5.2. Conclusions

Phototherapy by reducing the bilirubin level causes an increase in the serum zinc level which can make additional zinc supplementation the potential cause of zinc toxicity. Accordingly, it appears that using soluble zinc salts that can be absorbed into the blood system is not safe in hyperbilirubinemic neonates. Therefore, we suggest that future studies on inhibiting bilirubin enterohepatic circulation in hyperbilirubinemic neonates be done with low absorbable (insoluble) zinc salts.

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Footnote

Authors' Contribution: Ziba Mosayebi, designing the work; Maral Rahmani, drafting the work; Shahin Behjati Ardakani, revising it critically for important intellectual content; Mahdi Sheikh, analyzing the data; Mamak Shariat, interpretation of data for the work; Golnaz Rezaeizadeh, writing the article and final approval of the version to be published.

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