



Incidence of Zinc Toxicity as a Complication of Phototherapy

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Abstract

Background: Neonatal jaundice is one of the common newborn illness for which existing therapies are not only costly, time-consuming but also has some inherent risks. Phototherapy duration can be reduced by adding zinc salts. Unconjugated bilirubin in the intestine (bilirubin and zinc can form a complex in physiologic pH) is precipitated by zinc salts; 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.

Objective: Estimation of serum zinc level alterations before and after phototherapy, in jaundiced newborns

Materials and Methods: A prospective cohort study was performed at the newborn department of RMMCH. 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.

Background

Unconjugated bilirubin deposition in the neuronal membrane leads to permanent neuronal injury. Primary aim of detecting and treating neonatal hyperbilirubinemia is the prevention of bilirubin encephalopathy and its chronic sequelae. Therapeutic options for unconjugated hyperbilirubinemia in neonates, like phototherapy and blood exchange transfusion are costly, time-consuming and potentially risky. 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. Zinc salts have a potential to inhibit enterohepatic circulation of bilirubin probably by precipitating unconjugated bilirubin in the intestine. Accordingly some clinical trials have evaluated the effects of zinc supplementation on Hyperbilirubinemic neonates undergoing phototherapy.

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. Sobieszczanska et al. 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.

The chemical structure of bilirubin has the potential to chelate metal ions, such as zinc. 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.

Objectives

Estimation of serum zinc level alterations before and after phototherapy in hospitalized jaundiced newborns undergoing phototherapy

Materials and Methods

Subjects and protocol

The present study was a prospective cohort study performed at the RMMCH, Chidambaram from January 2016 to December 2016. Full-term, healthy 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 by research committee of RMMCH.

Measurements

Management of hyperbilirubinemia was performed largely based on American academy of pediatrics

(AAP) guidelines. Serum bilirubin was measured. 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/d: 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 (normal range :50-350 mg/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 s G6PD activity test were also performed in all cases in order to detect exclusion criteria.

Sample Size

A significant level of 95% (P < 0.05) and power of 90% the accepted minimum sample size was calculated at the 100 cases

Statistical Analysis

Data collected were analyzed by using SPSS 22 and the chi-square test, paired t-test and Fisher's exact test were also used. Pearson test was used to perform correlation analysis.

A,P value of < 0.05 was indicated as significant

Results

This cohort prospective study was conducted on 130 full term breastfed jaundiced neonates who were admitted to the RMMCH requiring phototherapy, At enrollment the mean \pm standard deviation (SD) for gestational age was 39.5 \pm 0.6 weeks; birth weight 3283 \pm 482 grams; neonatal age 6.8 \pm 2.8 days; admission weight was 3182 \pm 370 grams ; admission bilirubin level was 18.5 \pm 2.9 mg/dL; admission zinc level was 133.5 \pm 54.4 mg/dL; admission hemoglobin was 15.7 \pm 1.7 mg/dL ;and the duration of phototherapy was 2.4 \pm 0.6 days and zinc level after phototherapy was 145.8 \pm 52.1 mg/ dL ; Of the neonates 65(50%) were male, (66%) were born by cesarean

section(C/S) and (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 .

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 = 128 ± 60 , after phototherapy = 133 ± 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, $P=0.59$)

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 = 139 ± 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, $P=0.04$)

Discussion

In this cohort prospective study, a significant correlation which was inverse was detected between zinc and bilirubin levels in neonates with severe jaundice. Phototherapy was associated with a significant increase in the serum zinc levels in neonates with severe jaundice but not in those mild- moderate jaundice. In addition, phototherapy caused a significant increase in the rates of neonates with potentially toxic zinc levels

(zinc >200)among neonates with severe jaundice, while no significant change was observed among those with mild- moderate jaundice.

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 jaundice. 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 that 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 injure neurons⁽¹⁷⁾. Recently some studies have proposed using zinc salts for lowering bilirubin levels in neonates, jaundice or preventing the incidents of neonatal jaundice ^(6,7,9,10). The results of the studies should be considered when evaluating the effect of zinc therapy in hyperbilirubinemic neonates. Kumar et al. ⁽⁶⁾, Rana et al ⁽⁷⁾ and also Maamouri et al. ⁽⁸⁾ found that the incidents of hyperbilirubinemia and requirement of phototherapy did not differ with 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.

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.

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 can be absorbed into the blood system is not safe in hyperbilirubinemic neonates. Therefore, we suggest that studies on inhibiting bilirubin enterohepatic circulation in jaundiced neonates be done with low absorbable (insoluble) zinc salts.

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