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Efficacy of zinc sulfate in reducing unconjugated hyperbilirubinemia in neonates

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ABSTRACT

Hyperbilirubinemia is a common disease and unconjugated hyperbilirubinemia has been seen mainly in neonates. Severe form of unconjugated hyperbilirubinemia may cause kernicterus and even death. Conventional treatment for severe unconjugated hyperbilirubinemia consists of phototherapy and exchange transfusion that have several known disadvantages; specially exchange transfusion is associated with a significant morbidity and even mortality. These harmful effects indicate the need to develop alternative pharmacological treatment strategies for unconjugated hyperbilirubinemia. One of these pharmacological agents is zinc salts. Zinc has been shown to lower the bilirubin levels by inhibition of the enterohepatic cycling of unconjugated bilirubin. Oral zinc has been shown to reduce serum unconjugated bilirubin in animals, adolescents and low birth weight neonates. However, studies in healthy term neonates given oral zinc showed no reduction in hyperbilirubinemia based on daily measurement. In order to improve the accuracy, hyperbilirubinemia may be determined based on measurements every hour. More studies are needed to know the effect of zinc in neonatal jaundice.

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Introduction

In recent years, substantial researches have been carried out to predict neonates who are most likely to develop hyperbilirubinemia. Reliable prediction can reduce hospital stay for low-risk neonates resulting in their early discharge and identifying high-risk

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neonates facilitating their closer follow-up (1). In general, 60% of full-term newborns and 80% of preterm ones experience jaundice in their first week of life (2,3). The highest incidence of severe neonatal hyperbilirubinemia is in Asians; accounting for one third of infantile admissions in Iran (3). Jaundice in such cases is mainly physiologic and is diagnosed by ruling out other causes of icterus such as hemolysis, infection or metabolic diseases whereas 5-10% require intervention (3,4). The fundamental aim of detecting and treating severe neonatal jaundice is to prevent bilirubin encephalopathy and its chronic sequel (1,5). Such complications further necessitate the importance of treatment in this disease. Although up to now the phototherapy and blood transfusion have been the treatment of choice in such cases, both have several disadvantages (4). Exchange transfusion has the risk of Graft Versus Host Disease (GVHD) and a higher mortality rate (2). Phototherapy induces parental anxiety secondary to hospitalization and high cost of care. On the other hand, it disturbs mother-infant bonding; whereas drug therapy is more practical and has a lower cost of care.

In several studies, the association between micronutrients and icterus have been proposed and various substances have been introduced which bound to bilirubin in the small intestine, resisted against its absorption and therefore prevented enterohepatic circulation, but with inconsistent results (1,6).

Zinc is one of the essential elements in neonatal growth, protein synthesis and regulation of inhibitory and stimulatory synapses of the brain. Zinc lower the bilirubin levels by inhibition of the normal enterohepatic cycling of unconjugated bilirubin (UCB) (7-9). Therefore, the anticipated role of zinc supplementation in neonatal jaundice seems to be an attractive issue.

Discussion

Drug therapy has always been a method with highest compliance, low cost and the treatment method in cases of neonatal hyperbilirubinemia.

Clofibrate, phenobarbtal, bile salts, dipenycilamine, zinc compounds and etc. have been studied so far which act through different mechanisms such as inhibition of production, stimulation of hepatic clearance and enzyme inhibition (10). However, none has been proposed as a common therapeutic method so far.

Bilirubin is produced by the catabolism of heme in the intestine to form a structure that cannot be absorbed by the intestine into the blood stream and will be excreted in the feces resulting in decreased unconjugated bilirubin (UCB) blood. Based on this theory oral zinc is expected to reduce hyperbilirubinemia (11). To date, zinc salts have been demonstrated to be promising in both in vitro and in vivo conditions (1). In other words, the action of zinc in hyperbilirubinemia depends on its ability to reach the distal intestine where it precipitates the unconjugated bilirubin to prevent the enterohepatic circulation.

The first human study on this issue was performed by Mendez-Sanchez et al. on adult patients of Gilbert syndrome. This study was a small study with low sample size, enrolling only 20 patients. Authors reported that zinc sulphate administration decreased the serum unconjugated bilirubin significantly (7).

In another study by Rana et al. (1), the efficacy of oral zinc salt was investigated on the incidence of hyperbilirubinemia and the need of phototherapy in at-risk term and late-preterm neonates between 25 and 168 h of age. They concluded that twice-daily administration of oral zinc in a dose of 10 mg/day did not reduce the incidence of hyperbilirubinemia in such cases during first week of age (1).

Mafinejad et al. conducted a study in Iran in 2012. They showed that administration of zinc sulfate neither affected hyperbilirubinemia nor delayed jaundice appearance. However, fewer admissions and phototherapy duration was reported in the zinc group. Weight gain between 3rd and 7th day of age was also more significant among the zinc group (12).

In a study by Vitek et al. in 2005, the oral administration of zinc salts efficiently decreased serum bilirubin levels in hyperbilirubinemic rats, most probably due to the inhibition of enterohepatic circulation of bilirubin. They suggested that this approach might be useful in the treatment of severe unconjugated hyperbilirubinemia (8).

Nevertheless, Patton et al. studied the effect of oral zinc on 60 neonates with hyperbilirubinemia. The neonates were divided into the study group receiving 5mg oral zinc twice daily for five days and the control group. They reported that bilirubin level measurement on day 5 of treatment have showed no significant difference in the duration of hyperbilirubinemia between the two groups (11). No adverse effects have been seen in these studies.

Regarding several trials treating large number of children with diarrhea, measles, pneumonia, common cold and malaria, oral zinc has been found to be quite safe (13-15).

Conclusion

Administration of oral zinc sulfate in neonatal jaundice may reduce duration of phototherapy and the mean total serum bilirubin (TSB) levels in neonates. Therefore, zinc may be recommended as a safe and effective medication in neonatal jaundice beside phototherapy. Further studies with a larger sample size, different dosage, formulation of zinc and with more precise laboratory studies are recommended in the future to confirm these findings.

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Conflict of Interest

The authors declare no conflict of interest.

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