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Effect of zinc sulfate in prevention of jaundice in healthy term newborns

Leila Mehrabi Sharaf-Abadi[1], RakhshanehGoodarzi[2], Salma Naderi[2], Abolhasan Divband[2]

[2]*Clinical Research Development Center of Children Hospital/ Hormozgan University of Medical Science, Iran*
[1]*Department of Pediatrics, Faculty of Medicine, College/ Hormozgan University of Medical Science,Iran*

Abstract:
Background*: Neonatal jaundice or hyperbilirubinemia is a common problem in infants that increases serum bilirubin. Prevention of jaundice may be more reliable than conventional treatments such as phototherapy or blood transfusions. The aim of this study was to investigate the effect of oral zinc sulfate in prevention of jaundice in healthy term newborns.*
Materials and Methods*: In the present study, 120 infants weighing more than 2500 gr and gestational age over 37 weeks were divided into two equal control groups and case. After prescribing Zinc Sulfate oral syrup, they were asked to come back to Bandar Abbas Persian Gulf Hospital on the second and fourth days of birth for checking neonatal skin bilirubin (TcB). Then, in addition to measuring the skin bilirubin concentration, based on a pre-prepared questionnaire, other information such as newborn weight, gender, newborn and mother's blood type, gestational age, type of delivery and history of anewborn (with jaundice) were completed. Statistica 8 was used to analyze the data, and descriptive information was reported with the help of the mean percentage and the maximum and minimum standard deviation.Also, to analyze the relationship of quantitative variables, parametric or non-parametric test were used. R.3.6.3 program was used to investigate the effect of TcB concentration on the studied variables and a final and valid model was obtained using this program.*
Results*: In this study, the mean TcB concentration was recorded in the second and fourth days in the case group (5.25 ± 1.44 and 7.43± 1.4 mg/dL, respectively), which was lower than the control group (6.85 ± 1.23 and 10.44± 2.51 mg/dL, respectively). The comparison of these two groups showed a statistically significant differences (p = 0.000). Also, in both groups, the concentration of TcB in the second and fourth days was positively correlated with neonatal weight. Finally, the model obtained with the R.3.6.3 program showed the effect of TcB concentration on birth weight, breast feeding and gestational age, and the results of this model were statistically validated.*
Conclusion*: Preventive administration of oral sulfate at a dose of 5 mg per day to healthy term newborn is likely, reduce bilirubin. This result may be due to cessation of hepatic secretion or/and enterohepatic circulation happen.*
Key Word*: Hyperbilirubinemia, Jundice, healthy term newborns, Zinc Sulfate*

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I. Introduction

Neonatal jaundice means yellowing of the skin of infants, resulting increased levels of bilirubin as scientifically called hyperbilirubinemia[1]. Serum bilirubin concentrations generally increase from birth to reach a peak during the third to fifth days[2]. It becomes apparent when the total bilirubin in the serum is 5 mg /dL[1].It's known as one of the most common conditions that require medical attention in infants. In the first week of life, about 84% of term newborn[3]and 60% of infants experience jaundice[4,5]. Bilirubin is produced by catabolism of hem in the reticuloendothelial system. Un-conjugated bilirubin is released reversibly into the circulatory system while being firmly bound to albumin.When the compound bilirubin-albumin reaches the liver cell, it is transported to the liver cells, where there is a compound of an enzyme that produces (bilirubinmonoand diglucuronides) with glucuronic acid. The conjugate compound is catalyzed by (UGT-1A1: uridine diphosphate glucuronosyl transferase). The mono and diglucuronides compounds are then excreted in the bile and intestines. In infants, most of the conjugated bilirubin in the gut is hydrolyzed to non-conjugated bilirubin, a reaction catalyzed by the beta-glucuronidase enzyme in the intestinal mucosa. The un-conjugated bilirubin then re-enters into the blood through the intestinal circulation and injects some extra bilirubin into the liver. This part of the bilirubin circulation is called the enterohepatic cycle and plays a major role in some cases of jaundice in infants[6].

The role of zinc and its importance in physiological cycles is undeniable. The role of zinc can be divided into three groups: catalytic, structural, and regulatory functions[7,8]. In new born, deficiency of this micronutrient can negatively affect the growth, reduce immune system against infections, and even increasing mortality[9] and also cause idiopathic jaundice[10]. Although serum zinc makes up only 0.1 percent of the body's total, with the same amount of circulating, it quickly meets the needs of the body's various tissues[11]. Zinc is absorbed by the carrier-mediated mechanism in the small intestine [12]. Also,recently studies have shown that there is a different rate of absorption by ages[13]. The physiological need for zinc varies depend of ages. Accordingly, infants 6 to 12 days of age need 0.84 mg per day of zinc[14].

In order to Jundice description, as well as to evaluate the possibility of preventing and managing jaundice and thus reducing the destructive effects of this disease on infants, it is very important to pay attention to Total Serum ofBilirubin(TSB) and the age after birth. Research has shown about 95% correlations between TSB and transcutaneous bilirubin (TcB)[15,16]. Indeed, the TcB levels can accurately predict TSB in both preterm and term neonates and also at all measurement sites suchas forehead, sternum and abdomen[17]. The incidence and severity of jaundice can be changed to various dangerous, intermediate and low risks[18].

According to the American Academy of Pediatrics (AAP), blood transfusion and phototherapy are currently used to treat jaundice. Unfortunately, these methods each have their own side effects and can be dangerous[19,20,21]. Moreover, it is expensive also take a long time. In order to provide a preventive method in the future, this method should be a good alternative in compare to other common methods and also its side effects should be minimized and safe. Although, studies have been conducted in the past on the effect of zinc sulfate on the treatment of jaundice, it is necessary to conduct new studies in healthy term infants with a "preventive" view. In particular, these studies differ in terms of dose of zinc sulfate, conditions of sample, age of infants, genetic characteristics of the community. As a consequence, it seems that using the results of this group of studies with the aim of preventing jaundice can confuse researchers. Also, in many cases, infants with jaundice have been selected to study the effects of zinc sulfate, which can seriously challenge the accuracy of the results. Therefore, the necessity of designing and conducting new studies in a specific age group, maintaining non-intervening conditions is more obvious. The aim of this study was to investigate the effect of oral Zinc sulfate on the prevention of jaundice in healthy term infants based on type of delivery, birth weight, previous child jaundice history, neonatal sex and infant and maternal blood type.

II. Material And Methods

The present study was performed on healthy term newborns in Bandar Abbas Persian Gulf Hospital (Iran) after obtaining the approval of the ethics committee from Hormozgan University of Medical Sciences Research and obtaining written consent from the parents. Prior to the study, parents of newborns were given informed consent with full explanation of all stages of the study. At the same time, the necessary awareness was always given to the parents, including the confidentiality of the recorded information and the possibility of refraining from cooperating at any stage. The newborns were randomly selected according to the criteria of entry and exit from the study (as followed) and were divided into two equal groups (control and case), each of which was divided into 60 infants. The criteria for entering the study included healthy babies (start breastfeeding),older than 37 gestational age (weeks) and birth weight more than 2500 grams and the criteria for leaving the study included G6PD-deficiency, ABO and Rh infants, Sepsis symptoms, severe congenital anomalies, asifox ,IUGR, immune defects, hospital history and possible need for phototherapy or blood exchange. During the study, in the event of any physiological instability or other adverse effects of the intervention, these items were completely removed from the sampling list. Also, in order to complete the required information, including the newboen age, type of delivery, birth weight, history of a child with jaundice(HCWJ),gender and the newborn/mother’s blood type were collected in pre-designed questionnaires.

In the first group (control), where babies are healthy and normal, immediately after birth, they usually met with the mother in the hospital, and after the mother's discharge from the hospital, parents were advised to cooperate in the research on the second and fourth days of birth, to measure the amount of TcB, refer to the neonatal section of Bandar Abbas Persian Gulf Hospital daily. In the second group (case), in addition to the above, 5 mg of zinc sulfate syrup per day was prescribed at 1% with the volume of each glass of syrup equivalent to 60 ml as a single dose daily for 5 days[22,23]. As long as the newborn's mother was hospitalized, the infant's trained nurse continued to feed the sulfate syrup to the infant. After the mother's discharge from the hospital, a phone call was made to ensure that the medicine was received as programed before.

In the present study, according to the manufacturer's instructions and by a person trained in this field the amount of skin bilirubin was measured by BILINFANT device manufactured by ParsianAzteb Company, model YZB/SU0372/2007.

To analyze the data, statistical programs includes Statistica.8 and R.3.6.3 used. Descriptive information was reported with average percentage and maximum and minimum standard deviation. Parametric testing or non-parametric was also used to analyze the relationship of quantitative variables due to whether the distribution

was normal or not[24]. In addition, p value is considered to be less than or equal to 0.05. In order to investigate the effect of TcB in the second and fourth days of sampling, we used (Linear Model) by R program.

III. Result

In the present study, the gender of control and case group consisted of 68% and 57% (male) as well as 32% and 43% (female), respectively. The results of other categorical variables are shown in terms of percentage in the two groups (Table 1).

Table 1: Comparison of categorical variables in control and case group

Characteristics	Control Group Number (%)	Case Group Number (%)	*p* value
Gender			0.44
Mal	41(68)	34(57)	
Female	19(32)	26(43)	
Mode of delivery			0.74
Caesarian	13(22)	3(5)	
Vaginal	47(78)	57(95)	
Type of feeding			0.53
Breast Feeding	50(83)	58(97)	
Formulated Feeding	10(17)	2(3)	
Newborn Blood Type			0.87
A	15(25)	16(27)	
B	14(23)	15(25)	
AB	8(13)	5(8)	
O	23(39)	24(40)	
Mother Blood Type			0.75
A	10(17)	19(32)	
B	16(27)	16(27)	
AB	12(20)	7(11)	
O	22(36)	18(30)	
History of jaundice			0.14
Yes	10(17)	10(17)	
No	50(83)	50(83)	
Hospitalization			0.44
Yes	7(12)	3(5)	
No	53(88)	57(95)	

The concentration of TcB in the second and fourth days in the control group (red triangles) is mostly higher than the case group (green circles), while the maximum level of TcB concentration in both control and case groups was higher on the fourth day than on the second day of sampling (Figure1a ,b).

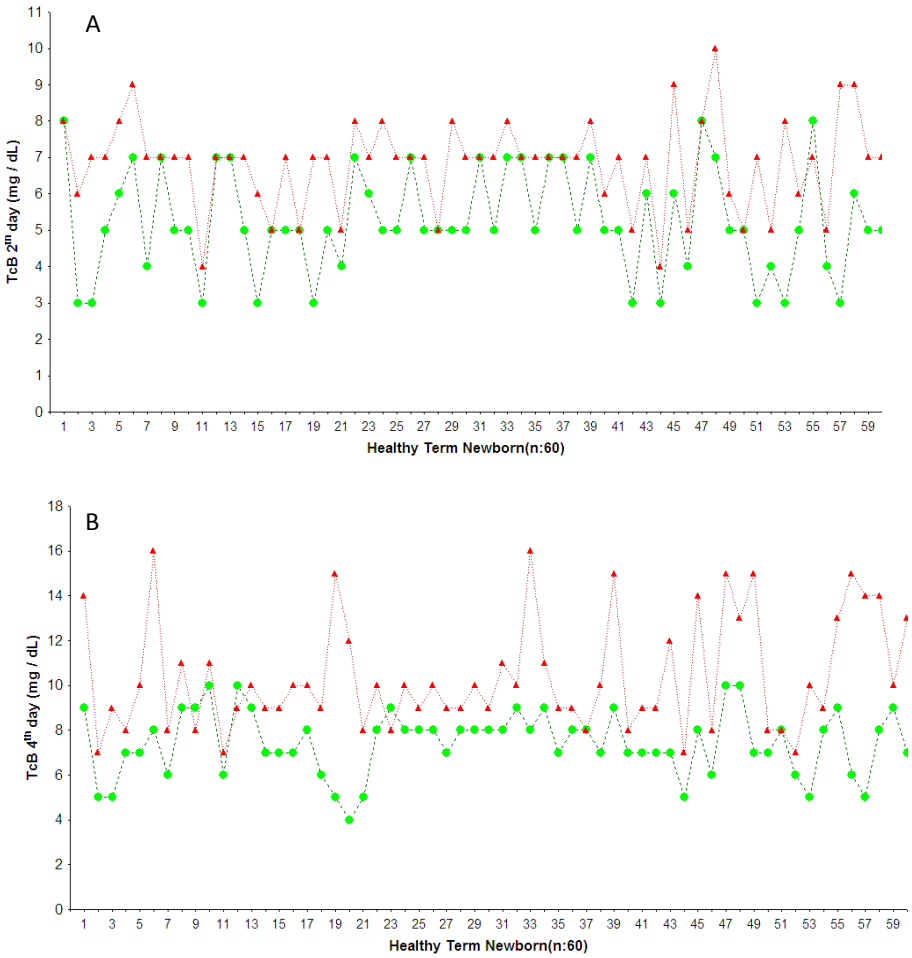

Figure 1.TcB concentration on the second day (A) and the fourth day (B).
control group (red triangle),case group(green circle)

The concentration of TcB in the control group shows higher value than case group on both second and fourth day (6.85 ± 1.23, 10.40 ± 2.51 and 5.25 ± 1.44, 7.43 ± 1.44 mg/dL, respectively). In terms of average weight, we obtained higher value in control group compared with case group (Table 2). Also, the mean TcB concentration (second day and fourth day) showed a significant difference between the control and the case groups (p value = 0.00) (Table 2).

Table 2: Comparison of continuous variables in control and case group

Characteristics	control Group (n = 60)	case Group (n = 60)	p value
Mean gestational age ± SD (weeks)	38.42 ± 0.92	38.52 ± 1.13	0.70
Mean STB at 2th day of age ± SD (mg/dl)	6.85 ± 1.23	5.25 ± 1.44	0.00
Mean STB at 4th day of age ± SD (mg/dl)	10.40± 2.51	7.43±1.44	0.00
Mean birth weight ± SD (gr)	2899.58 ± 243.68	3031.67 ± 334.12	0.15

Figure 2 shows the Boxplot of TcB concentration on the second and fourth day in the healthy term newborns. The mean concentration of TcB in both second and fourth days in the control group was higher than the case group. The results were statistically significant (Table 2).

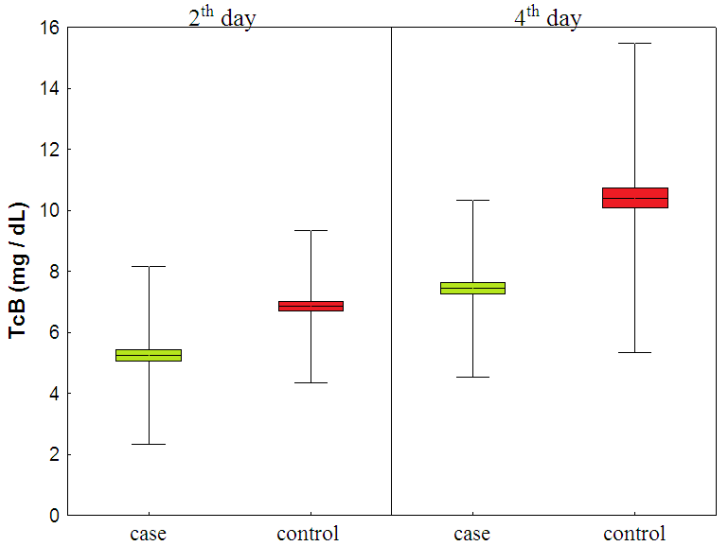

Figure 2. Median values (line), the 25_75% percentiles (box), and the non-outlier ranges (whisker) of the TcB concentration of healthy term newborns. Control group (red box), case group (green box)

The results of correlation between TcB concentration and healthy newborn weight on the second day in both control and case groups showed a positive correlation (r= 0.29 0.30; p value= 02, 03; r^2=08, 09). Also, the results of forth day for above variables showed a positive correlation (r= 0.25, 0.28; p value= 05, 04; r^2=07, 08) (Figure 3 a, b). In the same way, results of modeling with R.3.6.3 program showed the effect of TcB concentration on birth weight and type of food (breastfeeding), which was finally tested in terms of significance and validity, which was run in rcmdr environment and by installing the mass package.

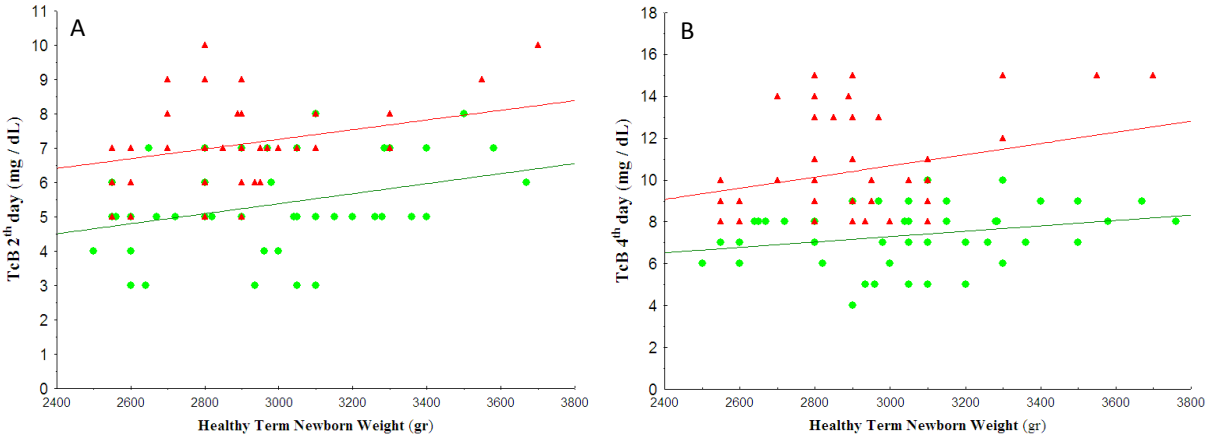

Figure 3. Scatterplots of TcB 2thvs. newborn weight (A) and TcB 4thvs. newborn weight (B). Red triangles are the values for the control groupand green circles are the values for the case group.Correlation lines are shown only when are statistically significant (p<0:05). Red line:control group; Green line: case group

IV. Discussion

Last studies on animals have shown that zinc binding to bilirubin and then prevent bilirubin reabsorption trough enterohepatic cycle, consequently reducing TSB concentration[25]. In other study, the amount of bilirubin secreted in Wistar rats with hyperbilirubinemia (using zinc sulfate) was investigated. The results showed that the bilirubin concentration dropped significantly from 45 to 25 nmol/h 100gr body weight[26]. The serum zinc levels showed lower value in infants with jaundice than in healthy[13]. As a result, they concluded zinc may have played a protective role against jaundice.In other studies, using 5 mg of zinc Sulfate in infants with jaundice(3 days prescribed and simultaneously treated with phototherapy) showed significant reduction from 9.00 ± 2.64 to 7.76 ± 2.28 (p=0.011)[23]. Same result obtained using 10 mg per day of zinc sulfate in the first week of life[27]. Although the results of zinc sulfate in neonatal term are similar to those in LBW infants[28.29], but in other studies, this effect has not led to a reduction of TSB[30,31,32]. It may be resulted due to differences in the

number of patients, simultaneous phototherapy, sampling conditions, or data analysis methods. Decreased TcB after zinc sulfate consumption associated with age and thus reduce the time of conventional therapies such as phototherapy[33].

Based on the results of this study, the TcB concentration of the case group in both study days (second day and fourth day) was clearly lower than the control group, which was statistically significant (p value =0.00). Babaeiet al.[2], used a volume of 5 mg per day to test preventive possibility of oral zinc sulfate for jaundice disease. They found that the concentration of TcB on the first and second day after birth did not differ significantly between the two groups, but from the third to the fifth day, the amount of skin bilirubin in the case group was significantly lower than the control group. This effect has been associated with accelerating the process of excretion of meconium and then reducing the enterohepatic cycle. Similar results were obtained in other studies[34,35].

Due to the limitation of hourly sampling of TcB concentration in the present study, it was not possible to investigate the correlation between age variability and TcB concentration. However, in both control and case groups, we observed an increase in TcB concentration from the second to the fourth day.This diferences was statistically significant. A study of about 3,000 newborns with a gestational age over 35 weeks and a birth weight of more than 2,500 grams found a correlation between age and bilirubin concentration [36]. Due to the inverse relationship between zinc concentration and TcB, the results of the present study can be compared with the results of Boskabadiet al.[13]. They found a strong and negative relationship between serum zinc concentration and infant age (pvalue=0.7), However, another study was not in accordance, which may have been influenced by concomitant phototherapy[37]. Considering the relationship between age and weight, it is obvious that the results of TcB concentration-age are consistent with the results of TcB concentration-weight. Accordingly, in the present study, a weak positive correlation was obtained between TcB concentration and weight in the control and case groups on the second and fourth day. However, in another study, no such correlation was reported[23].

Breast feeding-related jaundice occurs 2-4 days after birth. Before, studies have shown that there is a direct link between breast feeding and increased prevalence of neonatal hyperbilirubinemia in infants[38]. This type of jaundice appears to be associated with increased bilirubin in the first few days after birth. This happens in the first few days because until starts breastfeeding, babies receive fewer calories, and lowering their calorie intake is an important stimulus to increase intestinal circulation.

In this study, initial nutrition of newborn scheduled via breastfeeding. The level of bilirubin recorded in the control group is higher than the case group.This higher value may be interpreted as breastfeeding-related jaundice. This confusion with an attention to our results could interpret. In this study, case and control groups includes 83 and 97 percentage breastfeeding respectively also this differences was not significant statistically (p= 0.53).Then, the effect of oral zinc sulfate syrup and its importance in reducing TcB well appears. Also, in the obtained model, using the statistical program R, the effect of TcB on the type of nutrition (breastfeeding) was proved.

Based on the results, the comparison between the variables of type of delivery, gender, blood type, HCWJ, hospitalization in the control and case groups did not showed a significant difference.These results can be compared with the study of Boskabadiet al.[13]. They no report significant relationship (p = 0. 53, 0.34, 0.07, respectively), but it was significant for the history of hospitalization (p=0.014). In another study, instead of examining bilirubin, they studied statistical relationships between zinc and the above variables. Results did not showed significant relationship between gender, type of delivery and type of breastfeeding with zinc[27].Also, Nabavizadehet al.[39], no significant relationship was found between the discussed variables. According to this study, relationship between control group and case (p = 0.87, 0.75) was not significant in terms of blood group (p> 0.05).

V. Conclusion

According to the study, the concentration of TcB in the case group by receiving oral zinc sulfate syrup in the second and fourth days was clearly lower than the control group, so likely, oral zinc sulfate syrup play an important role in preventing jaundice in healthy term newborns. The reason for this preventive effect can be related to inhibition of un-conjugated bilirubin concentration, inhibition of production, stimulation of hepatic secretion or cessation of intrahepatic cycle.

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References

[1]. American Academy of Pediatrics Subcommittee on Hyperbilirubinemia(AAP). Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2014;114(1): 297-316.
[2]. Maisels MJ. Jaundice. In: MacDonald MG, Seshia MMK, Mullett MD, eds. Neonatology: Pathophysiology and Management of the Newborn. Philadelphia, Pa: Lippincott Co. 2005:768–846
[3]. Bhutani VK, Stark AR, Lazzeroni LC, et al. Initial Clinical Testing Evaluation and Risk Assessment for Universal Screening for Hyperbilirubinemia Screening Group. Predischarge screening for severe neonatal hyperbilirubinemia identifies infants who need phototherapy. J Pediatr. 2013;162(3):477-482.
[4]. Amos RC, Jacob H, Leith W. Jaundice in newborn babies under 28 days: NICE guideline. ArchDis Child EducPract Ed. 2017;102 (4): 207-209.
[5]. Michael K, Ronald JW, EricSibley DK. Neonatal jaundice and liver disease. In: Martin RJ, Fanaroff AA,Walsh MC. Neonatal-perinatal medicine diseases of the fetus and infant medicine. 9th ed. Philadelphia: Mosby Elsevier.2011: 1443-81.
[6]. Maisels JM. Neonatal Jundice. Pediatrics in Review.2006; 27: 443-454.
[7]. Cousins RJ. Zinc. In: Filer LJ, Ziegler EE, editors. Present Knowledge in Nutrition. 7th ed. Washington DC: International Life Science Institute Nutrition Foundation.1996: 293-306.
[8]. Brown KH et al. Effect of supplemental zinc on the growth and serum zinc concentrations of prepubertal children: a meta-analysis of randomized controlled trials. American Journal of Clinical Nutrition.2002;75:1062-1071.
[9]. Brown KH, PeersonJM, Baker SK, and Hess SE.et al. Preventive zinc supplementation among infants, preschoolers, and older prepubertal children. Food and Nutrition Bulletin. 2009; 30(1):12-36.
[10]. Tan H, Karakelleoğlu C,Akçay F, Akdağ R & Alp H. Serum concentrations of zinc, magnesium, manganese and copper in neonatal jaundice. Atatürk Üniversitesi Tıp Dergisi.2000; 32 (1): 9-12.
[11]. Brown KH, Rivera JA, Bhutta Z, GibsonRS, King JC, et al. International Zinc Nutrition Consultative Group (IZiNCG) technical document. Assessment of the risk of zinc deficiency in populations and options for its control. Food Nutr Bull.2004; 25: 99-203.
[12]. Cousins RJ. Absorption, transport, and hepatic metabolism of copper and zinc: Special reference to metallothionein and ceruloplasmin. Physiol Rev.1985; 65: 238-309.
[13]. Boskabadi H, MaamouriG, Mohsen Zadeh H, Shakeri MT, Ghayour-Mobarhan M, , Mohammadi S, Fern G. Comparison of Serum Zinc Level Between Neonates With Jaundice and Healthy Neonates. Shiraz E Medical Journal. 2015; 27392.
[14]. WHO (World Health Organization. Levels and trends in child malnutrition. Joint child malnutrition estimates. New York, NY: United Nations International Children's Fund. Geneva: Washington, DC: World Bank.2012.
[15]. Taylor JA, Anthony E. Burgos MD, Valerie Flaherman MD, Esther K, Chung MD et al. Discrepancies Between Transcutaneous and Serum Bilirubin Measurements. Pediatrics.2014;135(2): 224-231.
[16]. Christian V, Hulzebos ID, Deirdre E, Vader-van I, Bos AF, Dijk PH. Should transcutaneous bilirubin be measured in preterm infants receiving phototherapy? The relationship between transcutaneous and total serum bilirubin in preterm infants with and without phototherapy.plos one.2019;14(6): e0218131.
[17]. Vasava S and DagliPP.Transcutaneousbilirubinometry: Influence of gestational age and measurement site . Sri Lanka Journal of Child Health.2018; 47(1):27-32.
[18]. Maisels MJ. Jaundice. In: MacDonald MG, Seshia MMK, Mullett MD, eds. Neonatology: Pathophysiology and Management of the Newborn. Philadelphia, Pa: Lippincott Co; 2005:768–846
[19]. Matichard E, Le Henanff A, Sanders A, Leguyadec J, Crickx B, Descamps V. Effect of neonatal phototherapy on melanocytic nevus count in children. Arch Dermatol. 2006; 142(12):1599-604.
[20]. Dennery PA, Lorch S. Neonatal blue–light phototherapy could increase the risk of dysplastic nevus development. Pediatrics.2007; 119(6): 247-248.
[21]. Taksande A &Selvam S. Side Effects of Phototherapy in Neonatal Hyperbilirubinemia. ActaScientific Paediatrics.2018;1(5): 24-30.
[22]. Babaei H, Hemmati M, Fallahi V, Rezaei M. Effect of oral zinc sulfate in prevention of jaundice in healthy term newborns. Journal of Kermanshah University of Medical Sciences. 2014;17: 680-686.
[23]. ErfaniP,Gudarzi R. The effect of oral zinc sulfate on the treatment of jaundice in the first week of infancy. The final dissertation on the specialty of diseases of children and infants, Hormozgan University of Medical Science. 2015: 33-45(In Persian).
[24]. Millar RB, Anderson MJ. Remedies for pseudoreplication. Fisheries Research.2004;70: 397-407.
[25]. Mendez-Sanchez N, Roldan-Valadez E, Flores MA, Cardenas-Vazquez R, Uribe M. Zinc salts precipitate unconjugated bilirubin in vitro and inhibit enterohepatic cycling of bilirubin in hamsters. European Journal of Clinical Investigation.2001; 31:773-80.
[26]. Vitek L, Muchova L, Zelenka J, Zadinova M, Malina J. The effect of zinc salts on serum bilirubin levels inhyperbilirubinemic rats. J PediatrGastroenterol Nutr.2005; 40(2):135-40.
[27]. Agrawal K, Kumar S, Sethi RS. Efficacy of Oral Zinc Acetate in Reducing Hyperbilirubinemia in Full-Term and Near-Term High Risk Neonates. Journal of Dental and Medical Sciences (IOSR-JDMS). 2018;17: 221–230.
[28]. Mafinezhad SH, Bayani GH, BozorgniaY, Khodaparast M, Jodat SH. Effect of oral zinc sulfate on reducing hyperbilirubinemia among newborns under 1800 gram.Journal of North Khorasan University of Medical Sciences.2015; 7(4): 897-904.
[29]. Mohammadzadeh A, Farhat A, Ghasemian,A, Ramezani M, Esmaily H, Musavi BM. Effects of oral zinc sulfate on hyperbilirubinemia in low-birth-weight neonates. Iranian Journal of Neonatology.2016; 7: 1-14.
[30]. Rana N, Mishra S, Bhatnagar S, Paul V, Deorari AK, Agarwal R. Efficacy of zinc in reducing hyperbilirubinemia among at risk neonates: a randomized, double- blind, placebo controlled trial. Indian Journal of Pediatric.2011; 78:1073-1078.
[31]. Rachmadi PD, Sukadi A. Effect of oral zinc on hyperbilirubinemia in full term neonates. Paediatr Indones.2011; 51:107-110.
[32]. Maamouri G, Boskabadi H, Mafinejad S, Bozorgnia Y, Khakshur A. Efficacy of Oral Zinc Sulfate Intake in Prevention of Neonatal Jaundice. Iranian Journal of Neonatology .2013; 4:11-16.
[33]. Yang L, Wu D, Wang B, Bu X, Tang J. The influence of zinc sulfate on neonatal jaundice: a systematic review and meta-analysis. The J MaternFetal Neonatal Med.2018; 31 (10): 1311-1317.
[34]. SemmekrotBA, deVries MC, Gerrits GP, van Wieringen PM. Optimal breastfeeding to preventhyperbilirubinemia in healthy term newborns. NedTijdschr Geneeskd.2004; 148(41): 2016-19.
[35]. Chen J, Sadakata M, Ishida M, Sekizuka N, Sayama M. Baby massage ameliorates neonatal jaundice in fulltermnewborn infants. Tohoku J Exp Med. 2011; 223(2): 97-102.
[36]. Bhutani V, Gourley GR, Adler S, Kreamer B, Dalman C, JohnsonLH. Noninvasive measurement of total serum bilirubin in amultiracial predischargenewborn population to assess the risk ofsevere hyperbilirubinemia. Pediatrics. 2000;106(2):17.
[37]. Hashemian S, Mohammadzadeh A, Farhat A, Ramezani M, Seyedi SA. The Therapeutic Effect of Zinc Sulfate on Neonatal Hyper-bilirubinemia. Iranian Journal of Neonatology.2017; 8(2):14.

[38]. Kumral A, OzkanH,Duman N,Yesilirmak DC, Islekel H , Ozalp GY. Breast Milk Jaundice Correlates With High Levels of Epidermal Growth Factor. Pediatric Research. 2009; 66: 218–221.
[39]. Nabvizadeh H, Keshavarz K, Sadati S, Abidi H, Abdollapour S, Zoladl M. Effect of oral sulfate on neonatal jaundice (no symptoms). Yasouj University Research Journal. 2015; 20: 460-471(In Persian).

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