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Original article

Serum Zinc Level in Neonates with Indirect Hyperbilirubinemia

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ABSTRACT

Background: The most common cause of hospital admission in the first month of life is the neonatal jaundice. Some factors [e.g., prenatal, neonatal factors, maternal factors, and environmental factors (such as zinc) influence the frequency of neonatal jaundice. In terms of neonates, it is proposed that there is a correlation between serum zinc quality and hyperbilirubinemia.

Aim of the work: To evaluate the level of serum zinc in term neonates with indirect hyperbilirubinemia.

Patients and methods: A case control study carried out at the neonatal intensive care unit (NICU) and pediatric outpatient clinic of New Damietta, Al-Azhar University Hospital, from June 2018 to February 2019. It included 75 neonates with neonatal jaundice as cases group and 75 healthy neonates of matched age and sex as a control group. All were assessed clinically and serum zinc levels were determined and documented.

Results: Level of serum zinc in neonates with non-hemolytic hyperbilirubinemia (103.3±36.56 ug/dl) was significantly lower than healthy neonates without jaundice (128.62 ± 40.83 ug/dl) and zinc deficiency in jaundiced neonates (25.3%) was statistically significant more than healthy neonates (6.7%). There was no significant relation between the level of serum zinc and other factors like the maternal age, parity, pattern of feeding, gender and weight, but there was significant correlation with maternal zinc intake during pregnancy.

Conclusion: We concluded that serum zinc level in term neonates with neonatal jaundice was statistically significant decreased than healthy term neonates.

Keywords: Zinc; Indirect; Hemolytic; Hyperbilirubinemia; Neonates.

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INTRODUCTION

Neonatal jaundice is defined as yellow discoloration of the sclera, skin and mucous membranes caused by tissue deposition of bilirubin. When the total serum bilirubin level (TSB) is 5 mg/dL, it becomes apparent. [1] Neonatal jaundice is considered one of the most common conditions requiring medical attention in neonates; in the first week of life, approximately 80% of preterm neonates and 60% of term neonates experience jaundice.[2] Treatment in neonates for unconjugated hyperbilirubinemia, such as phototherapy and blood exchange transfusion, is costly, takes a long time and can be dangerous. Certain therapies to avoid bilirubin neurotoxicity by reducing the level of unconjugated bilirubin by enterohepatic circulation inhibition are available.[3]

Zinc is one of the critical trace elements for normal function and is therefore associated with tragic deficiencies when deficient.[4]

Zinc plays a vital role in a wide range of biological activities, including nucleic acid metabolism, immune function by serving as a co-factor in the development of more than 200 enzymes, e.g. metalloproteinases, phosphatases, oxide-reducatases, protein synthesis and cell function preservation.[5]

For intestinal bilirubin binding, several materials have been used to avoid its absorption; for example, the use of laxatives and oral agar. It has also been shown that oral zinc salts at normal body pH reduce the maximum bilirubin serum since they deposit unconjugated bilirubin.[6]

Inhibition of enterohepatic circulation is one important approach to preventing neonatal hyper-bilirubinemia. Zinc has been reported to decrease bilirubin levels by inhibition of enterohepatic circulation.[7]

Zinc sulfate supplementation has been reported to have some potential to decrease total serum bilirubin (TSB), hyperbilirubinemia, and photo-therapy time.[8]

AIM OF THE STUDY

Evaluation of serum zinc level in term neonates with indirect hyperbilirubinemia was the objective of this study.

PATIENTS AND METHODS

A case control study was carried out at the neonatal intensive care unit (NICU) and outpatient clinic of Al-Azhar university hospital (New Damietta), starting from June 2018 to February 2019. The study included 150 term neonates who were randomly selected, and fulfilled the inclusion criteria; 75 neonates with non-hemolytic neonatal jaundice as a study group and 75 healthy controls of matched age and sex.

Inclusion criteria included full-term neonates, of both genders, age 2-10 days and weight ≥ 2500g.

We **excluded** all infants with major congenital malformations, presence of any systemic illness (sepsis, infant of diabetic mother, hypoxic ischemic encephalopathy and respiratory distress), chronic disease of the mother and neonates with ABO incompatibility, Rh incompatibility and cephal-hematoma. During this study we excluded 8 infants with ABO and Rh incompatibility, 3 neonates with sepsis, 2 infants with cephalhematoma and 3 cases due to failure of sampling.

We explained to the guardians the purpose of the study and an informed consent was given by each guardian. Furthermore, confidentiality of all data was guaranteed. All newborns in the sample are subjected to complete history, detailed medical review, laboratory investigations (complete blood count (CBC), total serum bilirubin (TSB), Direct serum bilirubin (DSB), blood grouping, reticulocyte count and serum zinc level by commercially available spectrophotometric kits). The normal reference value was 80-120µg/dl according to test scope.[9] Low zinc deficiency recognized at serum levels of 60–79µg/dl, moderate zinc deficiency if levels <59µg/dl and extreme zinc deficiency if levels < 30 µg/dl.[10]

Statistical analysis: The statistical Package for social sciences, version 20.0 (IBM, SPSS Inc., Chicago, Illinois, USA) was used to coordinate, record and analyze data. For quantitative variables, mean and standard deviation (SD) were estimated, while for qualitative variables frequency and percentages were calculated. The student (t) was used to compare two concepts, while the Chi-square (x^2) was used to compare the ratios of two qualitative variables. The confidence interval was

95% and the accepted error margin was set at 5%. If (P-value < 0.05) the p-value was considered significant.

RESULTS

This study was conducted on 75 full-term neonates with neonatal jaundice; they were 42 males (56%) and 33 females (44%). In addition, 75 healthy control group of matched age and gender were included as well, males represented 39 (52.0%) and females were 36 (48.0%) of this group. Mean age of cases was 5.93±1.89 days. Multiparity accounted for 58.7% of cases and cesarean section (CS) accounted for 76.0% of cases, and there was no significant difference regarding all demographic data between both cases and control groups (Table 1).

Zinc deficiency was more frequent among cases (25.3%) than control group (6.7%) and this difference was statistically significant with (p. value = 0.002). In addition, mean serum zinc level was significantly (p= 0.001) decreased in cases (103.33 µg/dl) than control group (128.62 µg/dl) (Table 2).

There was no significant difference between deficient zinc in cases and control group regarding sex, gestational age (GA), feeding, maternal age, previous sibling with jaundice and 100% of mothers in both subgroups had no history of zinc supplementation. But, there was a statistically significant difference between cases and control regarding serum zinc level (Table3).

There was negative correlation between serum zinc with weight and TSB and positive correlation with other parameters (GA, age, onset of jaundice, maternal age and DSB); however, this correlation was statically non-significant (Table 4).

The mean serum zinc was 99.20±31.40ug/dl with multiparity and it was 88.90±24.60ug/dl in cases with previous sibling with jaundice and was higher with bottle feeding 120.10±54.90ug/dl than breast feeding and it was144.00±59.90µg/dl with maternal zinc intake, however; there was no significance except with maternal zinc intake (Table 5).

Table [1]: Difference between cases and control group regarding demographic data

Variables	Cases group (N=75)	Control group (N=75)	Chi square test\Independent t test	
			X^2/t*	P value
Sex (%) Males Females	42 (56.0%) 33 (44.0%)	39 (52.0%) 36 (48.0%)	0.242	0.623
Gestational age (week) (mean±SD)	38.15±1.19	38.13 ±1.11	0.071*	0.944
Age (days) (mean ± SD)	5.93 ±1.89	6.37±1.75	1.480*	0.141
Maternal age (years) (mean±SD)	25.25 ± 4.51	24.91 ± 4.31	0.481*	0.631
Multiparity (%) No Yes	31 (41.3%) 44 (58.7%)	35 (46.7%) 40 (53.3%)	0.433	0.511
Mode of labor (%) CS Vaginal	57 (76.0%) 18 (24.0%)	52 (69.3%) 23 (30.7%)	0.839	0.360

Table [2]: Difference between cases group & control group regarding serum zinc level (µg/dl)

Variables	Cases group (N=75)	Control group (N=75)	Chi square test\ Independent t test	
			X^2/t*	P value
Serum zinc (µg/dl) Deficient Normal	19 (25.3%) 56 (74.7%)	5 (6.7 %) 70 (93.3%)	9.722	0.002
Serum zinc level (ug/dl)(mean±SD)	103.33±36.56	128.62±40.83	3.996*	0.001

Table (3): Comparison between deficient zinc in cases group and deficient zinc in control group as regards serum zinc and demographic data

Variables		Deficient zinc in cases (n=19)	Deficient zinc in control (n =5)	Chi square test\Independent t test	
				X^2/t*	P value
Sex (%)	Males	8 (42.1%)	2(40.0%)		
	Females	11 (57.9%)	3 (60.0%)	0.007	0.932
Maternal zinc intake	No	19 (100.0%)	5 (100.0%)	NA	NA
	Yes	0 (0.0%)	0 (0.0 %)		
Feeding :	Breast	11 (57.9%)	4 (80%)		
	Bottle	2 (10.5%)	0 (0.0%)	1.018	0.601
	Mixed	6 (31.6%)	1 (20%)		
Maternal age (years)(mean±SD)		24.05 ± 3.29	25.66 ± 4.81	1.350	0.181
Previous sibling of jaundice (%):					
	No	15 (78.9%)	4 (80.0%)	0.003	0.959
	Yes	4 (21.1%)	1 (20.0%)		
Serum zinc level (µg/dl) (mean±SD)		67.67±5.74	74±3.16	-2.347	0.028
Gestational age (week) (mean ±SD)		37.95±1.08	37.80 ±0.45	0.295	0. 771

Table (4): Correlation between serum zinc level as other parameters in cases group

Variables	Serum zinc (µg/dl)	
	r	P value
GA (week)	0.146	0.211
Age(days)	0.126	0.282
Onset of jaundice (days)	0.090	0.442
Maternal age (years)	0.084	0.471
Weight (kg)	-0.034	0.775
TSB (mg/dl)	-0.075	0.520
DSB (mg/dl)	0.052	0.655
GA: Gestational age; DSB: Direct serum bilirubin; TSB: Total serum bilirubin.		

Table (5): Relation between serum zinc level as regard other parameters in cases group

Variables		Serum zinc (ug/dl)	Independent t test/ One-way ANOVA	
			t/f*	P value
Multi parity	No	109.20±42.70	1.117	0.243
	Yes	99.20±31.40		
Maternal zinc intake				
	No	101.60±34.90	2.006	0.049
	Yes	144.00 ±59.90		
Feeding				
	Breast	103.60±34.20	1.275	0.286
	Bottle	120.10±54.90		
	Mixed	95.90 ±32.80		
Previous sibling with jaundice (%)				
	No	105.80 ±37.80	1.424	0.159
	Yes	88.90 ±24.60		

DISCUSSION

This research was designed to assess the amount of serum zinc in neonates with indirect hyperbilirubinemia. Zinc (Zn) is considered a critical trace element with a range of biological effects depending on its structural and catalytic role in a large number of enzymes and "Zn-finger" proteins. Serum zinc deficiency can result in the development of deficient enzymes that act in the metabolism of bilirubin [11]. Zinc salts will potentially inhibit bilirubin and its enterohepatic circulation by precipitating unconjugated bilirubin in the intestine.[12]

Zinc may result in deficient synthesis of various enzymes that play a role in the metabolism of bilirubin, in particular the Z and Y proteins, resulting in neonatal jaundice. [13]

With respect to demographic data of studied groups, the percentage of males was 56 percent higher than 44 percent of females, the male to female ratio in cases was 1.2:1. This in agreement with **Boskabadi et al.** [3] who reported that male to female ratio was (1.2:1) and **Hasan** [4] who reported that male to female ratio was (1.3:1) with male predominance. In fact, male newborns are always more susceptible to neonatal jaundice, although the cause remains unknown.[14]

The control mean age was 6.37±1.75 days that was comparable to the study of **Boskabadi et al.** [3] who showed that the mean age 6.75 ± 4.88 days in the control group. In addition, the mean gestational age in cases was 38.15 ± 1.19 week and in control group was 38.13± 1.11 week that was comparable to the study of **Tan et al.** [15] who reported GA of 38.48±1.15 week in cases and 38.15±1.03 week in control group.

The difference of gender, gestational age and age between cases and controls were statistically nonsignificant. This was in agreement with **Al-HajjiahNasma**[16], **Boskabadi et al.** [3] and **Tan et al.** [15].

Majority of cases (76%) were delivered by caesarian section, which is more frequent in cases than control group and this was in agreement with the study of **Tavakolizadeh et al.**[17].

In the current work, serum Zn was significantly reduced in cases when compared to control group. This is in agreement with **Boskabadi et al.**[3] and **Al-HajjiahNasma**[16] who reported statistically significant relation between neonatal jaundice and zinc deficiency. In addition, **Hasan** [4] and **Tan et al.**[15] revealed similar results.

The prevalence of zinc deficiency in cases group was 25.3% and 6.7% in control group. This agree with **Al-HajjiahNasma [16].**

As in the present work, **Al-HajjiahNasma**[16] showed no significant association between neonatal jaundice and gestational age or parity (P> 0.05). Also, **Boskabadi et al.** [3] showed similar results. The same authors reported that there was no statistically significant association between level serum zinc and each of weight, sex, serum bilirubin, and maternal age which is consistent with the current study.

We found significant correlation between level of serum zinc of cases and maternal zinc intake during pregnancy which agrees with **Al-HajjiahNasma** [16].

In the current study, breast feeding was more frequent in both deficient zinc in cases (57.9%) and deficient zinc in control (80%), with significantly lower serum zinc levels among breast-fed when compared to formula fed neonates. This agrees with **Ali et al.** [18]. This could be explained by zinc deficiency and absence of zinc supplementation among mothers.

In conclusion, zinc deficiency in jaundiced cases (25.3%) is more frequent than healthy neonates (6.7%) and serum zinc levels are significantly lower in term neonates with hyperbilirubinemia than stable neonates without jaundice. Thus, zinc supplementation is recommended for pregnant mothers.

Financial and Conflict of interest disclosure

None

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