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Evaluation of the Relationship between Serum Vitamin D Level and Early Onset of Sepsis

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Abstract

***Background:** Neonatal sepsis is a critical condition caused by a generalized bacterial infection and is one of the most common causes of neonatal mortality and morbidity in the first month of life. Vitamin D is a steroid hormone that has numerous roles in the immune system and reduces inflammation. The purpose of this study was to evaluation of the relationship between serum vitamin D level and neonatal early onset of sepsis (EOS).*

***Materials and Methods:** In this case-control study, 43 newborns with EOS selected in the case group and 43 matched healthy children were selected as the control group. The demographic data such as gestational age, delivery method, birth weight and the results of blood and biochemical tests were collected and then analyzed by statistical methods in SPSS version 21.*

***Results:** In the case group, the mean age was 4.93 days and 72.1% were boy. The most common complaints in neonates were restless with 74.71%, jaundice with 67.44% and fever with 62.7%. The average age of mothers with a septic newborns was 26.83 years and 23.3% of mothers had received vitamin D supplementation during pregnancy. Dairy consumption in studied mothers was low and the majority of them had exposure with sunlight less than 15 minutes. A high percentage of infants (94.2%) had severe to moderate vitamin D deficiency that in septic neonates was higher than healthy neonates but no significant. Also, there was no significant relation between the level of vitamin D and incidence of sepsis.*

***Conclusion:** The results showed that there is no significant difference between vitamin D levels in mothers and their neonates but in the case group, there was a significant correlation between maternal and neonatal serum vitamin D level.*

Keywords: *Sepsis, neonate, serum Vitamin D, Ardabil.*

Introduction

Neonatal sepsis is characterized by signs and symptoms of infection that associated with or without accompanying by bacteremia occurring in the first month of life and is one of the main causes of life threatening and known as an important factor for mortality and morbidity in neonates [1,2]. Neonatal early onset of sepsis (EOS) is a severe multi systemic illness thatoften characterized by respiratory distress, digestive disorders, cardiovascular disorders, cerebrovascular and/or blood disorders. Pay attention to clinical and laboratory symptoms at diagnosis of neonatal sepsisis important. Clinical signs and symptoms of sepsis are intolerance to nutrition, temperature instability, apnea, need for oxygen, need for ventilation, hemorrhage, tachycardia and bradycardia, abdominal distension or vomiting and necrotizing enterocolitis and of laboratory symptoms we could pointed to the number of

platelets, neutrophil percent, WBC, B/C and CRP[3]. The association between infections and 25 hydroxy vitamin D (25(OH)D) deficiency was first described more than a century ago. Vitamin D deficiency may play a role in the pathogenesis of infections and low level of circulating vitamin D has been shown to be strongly associated with infectious diseases [4]. Hosienzadeh et al in a study showed that overall prevalence of vitamin D deficiencies (levels <30 ng/mL) in newborns was estimated to be 98.1% and the mean concentration of 25(OH)D for newborns is very low. Vitamin D deficiency is now considered a global pandemic, and more than one billion people are suffering from vitamin D deficiency [5].

Based on common types of sepsis, the incidence probability of sepsis is more ininfants which had at least one of clinical symptoms for sepsis such as CRP above 1 or at least two Paraclinical symptoms in addition to CRP while blood cultivationin them can be positiveor negative(3). Vitamin D is a steroid hormone that its role in optimizing performance of body systems changed to an attractive topic for scientists in worldwide[6]. Vitamin D in the body have classical effects on calcium homeostasis and bone metabolism but recently vitamin D deficiency have non classical effects including anti cancer activity [7], cardiovascular effects [8], effects on the immune system [9], insulin resistance, allergies, autoimmune disorders [10], effects on pregnancy and increasing the risk of gestational diabetes, preeclampsia and vaginosis Bacterial and IUGR, LBW and EOS[11-12]. Although, Vitamin D deficiency is one of the current problems inour community but of them pregnant women are at a higher risk of vitamin D deficiency. Vitamin D has effect on many actions during pregnancy such as response to infection and inflammation and has main role in the mother and the baby's immune system and taking enough vitamin D during pregnancy in prevention of EOS in term infants is essential[13]. The risk factors for Vitamin D deficiency are inadequate intake of vitamin D, low consumption of enriched foods, seasonal changes, skin color, inadequate exposure with sunlight, prematurity, body coverageand etc [14-15]. The aim of this study was to Evaluation of the relationship between serum vitamin D level and early onset of sepsis.

Methods

Study Design and Participants

This case-control study was approved by the Ethics Committee Ardabil University of Medical Sciences. After the interview with mothers of newborns and complete consent form by them, newborns entered in the study. 43 newborn with EOS selected as a case group and 43 healthy term neonates who were matched in age, sex and weight with case group were selected as control group. Data collectedby a checklist including demographic data of infants and mothers, primary complaint, type of delivery, birth season, birth weight and discharge time, complications and measures taken at admission, duration of hospitalization, WBC level, platelet and CRP, blood culture, maternal information such as education, socioeconomic status, job, history of illness, taking vitamin D supplementation in pregnancy duration, consumption dairy, sun exposure, coverage status and vitamin D levels in mothers.

Inclusion and Exclusion Criteria

Infants with metabolic diseases were excluded from the study.

Biochemical Parameter

Five mL venous blood samples from mothers and 5 mL blood from the umbilical cord of newborns were collected by a clinical pathologist. Samples were stored at -80 °C to be prepared for testing. Mother and newborns serum samples were collected to measure 25(OH)D by enzyme linked immunosorbent assay (ELISA) using a kit manufactured by EUROIMMUN company in Germany.

Definition of Vitamin D Deficiency

In this study, vitamin D cut-off was divided based on United States Endocrine Society; of 25(OH)D below 30 ng/mL was considered deficiencyand 30 ng/mLand up was considered sufficient.

Statistical Analysis

Data were analyzed using descriptive and analytical statistical methods in SPSS version 21. P values less than 0.05 were considered statistically significant.

Results

The case group consisted of 43 infants with EOS and the control group was 43 healthy infants who were hospitalized. The mean age of case group was 4.93 ± 1.45 and control group was 4. 58± 1.38 years. There was no significant difference between two groups. 31 neonates (72.1%) in case group and 27 neonates (62.8%) in control group were male and there was no significant difference between two groups. The most common complaint among infants in the case group was restlessness with 32 cases (74.41%) and in the control group was jaundice with 43 (100%).

The average birth weight in the case group was 3.33 ± 0.32 kg and control group 3.39 ± 0.5 kg and the difference was not significant. Most of neonates in case and control groups were born by cesarean section. Most of mothers in two groups had moderate economical status (Table 1). 21 (48.8%) neonates in case group and 17 neonates (39.5%) in control group were born in winter. The average age of mothers in the case group was 26.83 ± 5.94 years and in the control group was 27.23 ± 89.5 years and the difference wasn't significant. The majority of mothers had sun exposure for less than 15 minutes in daily and the difference wasn't significant between two groups. 19 mother (44.2%)of case group and 20 mothers (46.5%) of the control group consumed 2-3 dairy units per day and no significant difference was found between two groups (Table 2).

Table 1. *Demographic data of mothers in two groups*

Variables		case		control		p-value
		n	%	n	%	
education	Illiterate	0	0	3	7	0.343
	Under diploma	18	41.9	16	37.2	
	Diploma	12	27.9	10	23.3	
	University degree	13	30.2	14	32.6	
Economical condition	week	7	16.3	8	18.6	0.849
	moderate	34	79.1	32	74.4	
	good	2	4.7	3	7	
Occupation	housekeeper	43	100	42	97.7	0.314
	Free job	0	0	1	2.3	
underlying disease	+	15	34.9	12	27.9	0.486
	-	28	65.1	31	72.1	
Type of delivery	Vaginal	20	46.5	18	41.9	
	Cesarean	23	53.5	25	58.1	

Table 2. *Behavior of mothers about effective variables on absorption of vitamin D in two groups*

Variables		case		control		p-value
		n	%	n	%	
Exposure with sun daily (min)	<15	24	55.8	31	72.1	0.09
	15-60	17	39.5	8	18.6	
	>60	2	4.7	4	9.3	
Coverage status	Complete cover	2	4.7	0	0	0.36
	Only hand and face exposure with sun	39	90.7	41	95.3	
	More part of body exposure	2	4.7	2	4.7	
Receiving Vitamin D supplement	+	10	23.3	8	18.6	0.6
	-	33	76.7	35	81.4	
use of sunscreens	+	14	32.6	11	25.6	0.47
	-	29	67.4	32	74.4	
Rate of dairy use	< 2-3 unit	19	44.2	18	41.9	0.6
	2-3 unit	16	37.2	20	46.5	
	More than 2-3 unit	8	18.6	5	38.5	

The mothers of the newborns in the case group had significantly more abortions than the mothers of the control group. The average duration of hospitalization in the case group with 2.62 ± 6.22 days significantly lower than control group with 3.16 ± 1.36 days. It was observed that the level of vitamin D in infants could not significantly change the duration of hospitalization of newborns in both groups. In the case group, 29 infants (67.44%) received phototherapy during admission. There was no mortality and pneumothorax in infants. There was no meaningful relationship between the types of neonatal complications and the level of vitamin D. There was significant difference in the amounts of CRP, total bilirubin, monocyte, lymphocyte and PMN in neonates between two groups (Table 3).

Table 3. *Laboratory variables in two groups.*

variables		mean±SD	p-value
WBC	case	12920±4670	0.74
	control	12148±1445	
PMN	case	54±12	0.001
	control	39±9	
Lymphocyte	case	36±11	0.001
	control	47±13	
Monocyte	case	4±1	0.001
	control	6±1	
Eosinophil	case	3±1	1
	control	3±1	
Platelet	case	255000±82000	0.19
	control	277000±66000	
CRP	case	21.03±18.3	0.001
	control	5.13±4.12	
Bilirubin total	case	10.16±7.33	0.001
	control	17.26±3.95	
Bilirubin direct	case	2.79±0.78	0.52
	control	0.5±0.14	

There was significant difference between CRP and vitamin D levels incase group but in the control group this difference wasn't significant. The mean level of vitamin D in the neonates of the case group was significantly lower than that of the control group (12.4±7.25 v.s 15.55±7.49, p=0.048). The difference in the mean level of vitamin D in the mothers of neonates in two groups was not significant.

The majority of mothers and infants(93% v.s 7%) in both groups had vitamin D deficiency but no significant between two groups. Most of mothers in case and control groups had vitamin D deficiency but no significant. Most of neonates in case and control groups had vitamin D deficiency but no significant. The correlation between infant vitamin D levels and their mothers in case group waspositive and significant (r=0.74, p=0.001). But in the control group there wasn't significant correlation between infant vitamin D levels and their mothers vitamin. There was no relationship between neonatal vitamin D and WBC, neutrophil counts, lymphocyte, platelet and CRP levels .

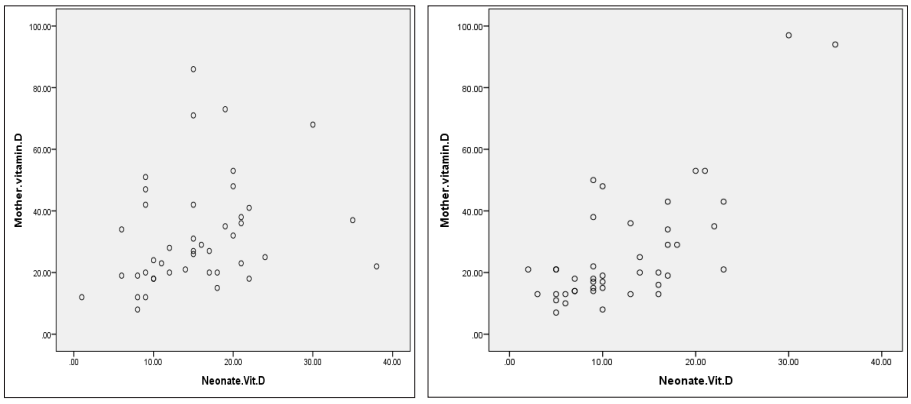

Fig1. *Correlation between mother and neonate vitamin D level in case (right) and in control (left)*

Discussion

In this study 43 neonates with sepsis were studied that their average age was 4.93 days and 72.1% were boys. Out of 86 cases of both case and control groups in this study, 58 (67.4%) cases were male and 28 (32.6%) were female. From the study of Cizmeci (2014) in Turkey, 27 (68%) were male and 13 (32%) were female in case group and 28 (65%) and 15 (35%) were male and female respectively. These results may be due to the fact that males are more affected than females in neonatal sepsis and may also due to small sample sizes [16]. The most common complaints in neonates were

restless with 74.71%, jaundice with 67.44% and fever with 62.7%. The average birth weight of neonates was 3300 gr and the gestational age was 38.2 weeks. Similarly, Cizmeci [16] in Turkey stated that birth weight of Mean ± SD in grams was 2877 ±652 in case group and 3120 ±440 in control group. The duration of hospitalization was 5.02 days.In the study of Adib and et al [17], 53% of infants were male and the average age was5.73 days, gestational age was 36.8 weeks and 59.3% had EOS and moaning, narcosis and not drink milk were the most common clinical signs of neonates. In the study of Shamsizadeh et al [18], 63.2% were boys, 29.4% had prematurity and 70.6% had endemic form of sepsis. In the study of Aftab [19] in India, 42% of newborns had EOS and others had late sepsis. In the study of Borna et al (20), the average age of infants with sepsis was 6.3 days, gestational age was 36.8 weeks and 52.6% were boy and fever, improper nutrition, icterus, tachypnea and respiratory distress were the common symptoms of infants. In Raffati and et al study[21], of infants with sepsis 63% were boy, 27% preterm, 20 % LBW and icterus, cough, seizure, hypoglycemia and respiratory distress syndrome were the most common symptoms of newborns. A review of the articles showed that neonatal septicemia is more common in boys than in girls which can be due to genes related to the sex involved in the immune system[22-23]. Also, fever, narcosis and impairment in infant feeding were the common causes that were observed in most of studies. Also, in this study 43 mothers with septicneonates were evaluated. In this study about 43% of postpartum mothers had severe to moderate vitamin D deficiency thatthis ratio in mothers with septic infants was significantly higher than other mothers. Also, in the case group there was a significant correlation between vitamin D levels in neonatal and their mothers. In the study of Cetinkaya and et al [24], there was positive correlation between the level of 25- OHD in both mother and neonate and the results showed that lower levels of 25 (OH) vitamin D in mother and infant were associated with neonatal EOS. In another study by Karatekin et al [25], serum levels of 25-OHD in mothers of the case group was 13.38 and control group was 22.79 ng / mL (P=0.012) and it was observed that concentration of 25-OHD in neonates was related to its concentration in mothers. Yang and et al [26]in their study showed that mothers with septic neonates had lower levels of vitamin D than healthymothers. Mohammad [27] in confirmation of earlier studies showed that vitamin D levels in mothers in case group are significantly lower than mothers with healthy infants.

Vitamin D status varies in different countries due to differences in exposure to sunlight, dietary intake of vitamin D, ethnicities and cultural factors. Similarly, according to the study of Cizmeci [16] in Turkey, 5 (12.5%) were sufficient (≥ 30 ng/mL) and 35 (87.5%) were low (<30ng/mL) in case group. Among the babies with low levels of cord blood 25-hydroxyvitamin D, 28(70%) were deficient and 7 (17.5%) were insufficient. 20 (46.5%) were sufficient (≥ 30 ng/mL), 23 (53.5%) were low (<30ng/mL) in control group. Among the babies with low levels of cord blood 25-hydroxyvitamin D, 22 (51.2%) were deficient and 1 (2.3%) were insufficient. Moreover, this study showed that cord blood 25-hydroxyvitamin D levels in case group were statistically significant lower than that of control group (Mean ± SD of 9.82 ±2.65 and 18.47 ±4.37 respectively), (p-value <0.001). Low levels of cord blood 25-hydroxyvitamin D levels were associated with increased risks of EONS. [3]

New evidence has recently been discovered the role of vitamin D during pregnancy. Researchers in Canada showed that vitamin D deficiency in pregnant women is likely to increase gestational diabetes and preeclampsia (28). Other studies have shown that taking vitamin Dis effective inthe development of the brain and the immune system of the fetus and the prevention of many autoimmune diseasessuch as DM type 1 and MS in elderly ages [29-30]. Many studies in Iran have concluded that pregnant women may suffer from vitamin D deficiency because of the type of clothing and use of sunscreens [29-33]. In addition, vitamin D deficiency is also common among men and clothing cannot be considered as the only cause of this deficiency.In other studies, the combination of factors such as geographical location, urbanization, lifestyle changes, diet, skin color, air pollution, or possibly genetic predisposition to vitamin D deficiency among. Asian people has been mentioned as factors influencing vitamin D status [34]. The mean concentration of 25 (OH) D in African and European newborns was 14 ng/mL, in Western Oceania was 22 ng/mL and in the American newborns was 32 ng/mL, respectively [35].

Most of studies showed a high mortality rate but mortality was not observed in the present study which can be probably due to several reasons such as early diagnosis of infants in the hospital before their status get worse, early onset of intravenous antibiotics, appropriate care in the neonatal areas and etc [36-39].

Easy access to the hospital by parents and follow up of mothers and their infants by health centers and giving mothers' health warnings can also be considered as an early reason for referring mothers.

In this study, a high percentage of newborns had severe to moderate vitamin D deficiency that this rate in neonates of case group was significantly more than neonates in control group. Also there was no significant difference between vitamin D level in neonates in two groups. Also there was no significant relationship between vitamin D level and outcome of neonates [16,24,26-27,40]. In our study similar to other studies, it was observed that a low level of vitamin D could increase the incidence of sepsis and the rate of vitamin D deficiency in all newborns was high which can be probably due to not taking vitamin D supplements in pregnant women. A high percentage of newborns and their mothers at birth time because of having acover on the body and organs and non-exposure of body with sunlight in mothers and their body and taking too much sunscreen even during pregnancy have a low level of vitamin D.

Conclusion

The results of this study showed that there was a significant difference between the mean levels of vitamin D in neonates in both groups but there was a significant difference between the mean levels of vitamin D in mothers in two groups. Also there was a significant correlation between mother and neonate's vitamin D level in case group but in the control group correlation wasn't significant.

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