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Research Article

The Comparison of Serum Vitamin D Level in the Term Neonates With and Without Sepsis in Children Hospital of Bandar Abbas City, Iran From 2016 to 2017

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Abstract

Background: Neonatal sepsis is one of the most important causes of infant's death, and the identification of its factors has been the subject of many studies. Some new evidence suggested the role of vitamin D in the occurrence of sepsis in infants.

Objectives: The aim of this study was to compare serum levels of vitamin D in neonates with sepsis in the first week of birth and healthy neonates.

Methods: This case-control study was performed on 72 term neonates (36 neonates with sepsis as case and 36 healthy neonates as control group) who refereed to Bandar Abbas children's hospitals, Bandar Abbas, Iran, during 2016-2017.

Results: Serum vitamin D levels were measured in all infants and their mothers in both sepsis and control groups. In addition, data collected, including sex, birth weight, C-reactive protein (CRP), and duration of hospitalization in neonates with sepsis. Mean serum level of vitamin D was 18.52 ±11.49 ng/mL in sepsis and 20.52 ±13.75 ng/mL in control group neonates ($P \geq 0.05$). The mean maternal serum level of vitamin D in sepsis group was 22.44 ±11.26 ng/mL and in control group was 24.36 ±12.82 ng/mL ($P \geq 0.05$). There was a positive correlation between maternal and neonatal vitamin D levels in the sepsis group (r=0.803) and the control group (r=0.756). However, there was no significant difference between vitamin D level and CRP ($P = 0.148$) and length of stay ($P = 0.396$) in the sepsis group.

Conclusion: Although the results of the present study showed a correlation between serums vitamin D levels in mothers and neonates with neonatal sepsis, there was no significant vitamin D level between neonates with and without sepsis.

Keywords: Serum Vitamin D, Sepsis, Neonate

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Background

Neonatal sepsis is characterized by systemic signs of infection that are accompanied by bacteremia in the first month of life (1, 2). It includes septicemia, pneumonia, meningitis, arthritis, osteomyelitis, and urinary tract infections (3).

The most common cause of infants' death is still sepsis that accounts for 30%-50% of total deaths annually in developing countries, and in Iran, it estimated up to 8% (4). Neonatal sepsis is divided into early-onset sepsis (EOS) and late-onset sepsis (LOS) (4-6). The clinical symptoms of EOS usually present within the first 72 hours of birth, although some physicians report the onset of sepsis before the first 7 days of birth, especially if it originates of group B streptococcal (GBS) as EOS (7). LOS is accompanied with symptoms occurring after day 3 to 7 of birth (8). Accordingly, the clinical manifestations of neonatal sepsis usually begin within the first 6 hours of birth and typically present within the first 24 hours of birth (9). In most neonates, manifestations begin with respiratory distress, which is similar to other cardiopulmonary diseases (7-9). During the first 24-48 hours of birth, 80%-90% of patients become symptomatic (10). As mentioned earlier, neonates with LOS have no clinical symptoms of sepsis at birth and subsequently, are affected by community-acquired sepsis after being discharge or during long-term hospitalization (11).

Vitamin D regulates cytokines by activating T cells and affects the synthesis of immunoglobulins by activating B lymphocytes (12). Indeed, the immune-modulating effects appear to be mediated by 25-OH vitamin D3 (12). Nearly most immune cells include B and T lymphocytes, monocytes and dendritic cells have specific vitamin D receptor (VDR). Vitamin D exerts a modulating effect on immune activity in mononuclear and polynuclear cells via the VDR receptor (13). Vitamin D has a direct

effect on macrophages and enhances the production and development of cytokines, acid phosphatase, and hydrogen peroxide as well as prevents the overproduction of inflammatory cytokines (14). Vitamin D also facilitates neutrophil motility and phagocyte function. It may improve prognosis, and decrease both local and systemic inflammatory responses (15).

According to the role of vitamin D in immune system function and the mortality and morbidity of neonatal sepsis, this study was designed to investigate the association between serum vitamin D level and the prevalence of neonatal sepsis.

Materials and Methods

Patients and Study Design

This case-control study was performed on 36 term (gestational age of 37 weeks or more) neonates who were admitted to the neonatal ward or neonatal intensive care unit of Bandar Abbas children's hospitals (Bandar Abbas, Iran) during 2016-2017, with diagnosis of neonatal sepsis as case group, and 36 term neonates with no sepsis who referred to the hospital or outpatient due to other causes as control group. Both case and control groups weighed at least 2500 g.

Inclusion and Exclusion Criteria

Inclusion criteria were GA≥ 37 weeks, birth weight ≥2500 g, and the onset of sepsis at first week of birth based High probable Sepsis and possible Sepsis according to Gitto criteria (16), and no signs of sepsis in control group. Also, neonate with congenital anomalies, onset of sepsis in control group, resuscitation and asphyxia at birth, known risk factors for sepsis (e.g., history of GBS infection in neonate, bacteriuria in recent pregnancy, prematurity, maternal fever of ≥38°C, chorioamnionitis, rupture of membrane more than 18 hours, and low APGAR score) were excluded from study.

Data Collection

Demographic information includes sex, birth weight, levels of vitamin D, complete blood count (CBC), C-reactive protein (CRP), duration of hospital stay were recorded. To determine the vitamin D level, plasma sample (2 cc) from both mothers and neonates of all groups were obtained, and the 25-OHD level was measured by commercial kit (Monobind, USA) according to the manufacturers' instructions. Besides, vitamin D deficiency was classified as severe deficiency (serum 25-OHD≥10 ng/mL), insufficiency (serum 25-OHD between 11 and 32 ng/mL) and adequate (serum 25-OHD between 32 and 100 ng/mL) (8). Also, blood samples for whole blood count, CRP, and culture were obtained before initiating antimicrobial therapy.

Statistical Analysis

Quantitative information was presented as mean, standard deviation, and number (or percentage). Data were analyzed using SPSS software version 23 (SPSS, version 16.0, Chicago, IL, USA) via Independent *t* test, chi-square, and Pearson correlation were used. The significant difference was set at less than 0.05.

Results

Demographic Data

In this study, 72 term neonates were studied. The mean GA of neonates in the case and non-sepsis (control) were 270.77±7.93 and 296.37±5.95 days, respectively (Table 1). Also, the mean weight of neonates with and without sepsis was 3159±418 grams and 3135±419 g. The demographic data of these neonates are presented in Table 1.

Serum Vitamin D level

The mean serum level of vitamin D in the sepsis and healthy neonates were 18.52 ± 11.49 ng/mL and 20.52 ± 13.75 ng/mL, respectively (Table 2). Independent *t* test showed no significant difference between two groups. Also, the mean serum level of vitamin D of mothers in case and control groups was 22.44 ±11.26 ng/mL and 24.36 ± 12.82 ng/mL, respectively. Independent *t* test showed no significant difference between mothers of two groups in terms of vitamin D level (Table 2).

Pearson correlation coefficient test showed no significant correlation between vitamin D level and neonates' weight in both sepsis (r= -0.188, $P=0.227$) and control groups (r=-0.117, $P=0.502$). Also, there was no significant difference between gender of neonates with serum vitamin D level ($P=0.148$).

The Severity of Vitamin D Deficiency

In this study, the level of vitamin D of neonates and

Table 1. Demographic Information of Neonates in Sepsis and Control Groups

Variables	Case Group	Control Group
Gestational age, day (mean ± SD)	270.77±7.93	296.37±5.95
Weight, g (mean ± SD)	3159±418	3135±419
Sex, n (%)		
Male	16 (44.4)	30 (83.3)
Female	20 (55.6)	6 (16.7)
Mode of delivery type, n (%)		
NVD	23 (63.9)	20 (55.5)
C/S	13 (36.1)	16 (44.5)

Table 2. Comparison of Vitamin D in Mothers and Neonates of two Studied Groups.

Vitamin D Level	Case Group (Mean ± SD)	Control Group (Mean ± SD)	*P* Value
Neonates (mL/ng)	18.52±11.49	20.52±13.75	0.5
Mothers (mL/ng)	22.44±11.26	24.36±12.82	0.5

mothers were divided into three groups; adequate, inadequate, and deficiency. According to chi-square test, the level of vitamin D deficiency was not significantly different in neonates of sepsis and control groups ($P=0.829$, Table 3). Moreover, chi-square test showed no significant difference in severity of vitamin D deficiency in mothers of sepsis and control groups ($P=0.448$, Table 3).

The Correlation Between Serum Vitamin D Level of Mothers and Neonates

Based on Pearson test, the strong positive correlation between serum vitamin D levels of mothers and neonates in case and control groups was observed (r=0.803 and r=0.756; $P<0.001$, respectively). As showed in Table 4, no significant difference was observed between the two groups in terms of severity ($P=0.625$).

The Relationship Between Serum Vitamin D With CRP and Length of Hospitalization in the Sepsis Group

Pearson Correlation Coefficient indicates a weak positive correlation between vitamin D level and CRP level in neonates with sepsis, which was not statistically significant (r=0.250, $P=0.142$, Figure 1). Also, the correlation between serum vitamin D level and the length of hospitalization in the sepsis group was 0.146 that indicates a weak positive correlation, which was not statistically significant ($P=0.396$). According to Table 5, no significant relationship between different levels of vitamin D and CRP levels ($P=0.213$) and length of hospitalization were observed ($P=0.055$).

Discussion

In the present study, we determined the serum vitamin D level in both neonates with sepsis and their mothers and compared it in healthy one. Also, some risk factors of sepsis in neonates were investigated. Our results showed that serum vitamin D level in both neonates and mothers was no difference compared to healthy subjects. However, in the sepsis group, a positive correlation was found between maternal and neonatal serum vitamin D.

In line with previous researches (7, 8), our study indicates that there was no significant between GA, weight, sex, length of hospitalization, and mode of delivery in neonates with sepsis comparison to healthy groups.

In the present study, although vitamin D level in neonates with sepsis was lower that of the control group; it showed no significant differences. In contrary to our findings, Gamal et al (7) in a study in Egypt that conducted on 50 neonates (25 full-term + 25 preterm infants) with sepsis and 30 age- and sex-matched healthy neonates as controls. They state that serum vitamin D levels were significantly lower in mothers and neonates with EOS than mothers

Table 3. Comparison of Severity of Vitamin D Deficiency in Mothers and Neonates in Sepsis and Control Groups

Severity of Vitamin D Deficiency		Group				*P* Value
		Case		Control		
		No.	%	No.	%	
Neonates	Deficiency	22	61.1	21	58.4	0.829
	Inadequate	8	22.2	7	19.4	
	Adequate	6	16.7	8	22.2	
Mothers	Deficiency	17	47.2	12	33.3	0.448
	Inadequate	13	36.1	15	41.7	
	Adequate	6	16.7	9	25	

Table 4. Correlation Between Serum Level of Vitamin D in Mothers and Neonates of Sepsis and Control Groups

Groups	Pearson Correlation Coefficient		*P* Value (Case and Control)
	Case (Mothers and Neonates)	Control (Mothers and Neonates)	
Correlation level	0.803	0.756	0.625
P value (mothers and neonates)	0.001>	0.001>	

Table 5. Comparison of CRP Level and Length of Hospitalization and Vitamin D Levels in Neonates with Sepsis

Variables	Vitamin D levels						*P* Value
	Deficiency		Inadequate		Adequate		
	Mean	SD	Mean	SD	Mean	SD	
CRP (mg/dL)	18.73	18.65	25.25	26.24	37.33	31.21	0.213
Length of hospitalization (days)	9.09	3.75	14.25	7.98	9.83	4.07	0.055

and neonates in the control group. There was also a significant reversely correlation between maternal and neonatal vitamin D levels and all sepsis markers. Also, the direct positive correlation between maternal and neonatal serum vitamin D levels was observed (7).

Seliem et al performed a study on 30 term neonates with EOS and 30 age-matched healthy neonates as controls. They demonstrated that neonatal and maternal vitamin D levels of sepsis group were lower than the control group. This study showed a negative correlation between vitamin D and CRP levels in neonates with sepsis (17). In our study, we found a negative correlation between vitamin D levels of sepsis group in comparison with control neonates; however, it was not statistically significant.

Cetinkaya et al indicated that serum vitamin D levels in mothers and neonates in case group were significantly lower than controls (8). Severe vitamin D deficiency was also more common in the group with sepsis (8). While in our study, there was no significant differences between vitamin D level severity and neonatal sepsis

Accordingly, in contrast with our findings, Karatekin et al (13), Cizmeci et al (11), Dhandai et al (18), and Ismail et al (19), Aye et al (20) found revealed serum vitamin D levels were lower in neonates with sepsis than those of controls. Also, vitamin D levels were lower in the mothers of sepsis group than those mothers of the control group.

In the line with our study, Barak et al (21) studied 43 neonates with EOS and 43 healthy neonates as the control group in Ardabil, Iran. A high percentage of neonates (94.2%) had moderate to severe vitamin D deficiency, which was higher in neonates with sepsis than in controls, but these differences were not significant. There was also no positive correlation between vitamin D levels and the incidence of sepsis (21). However, Saboute et al (22) showed maternal serum vitamin D was inversely correlated with neonatal sepsis occurrence.

Say et al (23) reported 63% of infants had vitamin D deficiency, 24% had insufficient vitamin D levels, and 13% had adequate vitamin D levels. There was no association between vitamin D levels and the risk of neonatal sepsis in preterm infants (23). In our study, most of neonate in both case and control groups have vitamin D deficiency.

In our study, there was no any significant difference between CRP with severity of vitamin D deficiency. In line with our results, Prasad et al (24) study in India showed there was no significant association between severity of vitamin D and CRP levels in neonates with sepsis.

Tao et al (25) showed in neonates with vitamin D levels less than 25 nmol/L, the increase in vitamin D level by 10 nmol/L resulted in a decrease of CRP by 1.42 mg/L. Moreover, in neonates with vitamin D levels between 25-49.9 nmol/L, increasing every 10 nmol/L vitamin D levels, a decline was observed for CRP by 0.49 mg/L. There was no correlation between serum CRP levels among infants with serum vitamin D levels ≥ 50 nmol/L (25).

Conclusion

The results of the present study showed no association between serum vitamin D levels of mothers and neonates with sepsis in comparison to control group. There was also no association between vitamin D level, neonates' weight, sex, CRP, length of stay as well as mode of delivery. Hence, future studies with more sample size are recommended to investigate vitamin D level in neonate with EOS and LOS as well as maturity of neonates.

Authors' Contribution

Study concept and design: SHS and TM; Analysis and interpretation of data: SHS and TM; Drafting of the manuscript: TM; Critical revision of the manuscript for important intellectual content: RG; Statistical analysis: FK.

Conflict of Interests

The authors declare that there is no conflict of interests.

Ethical Approval

The Ethics Committee of Hormozgan University of Medical Sciences (HUMS) approved the study protocol (HUMS.REC.1395.71). Informed parental consent was obtained for all neonates.

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Informed Consent

Informed parental consent was obtained for the parents of all neonates.

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