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COMPARISON OF THE LEVEL OF VITAMIN D IN PRETERM INFECTED AND UNINFECTED INFANTS

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Abstract. *Introduction.* Despite the substantial progress in intensive cares, sepsis is still an important cause of neonatal mortality. Given the role of vitamin D in infection control, this study was conducted to compare vitamin D level in infected and uninfected preterm infants. *Materials and methods.* This cross-sectional study was carried out on 87 preterm infants (45 infected infants and 42 uninfected infants) hospitalized in Mashhad Ghaem Hospital, Iran, during 2015–2017. The subjects were selected by using convenience sampling. The infected infants (n = 45) included babies with clinical and laboratory findings compatible with infection and/or positive blood or cerebrospinal fluid cultures. The serum levels vitamin D were measured in all infants. A researcher-made questionnaire containing demographic, clinical and laboratory features of infants was used. In addition, independent t-test and chi-square test were applied. SPSS was used to perform the statistical data analysis. *Results.* 83% of infants had vitamin D deficiency 34.5%, 26.4%, and 21.8% of whom exhibited severe (less than 10 ng/ml), moderate (10.1–20 ng/ml), mild deficiency (20.1–30 ng/ml), respectively. The mean vitamin D level of infants was 23.31±9.40 ng/ml in the control group and 11.02±8.64 ng/ml in the case group (p = 0.000). In the case group, the mean vitamin D was 8.14±5.53 ng/ml in early sepsis and 12.62±9.75 ng/ml in late-onset sepsis (p = 0.121). 95% of infected infants and 71% of uninfected infants had vitamin D less than 30 ng/ml (p = 0.003). *Conclusion.* Vitamin D deficiency is very common in preterm infants. Serum vitamin D levels in infants with sepsis were lower than those in uninfected infants. Therefore, the correction of vitamin D deficiency may contribute to better control of neonatal infection.

Key words: *preterm infants, vitamin D, sepsis, meningitis, infection, neonates.*

СРАВНЕНИЕ УРОВНЯ ВИТАМИНА D У НЕДОНОШЕННЫХ ИНФИЦИРОВАННЫХ И НЕИНФИЦИРОВАННЫХ НОВОРОЖДЕННЫХ

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Резюме. *Введение.* Несмотря на значительный прогресс в области интенсивной терапии, сепсис по-прежнему остается одной из основных причин неонатальной смертности. Поскольку уровень витамина D влияет на тяжесть течения инфекций, в настоящем исследовании было проведено сравнение уровня витамина D у инфицированных и неинфицированных недоношенных детей. *Материалы и методы.* Проведено поперечное исследование 87 недоношенных новорожденных (45 инфицированных и 42 неинфицированных младенца), госпитализированных в больницу Мешхед Гаем, Иран, в период с 2015 по 2017 г. Отбор пациентов осуществлялся

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методом случайной выборки. В группу инфицированных (n = 45) были включены младенцы с клиническими и лабораторными данными, соответствующими инфекции, и/или положительными высевами крови или спинномозговой жидкости. Уровни витамина D в сыворотке крови определяли у всех младенцев. Была использована разработанная нами анкета, содержащая демографические, клинические и лабораторные данные младенцев. Статистическая обработка данных проводилась в программе SPSS и включала оценку независимого t-критерия и критерия хи-квадрат. *Результаты.* У 83% младенцев был выявлен дефицит витамина D, при этом у 34,5, 26,4 и 21,8% установлена тяжелая (менее 10 нг/мл), умеренная (10,1–20 нг/мл) и легкая степень дефицита (20,1–30 нг/мл) соответственно. Средний уровень содержания витамина D у младенцев составил 23,31±9,40 нг/мл в контрольной группе и 11,02±8,64 нг/мл в основной (p = 0,000). При раннем и позднем сепсисе в основной группе средний уровень витамина D составил 8,14±5,53 и 12,62±9,75 нг/мл (p = 0,121) соответственно. У 95% инфицированных и 71% неинфицированных младенцев уровень витамина D был менее 30 нг/мл (p = 0,003). *Выводы.* Дефицит витамина D встречается у недоношенных детей довольно часто. Уровень витамина D в сыворотке крови у недоношенных новорожденных с сепсисом был ниже, чем у неинфицированных. Следовательно, коррекция дефицита витамина D может препятствовать развитию тяжелых форм неонатальной инфекции.

Ключевые слова: *недоношенные дети, витамин D, сепсис, менингит, инфекционное заболевание, новорожденные.*

Introduction

Neonatal sepsis, a serious disease with high mortality, remains a major challenge for neonatologist due to both non-specific symptoms and the lack of a definitive early diagnostic test. This condition leads to increased length of stay and higher treatment costs for families, communities and health systems, especially in developing countries with limited neonatal intensive care resources, limited space, and personnel [6].

The prevalence of neonatal bacterial sepsis varies from 1 to 4 cases per 1000 live births. It is estimated to be higher in the preterm infants, with at least 21% experiencing at least one episode of infection. Infections account for about one-quarter of causes of mortality in Mashhad Ghaem Hospital [6, 24, 31, 33]. Identifying risk factors for neonatal infections and making proper corrections can play a significant role in infection control. Prematurity is undoubtedly the most important risk factor for neonatal infection and immune system immaturity is a major predisposing factor for infection in preterm infants. Cellular and humoral defense mechanisms have not still yet developed sufficiently in preterm infants, and neutrophils are deficient in both quality and quantity [30].

Vitamin D, a fat-soluble vitamin, play a role in calcium metabolism and bone mineralization, as well as having a regulatory role in the immune system function, including macrophage [25]. Vitamin D is essential for proper functioning of the innate immune system via peptides in epithelial cells, neutrophils and macrophages [25, 30].

The mechanical barrier of skin and other epithelial surfaces are among the first protective barriers against infection, and activated vitamin D plays a vital role in maintaining the integrity of epithelial cells [5].

Prematurity is associated with an increased risk of vitamin D deficiency. Vitamin D deficiency (serum 25-hydroxy vitamin D level less than 50 nmol/L) differ between preterm infants worldwide, with 64%, 83% and 82% of preterm infants with vitamin D deficiency reported in America, India and Iran, respectively. Low vitamin D levels are associated with intrauterine growth retardation, preterm delivery, hypertension, and neonatal complications during pregnancy [6, 15].

Some studies have reported that insufficient vitamin D (deficiency and inadequacy) is one of the important causes of acute respiratory tract infection in infants and children [13, 32, 34]. There has been an association of vitamin D deficiency with respiratory syncytial virus infection during infancy [33]. On the other hand, vitamins and micronutrients can play an important role in supporting the human immune system, and their homeostasis is key in the response to infection. Micronutrient inadequacies and deficiencies constitute a global health issue, particularly among countries in the Middle East [2]. The deficiency of vitamins A and D is very common in mothers and children due to improper diet and the loss of these materials during periods of recurrent infection particularly in the Middle East and Asia [10, 17].

Vitamin D deficiency can be considered as one reason for weak immune system in preterm infants, leading to the prevalence of infection with increasing age through weakening innate and specific immune system. Given the high prevalence of infection in infants, especially in preterm infants and the possible role of vitamin D in immune system function; this study aimed to investigate the relationship between incidence of infection and vitamin D level in preterm infants.

Materials and methods

This cross-sectional study was carried out on 87 preterm infants with a birth weight of less than 2000 g or gestational age less than 34 weeks, hospitalized in Neonatal Intensive Care Unit (NICU) at Mashhad Ghaem Hospital, Iran, between 2015 and 2017. The subjects were selected through convenience sampling. After obtaining ethical approval and written informed consent from the parents, infants with clearly congenital anomalies, death in the delivery room, maternal substance abuse, and severe asphyxia were excluded from the study.

A 1.5 cc blood sample from the umbilical cord was collected following the birth. The prepared samples were centrifuged, and their serum was stored at –20°C and sent for laboratory evaluation. Vitamin D levels were measured using an Elisa Reader RT2100c (Germany) and Elisa Washing machine with the ELISA method. Vitamin D levels of the infants were divided into four categories: severe (25-hydroxy vitamin D level of less than 10 ng/ml), moderate (10.1–20 ng/ml), mild deficiency (20.1–30 ng/ml), and normal (> 30.1 ng/ml). Demographic characteristics of infants including birth age, sex, and birth weight were recorded in a checklist developed by the researcher. Apgar scores, need for resuscitation, intrauterine growth restriction, asphyxia, respiratory distress, blood culture, spinal cerebrospinal fluid culture, CBC, the number of blood platelets, ESR, C-reactive protein (CRP), intraventricular hemorrhage (IVH) and Respiratory distress syndrome (RDS) were recorded in the checklist. Then, the infants were followed up until hospital discharge, and if there was a clinical or definitely infection, they were followed up. The uninfected and infected infants groups were compared in terms of serum levels of vitamin D

Generally, definitive infection included the infants with positive blood culture (sepsis) or cerebrospinal fluid (CSF) (meningitis) and urine (urinary tract infection). Cases with CSF liquid cytology, white blood cells (WBC) > 30 with preferring neutrophil with or without protein > 150 mg/dl, and sugar less than 35 mg/dl were considered as cytological meningitis. Clinical sepsis was defined as two clinical signs accompanying (lethargy, apnea, respiratory distress, restlessness, seizures, need for mechanical ventilation, abdominal distention, hypotension and food intolerance) and two laboratory signs (20 000 ≤ WBC or ≤ 5000), thrombocytopenia (Plt ≤ 150 000/μL) and CRP ≥ 10 mg/dl)) without a positive culture. When the positive cultures were taken, early and late-onset sepsis were considered after the first three days. After collecting data and inputting it into SPSS, the study was examined using tables, diagrams, and statistical indicators. In order to evaluate the relationships among variables after controlling the normality, an independent t-test was used for normal cases. Chi-square test was used to analyze the relationships among variables with the nominal scale. A p-value less than 0.05 was considered statistically significant.

All statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 20.0 (IBM Corp., Armonk, NY, US). Depending on their distribution, the data were presented as mean and standard deviation or as median and interquartile range. Frequency measures were presented as numbers (n) and frequencies (%). Demographic characteristics were compared between the infection group and control groups. The independent sample t-test was used for normally distributed variables and the Mann–Whitney U-test was used for non-normally distributed variables to determine differences between the two groups. P values of less than 0.05 were considered to indicate statistical significance.

Results

Of the 87 cases, 45 (51.7%) of uninfected infants were in the control group, and 42 (48.3%) of infected infants were in the case group. The infants in the case group included 24 (27.6%) with sepsis, 3 (3.4%) with meningitis, 7 (8%) with meningitis plus sepsis, 4 (4.6%) with cytological meningitis, and 4 (4.6%) with clinical infection. Among the infants, 15 (35.7%) had early-onset infection and 27 (64.3%) had late-onset infection. The most common causes of admission were prematurity (66.7%) and respiratory problems, and the common diagnoses were prematurity, respiratory distress syndrome and infection.

In the present study, vitamin D levels of the infants evaluated showed that 83% of them had vitamin D deficiency, of whom 34.5%, 26.4%, 21.8%, and had severe (less than 10 ng/ml), moderate (10.1–20 ng/ml) and mild deficiency (20.1–30 ng/ml), respectively, and17.2% of cases were normal (30.1–45 ng/ml).

The mean birth weight of infants was 1395.51± 357.53 g in the control group and 1266.71±280.73 g in the case group (p = 0.078). The other features of the study subjects are given in Table 1.

No statistically significant difference were detected between the two groups with respect to WBC (p = 0.802), neutrophils (p = 0.590), lymphocytes (p = 0.450), ESR (p = 0.871), Plt (p = 0.238), hematocrit (p = 0.070), height (p = 0.127), weight (p = 0.078) and gestational age (p = 0.056) (p > 0.05, Table 2).

Statistically significant differences were found between the two groups in terms of CRP (p = 0.025) and serum vitamin D (p = 0.001), i.e. vitamin D, first minute Apgar scores, fifth-minute Apgar scores, and head circumference were higher while CRP of infants was lower in the control group (Table 1).

The mean vitamin D level of infants was 23.31±9.40 ng/ml in the control group and 11.02±8.64 ng/ml in the case group (p = 0.000). In the case group, the mean vitamin D was 8.14±5.53 ng/ml in early sepsis and 12.62±9.75 ng/ml in late-onset sepsis (p = 0.121).

Brain ultrasonography demonstrated intracranial hemorrhage in 4/45% of infants in the control group and 40% of ones in the case group (p = 0.021). There was positive culture in 32.5% of infants on the first day (p = 0.000) and 65.52% of infants after the third day (p = 0.000) in the case group (Table 2).

The mean serum vitamin D levels in infected infants were lower than those in the uninfected cases, with rate 5.30±1.65 ng/ml in the clinical infection and 7.10±2.15 ng/ml in the available cases along with sepsis plus meningitis (Table 3).

Table 1. Comparing the mean infant variables in the two control and case groups

Variables	Infants in the control group 45 (51.7) infants	Infants in the case group 42 (48.3) infants	Level of significance (T-test)
CRP	5.4±11.5	30.50±48.05	0.035*
ESR	8.80±3.70	7.11±2.10	0.871
WBC	11.66±5.17	12.34±7.43	0.802
Neutrophils (%)	45.00±7.07	51.14±15.18	0.590
Lymphocytes (%)	50.50±4.94	41.35±16.08	0.450
Platelets (μL)	330 084±76 026	370 180±61 132	0.238
Hematocrit (g/dl)	46.97±3.26	42.12±6.70	0.070
Vitamin D for infant (ng/ml)	21.23±9.83	11.47±11.35	0.001
Gestational age (weeks)	31.7442±2.08	30.7250±2.64	0.056
First minute Apgar score	7.29±1.48	6.15±2.02	0.005
Fifth minute Apgar score	8.62±1.12	7.73±1.55	0.004
Height (cm)	40.57±2.77	39.53±2.75	0.127
Head circumference (cm)	29.37±1.58	28.13±2.30	0.016
Weight (g)	1395.51±357.53	1266.71±280.73	0.078

Note. *Value is expressed as median±IQR. Others values are expressed as means±SD.

According to the results of this study, the incidence of infection reduced in infants as vitamin D levels increased (Fig.).

40 (95/2%) and 2 (4.8%) infected cases had vitamin D levels less and higher than 30 ngml while in the control group, 32 (71.1%) and 13 (28.9%) infants had low and normal vitamin D levels ($p = 0.003$).

Discussion

According to the results of the study, over four-fifth of preterm infants had Vitamin D deficiency, with 29%, 34%, and 14% experiencing severe, moderate, and mild deficiency, respectively. In the study by Park et al. (2015), 98.9% of preterm infants had vitamin D deficiency, with 50% having severe vitamin D deficiency (less than 10 ng/ml) [28]. In this study, the average serum vitamin D levels were doubled in infants up to 32 weeks compared to the infants less than 32 weeks. In a study conducted by Singh et al. (2016), vitamin D levels in preterm infants were lower than those in full-term infants. Vitamin D deficiency was 94.74%, 87.78%, and 82.67% in the infants below 32 weeks, 32 to 37 weeks, and over 37 weeks, respectively [32]. A significant difference was observed in vitamin D levels at different gestational ages ($p < 0.001$), with higher prevalence of severe and moderate vitamin D deficiency at lower gestational ages. On the other hand, infants with gestational ages over 32 weeks had higher levels of vitamin D (18.05±11.64 ng/ml) compared to those with gestational ages below 32 weeks (10.97±6.31) [8].

Infants' vitamin D status at birth depends on the mothers' vitamin D status during pregnancy. The results of a study showed that the low level of 25-hydroxy vitamin D in mother are associated with increased risk of tooth decay in infancy [30]. A study conducted by Choi et al. demonstrated that majority of Korean pregnant women suffer from vitamin D deficiency, which can play an effective role in reducing vitamin D levels in preterm infants [10]. Cetinkaya et al. (2015) showed that vitamin D levels were lower in newborns of mothers with vitamin D deficiency [9]. Therefore, vitamin D supplementation during

Table 2. Comparison of some neonatal variables in both control and case groups

Group / Variable	Infants in the contol group 45 (51.7) infants	Infants in the case group 42 (48.3) infants	Level of significance* (Statistical test (2))
Blood culture (first day)			
- positive	0 (0)	13 (32.5)	0.000
- negative	42 (100)	27 (67.5)	
Second blood culture			
- positive (after 3 first days)	0 (0)	19 (65.52)	0.000
- negative	33 (100)	10 (34.48)	
Cerebrospinal fluid culture			
- positive	0 (0)	10 (35.71)	0.081
- negative	6(100)	18 (64.29)	
Brain sonography			
- normal	43 (100)	30 (83.33)	0.021
- IVH1	0(0)	5 (13.89)	
- IVH2	0(0)	1 (2.78)	

Note. $p < 0.05$ was considered statistically significant.

Table 3. Mean serum vitamin D levels in the types of infant infections

Infection status	Serum vitamin D levels Mean±SD
Lack of infection (normal)	23.31±9.40
Sepsis	12.21±9.27
Meningitis	21.30±14.06
Clinical Infection	5.30±1.65
Meningitis + sepsis	7.10±2.15
Cytologic meningitis	8.75±3.92

pregnancy improves 25-hydroxy vitamin D levels and can prevent maternal and neonatal complications [9].

Ninety-five percent of our infected infants exhibited low vitamin D levels and 62% of them suffered from severe vitamin D deficiency. In the study of Workneh et al. (2020), Low levels of vitamin D in the cord and maternal blood were significantly associated with neonatal sepsis. Therefore, vitamin D supplementation for pregnant newborns and women could decrease neonatal sepsis [35].

In a study performed by Kanth et al. (2016), 36% of infants in the case group (with early sepsis) and 13% of cases in the control group (without clinical and laboratory evidences of infection) had severe vitamin D deficiency (less than or equal to 12 ng/ml) [18]. In the study of Rech et al. (2014), the incidence of sepsis was significantly higher in cases of vitamin D deficiency (37.3%) than in inadequate (28.6%) or adequate (22.1%) vitamin D levels [29]. In the study of Delrue et al. (2023), the vitamin D status was investigated in prenatal sepsis. In the sepsis group's maternal and neonatal 25(OH) D concentrations were noticeably lower than those of the non-sepsis group ($p < 0.001$ [12]. The sepsis group had a significantly higher percentage of severe vitamin D deficiency than the non-sepsis group.

As the problems of infants with sepsis increase, the mechanism of vitamin D deficiency may be due to the immunological effects of vitamin D; however, the mechanism of vitamin D is complex in immune system [1]. According to a study, there was a significant relationship between vitamin D deficiency in mothers and infants and prolonged rupture of the membranes, with the likelihood of PROM rising as the neonatal sepsis increased [1].

The important role of vitamin D as a regulator of calcium and bone metabolism is well-known; however, vitamin D plays a role in regulating the innate immune system through the production of antimicrobial peptides in epithelial cells, neutrophils, and macrophages [11, 16]. Vitamin D plays a crucial role in prevention sepsis and neonatal diseases [9] as its function is present in almost all types of immune cells, and the response to pathogens by vitamin D receptors [4]. The expression of vitamin D receptors in some immune cells is controlled by safety signals. The increase in the number of vitamin D receptors in the immune system and their regulating by safety

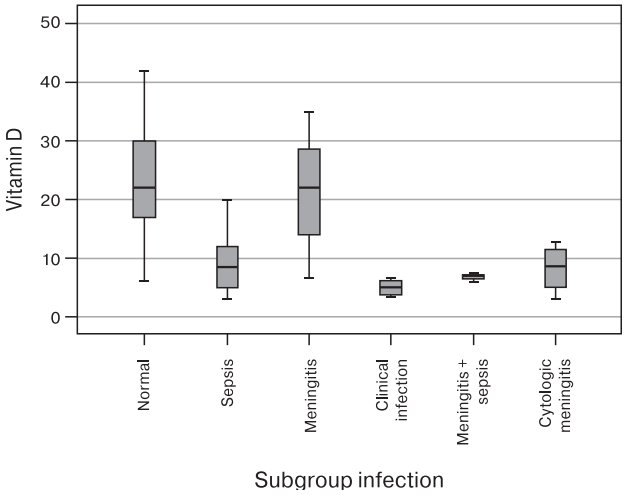

Figure. Relationship between infection and vitamin D level

signals highlight an important role for this hormone as a regulator of immune responses [4]. In addition to influencing hormonal response to sepsis, vitamin D can play a role in the local response of tissue to infection [26]. 1,25-hydroxy vitamin D3 as the active form of vitamin D, regulates the immune system and targets immune cells such as monocytes, macrophages, dendritic cells, and T and B lymphocytes, thereby regulating both innate and adaptive immune responses. Furthermore, immune cells produce the enzymes that activating vitamin D, allowing local conversion of inactive vitamin D to 1,25-hydroxy vitamin D3 in the immune system [4]. Vitamin D can reduce the risk of sepsis by increasing LL-37 Cathelicidin levels, which acts an endogenous antimicrobial peptide and plays a defensive role against a wide variety of infectious factors such as Gram-positive and Gram-negative bacteria, fungi, and micro-bacteria [22, 23]. LL-37 is known as the only member of the Cathelicidin family of host defense peptides in humans so that it is primarily produced by leukocytes and epithelial cells. It regulates a wide range of biological responses, including direct killing of microorganisms, chemotaxis and chemokine induction, regulation of inflammatory responses, angiogenesis, and wound healing [27].

In our study, 95% of infected infants had vitamin D levels less than 30 ng/ml, while in the control group, 71% of cases had vitamin D deficiency ($p = 0.003$). Aydemir et al. (2014) conducted a study on children with sepsis, and the cutoff point of 20 ng/ml for vitamin D Hydroxy exhibited a sensitivity and a specificity of 84% and 76% for diagnosing sepsis as compared with controls [3]. Therefore, serum levels of vitamin D can be utilized as a diagnostic marker with high sensitivity, but low specificity or the diagnosis of infection.

Vitamin D levels in infants with early sepsis is approximately 4 ng/ml lower than those in late-onset sepsis. Although vitamin D plays a role in the incidence of respiratory tract infections in children

and adults, its role in the prevention of neonatal sepsis is still not entirely clear. In their study, Cetinkaya et al. (2015) investigated 25-hydroxy vitamin D levels in healthy infants and infants with early sepsis, and the results showed that lower levels of vitamin D are associated with early sepsis, and severe vitamin D deficiency is very common in the infants with sepsis [9]. In a study conducted by Alves et al. (2015), severe vitamin D deficiency (less than 10 ng/ml) was obsrved in 69.2% of patients with sepsis and 48% of patients without sepsis [2]. Ginde et al. (2011) evaluated the relationship between the concentration of vitamin D and severity of sepsis and found that serum vitamin D levels in patients with severe sepsis were lower than those in the patients with sepsis without organ dysfunction [14]. The results of a prospective study conducted by Uday Kanth et al. (2016) demonstrated that 25-hydroxy vitamin D levels in infants with early sepsis were significantly lower than those in healthy infants, and about 36% of infants with early sepsis exhibited 25-hydroxy vitamin D levels less than or equal to 12 ng/ml [18]. Innate and adaptive immune cells can express vitamin D receptors and respond to stimulations using 1,25-hydroxy vitamin D. Vitamin D-binding protein levels are decreased in the patients with sepsis, leading to exacerbating vitamin D deficiency [34].

The limitation of this study was the hospital control group which was unavoidable due to the significance of gestational age as an intervention factor.

Conclusion

The results of the present study showed that 83% of preterm infants had vitamin D deficiency, of whom almost one-third of infants had severe vitamin D deficiency (less than 10 ng/ml). Also, the low serum levels of vitamin D were associated with an increased incidence of neonatal sepsis. Therefore, given the inverse relationship between serum vitamin D levels and the incidence of sepsis, the use of serum vitamin D level assay is useful as a valuable diagnostic marker with high sensitivity.

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Conflicts of interest

None declared.

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