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Original Article / Orijinal Araştırma

The Evaluation of the Effect of Vitamin D Levels on Neonatal Sepsis in Very Low Birth Weight Infants

Çok Düşük Doğum Ağırlıklı Bebeklerde D Vitamini Düzeylerinin Neonatal Sepsis Üzerine Etkisinin Değerlendirilmesi

Handan HAKYEMEZ TOPTAN, Nilgün KARADAĞ, Sevilay TOPÇUOĞLU, Emre DİNCER, Abdülhamit TÜTEN, Selahattin AKAR, Tülin GÖKMEN YILDIRIM, Elif ÖZALKAYA, Güner KARATEKİN, Hüsnü Fahri OVALI

University of Health Sciences Turkey, Zeynep Kamil Maternity and Children's Disease Health Training and Research Hospital, Clinic of Neonatology, İstanbul, Turkey

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ABSTRACT

Objective: The objective of this study was to investigate the association between 25-hydroxy vitamin D [25 (OH)D] levels and early- and late-onset sepsis in very low birth weight (VLBW) infants.

Methods: This study was conducted between November 2016 and November 2017. VLBW of infants below the 32nd gestational week were included in the study. Serum 25 (OH)D levels were measured on the 1st day and after one week. The infants' demographic data such as gender and gestational week, birth weight, maternal age, presence of early and late sepsis, mechanical ventilation duration, length of hospital stay, and mortality rate were recorded.

Results: Sixty-six newborns followed up in the neonatal intensive care unit of our hospital were enrolled in this study. The median value of 25 (OH)D level on the 1st day was 18.2 (5.2-28.0) ng/mL and the median value of 25 (OH)D after the first week was 15.5 (7.5-37.8) ng/mL. A significant correlation was found between low sepsis and 25 (OH)D levels (<20 ng/mL) measured on the first day (r=-0.557, p=0.003).

Conclusion: There was a significant association between early sepsis and low 25 (OH)D levels measured on the first day. In addition, significant correlations were found between vitamin D deficiency and duration of hospitalization. However, more studies are needed to reach a definite conclusion on this issue.

Keywords: Vitamin D, 25 (OH)D, neonatal sepsis, very low birth weight

ÖZ

Amaç: Bu çalışmada çok düşük doğum ağırlıklı (ÇDDA) bebeklerde 25-hidroksi D vitamini [25 (OH)D] düzeyleri ile erken ve geç başlangıçlı sepsis arasındaki ilişkiyi irdelemeyi amaçladık.

Yöntem: Bu çalışma Kasım 2016 ile Kasım 2017 tarihleri arasında yapılmıştır. Otuz ikinci gebelik haftasının altında ÇDDA bebekler çalışmaya dahil edildi. Serum 25 (OH)D düzeyleri 1. gün ve 1. haftadan sonra ölçüldü. İnfantların cinsiyet ve gebelik haftası gibi demografik verileri, doğum ağırlığı, anne yaşı, erken sepsis ve geç sepsis varlığı, mekanik ventilasyon süresi, hastanede kalış süresi ve mortalite oranları kaydedildi.

Bulgular: Hastanemiz yenidoğan yoğun bakım ünitesinde izlenen 66 yenidoğan çalışmaya dahil edildi. 25 (OH)D seviyesinin 1. gün ortanca değeri 18,2 (5,2-28,0) ng/mL ve 1. haftadan sonra 25 (OH)D ortanca değeri 15,5 (7,5-37,8) ng/mL idi. Birinci gün ölçülen düşük 25 (OH)D düzeyleri (<20 ng/mL) ile sepsis arasında istatistiksel olarak anlamlı korelasyon vardı (r=-0,557, p=0,003).

Sonuç: İlk gün ölçülen düşük 25 (OH)D seviyeleri ile erken sepsis arasında anlamlı bir korelasyon vardı. Ayrıca D vitamini eksikliği ile hastanede kalış süresi arasında anlamlı korelasyonlar bulundu. Ancak bu konuda kesin bir sonuca varmak için daha fazla çalışma yapılmasına ihtiyaç vardır.

Anahtar Kelimeler: D vitamini, 25 (OH)D, yenidoğan sepsisi, çok düşük doğum ağırlığı

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Corresponding Author/ Sorumlu Yazar:

Handan HAKYEMEZ TOPTAN MD,

University of Health Sciences Turkey, Zeynep Kamil Maternity and Children's Disease Health Training and Research Hospital, Clinic of Neonatology, İstanbul, Turkey

Phone: +90 216 391 06 80

mdhandanhakyemez@gmail.com

ORCID: 0000-0002-6966-8514

INTRODUCTION

Classically, vitamin D regulates calcium and is involved in phosphate metabolism. Vitamin D plays a critical role in maintaining a healthy mineralized skeleton and immunomodulatory hormone.[1,2] Studies have shown that vitamin D has significant biologic activities on the adaptive and innate systems by inducing antimicrobial peptides in macrophages, neutrophils and epithelial cells.[3,4] Vitamin D plays an immunomodulatory role in pediatric age groups and newborns and deficiency of this vitamin has been associated with asthma and respiratory infections.[5] Nguyen et al.[6] reported that vitamin D has a crucial role in the interactions between alveolar epithelial cells and mesenchymal cells, and it is involved in the maturation process of the fetal lungs. Vitamin D receptors are expressed by type 2 alveolar cells that take place in the secretion and synthesis and surfactants in response to vitamin D. As a new field of study, researchers have focused on the role of vitamin D in pulmonary maturation and development and postnatal respiratory diseases. The levels of vitamin D in the fetus and neonates reflect those of the mother. Very low birth weight (VLBW) infants born less than 1500 g are deprived of nutrients that are absorbed by the fetus during the last trimester. Low levels of vitamin D are common in women during pregnancy, and the levels tend to be even lower in the cord blood.

Vitamin D deficiency has been associated with an increase in the risk of initiation and development of viral and bacterial infections and development of viral and bacterial infections.[3]

Neonatal sepsis is an important cause of morbidity and mortality in infants and is characterized by signs and symptoms of infection with or without bacteremia in the first month of life.[7] The clinical manifestations of neonatal sepsis range in a wide spectrum from simple subclinical infection to severe focal or systemic disease. Neonatal sepsis is especially evident in premature or low birth weight infants and prolonged hospitalization and requirement of invasive procedures put them at an increased risk for nosocomial infections.[8] Lower levels of neonatal 25-hydroxy vitamin D [25 (OH)D] have been correlated with early-onset neonatal sepsis, late onset sepsis, and increased risk of lower respiratory infections in newborn.[9-12] The objective of this study was to investigate the association between 25 (OH)D levels and early-onset and late-onset sepsis in VLBW infants.

METHODS

This study was performed between November 2016 and November 2017 as a prospective cross-sectional trial and was conducted in VLBW infants below the 32nd gestational week. Infants with congenital anomalies and a history of maternal immunosuppressant therapy in the antenatal period and infants receiving vitamin D before enrollment were excluded from the study. Serum 25 (OH)D levels were measured on the 1st day and after one week. Oral vitamin D 400 U was administered to infants receiving enteral nutrition and 4 cc/kg/day (Vipalipid N infant) in infants receiving parenteral nutrition. A vitamin D level <20 ng/mL is considered low in premature infants.[13,14] Therefore, the infants were divided into two groups as those with a level of vitamin D <20 ng/mL (group 1) and those with a vitamin D level ≥20 ng/mL (group 2) both at the time of admission and after the first week.

Infants' demographic and anthropometric data such as gender and gestational week, birth weight, maternal age, mode of delivery, duration of mechanical ventilation, duration of hospitalization, mortality status, presence of eclampsia, antenatal steroids use, pneumonia, oligohydramnios, 1st and 5th minute Apgar scores were recorded, and early- and late-onset sepsis status was recorded as well. Sepsis seen within the first week of life is considered as early sepsis, and sepsis seen after the first week is considered late sepsis.

All infants included in the study needed early surfactant administration. Briefly, ventilation was performed with PSV TG in accordance with the protocol of our unit and the patients were extubated.

All included infants were assessed by echocardiography for the presence of patent ductus arteriosus (PDA) on the third day of life. When hemodynamically significant PDA was diagnosed, a medical closure protocol (PO ibuprofen for three days) was applied in accordance with our unit protocol.

Whether there is a correlation between 25 (OH)D levels measured on the first day and end of the first week and early and late-onset sepsis was investigated. Respiratory disorders, surfactant requirement, length of hospital stay, and mortality were recorded. At the same time the correlation between 25 (OH)D levels measured on the first day and end of the first week and surfactant requirement was also recorded. Therefore, the blood samples of the infants included were collected on the first day of admission to the neonatal intensive care unit (NICU) and after one week. Plasma samples of neonatal samples were separated and stored at -80°C. 25 (OH)D levels were determined utilizing the Shimadzu LC-20AT model high-performance liquid chromatography system.

Ethics Approval

The study was approved by the Ethics Committee of Zeynep Kamil Maternity and Children's Disease Health

Training and Research Hospital (decision no: 159, date: 25.11.2016). The parents of the infants were informed about the objectives of the study and gave written informed consent. This study was conducted in accordance with the Declaration of Helsinki revised 2013.

Statistical Analysis

Data obtained in this study were statistically evaluated using Statistical Package for Social Sciences (SPSS) version 21.0 (SPSS, IBM Inc., Chicago, IL, USA) software. The data were assessed for normality using visual and analytic methods. Data were tested for normality with the Kolmogorov-Smirnov test and expressed as a mean standard deviation (SD) or median interquartile range (IQR) as appropriate. Categorical variables were expressed as frequencies (n; %), normally distributed continuous variables as mean±SD, and non-normally distributed continuous variables as median (IQR: p25-p75) based on the Kolmogorov-Smirnov test. Pearson correlation analysis was used to assess the correlation between 25 (OH)D studied on the first day and after one week and early and late onset sepsis, $p<0.05$ values were considered statistically significant.

RESULTS

A total of 66 VLBW newborns followed up in the NICU of our hospital were enrolled in the study. Of all newborns, 54.5 (n=36) were male and 45.5 (n=30) were female. The median maternal age was 32 (21-46) years. Antenatal and demographic data of the patients are presented in Table 1.

The median value of 25 (OH)D level on the 1st day was 18.2 (5.2-28.0) ng/mL and the median value of 25 (OH)D after the first week was 15.5 (7.5-37.8) ng/mL. The distribution of patients according to 25 (OH)D is shown in Figure 1.

Pre-eclampsia was observed in 19 (28.79%) and oligohydramnios in 6 (9.09%) mothers. Surfactant was required in 54 (81.82%) patients and antenatal steroids in 32 (48.48%) patients. The median days of mechanical ventilation was found to be 2 (0-56) days. Twenty (30.30%) newborns had congenital pneumonia. The median total parenteral duration was 15 (2-52) days and the median day to transit to enteral feeding was 14.5 (0-53) days. Early-onset sepsis was found in 23 (38.85%) and late-onset sepsis in 28 (44.42%) infants. The median hospitalization duration was found to be 41.5 (2-121) days. Mortality occurred in 11 (16.67%) newborns.

Table 1. Antenatal and demographic features of the patients

Antenatal and demographic findings		
Female/male infants (n, %)		45.5/54.5% (30/36)
	Mean±SD	**Median (IQR)**
Gestational week	27.61±2.33	28 (26-30)
Birth weight	1000.61±266.38	985 (756-1253) g
25 (OH)D value at the 1st day	80.05±7.21	18.2 (5.2-28.0) ng/mL
25 (OH)D value after the 1st week	13.19±5.19	15.5 (7.5-37.8) ng/mL

25 (OH)D: 25-hydroxy vitamin D, SD: Standard deviation, IQR: Interquartile range

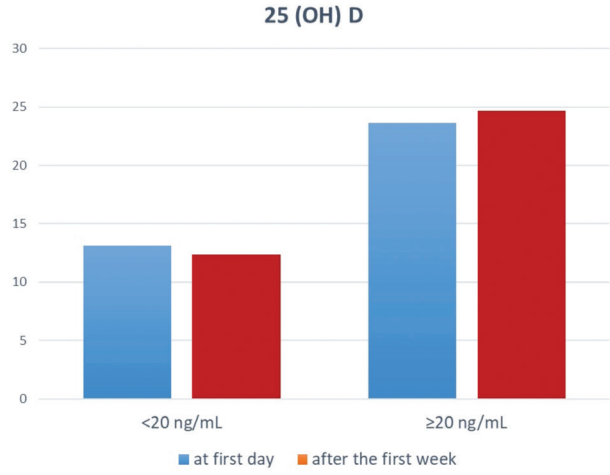

Figure 1. Distribution of 25 (OH)D values on the first day and after the first week

25 (OH)D: 25-hydroxy vitamin D

There was a significant correlation between low 25 (OH) D levels (<20 ng/mL) measured at the first day and sepsis (r=-0.557, p=0.003). However, no statistically significant correlation was observed between low levels of 25 (OH)D (<20 ng/mL) measured after the first week and late sepsis (r=0.97, p=0.094). There was a statistically significant negative relationship between hospitalization duration and 25 (OH)D levels in the first 24 h of life (p=0.001). No correlation was observed between 25 (OH)D levels in the first 24 h and mortality (r=0.492, p=0.931).

DISCUSSION

In this study, we investigated the relationship between vitamin D and early and late sepsis. We found that low levels of vitamin D (<20 ng/mL) were significantly correlated with early-onset sepsis but not with late-onset sepsis. In Behera et al.,[15] low maternal and neonatal vitamin D levels were correlated with neonatal sepsis. In a systematic review and meta-analysis of studies investigating the effects of vitamin D on sepsis, low levels of vitamin D in the cord blood were significantly correlated with neonatal sepsis. The prevalence of vitamin D deficiency was significantly higher among neonates with neonatal sepsis. The authors concluded that vitamin D supplementation for pregnant women and newborns could decrease neonatal sepsis.[16] Studies have shown that vitamin D deficiency among newborns with sepsis differs between 50% and 98.8%.[17] In our study, 84.8% of the infants with early or late-onset sepsis had vitamin D deficiency. Singh et al.[18] reported vitamin D deficiency in 94.74% neonates born <32 weeks. Similarly, Jeengar et al.[19] stated that the 25 OH-D level was significantly lower in the early-onset neonatal group compared to the control group. Terek et al.[20] found that infants with intrauterine growth restriction had vitamin D deficiency in more than half of the cases. Our finding is consistent with the range reported in the literature. In Abdelmaksoud et al,.[21] vitamin D deficiency was correlated with late-onset sepsis. In addition, Dhandai et al.[22] found that neonates with vitamin D deficiency are at greater risk of LOS than those with sufficient vitamin D levels. In our study, we could not find such correlation. We attributed this to the fact that the relationship between vitamin D and sepsis does not necessarily imply causation, and the relationship between vitamin D levels and sepsis is complex and still the subject of ongoing research. In our study, we included only VLBW infants. The median birth weight was 985 (756-1253) g and the median gestational week was 28.

Neonatal sepsis is an infectious disease that is seen within the first 28 days of life, including bloodstream infections, pneumonia and meningitis.[23] Despite the advancement in obstetrics and delivery rooms, neonatal sepsis is still an issue of concern in all gestational ages and various risk factors must be identified for the prevention of neonatal sepsis.[15]

In addition to the extraskeletal system, the demonstration of vitamin D receptors in the cells of the immune system has drawn attention to the effects of vitamin D deficiency on the immune system, especially in relation to sepsis; however, the underlying process is not clear.[11] Studies investigating the relationship between neonatal vitamin D levels and sepsis are limited.[9,24-26] Studies have reported that vitamin D has antimicrobial implications.[27] Vitamin D both enhances the innate immunity and downregulates the acquired immune response.[28] Studies conducted on the innate immune system reported that vitamin D activates toll-like receptors, which promote the production of peptides such as cathelicidin and beta-defensin that have antimicrobial effects on bacteria, viruses, and fungi.[3] Vitamin D has been reported to inhibit the growth and/or kill strains of *Escherichia coli*, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Klebsiella pneumoniae*.[15] Vitamin D has also been found to prevent direct invasion of pathogenic bacteria at sites such as the respiratory tract by enhancing the clearance of these invading organisms. Numerous studies have associated inadequate vitamin D concentrations with respiratory tract infections.[29] In our study, 40.91% of the VLBW infants had low vitamin D levels (less than 20 ng/mL).

In our study, there was a statistically significant negative correlation between hospitalization duration and 25 (OH)D levels in the first 24 h of life (p=0.001). No correlation was observed between 25 (OH)D levels in the first 24 h and mortality (r=0.492, p=0.931). In Mosayebi et al.,[30] no association was found between the duration of hospitalization and the rate of neonatal mortality with vitamin D status (p=0.876). We think the difference between hospitalization outcomes might be attributed to the fact that we included only VLBW infants and this could prolong the length of stay in the hospital.

Study Limitations

This study has some limitations. The major limitation is the small number of patients. In addition, we could include a group with normal birth weight. Finally, given the limited number on the effects of vitamin D on neonatal sepsis in VLBW infants, we could not compare our results exactly. However, this is one of the limited studies in the literature on this issue, and we believe that our findings will guide future studies.

CONCLUSION

The results of our study indicate a significant correlation between low 25 (OH)D levels measured on the first day and early sepsis. In addition, significant correlations were found between vitamin D deficiency and duration

of hospitalization. The results of this study indicate the importance of low 25 (OH)D levels measured on the first day in terms of morbidity, thus emphasizing that vitamin D levels should be monitored more closely. Our results need to be confirmed by further comprehensive randomized controlled studies with a larger series of patients.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of Zeynep Kamil Maternity and Children's Disease Health Training and Research Hospital (decision no: 159, date: 25.11.2016).

Informed Consent: The parents of the infants were informed about the objectives of the study and gave written informed consent.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: H.H.T., N.K., S.T., E.D., A.T., S.A., T.G.Y., E.Ö., Concept: H.H.T., N.K., G.K., H.F.O., Design: H.H.T., N.K., S.T., E.D., A.T., S.A., T.G.Y., E.Ö., Data Collection or Processing: H.H.T., N.K., A.T., S.A., Analysis or Interpretation: H.H.T., G.K., H.F.O., Literature Search: H.H.T., S.T., E.D., A.T., E.Ö., Writing: H.H.T.

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REFERENCES

1. Prietl B, Treiber G, Pieber TR, Amrein K. Vitamin D and immune function. Nutrients. 2013;5:2502-21.
2. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord. 2017;18:153-65.
3. Aranow C. Vitamin D and the immune system. J Investig Med. 2011;59:881-6.
4. Clancy N, Onwuneme C, Carroll A, et al. Vitamin D and neonatal immune function. J Matern Fetal Neonatal Med. 2013;26:639-46.
5. Igde M, Baran P, Oksuz BG, Topcuoglu S, Karatekin G. Association between the oxidative status, Vitamin D levels and respiratory function in asthmatic children. Niger J Clin Pract. 2018;21:63-8.
6. Nguyen TM, Guillozo H, Marin L, Tordet C, Koite S, Garabedian M. Evidence for a vitamin D paracrine system regulating maturation of developing rat lung epithelium. Am J Physiol. 1996;271(3 Pt 1):L392-9.
7. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr. 2008;75:261-6.
8. Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis. Lancet. 2017;390:1770-80.
9. Gamal TS, Madiha AS, Hanan MK, Abdel-Azeem ME, Marian GS. Neonatal and Maternal 25-OH Vitamin D Serum Levels in Neonates with Early-Onset Sepsis. Children (Basel). 2017;4:37.
10. Cizmeci MN, Kanburoglu MK, Akelma AZ, et al. Cord-blood 25-hydroxyvitamin D levels and risk of early-onset neonatal sepsis: a case-control study from a tertiary care center in Turkey. Eur J Pediatr. 2015;174:809-15.
11. Ozdemir AA, Cag Y. Neonatal Vitamin D status and the risk of neonatal sepsis. Pak J Med Sci. 2019;35:420-5.
12. Karatekin G, Kaya A, Salihoğlu O, Balci H, Nuhoğlu A. Association of subclinical vitamin D deficiency in newborns with acute lower respiratory infection and their mothers. Eur J Clin Nutr. 2009;63:473-7.
13. Tofe-Valera I, Pérez-Navero JL, Caballero-Villarraso J, Cañete MD, Villa-Jiménez R, De la Torre-Aguilar MJ. Vitamin d deficiency with high parathyroid hormone levels is related to late onset SEPSIS among preterm infants. BMC Pregnancy Childbirth. 2023;23:23.
14. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-30. Erratum in: J Clin Endocrinol Metab. 2011;96:3908.
15. Behera CK, Sahoo JP, Patra SD, Jena PK. Is Lower Vitamin D Level Associated with Increased Risk of Neonatal Sepsis? A Prospective Cohort Study. Indian J Pediatr. 2020;87:427-32.
16. Workneh Bitew Z, Worku T, Alemu A. Effects of vitamin D on neonatal sepsis: A systematic review and meta-analysis. Food Sci Nutr. 2020;9:375-88.
17. Aye A, Yu Y, Khaing K, Wai L. Serum vitamin D levels in term neonates with early onset sepsis. Pediatr Neonat Biol. 2018;3:124.
18. Singh G, Singh G, Brar HK, Malik S. Vitamin D levels in preterm and term neonates at birth. Int J Contemp Pediatr. 2017;4:48-52.
19. Jeengar B, Gothwal S, Meena KK, et al. Vitamin D Levels and Early Onset Sepsis in Newborns. Journal of Neonatology. 2021;35:64-9.
20. Terek D, Özcan G, Ergin F, et al. Vitamin D Deficiency in Premature Infants and Its Effects on Neonatal Prognosis. J Pediatr Res. 2018;5:37-40.
21. Abdelmaksoud SR, Mostafa MA, Khashaba RA, Assar E. Lower Vitamin D Level as a Risk Factor for Late Onset Neonatal Sepsis: An Observational Case-Control Study. Am J Perinatol. 2021.
22. Dhandai R, Jajoo M, Singh A, Mandal A, Jain R. Association of vitamin D deficiency with an increased risk of late-onset neonatal sepsis. Paediatr Int Child Health. 2018;38:193-7.
23. GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390:1151-210.
24. Grant WB. Vitamin D supplementation of mother and infant could reduce risk of sepsis in premature infants. Early Hum Dev. 2010;86:133.
25. Seliem MS, Abdel Haie OM, Mansour AI, Salama SSME. The relation between vitamin D level and increased risk for earlyonset neonatal sepsis in full term neonate. Med Res J. 2016;15:16-21.
26. Yu YK, Khaing KW, Wai LT, Aye A. Serum vitamin D levels in term neonates with early onset sepsis. Pediatr Neonat Biol. 2018;3:124.
27. Youssef DA, Miller CW, El-Abbassi AM, et al. Antimicrobial implications of vitamin D. Dermatoendocrinol. 2011;3:220-9.

28. Di Rosa M, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immuno-modulator. Immunology. 2011;134:123-39.
29. Esposito S, Lelii M. Vitamin D and respiratory tract infections in childhood. BMC Infect Dis. 2015;15:487.
30. Mosayebi Z, Sagheb S, Mirzendedel M, Movahedian AH. Serum Vitamin D Deficiency in NICU Hospitalized Neonates and Its Association With Neonatal Outcomes. J Family Reprod Health. 2021;15:99-105.