

A Review on the Relation between Sepsis and Vitamin D Level among Neonatal Intensive Care Unit Infants

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Abstract

Background

Neonatal sepsis is a critical condition caused by a generalized bacterial infection in the first month of life. The present study aimed to investigate the relationship between serum vitamin D levels and neonatal sepsis.

Materials and Methods: A search of online databases (Medline, Cochrane Library, Web of Science, EMBASE-Ovid, and Scopus) were carried out for randomized control trials and non-randomized prospective or retrospective clinical studies published in English till April 2020. Two reviewers selected the studies.

Results: In the first study, the level of 25-hydroxyvitamin D [25(OH)D] in the cord-blood sample of infants in the Early-Onset Neonatal Sepsis (EONS) group was significantly lower compared to the control group. 25(OH)D level (19 ng/ml) in the control group were significantly higher compared to the 25(OH) level (8.6 ng/ml) in the sepsis group. In the third study, the serum 25(OH) level showed a significant decrease in the affected neonates (6.4 nmol/L) compared to healthy neonates (42.5 nmol/L). In the fourth study, the sepsis and control group had a significant difference in the level of 25(OH)D (69±7.5ng/ml and 35±19ng/ml). According to the fifth study, the serum 25(OH)D level was insufficient in the case group and sufficient in the control group (p<0.0001). In the sixth study, the odds of very-early-onset neonatal sepsis among the neonates who had the serum 25-hydroxyvitamin D deficiency were lower compared to the odds among neonates who did not have serum 25-hydroxyvitamin D deficiency.

Conclusion

The level of 25-hydroxyvitamin D in the blood sample of infants in the sepsis group was significantly lower compared to the control group; further studies required to confirm the results by considering more confounders.

Key Words: Infants, Sepsis, Neonatal Intensive Care Unit, Vitamin D.

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1- INTRODUCTION

Neonatal sepsis is a risk that includes over 40% of neonatal mortality, with more than 3 million neonate deaths annually worldwide (1). The prevalence of the disease has been reported 1-8 cases out of 1000 live births (2). The term neonatal septicemia is earmarked to conditions of bacterial, viral, and fungal infections that exhibit hemodynamic changes, as well as other clinical manifestations, and accompanies considerable somatic injuries and mortality potential. Despite the experience of caring for the suspected neonates or its definite diagnosis for several years, there are still challenges of the consensus in describing neonatal sepsis (3). The clinical diagnosis of the disease is difficult due to its nonspecific symptoms and manifestations, and neonate specialists confront challenges in diagnosing and managing neonatal sepsis contrary to the presence of laboratory tests (4).

Although the survival probability of the infected neonates has enhanced as a result of treatments using the antibiotic regimens, dissatisfaction with its therapeutic management persists (5). Although the symptoms of neonatal sepsis have been identified for a long time, researchers have not yet attained any convincing success (6). Early neonatal sepsis includes the emergence of symptoms during 72 hours after birth and mainly results from the group B streptococcus that manifests during delivery and as a result of vertical mother-to-fetus transmission. The later version emerges from the 3rd-7th day after birth owing to environmental contacts with the hospital and the atmosphere of the outdoors. A premature birth (before the due date), and an increase in hospitalization time are of the factors, which raise the potential risk of sepsis. However, some cases of late neonatal sepsis have been reported in the first week to the third month after birth (7). The sepsis-suspicious neonates are examined

using the symptoms of skin colour, Hypotonia, Bradycardia, Apnea, respiratory distress, liver enlargement, digestive symptoms, outnumbered leukocytes, Thrombocytopenia, and metabolic acidosis (8). Consideration of predisposing factors such as hospitalization in an intensive care nursery and the weakness of the immune system, especially in premature neonates, along with maternal factors such as the long-term rupture of the embryonic membrane, unpleasant smell rising from the amniotic fluid during delivery, low-weight, and neonatal anomalies is crucial in diagnosing and managing this disease since they increase the risk of septicemia (9, 10).

Besides, different studies have addressed the low level of 25-hydroxyvitamin D, which is related to aborning low weight, pregnancy age, and even aborning Apgar score (10). The results of studies have referred to the direct relationship between vitamin D deficiency, as a potential risk factor in the weakness of the immune system, and the heightened probability of sepsis pathogenesis. In this respect, the association between deficiency at the average vitamin D level of mothers and the possibility of early neonatal sepsis has been posed (11). According to the results of some studies, the 25-hydroxyvitamin D level deficiency in the cord blood is linked to the emergence of sepsis in the first year after birth (12).

Since neonatal sepsis still imposes a heavy burden on the health system even after many years, perceiving the disease phases and controlling them are of utmost importance. In this regard, it is essential to accurately measure the vitamin D serum level of mothers based on the instructions of the health system. Besides, scientific evidence has shown noticeable variations in conditions such as inflammation and stress perception during the assessment of the 25-hydroxyvitamin D levels of pregnant mothers. Thus, more precise

measurement and further studies are recommended (13) so that the preventive and therapeutic role of vitamin D in the manifestation and pursuance of neonatal sepsis is clarified (6). The present study aimed to review the studies conducted on determining the mothers' and neonates' vitamin D serum levels, which are associated with neonatal sepsis.

2- MATERIALS AND METHODS

2-1. Information sources

Following electronic databases were search to find the Relation between Sepsis and Vitamin D Level among neonatal intensive care unit infants: Medline (via PubMed), Cochrane library, EMBASE-Ovid, Web of Science and Scopus for randomized control trial and non-randomized prospective or retrospective clinical studies. The studies published in English to April 2020. The search was carried out independently in duplication by two reviewers, and the supervisor dissolved any disagreement between the reviews.

2-2. Search

Keywords were a combination of: "Neonatal sepsis/ Sepsis/" AND "Ergocalciferols OR Vitamin D" AND "Infant/Neonate".

2-3. Study selection

A database search was carried out for possible studies. Moreover, the abstracts of the studies were screened for identification of eligible studies and the full-text articles were obtained, assessed, and a final list of included studies was made. This process was carried out independently and in duplication by two reviewers, and the third reviewer resolved any disagreement.

3- RESULTS

Finally six studies were included in this systematic review. According to the 18-month study by Cizmeci et al., the

number of NICU infants with suspected Early-Onset Neonatal Sepsis (EONS) was 53 out of 2,571 live births. The level of 25(OH)D in the cord-blood sample of infants in the study group 12.6 ng/mL (3.1 to 78.9) was significantly lower compared to the control group (median 21 ng/mL (5 to 118) ($p=0.038$). The multivariate models showed a relationship between high risk of EONS and low cord-blood 25(OH)D level of <30 ng/ml (OR: 5.6; 95 % CI: 1.3–23.5) (13).

Cizmeci et al. reported that neonatal 25-OHD levels (19 ng/ml) in the control group were significantly higher compared to the sepsis group. There was a direct correlation between neonatal and maternal 25-OHD levels. The sepsis group exhibited significantly severe vitamin D deficiency (14). In a study conducted by Gamal et al., 50 neonates with early-onset sepsis (25 full-term and 25 preterm infants), and 30 age and sex-matched healthy neonates as controls were included. The mean gestational age was 34.1 ± 1.26 for preterm neonates with sepsis and 37.5 ± 0.98 for full-term with sepsis. The serum 25-OH D level was significantly lower in the infected neonates (6.4 ± 1.8 and 24.6 ± 2.2 nmol/L) compared to healthy neonates (42.5 ± 20.7 and 50.4 ± 21.4 nmol/L).

There were significant negative correlations between neonatal and maternal 25-OH vitamin D serum levels and all sepsis markers. Moreover, there were significant positive correlations between neonatal and maternal 25-OH vitamin D levels (11). Çekmez et al. included 106 term babies consisted of 20 controls in their study. Newborn blood samples were collected from the first day of sepsis. The patients with sepsis and controls showed a significant difference in the level of 25(OH)D (69 ± 7.5 ng/ml and 35 ± 19 ng/ml, $p=0.01$) (6). In Das et al.'s study, the serum 25(OH)D was assessed, the primary circulating form of vitamin D on 120 subjects in a case-control approach,

recruiting 60 subjects in each category. The serum 25(OH)D level was insufficient (median = 12.16 ng/ml, 95% CI: 3.84–22.22) in the case group, and sufficient in the control group (median = 30.22 ng/ml, 95% CI: 20.08–46.78; $p=0.0001$), highlighting the higher prevalence of vitamin D deficiency in case group (15). Oleo et al. conducted a case-control study on maternal serum 25(OH)D levels and the risk of very early-onset neonatal sepsis. The odds of very-early-onset neonatal sepsis among the neonates who were serum 25(OH)D deficient was lower compared to the odds among neonates who were not serum 25(OH)D deficient (OR: -0.40, 95% CI: 0.13-1.15, $p=0.059$) (16).

4- DISCUSSION

This study aimed to investigate the relationship between serum vitamin D levels and neonatal sepsis. Six studies were included into the systematic review. The level of 25-hydroxyvitamin D in the sepsis group was significantly lower compared to control groups. There was a direct correlation between neonatal and maternal 25-OHD levels. Although deficiency at the average level of vitamin D of mothers is a global issue stemming from inappropriate regimens, skin coverage, and insufficient exposure to sunlight, therefore the utilization of the 25-hydroxyvitamin D supplement during pregnancy seems necessary if needed (11).

The role of vitamin D deficiency and its direct association with the pathogenesis power of infections in other diseases have been also posited (17). Various studies has revealed that vitamin D and its metabolites are related to several illnesses, including cancer, diabetes, asthma, and sepsis. Since the innate immune systems of neonates are not fully developed, they are more susceptible to be afflicted by various infections. Hence, the exposure of neonates to sunlight as a conventional method justifies this problem that it can

fortify the neonate's immune system and protect them from other infections (15). Concerning the early sensitivity of neonates to vitamin D deficiency in this period, it may also play the significant role in the growth of uterine lungs. It seems that vitamin D deficiency noticeably reduces lung volume. Moreover, vitamin D deficiency disposes neonates to respiratory infections by reducing their breathing storage (18). However, the neonates whose vitamin D level of their cord blood has been reported normal less suffer from acute respiratory infection (19).

The neonates of the mothers with vitamin D deficiency at their pregnancy show more stertor rate and are at risk of severe respiratory diseases in the first three months of their lives (18). The effect of the serum level adequacy of vitamin D associates with the decreased risk of the vertical transmission of infection from mothers suffering from HIV to fetuses (19). Recent studies have proved the importance of vitamin D besides antibiotic regimens on increasing the survival chance of infants with acute and chronic diseases.

The immediate reception of vitamin D supplements, and consequently, fortifying their immune system against infections, protects susceptible neonates from the emergence of early and late neonatal sepsis (15). Of course, the serum level adequacy of 25-hydroxyvitamin D of mothers is important in the first three months of pregnancy in supplying fetus storage and reinforcing their immune system. This issue is specifically noticed in neonates that are born before the 32nd week of pregnancy (11). Nevertheless, deficiency in the vitamin D storage of mothers in European countries, Canada, and Middle East countries is a global problem, and two-third of young and healthy women suffer from its storage deficiency (20). The risk of affliction by acute respiratory infection is higher among neonates suffering from vitamin D deficiency, and

this sequel is the common reason for neonatal mortality, particularly in developing countries (18). However, the effect of vitamin D on the immune system has not been well documented; there is dispersed evidence on its effect on neonatal consequences (13). Likewise, the most suitable dose and consumption time of vitamin D by mothers in their pregnancy period for the conservation of sufficient rates in mothers and neonates are not specified. Nevertheless, supervising the agreement of mothers with vitamin D supplements and personalizing the rate of vitamin D supplement based on the measured vitamin D improve vitamin D level in neonates. Some caution concerning the importance of proper nutrition, vitamin D supplement, and exposition to the sunlight should be given to mothers in their pregnancy period (18). Longitudinal studies are required to confirm our results and develop mechanisms between the 25-hydroxyvitamin D and ALRTI serum levels in neonates contriving these observations.

5- CONCLUSION

The level of 25-hydroxyvitamin D in the blood sample of infants in with sepsis group was significantly lower compared to the control group. There was a direct correlation between neonatal and maternal 25-OHD levels. Further studies are required to confirm the results by considering more confounders.

6- CONFLICT OF INTEREST: None.

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