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Original Article

Vitamin A and D Levels in Preterm Neonates: The Relationship with Morbidities and Clinical Considerations

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ABSTRACT

Background: Vitamin A and D deficiency are more prevalent in preterm neonates than in term. Preterm neonates are more susceptible to various complications and morbidities, including respiratory issues, sepsis, retinopathy of prematurity, hyperbilirubinemia, anemia, and intraventricular hemorrhage. This study aims to investigate potential relationships between vitamin A and D deficiency and neonatal morbidities.

Methods: Forty-four neonates, all with gestational age less than 32 weeks or birth weight less than 1500 grams, were enrolled. Serum levels of vitamin A and D were assessed, and neonates were categorized into deficient and sufficient. Comparative analysis was conducted between groups using various statistical tests, including Chi-square test, Wilcoxon signed rank test, Kruskal-Wallis test, independent t-test, and Mann-Whitney test.

Results: The mean gestational age was 30.5±1.7 weeks, and the mean birth weight was 1322.95±286.67 grams. The mean vitamin A and D levels were 20.95±9.79 µg/dl and 22.8±11.5 ng/ml, respectively. Vitamin A deficiency was observed in 19 individuals (43.2%), while 29 individuals (65.9%) exhibited vitamin D deficiency. A significant association was observed between vitamin D deficiency and both duration and type of oxygen support (p-value 0.04, 0.04). However, no significant differences were found between the two groups regarding other morbidities or vitamin A status.

Conclusion: Limited studies have evaluated the association of vitamin levels with neonatal morbidities. Vitamin D deficiency is common among preterm neonates and is associated with the duration and type of respiratory support. Further investigations are warranted to explore potential links between vitamin deficiencies and various neonatal morbidities.

Keywords: Bronchopulmonary dysplasia, Morbidity, Newborn, Respiratory distress syndrome, Vitamin A deficiency, Vitamin D deficiency

Introduction

Prematurity, defined as birth occurring before 37 weeks of gestation(1), accounts for 11% of live births worldwide and 35% of neonatal mortalities(2, 3). Premature infants suffer from multiple complications and morbidities, including sepsis, intraventricular hemorrhage (IVH), necrotizing enterocolitis, retinopathy of prematurity (ROP), bronchopulmonary dysplasia (BPD), patent ductus arteriosus (PDA), and hyperbilirubinemia. Consequently, understanding the factors that influence their health outcomes becomes paramount. Among crucial determinants of neonatal health are vitamins A and D, which play pivotal roles in growth, development, and immune function.

Vitamin D deficiency is more prevalent in preterm neonates compared to term neonates (4). Both maternal and neonatal vitamin D deficiency are common and significantly associated with

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each other (5, 6). The relationship between vitamin D levels and an elevated susceptibility of lower respiratory tract infections and wheezing is probably attributed to its immune-modulating and anti-inflammatory effects (7) as well as its role in lung maturation(1). Nevertheless, certain studies have found no association between vitamin D levels and lower respiratory tract infections(8). Animal studies have indicated that vitamin D deficiency might hinder the proliferation of alveolar type 2 and fibroblasts, which play a critical role in lung development and function(9, 10). Current investigations are underway to explore the potential contribution of vitamin D in the prevention of BPD(11, 12).

Vitamin A is of significant importance in neonatal respiratory disease due to its role in activating SP-B mRNA transcriptase, which is crucial for surfactant synthesis(13). Vitamin A deficiency can lead to decreased expression of genes involved in fatty acid synthesis, as well as mRNA levels of SP-A, SP-B, and SP-C. (14, 15) Additionally, it possesses antioxidant effects that are important for preventing respiratory diseases in newborns (16). Vitamin A also promotes the growth and differentiation of the epithelial cells. Vitamin A insufficiency can impair the normal re-epithelialization process of the lung tissue following acute injuries, such as barotrauma and oxygen toxicity (17-19).

The role of vitamin A and D in other morbidities such as ROP, hyperbilirubinemia, anemia, and more has received limited attention in the literature. This study aims to evaluate the relationship between vitamin A and D levels and neonatal morbidities in preterm infants.

Methods

This cross-sectional analytic study was conducted among preterm neonates with a gestational age (GA) of less than 32 weeks or birth weight (BWT) below 1500 grams, who were hospitalized for at least 14 days at Hafez and Namazi Hospital, Shiraz, Iran. A total of 50 neonates were enrolled over one year in 2021. Six neonates who died during the study were excluded.

Exclusion criteria for this study included neonates with asphyxia (Apgar in 5 minutes < 6, cord PH<7, BE<-12), congenital anomalies, Intra-Ventricular Hemorrhage (IVH) grade 3 and 4, congenital heart disease except for Patent ductus arteriosus (PDA).

Respiratory support was defined as the administration of oxygen, Continuous Positive Airway Pressure (CPAP), or a ventilator. All patients were monitored throughout their hospital stay. The selection of respiratory support for the patients followed the latest recommendations by the European consensus for neonatal respiratory support(20) and was based on clinical and paraclinical indicators. Neonates with lower oxygen saturation levels without respiratory distress were given oxygen until their saturation reached the target range of 90-94%. CPAP was utilized for neonates at birth who were at a higher risk of developing RDS, such as infants with GA < 30 weeks who did not require intubation. Intubation was performed for the neonates when all other methods failed to maintain the target of oxygen saturation range (90-94%).

To measure the serum levels of vitamins A and D, a 2cc serum sample was obtained by trained NICU nurses using clot tubes. To account for the respective half-life of vitamin D (approximately 6 hours) and vitamin A (ranging from 2 to 9 hours), administration of these vitamins was discontinued if the patient had received them within two days before sampling to neutralize their effects. The High-performance liquid chromatography (HPLC) method was utilized to measure the levels of vitamins. Blood samples were promptly sent to the laboratory immediately after collection.

The serum levels of vitamins A and D were measured when neonates reached 14±2 days. Based on the serum levels, neonates were categorized into deficient and sufficient groups for each vitamin A and vitamin D. The normal range for vitamin D was defined as 30 ng/ml or above, while vitamin A deficiency was determined as a level lower than 20 µg/dl.

Neonatal morbidities, including the need for oxygen support and its duration, sepsis, anemia requiring packed red blood cells, PDA, IVH 1, and hyperbilirubinemia requiring phototherapy, and the necessity for ROP treatment were recorded from hospital records and tracked for ROP in a 6-month follow-up.

Sepsis was defined as clinical characteristics such as poor feeding or lethargy, the positive c-reactive protein, or positive culture. PDA was assessed by echocardiography. Brain sonography was used for any hemorrhage. The treatment of hyperbilirubinemia is based on the guidelines for initiating phototherapy in premature infants(21). All these preterm neonates were examined by an expert ophthalmologist for ROP at day 28 and then had follow-ups.

Statistical analysis

Descriptive statistics, including mean ±

standard deviation (SD), were reported for continuous quantitative data, while percentages were used for quantitative data. The relationship between vitamin deficiency and oxygen dependency was assessed using the Chi-square test, the Wilcoxon signed rank test, and the Kruskal-Wallis test. Independent t-test and Mann-Whitney test were employed to compare normal continuous and non-normal data between the two groups. Statistical analysis was performed using SPSS software version 21 (SPSS Statistics Inc., Chicago) with a significance level set at 0.05.

Ethical Approval

This study was conducted on infants admitted to Namazi and Hafez hospitals in Shiraz, Iran. The study protocol was approved by the Medical Ethics Committee of Shiraz University of Medical Sciences (Ethics code: IR.sums.med.rec.1400.521). All methods were performed according to the relevant guidelines, and informed consent was obtained from a parent and/or legal guardian of all participants.

Results

Among 44 preterm neonates enrolled in the study, the mean GA was 30.5±1.70 weeks, ranging from 28 to 34 weeks. The average BWT was 1322.95±286.67 grams, ranging from 750 to 1900 grams. The Apgar score at the 1st minute and 5th minute were 6.36±1.44 and 8.32±0.82, respectively. The mother's mean age was 32.29±4.7 years, ranging from 25 to 50 years. Table 1 displays the demographic and clinical characteristics of these neonates.

The mean vitamin D level measured was 22.8±11.5 ng/ml (ranging from 4.1 to 44.6 ng/ml). Out of the total neonates, 29(65.9%) neonates displayed vitamin D deficiency, while 15(34.1%) exhibited adequate vitamin D levels. Table 2

Table 1. Demographic and clinical characteristics of preterm neonates

	N(%)
Sex	
Male	25(56.8%)
Female	19(43.2%)
Pregnancy-related factors	
IUGR[1]	13(29.5%)
Multiple births	20(45.5%)
Preeclampsia	10(22.7%)
GDM[2]	10(22.7%)
hypothyroidism	9(20.5%)
Feeding	
Breast milk	30(68.2%)
Formula	13(29.5%)
NPO	1(2.3%)
Oxygen dependency (day 14)	
No Oxygen	23(52.3%)
O2 with hood	14(31.8%)
CPAP	4(9.1%)
Intubate	3(6.8%)
Morbidities	
IVH 1	19(43.2%)
PDA	15(34.1%)
Sepsis	20(45.5%)
Phototherapy	34(77.3%)
Packed cell	30(68.3%)
ROP	2(4.5%)
Vitamin deficiency	
Vitamin A	19(43.2%)
Vitamin D	29(65.9%)

[1] intrauterine growth restriction, [2] gestational diabetes

Table 2. Comparison of neonates with vitamin D deficiency and adequate vitamin D levels

	Vitamin D deficient (N=29)	Vitamin D sufficient (N=15)	p-value
GA	30.24±1.55	31±1.92	0.67
Birth weight	1280.86±290.47	1404.33±269.99	0.28
Oxygen dependency			
NO	12(41.3%)	11(73.3%)	
Oxygen	13(44.8%)	1(6.7%)	0.04
CPAP	3(10.3%)	1(6.7%)	
Intubate	1(3.4%)	2(13.3%)	
Oxygen duration			
<7days	9(31.03%)	7(53.8%)	
7-14days	4(13.7%)	2(15.4%)	0.04
14-28days	4(13.7%)	4(30.8%)	
>28days	12(41.3%)	0	
Sepsis	14(48.2%)	6(40%)	0.75
Brain sonography			
IVH 1	10(34.4%)	9(60%)	0.123
NL	19(65.5%)	6(40%)	
Echocardiography			
PDA	9(31.03%)	6(40%)	0.738
NL	20(68.9%)	9(60%)	
Packed cell transfusion	21(72.4%)	9(60%)	0.5
Phototherapy	22(75.8%)	12(80%)	0.913
ROP	2(6.8%)	0	0.325
Duration of hospitalization	34.39±14.5	35.46±32.37	0.26

Table 3. Comparison of neonates with vitamin A deficiency and adequate vitamin A levels

	Vitamin A deficient (N=19)	Vitamin A sufficient (N=22)	p-value
GA	30.42±1.77	30.59±1.73	0.32
Birth weight	1258.95±322.55	1367.7±260.6	0.43
Oxygen dependency			
NO	6(31.6%)	15(68.2%)	
Oxygen	8(61.5%)	5(22.7%)	0.127
CPAP	3(15.8%)	1(4.5%)	
Intubate	2(10.5%)	1(4.5%)	
Oxygen duration			
<7days	6(33.3%)	9(42.9%)	
7-14days	3(16.7%)	3(14.3%)	0.47
14-28days	2(11.1%)	5(23.8%)	
>28days	7(38.9%)	4(19%)	
Sepsis	9(47.4%)	10(45.5%)	0.57
Brain sonography			
IVH 1	7(38.9%)	11(50%)	0.53
NL	12(63.2%)	11(50%)	
Echocardiography			
PDA	7(36.8%)	7(31.8%)	0.75
NL	12(63.2%)	15(68.2%)	
Packed cell transfusion	11(57.9%)	17(77.3%)	0.313
Phototherapy	13(72.2%)	5(27.8%)	0.26
ROP	1(7.1%)	1(6.7%)	0.96
Duration of hospitalization	35.23±16.8	35.33±25.95	0.64

provides a comparison between these two groups.

In this study, 19(43.2%) neonates exhibited vitamin A deficiency, while the remaining neonates had sufficient amounts of vitamin A. The mean level of vitamin A was 20.95±9.79 µg/dl, ranging from 4.6 to 45.3 µg/dl. Table 3 compares the deficient group and those with sufficient vitamin A levels, considering various morbidities.

Discussion

In this study conducted among preterm neonates, the majority of them exhibited vitamin D deficiency. Neonates deficient in vitamin D experienced a statistically significant longer duration of oxygen therapy compared to those with sufficient levels of vitamin D. The occurrence of other morbidities was similar in both groups. when comparing vitamin A deficient and vitamin A sufficient neonates, no significant difference in morbidities was observed.

Vitamin D, in conjunction with its receptor, plays a crucial role in exhibiting essential anti-inflammatory, membrane stabilizing, and antimicrobial properties at barrier sites like the gastrointestinal tract, respiratory system, and skin. Within the innate immune system, vitamin D holds significant importance as it stimulates the production of cathelicidins and other defensive components that possess antimicrobial and antiendotoxin activities(22, 23). In our study, although the majority of sepsis cases (70%) were vitamin D deficient, the association between vitamin D deficiency and sepsis was not statistically significant. This could be attributed to the small number of neonates with sepsis in this study. In a systematic review and meta-analysis, a significant inverse association between maternal vitamin D level and neonatal sepsis was discovered, the lower vitamin D status was associated with a higher susceptibility to sepsis in neonates. The lower cord vitamin D level was also linked to neonatal sepsis(24). Ozdemir et al. in their prospective study of 107 term neonates, demonstrate a significant difference between neonates with and without sepsis, with the mean vitamin D level being lower in the sepsis group(25). Dhandai et al. also reported that late-onset sepsis occurred more frequently in neonates with low vitamin D levels(26).

In our comparison between vitamin A-sufficient and vitamin A-deficient groups, we found no statistically significant difference. In contrast to our results, Zhang et al. in their study among children, found a significant association between vitamin A deficiency and sepsis or septic shock(27). There is limited information available

regarding the role of vitamin A in neonatal sepsis. Retinoic acid, an active metabolite of vitamin A, plays a significant role in promoting the differentiation of anti-inflammatory regulatory T cells and inhibiting pro-inflammatory T helper 17 cells induced by interleukin -6. This contributes to a balanced immune response with both pro and anti-inflammatory aspects (28). Vitamin A deficiency can lead to well-known manifestations like nyctalopia, but extensive research suggests that it is also associated with adverse health outcomes in children due to an increased risk of infections. Vitamin A deficiency impacts immunity at multiple levels, including disruption in the gastrointestinal mucosal barrier, reduced numbers of monocytes and natural killer cells, and Impaired function of macrophages, dendritic cells, and neutrophils(29, 30).

Our results revealed a statistically significant association between the duration of oxygen dependency and vitamin D deficiency (p-value 0.04). Additionally, a significant difference was observed between the vitamin D deficient and sufficient groups concerning the type of oxygen dependency (p-value 0.04). These findings are consistent with those of Jafari et al.(31) who reported a significant association between vitamin D deficiency and conditions such as RDS or the need for non-invasive ventilation in preterm infants. Furthermore, a meta-analysis conducted by Park et al.(9) demonstrated that 80% of preterm infants had vitamin D deficiency and highlighted a significant correlation between the umbilical cord or serum vitamin D levels on the first day of life and the development of BPD. Zhang et al. (32) also identified a link between lower vitamin D levels and more more severe respiratory problems. Additionally, Boskabady et al. (33) found that the mean maternal vitamin D level in neonates with RDS was five ng/dl lower compared to those without respiratory problems.

In our study, most of the patients who required respiratory support were vitamin A deficient; however, there was no statistically significant difference between the groups for the type and duration of oxygen support. Similar findings were reported by Tammela et al.(34), who found no significant difference in vitamin A levels between infants with RDS and those without. It is important to note that vitamin A deficiency can lead to impaired lung growth and repair, compromised secretion clearance, loss of cilia, and reduced ability to repair lung injuries (35). Mechanical ventilation can pose risks to underdeveloped lungs, including baro-volume trauma and oxygen toxicity, which can result in increased inflammatory responses(36). In contrast to our results, A recent study discovered an association between mechanical ventilation and retinol concentration, independently of IL-6. This suggests that the inverse relationship between mechanical ventilation and vitamin A status may not be solely attributed to inflammatory reactions but could also be due to increased utilization of vitamin A for lung repair or as a response to counteract oxidative stress(37).

Various studies have examined the relationship between serum vitamin D levels and the duration of hospitalization in the NICU yielding differing results. Some studies, such as our study, as well as those conducted by Mosayebi et al., Rey et al., and Rippel et al., did not find a significant association between vitamin D deficiency and the length of hospital stay(38-40). However, McNally et al. and Sankar et al. reported somewhat different results, showing a link between longer hospital stays and vitamin D deficiency(41, 42).

Our results showed no difference in the duration of hospitalization between neonates with normal vitamin A levels and those with deficient amount. In a randomized control trial by Basu et al. among very low birth weight neonates, the duration of hospital stay was significantly lower in neonates receiving vitamin A supplementation compared to those receiving a placebo(43). However, in Kositamongkol et al. ‘s study, there was no difference in the duration of hospitalization between neonates with normal vitamin A levels and those who were deficient (44), which aligns with our results.

Although the majority of neonates with hyperbilirubinemia (22 out of 34 neonates) had low levels of vitamin D, we found no statistically significant relationship between vitamin D deficiency and hyperbilirubinemia. However, in a comparison of term neonates with hyperbilirubinemia and those without, lower vitamin D levels were observed in the first group(45). In another study by Zia et al., an association was found between maternal vitamin D deficiency and the risk of hyperbilirubinemia in term neonates(46). It’s worth noting that further studies are needed to determine if there is a consistent association between vitamin D deficiency and hyperbilirubinemia.

In our study, we did not find any association between vitamin A deficiency and hyperbili-rubinemia. A search in PubMed and Google

Scholar with mesh terms “hyperbilirubinemia” and “vitamin A deficiency” did not yield any relevant articles.

Among the participants, two neonates had retinopathy of prematurity requiring treatment. Both of them had vitamin D deficiency, and one of them had vitamin A deficiency. There is evidence of the efficacy of supplementary vitamin A treatment in premature infants for the development of the retina(47). Additionally, some studies have shown an association between lower vitamin D levels and the occurrence and need for treatment of retinopathy of prematurity(48, 49). We suggest conducting a study among premature neonates with retinopathy of prematurity to investigate any potential association between vitamin deficiencies and ROP.

Although most of the neonates who had anemia and required transfusion of packed red blood cells had vitamin D deficiency, we did not observe a significant association. Similarly, we found no significant association between vitamin A deficiency and anemia. Further studies are needed among neonates to explore potential associations in more detail.

Although most studies have focused on the impact of vitamin supplementation on BPD occurrence (50-52), this study specifically investigated the levels of vitamin A and D in question. We also examined additional morbidities beyond respiratory issues among preterm neonates. However, due to the small sample size which limits the generalizability of the findings, further research is necessary to confirm these findings and explore potential interventions. Further studies should consider larger sample sizes or randomized control trials in different regions to better understand the relationship between vitamin levels and neonatal morbidities and the effectiveness of supplements. The findings from this study may have important implications for the care and treatment of preterm neonates, and further research is needed to fully explore this relationship.

Conclusion

In conclusion, our study investigated the association of vitamin A and D levels with a range of neonatal morbidities, including respiratory problems, hyperbilirubinemia, anemia, sepsis, and others. While we observed association in some instances, such as vitamin D deficiency being linked to longer oxygen dependency and more oxygen support, the overall findings indicate a need for further research to better understand the complex interplay between these vitamins and neonatal health. These preliminary results emphasize the importance of considering vitamin A and D status in neonatal care, particularly in cases of prematurity and respiratory distress syndrome, but underscore the need for larger studies to confirm these associations and elucidate potential interventions for improving neonatal outcomes.

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Conflicts of interest

The authors declare that they have no competing interests.

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