The Effect of Cord Blood Vitamin D Level on Bronchopulmonary Dysplasia and Other Neonatal Morbidities in Preterm Infants

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ABSTRACT

OBJECTIVES: We aimed to investigate the relationship between cord 25-hydroxyvitamin D level and bronchopulmonary dysplasia and other neonatal morbidities (sepsis, necrotizing enterocolitis, intraventricular hemorrhage, patent ductus arteriosus, respiratory distress syndrome, retinopathy of prematurity) in preterm neonates.

STUDY DESIGN: Infants aged <32 gestational weeks who were admitted to the neonatal intensive care unit between March 2014 and November 2014 were enrolled in this prospective study. Cord blood samples were obtained during delivery. 25-hydroxyvitamin D level was measured using an automatic biochemical analyzer. Patients were divided into two groups according to their 25-hydroxyvitamin D levels: 25-hydroxyvitamin D <20 ng/mL and 25-hydroxyvitamin D ≥20 ng/mL. We used descriptive statistics and multiple regression models to identify risk factors associated with bronchopulmonary dysplasia.

RESULTS: Sixty premature infants were analyzed in this study. The mean cord 25-hydroxyvitamin D level was 13,8±6,8 ng/mL (range 3,5-30,7 ng/mL). Eighty percent of the patients (48/60) had 25-hydroxyvitamin D levels <20 ng/mL. Among the infants, 21 (35%) developed bronchopulmonary dysplasia. Infants with bronchopulmonary dysplasia had higher frequencies of 25-hydroxyvitamin D deficiency than the non-bronchopulmonary dysplasia group (p=0.028). Duration of hospitalization was also longer in infants with low levels of cord 25-hydroxyvitamin D. On the other hand, there was no significant difference between infants with and without vitamin D deficiency with respect to respiratory distress syndrome, patent ductus arteriosus, retinopathy of prematurity, necrotizing enterocolitis, sepsis, and intraventricular hemorrhage.

CONCLUSION: This study shows the high rate of vitamin D deficiency in pregnant women in the central Anatolian region (Sivas) of Türkiye. Low cord 25-hydroxyvitamin D levels were associated with an increased risk of bronchopulmonary dysplasia and prolonged hospitalization in very preterm infants. These data strengthen the necessity for vitamin D supplementation during pregnancy.

Keywords: Bronchopulmonary dysplasia, Neonatal morbidities, Premature, Vitamin D deficiency

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Introduction

Preterm births constitute 12% of all births and its rate is higher in African Americans, those with low socioeconomic status, young and obese women. Among preterm babies, Vitamin D deficiency is more common than mature newborns (1,2) vitamin D has effects on the skeletal, cardiovascular, and immune systems. The studies conducted in the last decade shows that vitamin D deficiency is associated with not only calcium and bone metabolism disorders (2,3), it is also related to the development of common chronic diseases (multiple sclerosis, type 1 diabetes, inflammatory bowel disease, metabolic disorders, asthma) (4-6). Low 25-hydroxyvitamin D (25-OHD) level during pregnancy is associated with preeclampsia, intrauterine growth retardation, and gestational diabetes and is a risk factor for preterm births (7).

With the increase in premature survival rates, bronchopulmonary dysplasia (BPD) emerges as an important health problem in the short and long term. Bronchopulmonary dysplasia is defined as the presence of radiological findings of BPD in addition to oxygen dependency in term and near-term preterm newborns, although they reach the postnatal 28th day or when the corrected gestational age reaches 36th week in immature premature newborns (below 32 weeks) (8). In recent years, Mandell et al. (9) reported that vitamin D was effective in the vascular and alveolar development of the lungs in rats that developed BPD with endotoxin exposure. Mao et al. (10) found that 25-OHD levels were significantly lower in preterm babies with BPD at 28th-31st weeks of age. However, Joung et al. (11) did not find any relationship between low vitamin D levels and pulmonary morbidities in premature babies. Although many other reports support that low vitamin D levels affect BPD predisposition in premature babies (10,12-14), its effects on other morbidities have not been clearly defined.

In the present study, we aimed to investigate the effect of cord vitamin D level on BPD and other neonatal morbidities [sepsis, necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), retinopathy of prematurity (ROP)] in preterm babies.

Material and Method

The cross-sectional study was conducted in a tertiary-level neonatal intensive care unit at Cumhuriyet University, Faculty of Medicine, Sivas, between March 2014 and November 2014. For the present study, preterm infants who were born at <32 weeks of gestation with a birth weight of <1500 g were eligible for inclusion. Infants with congenital and chromosomal anomalies, any organic diseases, those whose mothers have calcium metabolism disorders, and those who died in the first 48 hours of life were excluded from the study. The study protocol was approved by the ethical committee of the Faculty of Medicine, Cumhuriyet University (Approval Number: 2014-04/03) and was performed in accordance with the ethical principles described by the Declaration of Helsinki. Informed parental consent was obtained from the parents.

The trained researcher collected the data of gestational age, maternal age, number of births, history of premature rupture of membranes, preeclampsia, antenatal steroid usage, gestational diabetes mellitus, sex, delivery mode, APGAR scores, and need for resuscitation (or oxygen supplementation, positive pressure ventilation, and intubation). Use of surfactant, duration of invasive and noninvasive ventilation, hospital stay, and death were also recorded.

Blood samples

Blood samples were taken from the umbilical cord at delivery. Samples were centrifuged at 3500 rpm (revolutions per minute) for 5 minutes, and the serum was separated and stored at -80°C until analysis. Plasma samples were used for the measurement of 25-OHD, calcium (Ca), phosphate (*P*), alkaline phosphatase (ALP). All samples were analyzed by a single technician to avoid any interobserver variation. The limit of detection was 2μU/mL with intraassay and interassay coefficients of variation of <7.3% for quality control, in accordance with the manufacturer's standards. The serum level of 25-OHD was measured by competitive immunoassay using Roche Diagnostic commercial kits and a multichannel automatic analyzer (Roche Cobas 6000-E 601, Rotkreuz, Switzerland). Vitamin D status was categorized into 4 groups in accordance with Endocrine Society Clinical Practice: ≥30 ng/mL (sufficiency), 20-29 ng/mL (insufficiency), and 12-19 ng/mL (deficiency), <12 ng/mL (severe deficiency) (15). The patients were divided into two groups for tests of association with clinical outcomes based on 25-OHD levels: vitamin D <20 ng/mL and vitamin D ≥20 ng/mL. serum levels of Ca, P, and ALP were measured on Cobas Integra 800 (Roche Diagnostics, Mannheim, Germany) instrument using the commercial kit, and reference intervals for biochemical parameters were accepted as follows: Ca: 5.9-9.7 mg/dL, *P*: 5.4-10.9 mg/dL, ALP: 145-420 U/L

Respiratory management

At admission, all infants received continuous positive airway pressure (CPAP) treatment produced by a neonatal ventilator, which was set at 5-6 cm H_2O and increased to 8 cm H_2O if needed. The fraction of inspired oxygen was adjusted continuously to maintain SpO_2 levels between 90%-95%. Short binasal prongs or masks were used as an interface. Continuous positive airway pressure failure was defined as the persistence of at least one of the following: hypoxemia [FiO_2 of 0.40 or greater to maintain SpO_2 of 88%; respiratory acidosis (pH <7.25 and PCO_2 >60 mmHg)] despite the maximum CPAP support; cardiovascular instability. These infants were intubated, all of whom were ventilated with a ventilator mode with of volume-targeted upon the discretion of the treating clinician. Ventilator settings were adjusted to keep blood gas analysis in normal ranges. Spontaneously breathing infants were extubated to nasal CPAP (nCPAP) when clinically stable. When the clinical signs of respiratory distress disappeared oxygen saturation was >95% without oxygen, and the respiratory rate was <60 breaths/min, respiratory distress was considered to be improved.

Definition of variables

Gestational age was determined by early fetal ultrasound and a new Ballard score after birth. Preterm rupture of membranes was defined as rupture of membranes 18 hours or more before delivery in preterm infants. Preeclampsia was defined as the development of hypertension with a blood pressure of 140 mmHg systolic or a diastolic pressure of 90 mmHg or greater arising after 20 weeks of gestation in a woman who was normotensive before 20 weeks of gestation and proteinuria of at least 300 milligrams per 24 hours (16). Respiratory distress

syndrome was diagnosed according to clinical findings (tachypnea, retractions, nasal flaring, cyanosis) blood gases, and radiological findings (reticular granular pattern, air bronchograms) (17). Sepsis was considered in infants who met two or more of the following criteria associated with positive blood culture: fever or hypothermia, tachycardia, tachypnea or apnea, and abnormal blood cells or increase in band/total neutrophils (18). Hemodynamically significant patent ductus arteriosus was defined based on cardiac ultrasound examination which requires pharmacological therapy or surgical ligation. The criteria of Bell were used for the diagnosis and staging of necrotizing enterocolitis (19). The diagnosis of IVH was based on the results of cranial ultrasound examinations on days 7 and 21 of life, which were graded according to Papile et al. (20). Retinopathy of prematurity was classified following the International Committee for Classification of ROP (21). Bronchopulmonary dysplasia was diagnosed according to the criteria of the National Institute of Child Health and Human Development/National Heart, Lung, and Blood Institute/Office of Rare Diseases Workshop and was classified as mild, moderate, severe in terms of BPD severity (8).

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 15.0 program was used for statistical analysis. Data were presented as mean ± standard deviation, median (interquartile range), or percentage. Differences between the two groups were analyzed by Student t-test or Mann-Whitney U test. A Chi-square test was performed for categorical variables. Pearson's Correlation was used to analyze the correlation between variables. Logistic regression analysis was used to assess the risk factors of BPD and $p<0.05$ was considered statistically significant.

Results

During the study period, 66 preterm babies were involved. Two babies with congenital anomalies and four babies who were 34 weeks of gestational ages according to their physical findings were excluded from the study. The remaining 60 infants were eligible for the analysis. The mean birth weight and gestation ages were 1610 ± 390 gr and 30 ± 1 weeks, respectively. The mean umbilical cord 25-OHD level was 13.8±6.8 ng/ml (range 3.5-30.7 ng/mL). The mean cord blood calcium level was 7.6 ± 1.7 mg/dL, phosphorus was 5.6 ± 1.4 mg/dL, alkaline phosphatase was 108±56 U/L.

Based on the cord blood 25-OHD levels, 1 (1.7%) patient was diagnosed as vitamin D sufficient (25-OHD level >30 ng/ml), 11 (18.3%) patients as vitamin D insufficient, 18 (30%) patients as vitamin D deficient and 30 (50%) patients as severe vitamin D deficient. The patients were divided into two groups based on a 25-OHD deficiency cutoff of 20 ng/mL before evaluation of the association with clinical outcomes: vitamin D <20 ng/mL and vitamin D ≥20 ng/mL. The number of neonates with vitamin D deficiency was 48 (80%), and 12 (20%) had vitamin D insufficiency or sufficiency.

The mean birth weight of babies who had vitamin D deficiency was lower than the birth weight of babies with vitamin D levels ≥20 ng/mL (Table I, $p=0.02$).

Out of 60 participating in the study, 26 (43.3%) required supplementary oxygen, positive pressure ventilation for 23 (38.3%), tracheal intubation for 11 (18.3%) in the delivery room. Four patients (4.4%) received only supplemental oxygen, whereas nCPAP was used in 56 (93%) patients, 10 (16.8%) required intubation during follow-up in the intensive

Table I: *Demographic and some prenatal and natal features of the study population*

	25(OH)D <20 ng/mL (n=48)	25(OH)D ≥20 ng/mL (n=12)	*p*
Gestational age (week)*	30.4±1.9	31.3±1.2	0.15
Birth length (cm)*	39.8±3.3	41.6±3.2	0.84
Birth weight (gr)*	1555±391	1840±294	0.02
Head circumference (cm)*	28.4±2.8	30.1±2.1	0.05
Maternal age (years)*	27.4±5.9	30.2±4.7	0.07
Multiple births, n (%)	14 (29.2)	3(25)	0.77
Male sex, n (%)	27 (56.3)	7 (58.3)	0.89
Small for gestational age, n (%)	8 (16.7)	3 (25)	0.50
Caesarean section, n (%)	43 (89.6)	11 (91.7)	0.83
Apgar score at 1 min*	6.9±1.2	7.4±1	0.14
Apgar score at 5 min*	8.4±0.8	8.8±1	0.92
Antenatal steroid treatment, n (%)	47 (97.9)	12 (100)	0.61
Maternal history			
PROM, n (%)	4 (8.3)	2 (16.7)	0.71
Preeclampsia, n (%)	14 (29.2)	0(0)	-
Gestational diabetes mellitus, n (%)	3 (6.3)	1 (8.3)	0.45
Delivery room resuscitation, n (%)	48 (100)	11 (91.7)	0.44

** mean ± SD; PROM: Premature rupture of membranes.*

care unit. The mean duration of mechanical ventilation was 4.4±3.8 days (Table II). We also evaluated the correlation between ventilation and cord blood 25-OHD levels. Cord vitamin D level was negatively correlated with the duration of noninvasive and invasive ventilation (r:-0.14, p=0.31;r: -0.12, *p* =0.97).

Twenty-one infants (35%) developed BPD. Babies with BPD had more frequent vitamin D deficiency (<20 ng/mL) than the babies with non-BPD (p=0.028, Table III). When we subsequently assessed the association between other morbidities and vitamin D levels, no significant difference was found between infants with and without vitamin D deficiency with respect to RDS, PDA, ROP, NEC, sepsis, and IVH. However, the patients with vitamin D < 20 ng/ml had a higher rate of BPD (Table II, *p* =0.03). The median day of hospital stay was 22.5 days (3-60 days). The median duration of hospitalization was significantly longer in patients with low vitamin D (<20 ng/ml) compared with those who had 25-OHD ≥ 20 ng/ml (Table II, *p*=0.005). Intensive care unit (ICU) stay was also negatively correlated with cord 25-OHD levels (r=-0.22, *p*=0.08).

Among the infants with BPD, 21 (66.6%) had mild BPD, 5 (23.4%) had moderate BPD, and 2 (10%) had severe BPD. Median (interquartile range) 25-OHD concentration of mild, moderate and severe BPD was 11.1 ng/mL (8.4-17 ng/mL), 17 ng/mL (13-21 ng/mL), 5.9 ng/mL (4.1-15.7 ng/mL), respectively. Only two infants had severe BPD. Vitamin 25-OHD levels of these 2 patients were 6.5 and 13.7 ng/mL, respectively. As shown in figure 1, there were no significant differences among all groups according to 25-OHD levels of cord blood.

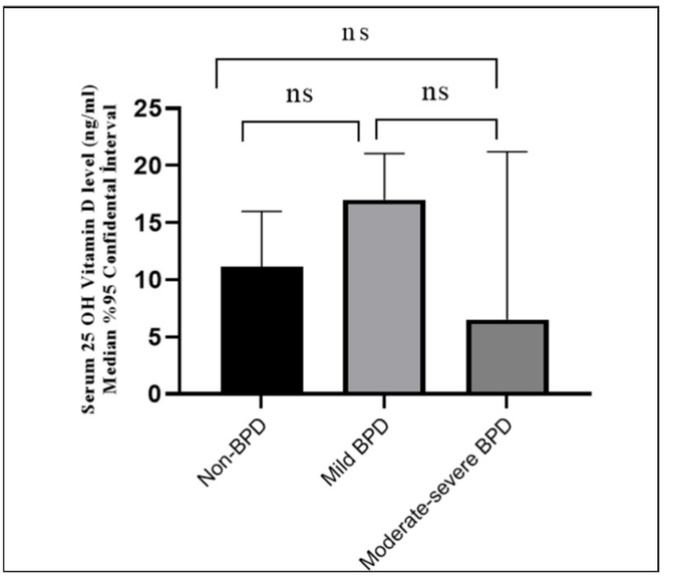

Figure 1: *Vitamin D levels according to the severity of bronchopulmonary dysplasia*

We also performed multivariate logistic regression analyses to assess the relationship between cord concentrations of 25-OHD and BPD. Vitamin D level was not significantly associated with BPD in this study. Unfortunately, the small sample size of the present study limited the statistical power to analyze 25-OHD as a risk factor for BPD (Table IV).

Table II: *Clinical outcomes of preterm infants*

	25(OH)D <20 ng/mL (n=48)	25(OH)D ≥20 ng/mL (n=12)	*p*
Duration of mechanical ventilation (day)*	3 (2.5-4)	3 (3-3)	0.42
Duration of noninvasive usage (day)	3 (2-5)	2 (2-6)	0.80
Surfactant ≥1 dose	27 (56.3)	5 (41.7)	0.36
Neonatal diseases, n (%)			
RDS	36 (75)	8 (66.7)	0.56
BPD	20 (41.7)	1 (8.3)	0.03
PDA	11 (22.9)	0 (0)	-
ROP	14 (29.2)	1 (8.3)	0.13
NEC	4 (8.3)	0(0)	-
Sepsis	15 (31.3)	1 (8.3)	0.21
IVH	3 (6.3)	1 (8.3)	0.79
Hospitalization period (day)	25 (14-37)	11.5 (8-20.5)	0.005
Death before discharge, n (%)	3 (6.3)	1 (8.3)	0.79

**Median (interquartel range); BPD: Bronchopulmonary dysplasia; RDS: Respiratory distress syndrome; ROP: Retinopathy of prematurity; NEC: Necrotising enterocolitis; IVH: Intraventricular haemorrhage; PDA: Patent ductus arteriosus.*

Table III: *Frequency of bronchopulmonary dysplasia according to vitamin D deficiency*

25-OHD	Normal, ≥20 ng/mL (n=12/60)	Low, <20 ng/mL (n=48/60)	*p**
BPD positive	1/12 (8.3%)	20/48 (41.7%)	0.028
BPD negative	11/12 (91.7%)	28/48 (58.3%)	

**Fisher's Exact test; 25-OHD: 25 hydroxy vitamin D; BPD: Bronchopulmonary dysplasia*

Table IV: *Logistic regression analyses of factors associated with bronchopulmonary dysplasia development*

Risk factors	Odds ratio	95% confidence interval	p
Gestational age	1.09	0.85-1.41	0.46
25 0H Vitamin D deficiency	0.14	0.01-17.6	0.24
Duration of mechanical ventilation	0.85	0.26-2.56	0.78

Discussion

There are positive findings that vitamin D has a role in the saccular and alveolar stages during the maturation of the fetal lung. To determine how vitamin D affects lung development, Zosky et al. (22) made an experimental study. In this study, lung volume, structure, and mechanics were examined in mice with vitamin D deficiency. They found, in the case of vitamin D deficiency, somatic growth does not decrease, but lung volume and alveoli number decrease. Rehan et al. (23) examined the metabolism of 1α25 (OH) 2D3 and 1α, 25 (OH) 2D-3-epi-D3, a metabolite of 1α, 25 (OH) 2D3, on alveolar type II cells in lung adenocarcinoma cells. They showed that 1α, 25 (OH) 2D-3-epi-D3 was produced in alveolar type II cells and stimulated surfactant phospholipids' synthesis, increased surfactant SP-B mRNA gene expression, and increased surfactant SP-B protein synthesis and also put forward the view that 1α, 25 (OH) 2D-3-epi-D3 played an important role in lung development and function.

In a meta-analysis which has done by Park et al. (14), it has been shown that low vitamin D levels at birth are associated with BPD. Kazzi et al. (13) also found severe RDS and BPD are associated with low 25-OHD levels. Cetinkaya et al. (12) showed maternal and infant 25-OHD levels were a significant predictor for BPD. Onwuneme et al. (24) found that low 25-OHD is associated with a greater need for assisted ventilation and positive–pressure ventilation during resuscitation at the delivery room. In our study, we found, the BPD frequency was higher among the babies with vitamin D deficiency (Table II), hospitalization time was longer among vitamin D deficient babies and there was a negative correlation between the duration of invasive-noninvasive ventilation and cord vitamin D levels.

However, when we performed the multivariate logistic regression analyses to assess the relationship between umbilical cord concentrations of 25-OHD and BPD, vitamin D level was not significantly associated with BPD. This was attributed to our low number of cases, Since the ventilation, duration was negatively correlated with the vitamin D levels our results supported the literature findings that vitamin D might play a role in the development of the respiratory system but we could not say that the umbilical cord vitamin D was an independent risk factor for BPD. However, with other risk factors, it could be a contributing factor for the development of BPD.

In our study, there was not a difference between the vitamin D deficient and sufficient groups according to the frequency of sepsis. However, there are some studies that vitamin D has been reported to modulate different processes in host defense, inflammation, and immune regulation in recent years. Vitamin D ligands increase the phagocytic activity of natural killer cells and macrophages. In addition, vitamin D increases the production of cathelicidin, an antimicrobial peptide triggered by bacteria, viruses, and fungi and produced by macrophages (25). We found also the hospitalization period was longer among the vitamin D deficient group (Table II). In a study conducted in India, the duration of hospitalization was longer among the patients with low vitamin D levels but it was not statistically significant (26). We thought that the relationship between vitamin D level and duration of hospitalization should be investigated by studies with larger study groups.

In our study, only 20% (12/60) babies had a cord blood vitamin D level above the desired level of 20 ng/ml, and 48 (80%) babies had a cord blood vitamin D level below 20 ng/ml. Since the vitamin D level in the cord blood is 80-90% of the maternal vitamin D level (27), we can say that vitamin D deficiency in pregnant women is a very serious health problem for both mother and baby in Türkiye. Finally, we want to emphasize, vitamin D support for women during pregnancy is a very important issue in Türkiye.

The limitation of our study is the low number of cases and it might have played a role in obtaining these results.

Conclusion

In the current study, BPD frequency was higher in the vitamin D deficient group. There was a negative correlation between the cord vitamin D level and duration of noninvasive-invasive ventilation and ICU stay. There was no significant difference between vitamin D deficient and sufficient groups according to the frequencies of RDS, PDA, ROP, NEC, and IVH. Since the ventilation duration was negatively correlated, with the vitamin D levels our results supported the literature findings that vitamin D might play a role in the development of the respiratory system but we could not say that the umbilical cord vitamin D was an independent risk factor for BPD. However, with other risk factors, it could be a contributing factor for the development of BPD. This study also shows the high rate of vitamin D deficiency in pregnant women in the central Anatolian region (Sivas) of Türkiye. We want to emphasize that low cord 25-OHD levels are associated with an increased risk of BPD and prolonged hospitalization in very preterm infants. These data strengthen the necessity for vitamin D supplementation during pregnancy. Finally, we con-

cluded that further studies with a higher number of cases are needed to explain the vitamin D effects of vitamin D premature infants' mortality and morbidities.

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