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Original Article

Serum Vitamin D Levels in Premature Neonates with Retinopathy of Prematurity; Prevalence, Severity, and Types of Treatments; A Cross-Sectional Study from Iran, 2019-2020

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ABSTRACT

Background: Retinopathy of prematurity (ROP) is the leading cause of preventable blindness in premature infants. 1, 25-dihydro vitamin D (Vitamin D) is a critical metabolite for the homeostasis, growth, and development, with its receptors widely present in the structure of the eyes. This study aimed to investigate the potential relationships between serum vitamin D level and the prevalence, severity, and treatment types of ROP among neonates admitted to the neonatal intensive care unit (NICU).

Methods: A cross-sectional study was conducted in Tehran, Iran, from 2019 to 2020. Seventy-five preterm neonates, either with a birth weight of ≤2000 grams or unstable conditions, were included in the study. Serum vitamin D levels were measured for all neonates immediately upon admission to the NICU. Additionally, a comprehensive eye examination was performed for ROP screening. Neonates who developed ROP were categorized into two groups: Type 1 (required treatment) and Type 2 (required no treatment or only close monitoring). The relationships between vitamin D levels and the severity and type of ROP treatment were then analyzed.

Results: Among 75 newborns, ROP developed in zone 1 in 10 cases (13%), zone 2 in 50 cases (67%), and zone 3 in 15 cases (20%). Of all, 18 cases (24%) were classified as Type 1 and required treatment. The mean gestational age of neonates with Type 1 ROP was significantly lower than that of neonates in the other group (P= 0.028). Of all neonates, 38 (51%) had sufficient vitamin D levels, 15 (20%) had insufficient levels, and 22 (29%) were vitamin D deficient. When comparing vitamin D status between the groups, the results showed that the mean vitamin D level was lower in neonates with Type 1 ROP compared to those with Type 2 ROP. Additionally, the mean vitamin D level in neonates with zone 3 ROP was significantly higher (P=0.04) than in those with zones 1 and 2.

Conclusion: The results of this study demonstrated a positive relationship between vitamin D levels and the zones affected by ROP. This finding suggests that prenatal vitamin D supplementation may have a beneficial effect in preventing abnormal angiogenesis and reducing the involvement of the posterior retinal pole.

Keywords: Infant, Premature, Retinopathy of prematurity, Vitamin D

Introduction

Retinopathy of prematurity (ROP) is a vasoproliferative disorder and a common cause

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(24-47%) of preventable blindness in premature infants (1, 2). Although various factors contribute to the development of ROP, the primary risk factors include prematurity, low birth weight, and oxygen exposure are the crucial risk factors. Despite extensive advances in neonatal medical care, ROP continues to be a serious concern in neonatal health (3).

Fortunately, ROP regresses spontaneously in most cases, with less than 10% of affected infants requiring treatment (4). Laser photocoagulation is the gold standard for ROP treatment, though it can sometimes result in unfavorable ocular outcomes. Recently, there has been a concerted effort to develop new methods for preventing ROP-related neovascularization and preserving effective vision in infants. The use of anti-vascular endothelial growth factor (anti-VEGF) drugs has shown promising therapeutic outcomes (5). Ongoing research is exploring the application of other biological and biochemical agents, including recombinant human insulin-like growth factor-1 (IGF-1) with IGF-binding protein-3, propranolol, antioxidants, vitamin A, caffeine, corticosteroids, and more (6). Surgical procedures such as scleral buckling or vitrectomy may be implemented for ROP cases with partially/completely retinal detachment (7).

Vitamin D is a fat-soluble metabolite. The effects of vitamin D are mediated through vitamin D receptors (VDR) that are expressed in many cells and tissues (8). In the eye, this receptor is present in the retinal ganglion cell layer, inner nuclear layer, retinal photoreceptors, retinal pigment epithelium, corneal epithelium, lens, and ciliary body. Vitamin D, besides its significant role in mineral homeostasis, has pleiotropic effects on cell proliferation, differentiation, and apoptosis (9). Several studies have pointed to its anti-inflammatory, anti-angiogenic, and anti-fibrotic properties. Vitamin D, as a potent inhibitor of neovascularization, affects the activity and morphogenesis of endothelial cells and inhibits their proliferation and growth (10).

Very few studies have examined the relationship between ROP and vitamin D status. One investigation assessed serum vitamin D concentrations in low-birth-weight neonates and identified vitamin D deficiency as a risk factor for ROP and the need for treatment (11). Another study found a correlation between developing ROP and persistent vitamin D deficiency during the first weeks of life in low-birth-weight and preterm neonates (12). Additionally, research from Iran showed an inverse association between the incidence and stages of ROP and both maternal and neonatal serum vitamin D levels (13).

The prevalence of vitamin D deficiency is notably high among the Iranian population, particularly among pregnant women and their offspring (14, 15). This study aimed to determine the prevalence, severity, and treatment requirement of ROP in hospitalized neonates. Providing more informative data, the relationships between serum vitamin D levels as an anti-angiogenic factor and ROP-related variables were also assessed.

Methods

A descriptive, analytical, and cross-sectional study was conducted in the NICUs of two teaching hospitals, Shariati and Yas, affiliated with the Tehran University of Medical Sciences (Tehran, Iran; 2019-20). According to national protocol, ROP screening is recommended for all preterm and low-birth-weight neonates at a chronological age of 4-6 weeks.

Preterm neonates (gestational age ≤34 weeks), those with a birth weight ≤ 2000 grams, or neonates with unstable conditions admitted to the NICU were included in the study. Written informed consent was obtained from the parents of the neonates before enrolment. Cases with congenital anomalies, incomplete data, or death before the eye examination were excluded.

Serum vitamin D levels were measured for all neonates immediately upon NICU admission, prior to any vitamin D supplementation. Samples of venous blood were collected for routine blood tests and vitamin D measurements. The samples were centrifuged, stored at -20° C, and sent to the laboratory. Neonatal serum 25-hydroxy vitamin D (vitamin D) levels were assayed using the Electrochemiluminescence immunoassay method. Vitamin D status was categorized as follows: deficiency (serum vitamin D <20 ng/ml), insufficiency (20-30 ng/ml), and sufficiency (>30 ng/ml) (14, 15).

A comprehensive eye examination for ROP screening was performed by an expert ophthalmologist who was blinded to the study's purpose. The examination was conducted using a binocular indirect ophthalmoscope and a 20-diopter lens, following the application of a pharmacological mydriasis agent and topical anesthesia. ROP classification was based on the International Classification of ROP (ICROP) (16). According to the Early Treatment for Retinopathy of Prematurity (ETROP) protocol (17), cases of ROP were categorized into two groups: Type 1

(requiring treatment) and Type 2 (requiring no treatment or only close monitoring).

The demographic and clinical characteristics of the participants including gender, mode of delivery, gestational age, birth weight, weight gain, nutritional status, duration of hospital admission, and respiratory support requirements including invasive and non-invasive positive pressure ventilation; NIPPV, periods of undergoing mechanical ventilation, high-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP), serum vitamin D status, and results of eye examination (ROP Sages, zones, and presence of plus disease) (18) were collected and recorded in a checklist. Any available data on maternal vitamin D levels or history of vitamin D supplementation during pregnancy were also retrieved from maternal medical records and included in the analysis.

The primary outcome of the study was to determine the relationship between neonatal vitamin D levels and ROP status among NICU-hospitalized neonates. As secondary outcomes, the study also assessed correlations between other neonatal variables and ROP status to identify potential risk factors related to ROP.

Sample size

Based on the results of a study by Kabataş et al. (11), the mean vitamin D level in premature neonates with ROP was 10.7±6.5 ng/ml. Using the comparing means formula with a presumptive deviation value of 1.5 based on the reported standard deviation (6.5), a power of 80% (β error=20%), and a significant level of 95%, the calculated sample size was 75.

Data analysis

The SPSS version 26.0 (SPSS Inc., Chicago, Illinois, USA) was used for analyses of data. Descriptive statistics are expressed in absolute and relative frequency for qualitative variables, as well as in mean and standard deviation for quantitative variables. The normality of data distribution was examined by the Kolmogorov-Smirnov. All variables had normal distribution and the ANOVA test was utilized. Qualitative variables were also analyzed by the Chi-square and Fisher Exact tests. P values<0.05 were considered significant levels.

Ethical Approval

The present study was approved by the Ethics Committee of the Tehran University of Medical Sciences according to the Helsinki Declaration (IR.TUMS.CHMC.REC.1398.046). Participants' data were considered confidential and no extra costs were imposed on the patients.

Results

Seventy-five eligible newborns were enrolled. Among them, 39 subjects (51%) were female and 62 neonates (83%) were born via cesarean section. The mean gestational age was 30±2.0 weeks (range: 26 to 34 weeks), and the mean birth weight was 1361±45.0 grams (range: 610 to 2285 grams). The mean length of hospitalization was 55.0±26.0 day (range: 18 to 154 days). Most of the neonates (70) were admitted for respiratory distress syndrome (RDS). The mean weight at hospital discharge was 1779±1312 g. The mean maternal age was 29±4.0 years.

According ICROP criteria, ROP developed in zone 1 in 10 cases (13%), zone 2 in 50 cases (67%), and zone 3 in 15 cases (20%). The distribution of ROP stages was as follows: Stage 1 in 40 neonates (53%), Stage 2 in 32 neonates (43%), and Stage 3 in 3 neonates (4%). Plus disease was presented in 4 cases (5%). Among the 75 cases with ROP, 18 cases (24%) were classified as Type 1 and required treatment. Of these, 6 neonates received laser photocoagulation, and 12 neonates were treated with Avastin injection. The remaining 57 neonates (76%) were classified as Type 2 and required only close monitoring.

The mean serum level of vitamin D among the 75 participants was 29.0±13.0 ng/ml (range: 10 to 70 ng/ml). Of all neonates, 38 (51%) had sufficient vitamin D levels, 15 (20%) had insufficient levels, and 22 (29%) were vitamin D deficient. Serum vitamin D concentrations were available for 45 mothers, with a mean level of 32.0±16.0 ng/ml (range: 8 to 74 ng/ml). Regarding prenatal vitamin D supplementation, 13 mothers received regular supplementation, 14 received irregular supplementation, and 18 received no supplementation. A positive correlation was found between maternal and neonatal serum vitamin D levels (P=0.042, r=0.63).

The demographic and clinical variables were compared between the groups, with detailed data provided in Table 1. The results revealed a statistically significant difference in gestational age between the ROP Type 1 and Type 2 groups (P= 0.028); neonates in the Type 1 group had a significantly lower mean gestational age compared to those in the Type 2 group. The mean duration of oxygen therapy and mechanical ventilation was significantly longer in the Type 1

Table 1. Demographic and clinical characteristics of participants based on treatment requirement

Variables	Type 2 ROP (n=57)	Type 1 ROP (n=18)	P value
Birth weight (g; mean± SD)	1439.0±470.0	1114.0±297.0	0.769
Gestational age (week; mean± SD)	30.0±1.0	28±1.0	0.028
Gender (Female/Male)	30/27	9/9	0.509
Type of delivery (Cesarean/Vaginal)	46/11	17/1	0.456
Vitamin D level (ng/ml; mean± SD)	30.0±12.0	27.0±13.0	0.133
Vitamin D status (n %)			
Sufficient	31 (54)	7 (38)	0.355
Insufficient	10 (17)	5 (27)	
Deficient	16 (28)	6 (33)	
Hospitalization period (Day; mean± SD)	45.0±15.0	85±33.0	0.055
Nutritional status (Day; mean± SD)			
Noting by mouth	10.0±6.0	30.0±16.0	0.202
Total parenteral nutrition	29.0±13.0	73.0±32.0	0.517
Weight gain (g/kg/day; mean± SD)	7.0±3.0	7.0±2.0	0.034
Duration of oxygen therapy (Day; mean± SD)	35.0±13.0	75.0±31.0	0.028
Duration of mechanical ventilation (Day; mean± SD)	5.05±4.85	30.0±21.0	0.006
CPAP and NIPPV (Day; mean± SD)	11.0±10.9	12.0±8.0	0.354
HFNC (Day; mean± SD)	17.0±10.0	32.0±14.0	0.340

group than in the Type 2 group (P= 0.028 and P=0.006, respectively). The mean weight gain among neonates with Type 2 ROP was statistically higher than cases with Type 1 ROP (P=0.034). Regarding vitamin D status, the mean vitamin D level was lower in neonates with Type 1 ROP compared to those with Type 2 ROP. Moreover, vitamin D deficiency and insufficiency were more frequent among participants in the Type 1 group; however, the differences regarding the mean value and vitamin D status were not significant between the groups (P= 0.133 and P= 0.355). Furthermore, no statistically significant differences (P>0.05) were observed between the groups concerning birth weight, gender, mode of delivery, type of nutrition, duration of hospital admission, or the mean days of CPAP, NIPPV, and HFNC requirements.

Further analyses were conducted to explore any relationships between ROP-related variables and serum vitamin D levels. The mean vitamin D level in cases with zone 3 ROP was significantly higher (P=0.04) compared to cases with zones 1 and 2. The results showed no significant association between the serum vitamin D levels and the Stages of ROP (P=0.375). The mean vitamin D level in 4 cases with plus disease was 29.2±22.0 ng/ml and there was no significant difference in vitamin D levels between neonates with plus disease and those without (P=0.91). Additionally, no statistical difference in vitamin D levels was observed between ROP cases treated with Avastin and those treated with Laser therapy (P=0.67). Detailed data are provided in Table 2.

Table 2. Relationships between ROP status and serum vitamin D levels

ROP-related variables	Vitamin D level (ng/ml)	P value
ROP zones		
Zone 1	22.5 ± 9.9	0.001
Zone 2	29.6 ± 11.7	
Zone 3	35.7 ± 16.8	
ROP stages		
Stage 1	31.6 ± 14.4	0.375
Stage 2	28.3 ± 11.5	
Stage 3	23.1 ± 3.5	
Plus disease		
Yes	29.2 ±22.0	0.91
No	29.9±12.6	
Treatment		
Avastin injection	27.6 ±9	0.67
Laser therapy	27.2 ±21	

Discussion

The relationship between vitamin D deficiency and eye complications with retinal neovascular-rization characteristics (e.g. diabetic retinopathy and age-related macular degeneration) has been demonstrated (19, 20). ROP is a complex condition and several factors are involved in its occurrence and severity (21). This study evaluated the relationship between serum vitamin D status and the prevalence and severity of ROP in hospitalized neonates to determine the potential benefits of vitamin D supplementation.

The results of this study revealed a statistically significant relationship between the zones affected by ROP and serum vitamin D levels; cases with zone 3 involvement exhibited higher levels of vitamin D. According to the results, neonates with zone 3 ROP had sufficient vitamin D status, whereas those with zone 1 and 2 ROP had insufficient levels. This finding supports the potential preventive role of vitamin D and its receptors in the development of retinal vasculature. Calcitriol, the active form of vitamin D, is a potent inhibitor of neovascularization (22). The presence and distribution of vitamin D receptors in eye structures, including the retina, are also well-documented (23). In a review, Jamali et al. (24, 25) highlighted that the expression of vitamin D receptors plays a crucial role in regulating vascular development, particularly in its later stages. Additionally, their animal-model investigation demonstrated that vitamin D and the expression of its receptors could significantly inhibit retinal neovascularization in mice during retinal maturation in oxygen-induced ischemia retinopathy. Compatible with our finding, Kabata et al. reported a significant association between low vitamin D levels in the first days of life and the severity of ROP among 71 premature newborns (Zone 3: 17.9±5.5 ng/ml; sufficient status vs. Zone 2: 8.7±5.1 ng/ml and Zone 1: 5.4±1.5 ng/ml; both in deficient status subgroup) (11).

Out of 75 ROP cases, 18 (24%) were classified as Type 1 and required treatment. The results showed a statistically significant relationship between Type 1 ROP and lower gestational age and delayed weight gain, as well as prolonged periods of oxygen therapy and mechanical ventilation. Although the mean vitamin D level was lower in neonates with Type 1 ROP compared to those with Type 2, the differences in mean values and vitamin D status were not statistically significant. Consistent with our findings, other investigations have confirmed the positive association between the progression of ROP or the need for treatment with different variables like low gestational age, delayed weight gain, and extended durations of oxygen therapy and mechanical ventilation (11, 26-28). It is important to note the proven impact of vitamin D deficiency on the incidence and severity of various neonatal morbidities, such as RDS, sepsis, intraventricular hemorrhage, and necrotizing enterocolitis, which often necessitate prolonged oxygen therapy and mechanical ventilation (29-33). Such evidence may suggest the indirect effects of vitamin D deficiency on the incidence or severity of ROP. In other words, beyond its direct effects on the retina and its vasculature, vitamin D deficiency could increase the incidence and severity of ROP by affecting ROP risk factors through the aggravating prematurity complications. Another noteworthy point is the role of oxidative stress in the etiology and pathogenesis of prematurity-related complications, including ROP (34-36). Reactive oxygen species (ROSs), by affecting the vascular endothelial growth factor (VEGF) pathway and other molecular mechanisms, can disrupt the angiogenesis process, resulting in retinal damage (36). Several studies have highlighted the potential role of vitamin D as a protective agent against ROS and free radicals produced during physiological process, such as energy production in the mitochondria. The literature has also delineated the anti-inflammatory reactions of vitamin D against retinopathy associated with ROP or diabetes (37, 38).

In line with the results of other studies (39, 40), our findings also showed a positive correlation between maternal and neonatal serum vitamin D levels. The mean serum vitamin D levels were 32.0±16.0 ng/ml for mothers and 29.0±13.0 ng/ml for their neonates. Despite the sufficient status of vitamin D in mothers, their neonates fell into the insufficient category, likely due to preterm birth. Since vitamin D is mainly transferred via the placenta during the third trimester of gestation, prematurity may prevent neonates from receiving adequate amount of vitamin D.

In our study, 18 neonates required treatment for ROP. Of these, 12 were treated with Avastin, while the remaining underwent laser therapy. The analysis showed no statistically significant relationship between serum vitamin D levels and the type of treatment administered. Moreover, serum vitamin D levels were not an influencing factor for the stage of retinal involvement or the presence of plus disease. These findings may correlate with the small sample size, as there were

only 4 cases of severe ROP at the first examination. It should be also noted that the minimum vitamin D level among our participants was 10 ng/ml, with no cases of severe vitamin D deficiency. Consequently, we were unable to assess any potential relationships between ROP-related characteristics and severe vitamin D deficiency. Further investigations with larger sample sizes are needed to explore possible relationships.

Limitation

The main limitation was the small sample size. We did not also measure serum vitamin D levels in all mothers because of financial constraints. Further investigations with larger sample sizes and more included variables are suggested.

Conclusion

The results of the present study demonstrated a significant positive relationship between vitamin D levels and ROP-affected zones. Data analyses also showed a correlation between maternal and neonatal serum vitamin D levels. This finding may highlight the potential benefit of prenatal vitamin D supplementation in preventing abnormal angiogenesis and involvement of the posterior retinal pole. No significant correlations were observed between serum vitamin D levels and the severity of ROP or treatment requirement. Further investigations with larger sample sizes and additional variables can provide more comprehensive data.

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Author's Contributions

Dr. Z. M. and Dr. M. M. carried out the design of the study and participated in most of the experiments. Dr. M.S. analyzed the data. Dr. S.S. and Dr. M.R.Z. participated in the experiments and manuscript preparation. All authors read and approved the content of the main text.

Conflicts of interest

The authors declare no conflict of interest.

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