Original Article

Comparison of Daily Dose of 400 and 600 Units of Vitamin D in the Prevention of Osteopenia of Prematurity in Infants with a Gestational Age of Less Than and Equal to 32 Weeks

Abstract

Background: The use of vitamin D in premature infants is one of the important preventive factors for osteopenia of prematurity, but there are conflicting results on the appropriate doses, so this study aimed to compare the doses of 400 and 600 units of vitamin D in the prevention of osteopenia of prematurity in infants with a gestational age ≤32 weeks. **Methods:** This clinical trial study was conducted on 108 premature infants divided into two groups of 54 with a gestational age of ≤32 weeks born between 2020 and 2021 in Shahid Beheshti and Al-Zahrai hospitals in Isfahan. In the first group, daily vitamin D was 400 units from the 7th day of birth, and in the second group, it was 600 units. At the age of 5 weeks, levels of calcium, phosphorus, alkaline phosphatase (ALP), and vitamin D were evaluated. If the ALP level was above 1000, wrist radiography was requested. Also, the baby was examined for clinical symptoms of rickets at the age of 5 weeks. The data were analyzed by Statistical Package for the Social Sciences (SPSS) software version 26, and a P value <0.05 was considered significant. **Results:** In this study, there was no significant difference between the levels of ALP in the two groups ($P = 0.596$), but the level of vitamin D was significantly higher in the 600 units of vitamin D group ($P < 0.001$). The level of calcium was higher in the 400 units of vitamin D group, but this difference was slightly significant ($P = 0.062$). The level of phosphorus in the 600 units of vitamin D group was higher than in the 400 units of vitamin D group, and the difference was slightly significant ($P = 0.062$). **Conclusions:** This study showed that daily doses of 600 and 400 units of vitamin D in infants with a gestational age of ≤32 weeks had no effect on the incidence of clinical symptoms and radiological findings of rickets at the age of 5 weeks.

Keywords: *Alkaline phosphatase, calcium, osteopenia of prematurity, phosphorus, vitamin D*

Behzad Barekatain[1], Shima Hamidipour[2], Zohreh Badiei[3], Maryam Farghadani[4]

[1]Associate Professor of Pediatrics, Neonatologist. Department of Pediatrics, Division of Neonatology, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Neonatologist, Department of Pediatrics, Division of Neonatology, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [3]Professor of Pediatrics, Neonatologist. Department of Pediatrics, Division of Neonatology, Child Growth and Development Research Center, Isfahan University of Medical Sciences, Isfahan, Iran, [4]Associate Professor of Radiology, Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran

Address for correspondence:
Dr. Shima Hamidipour, Fellowship of Neonatology. Department of Pediatrics, Division of Neonatology, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: hamidi201365@yahoo.comyahoo.com

Introduction

Preterm infants are exposed to an increased risk of bone disease, which is caused by a decline in the level and content of minerals in the body. This bone disease is known as osteopenia of prematurity or metabolic bone disease or rickets of prematurity and is more related to gestational age and birth weight. About 50% of infants with a birth weight of less than 1 kg and 23 to 32% of infants with a birth weight of less than 1.5 kg suffer from this disease.[1] The peak incidence of this disease is 4 to 8 weeks after birth. Most infants are asymptomatic at the time of diagnosis, and symptoms often appear 5 to 11 weeks after birth.[2]

Some show nonspecific symptoms, such as anorexia, vomiting, constipation, and rarely diarrhea. Infants are often lethargic, dehydrated, and hypotonic and may have seizures or failure to thrive (FTT). Bone fractures and rickets are major symptoms of this disease.[1] They may show an increase in respiratory work due to rib fractures and an increase in the size of brain sutures and frontal bossing.[2]

Risk factors for metabolic bone disease include placental insufficiency, preeclampsia, neuromuscular disorders, chorioamnionitis, total parenteral nutrition (TPN) for more than 4 weeks, male sex, liver and kidney disease, necrotizing enterocolitis, periventricular leukomalacia, intraventricular hemorrhage, bronchopulmonary dysplasia, and the use of drugs such as loop diuretics, methylxanthines, and glucocorticoids.[2] A simple X-ray of the wrist in infants with clinical symptoms of rickets and high alkaline phosphatase (ALP) is a practical measure to evaluate bone changes.[1] Biochemical tests to diagnose metabolic bone disease in premature infants

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include the evaluation of calcium, phosphorus, ALP, and vitamin D levels.[3] In this disease, serum calcium concentration is usually normal and serum phosphorus concentration is normal or low. Also, the concentration of ALP increases during this disease.[1] Hypophosphatemia is the first sign of the destruction of mineral metabolism and occurs around 7 to 14 days after birth.[2] A serum phosphorus level of less than 3.6 mg/dL (1.16 mmol/L) in breastfed infants is considered a risk factor for metabolic bone disease.[2] A serum phosphorus level of less than 5.6 mg/dl (<1.8 mmol/l) is strongly associated with the presence of radiological rickets in premature infants with a mean gestational age of 30.3 weeks and a mean birth weight of 1490 grams.[4]

Alkaline phosphatase increases in the first 3 weeks of life and reaches its peak in 6 to 12 weeks. Its level of more than 500 units/liter is associated with bone homeostasis destruction, and its level of more than 700 units/liter is associated with bone demineralization.[2] Also, the level of more than 900 units/liter is a reliable indicator for osteopenia of prematurity, so the simultaneous measurement of phosphorus and ALP is a suitable method for screening.[1] However, for screening, the serum calcium level is not very reliable, as it can be normal despite the loss of bone calcium.[2] Hypocalcemia in infants refers to a serum calcium level of less than 8 mg/dl (2 mmol/l).[1]

Vitamin D is active in the regulation of calcium and phosphorus and supports the cellular processes of bone mineralization and neuromuscular activity.[4] Vitamin D deficiency is common in preterm infants as a result of problems with adequate enteral nutrition and lack of contact with sunlight that occurs during hospitalization. According to the American Institute of Medicine, 20 ng/ml (50 nmol/l) of vitamin D and above is usually considered sufficient.[1] Neonates often have little time to store maternal vitamin D, which is due to the decrease in vitamin D transferring through the placenta, so this problem leads to a higher need of vitamin D because it is an essential element to activate calcium absorption.[1] Also, infants who use only breast milk are more exposed to vitamin D deficiency.

To prevent osteopenia of prematurity in preterm infants, different doses of vitamin D are recommended from various sources, so this study aimed to compare the two different doses of vitamin D (400 units and 600 units) in preterm infants of less than and equal to 32 weeks.

Methods

This double-blind clinical trial was conducted in Al-Zahra and Shahid Beheshti hospitals in Isfahan in 2020–2021. After obtaining written consent from the parents of the infants, the study was approved by the ethics committee of Isfahan University of Medical Sciences with the code ID IR.MUI.MED.REC.1399.869, and it has been registered on the clinical trial site as number IRCT20150423021910N7. Then, 108 infants were selected according to the inclusion criteria and divided into two groups based on the random number table. The inclusion criteria were premature infants with a gestational age of less than and equal to 32 weeks who were fed breast milk and fortifier at the rate of one scoop per 25 cc. Infants' total parenteral nutrition (TPN) was stopped during the first 10 days of birth, and they received full enteral nutrition equal to 100 CC/kg/day.

The exclusion criteria were the presence of maternal vitamin D deficiency or diabetes, asphyxia at birth, receiving drugs affecting vitamin D metabolism such as diuretics, corticosteroids, anticonvulsant drugs, and intrauterine growth restriction of infants.

Then, the samples were selected among the eligible subjects and were randomly selected by permutation block methods with four blocks in each of the two groups.

In the first group, from the 7th day of birth, the consumption of daily dose of 400 units of vitamin D drops was started, and in the second group, the consumption of daily dose of 600 units of vitamin D drops was started. Based on the current protocols, tests of calcium and phosphorus, ALP, and vitamin D serum levels were performed for the patient at the age of 5 weeks.

If the ALP level was above 1000, a wrist radiography was requested and the changes were reported by the radiologist.

The prescription of different doses of vitamin D was performed by a superspecialist, and the evaluation at the 5th week of birth and the recording of test results were performed by a superspecialist assistant. By following up on the patient and infants' examination at the age of 5 weeks, the superspecialist assistant checked the clinical symptoms of rickets (wide fontanel, wide wrist, hypotonia, and craniotabes) and registered the information in a form and laboratory and radiological results. The neonatal superspecialist assistant and the radiologist did not know about the prescribed dose of vitamin D.

Wide fontanel refers to the size of the anterior fontanel greater than 3 × 3 cm. Craniotabes means excessive softening and thinning of a part of the skull bones. These changes may occur in the course of rickets.

For the infants with disorders in the initial examinations or clinical symptoms of rickets, the treatment with calcium and phosphorus salt was started and the tests were repeated weekly and the follow-up continued.

Quantitative variables were reported with mean (median) and standard deviation (SD) (interquartile range) and qualitative variables with frequency and percentage. The numerical variables between the two groups were compared with a two-paired independent *t*-test and analysis of covariance (ANCOVA) in the case of confounders. A comparison of qualitative variables between the two groups was performed with the Chi-square test and Fisher's test.

The normality of continuous data was evaluated using the Kolmogorov-Smirnov test and Q-Q plot. Nonnormally positive skewed data were subjected to logarithmic transformation. Continuous and categorical data are presented as mean ± SD and frequency (percentage). The normality of continuous data was evaluated using the Kolmogorov-Smirnov test and Q-Q plot. Nonnormally positive skewed data were subjected to logarithmic transformation. Continuous baseline variables were compared between two groups by an independent-samples *t*-test. Continuous main variables (Total calcium, Phosphorus, Alkalin Phosphatase, vitamin D) were compared between study groups by an independent-samples *t*-test in the crude model and for adjusting the effect of confounding variables by ANCOVA in adjusted models. All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 26 (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.).

Results

This study was conducted on 108 premature infants with a gestational age of less than and equal to 32 weeks who were born in Shahid Beheshti and Al-Zahrai hospitals affiliated with Isfahan University of Medical Sciences between 2021 and 2022. Infants were divided into two groups of 54 people (the first group received 400 units of vitamin D daily and the second group received 600 units of vitamin D daily from the 7th day of birth). The mean gestational age in the group of daily dose of 400 units of vitamin D was 28.40 ± 1.96 and that in the group of daily dose of 600 units of vitamin D was 29.79 ± 1.34, and a significant difference was observed between the two groups (P < 0.001). The mean birth weight in the group with daily dose of 400 units of vitamin D was 1078.05 ± 271.41 and that in the group with daily dose of 600 units of vitamin D was 1224.53 ± 209.92 grams, and the difference between the two groups was significant (P = 0.002). In terms of gender, there were 26 (48.1%) boys and 28 (51.9%) girls in the group of 400 units of vitamin D and 29 (53.7%) boys and 25 (46.3%) girls in the group of 600 units of vitamin D. No significant difference was observed between the two groups (P = 0.56). However, there was a significant difference between the two groups in terms of gestational age and birth weight (P < 0.05) [Table 1].

Table 1 shows the demographic information of the studied population.

Infants were evaluated for clinical symptoms at the age of 5 weeks. The frequency of hypotonia was 0 case (0%) in the group of 400 units of vitamin D and 1 case (1.9%) in the group of 600 units of vitamin D daily, and no significant difference was observed between the two groups (P > 0.99).

The frequency of wide fontanel was 0 case (0%) in the group of 400 units of vitamin D and 1 case (1.9%) in the group of 600 units of vitamin D, and no significant difference was observed between the two groups (P > 0.99). The frequency of craniotabes and wide wrist was 0 in both groups, and there was no significant difference (P > 0.05) [Table 2].

Table 2 shows the comparison of clinical symptoms in two groups.

In terms of radiologic criteria, a wrist X-ray examination was performed by the radiologist in cases of ALP above 1000 at 5 weeks of age; regarding bone fractures and couping, the widening frequency was 0 cases (0%) in both groups. Fraying was found in two cases (3.7%) in the 400 units of vitamin D group and one case (1.9%) in the 600 units of vitamin D group, and there was no significant difference between the two investigated groups (P > 0.99). In terms of reduction in bone density, there were four cases (7.4%) in the group of 400 units of vitamin D and three cases (5.6%) in the other group, and the difference between the two groups was not significant (P > 0.99) [Table 3].

Regarding the laboratory symptoms, the level of calcium at the age of 5 weeks was 9.93 ± 0.88 in the group of 400 units of vitamin D and 9.51 ± 0.89 in the group of 600 units of vitamin D. If the effect of confounders such as gestational age and birth weight was not removed, the level of calcium was significantly higher in the first group (P = 0.016).

Table 1: Mean of demographic information in two groups

Variable	600; IU/day	400; IU/day	*P*
Gender			
Male	29 (53.7%)	26 (48.1%)	0.56
Female	25 (46.3%)	28 (51.9%)	
Gestational age; week	29.79±1.34	28.40±1.96	<0.001
Birth weight; gr	1224.53±209.92	1078.05±271.41	0.002

Table 2: Comparison of clinical symptoms in the two groups

Dose	Hypotonia	Wide fontanel	Wide wrist	Craniotabes
600; IU/day	1 (1.9%)	1 (1.9%)	0 (0%)	0 (0%)
400; IU/day	0 (0%)	0 (0%)	0 (0%)	0 (0%)
P	>0.99	>0.99	0.000	0.000

Table 3: Comparison of radiological criteria in two groups

Dose	Widening	Couping	Fraying	Bone FX	Reduced bone density
600; IU/day	0 (0%)	0 (0%)	1 (1.9%)	0 (0%)	3 (5.6%)
400; IU/day	0 (0%)	0 (0%)	2 (3.7%)	0 (0%)	4 (7.4%)
P	0.000	0.000	>0.99	0.000	>0.99

By adjusting the effect of confounders using statistical methods, the difference between the two groups was weakly significant ($P = 0.062$)). Regarding the phosphorus level, it was 5.62 ± 1.27 units in the group of 400 units and 6.20 ± 0.90 in the other group. In this case, if the effect of confounders was not removed, the level of phosphorus was significantly higher in the second group ($P = 0.008$), and after adjusting the effect of confounders, the difference between the two groups was slightly significant ($P = 0.062$).

The level of ALP in the group of 400 units of vitamin D was 871.00 ± 366.44, and in the group of 600 units of vitamin D, it was 792.44 ± 321.99, with no significant difference between the two groups (with and without adjusting the effect of confounders). The level of significance with and without adjusting the effect of confounders was $P = 0.596$ and $P = 0.239$, respectively.

The amount of vitamin D in the group of 400 units of vitamin D was 37.51 ± 14.4, and in the group of 600 units of vitamin D, it was 57.77 ± 24.79, and a significant difference was observed between the two groups (with and without adjusting the effect of confounders) ($P < 0.001$) [Table 4].

Discussion

Osteopenia of prematurity is one of the premature infant diseases that can be associated with long-term physical and developmental complications. Vitamin D deficiency is common in preterm infants and is caused by the lack of proper transfer of vitamin D through the placenta (usually occurs after 32 weeks), insufficient enteral nutrition, and lack of exposure to ambient light due to long-term hospitalization. Evaluation of premature infants at risk of osteopenia of prematurity is performed by screening total or ionized calcium, phosphorus, and ALP activity.[5]

When these laboratory values are clearly abnormal, a wrist plain radiography is performed often to evaluate the bones for osteopenia, rickets, or possible fractures. Usually, when serum ALP is more than 800 IU/L, a radiographic evaluation is recommended. It is true especially if serum phosphorus is less than 4.5 mg/dl at the same time.[6] Some sources have reported that ALP greater than 800–1000 IU/L or clinical evidence of fracture should be associated with radiographic evaluation of rickets.[1]

Taking vitamin D supplements during pregnancy is associated with an increase in the amount of 25-hydroxyvitamin D in the cord blood. According to the research findings, infants born to mothers who received vitamin D supplements had more weight and height than infants whose mothers did not.[7] Moreover, infants born to mothers with severe vitamin D deficiency were smaller in height and weight, and their head circumference was smaller than infants born with normal vitamin D levels.[8]

Table 4: Comparison of laboratory results in two groups

Dose	Serum Ca	Serum P	Alkaline phosphate	25 (OH) D serum
600; IU/day	9.51±0.89	6.20±0.90	792.44±321.99	57.77±24.79
400; IU/day	9.93±0.88	5.62±1.27	871.00±366.44	37.51±14.40
P (unadjusted)	0.016	0.008	0.239	<0.001
P (adjusted)	0.062	0.062	0.596	<0.001

Data shown mean±SD

In addition, insufficient levels of vitamin D in the cord blood were associated with the prevalence of severe respiratory tract infections in the first year of life and decreased bone density in childhood.[9,10]

In general, the condition of vitamin D in mothers is very inappropriate worldwide, especially in countries where vitamin D supplements are not used, there is little sunlight exposure, and they wear a lot of clothes or have very dark skin, so the level of vitamin D deficiency in cord blood (less than 20 nmol/l) in European societies may be up to 70%.[1] Vitamin D is important for supporting a large number of physiological processes, such as bone mineralization, immunomodulatory functions, and early lung development. Additionally, recent studies have indicated that low vitamin D levels predispose to an increased risk of rickets, immune system dysfunction, asthma, type 1 diabetes, and respiratory tract infections in infancy.[11,12] Moreover, vitamin D is vital for the cellular absorption of calcium that is performed through the active form of vitamin D (1.25-dihydroxyvitamin D). Vitamin D is converted into 25-hydroxyvitamin D in the liver and then transferred to the kidney, where it is converted into 1 and 25-dihydroxyvitamin D.

Furthermore, calcium absorption is mainly paracellular in the first weeks of life in premature infants and probably in term infants, and it is not dependent on vitamin D.[13] Vitamin D-dependent absorption of higher calcium levels may not happen until 1 to 2 months; in fact, the exact time is not known.[14]

Absorption of higher amounts of calcium dependent on vitamin D may not happen for 1 to 2 months, but the exact time is not known.[14]

Vitamin D may interfere with drugs such as antibiotics and glucocorticoids that are used to treat sepsis and bronchopulmonary dysplasia (BPD)[15]. Moreover, all premature infants need vitamin D to prevent premature rickets, but the recommended amount is different in various protocols.[16,17] The studies conducted in Europe have recommended a daily dose of 800–1000 IU vitamin D.[14] However, based on the recent recommendations of the European Association for Gastroenterology, the required amount of vitamin D is 800 to 1600 IU per day.[18,19] In other sources, the recommended dose is from 400 to 1000 IU/day.[20,21] According to the protocol of the American Academy of Pediatrics for infants, the recommended amount of vitamin D per day is 400 units.[22]

Considering the effective role of vitamin D in the prevention of osteopenia of prematurity and given that all three radiological, clinical, and biochemical criteria have been evaluated simultaneously in limited studies, this study was conducted with the aim of comparing the different doses of vitamin D (400 IU daily and 600 IU daily) in premature infants with ≤32 weeks of gestation. The infants under 32 weeks were divided into two equal groups, and their gestational age, birth weight, and gender were checked. In terms of gestational age and birth weight, the difference between the two groups was significant, and therefore, to eliminate any possible confounding factor with statistical methods, the effect of these confounders was adjusted.

The amount of calcium measured at the age of 5 weeks in the 400 units of vitamin D group was slightly higher than the other group.

Without removing the effect of confounders, this difference between the two groups was significant. However, by removing this effect, the difference in calcium levels between the two groups was slightly significant. The measured amount of phosphorus in the group of daily dose of 600 units of vitamin D was higher than in the other group. Without removing the effect of confounders, the difference between the two groups was significant, while with the removal of this effect, the difference in the level of phosphorus between the two groups was slightly significant. In the present study, the amount of vitamin D at the age of 5 weeks in the group of 600 units was higher than that in the group of 400 units of vitamin D. Furthermore, the level of ALP was higher in the group of 400 units of vitamin D. However, this difference was not significant, and therefore, there was no difference between the two groups.

The World Health Organization (WHO) has recommended a dose of 400–1000 units per day for premature infants.[23] According to the clinical guidelines of the Endocrine Society, the amount of vitamin D required for infants, from birth to 1 year of age, is 400–1000 units per day.[24] In some sources, for infants who are breastfed or those who use less than 1 liter of formula per day, the daily amount of vitamin D is 400 units per day.[25] Some sources have recommended the amount of vitamin D needed from birth to 6 months as 400 units per day.[26] In other sources, the amount of vitamin D in premature infants with a birth weight of less than 1500 gr is 200–400 units per day, and in premature infants with a birth weight of more than 1500 gr, 400–1000 units per day are recommended.[10] According to the protocol of the American Academy of Pediatrics for infants, the recommended amount of vitamin D is 400 units per day.[22,27]

So far, various studies have been conducted on the effect of vitamin D on the prevention of osteopenia of prematurity. In a study conducted in America by Anderson-Berry *et al*.,[28] it was found that taking a daily dose of 800 units of vitamin D for infants less than 32 weeks improved the level of 25-hydroxyvitamin D at 4 weeks, bone density, and linear growth. In a study by Alizadeh Taheri *et al*. (2013),[29] 60 premature infants were examined. One group received daily dose of 400 units of vitamin D and the other group received 200 units, but there was no difference between the levels of calcium, phosphorus, and ALP in the two groups.

In terms of clinical criteria, there was no difference in wide fontanel and wide wrist in Taheri's study, which was consistent with the present study. Besides, in terms of radiological criteria, there was no difference between the two groups, which was in line with the present study.

In a study conducted by Yang *et al*. (2018),[30] no difference was observed between the amounts of calcium, phosphorus, and vitamin D in a high dose (800–1000 units per day) and a low dose of vitamin D (400 units per day), while the results related to height and head circumference growth and immune system function were better in the higher dose group.

In a study by Alizadeh *et al*. (2006),[31] premature infants under 38 weeks with a birth weight of less than 2000 gr were evaluated, and one group was treated with 400 units of daily vitamin D and the other group was treated with 1000 units. The results showed that the mean levels of calcium, phosphorus, and ALP were not significantly different in the two groups. Moreover, none of the two groups showed clinical or radiological symptoms of rickets, so a lower dose of vitamin D was suggested to prevent osteopenia of prematurity. In the present study, there was no difference in the occurrence of clinical or radiological symptoms of rickets between the two groups, which was in line with the study of Alizadeh *et al*.

A dual-energy X-ray absorptiometry (DEXA) method is used to evaluate bone mineral content (BMC), but this method is only possible in a number of centers and it is expensive.[1,32]

Standard X-ray films are not an accurate assessment of bone demineralization because the BMC must decrease by 20%–30% or more to be detected by this method.[3] However, they can detect bone FX, osteopenia, couping, widening, and fraying.[3] Wrist or knee radiography in the 4th to 5th weeks of birth or afterward in high-risk infants is a practical method in the case of clear rickets.[1]

Backström *et al*.[33] used two different doses of vitamin D (200 and 960 daily units) in premature infants up to the age of 3 months and checked the BMC using the DEXA method, and no difference in the incidence of premature osteopenia was seen in these two groups.

Limitations

One of the limitations of this study was the small sample size in each week of gestational age, which was too small for generalization. It is recommended to do similar studies with a larger sample size.

Conclusions

According to the results of this study, after adjusting the effect of confounders such as birth weight and gestational age between the two investigated groups in premature infants ≤32 weeks of gestation, the amount of calcium in the group of daily dose of 400 units of vitamin D was higher than in the group of 600 units of vitamin D, but this difference was weakly significant. Also, the level of phosphorus in the group of 600 units of vitamin D was higher than that in the group of 400 units of vitamin D, and this difference was slightly significant. The level of ALP was not significantly different between the two groups. Also, vitamin D level was significantly higher in the group of 600 units, but no difference was observed between the two groups in terms of clinical and radiological symptoms of rickets.

Ethical approval

The study protocol was approved by the ethical committee of Isfahan University of Medical Sciences (code: IR.MUI.MED.REC.1399.869).

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Conflicts of interest

There are no conflicts of interest.

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