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Original Article (Pages: 18669-18680)

A Comparative Study of the Effect of Vitamin D Administration with a Dose of 400 and a Dose of 800 Units on the Establishment of Normal Serum Levels in Premature Infants

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Abstract

Background: This study was conducted to evaluate the impact of two different dosages of vitamin D (400 units versus 800 units) on achieving normal serum levels in premature infants.

Methods: In this randomized clinical trial, premature infants aged between 28 and 34 weeks, with a weight range of 1000 to 2000 grams, were randomly assigned to two groups: one receiving 400 units and the other 800 units of oral vitamin D drops daily.

Results: The results indicated that alterations in calcium and alkaline phosphatase (ALP) levels were not statistically significant. However, it was observed that the mean level of phosphorus within the first 24 hours and at the two-week mark was significantly lower in the group administered 800 units compared to those receiving 400 units ($P < 0.05$). Repeated measures ANOVA revealed that the overall changes in phosphorus levels were not statistically significant, suggesting that the observed differences at 24 hours and two weeks can be attributed to baseline variations between the groups. Additionally, it was found that vitamin D levels in infants receiving 800 units were significantly elevated at both the second and fourth weeks when compared to those receiving 400 units ($P < 0.001$).

Conclusion: The findings from this study demonstrate that infants receiving a high dosage of 800 units of vitamin D exhibited significantly higher vitamin D levels at both the second and fourth weeks compared to those receiving the standard dosage of 400 units.

Key Words: Premature Infants, Vitamin D, Comparative Study, Serum Levels.

* Please cite this article as: Saeidi R, Fatahi S, Amiri H, Abbasi A. A Comparative Study of the Effect of Vitamin D Administration with a Dose of 400 and a Dose of 800 Units on the Establishment of Normal Serum Levels in Premature Infants. Int J Pediatr 2024; 12 (03):18669-18680. DOI: **10.22038/ijp. 2024.64592.4898**

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Received date: Apr.03,2022; Accepted date: Mar.21,2024

1- INTRODUCTION

Vitamin D deficiency remains one of the five most prevalent health concerns in developing countries (1). The body acquires vitamin D from two primary sources: endogenous synthesis through skin exposure to sunlight and exogenous intake through diet or supplementation (2). Research conducted in Australia and New Zealand identifies maternal vitamin D deficiency during pregnancy as a significant contributor to vitamin D deficiency in infants (3). Additional factors influencing this deficiency include the degree of skin pigmentation, the use of sunblock with high SPF, and insufficient direct sunlight exposure (3).

Vitamin D receptors are present in various cells and tissues, including the brain, prostate, breast, colon, and immune cells, which respond to the active form of vitamin D. This active form is known to directly or indirectly regulate over 200 genes (4). The importance of vitamin D in mitigating the risk of numerous chronic diseases such as certain cancers, autoimmune disorders, infectious diseases, cardiovascular ailments, schizophrenia, multiple sclerosis, psoriasis, and oral health issues has been well-documented (3, 5). Furthermore, a deficiency in vitamin D can lead to osteoporosis in older adults (6). In childhood, insufficient vitamin D intake can result in complications such as rickets, osteomalacia, reduced bone density, bone pain, and pathological fractures. These conditions may be exacerbated by factors including the use of anticonvulsants, rapid growth, and malabsorption issues related to fats and vitamins (7).

The American Institute of Medicine recommends an international intake of 200 International Units (IU) of vitamin D per day for children and adults under 50 years of age, 400 IU/day for individuals aged 51 to 70, and 600 IU/day for those over 70 years (8). However, a number of experts argue that these recommended levels are insufficient, advocating for a daily intake of 800 to 1,000 IU for all adults over the age of 50 (8). The maximum allowable dose of vitamin D, defined as the highest level that can be safely consumed, is established at 12,000 IU/day for adults and children over the age of one (9).

Research has demonstrated the beneficial impact of vitamin D on the accelerated healing of hyaline membrane disease (respiratory distress syndrome, RDS) and the reduction of neonatal sepsis (10). Additionally, it has been associated with a decreased risk of cardiovascular diseases, preeclampsia, diabetes, and preterm birth. The serum levels of vitamin D in infants are influenced by maternal serum concentrations; given that the majority of this vitamin is transferred from the placenta to the fetus during the third trimester, premature infants are particularly susceptible to vitamin D deficiency (10). This deficiency is especially pronounced in infants born before 32 weeks of gestation, with those born before 28 weeks being at even greater risk. Contributing factors to vitamin D deficiency in pregnant women and infants include air pollution, inadequate dietary intake of vitamin D by the mother, urban living patterns, and darker skin pigmentation (11).

Breast milk contains approximately 15 International Units (IU) of vitamin D per deciliter (12). In contrast, the concentration of vitamin D in standard infant formula or human milk fortifiers (HMF) is about 180 IU per deciliter (12). Consequently, it is recommended that all infants, regardless of whether they are breastfed or formula-fed, receive a vitamin D supplement (12). The American Academy of Pediatrics suggests an oral vitamin D supplementation dose of 400 IU daily for preterm infants, aligning with the dosage recommended for term infants. Conversely, the European Society for Pediatric Gastroenterology, Hepatology,

and Nutrition (ESPGHAN) advocates for a higher daily intake of 1000–200 IU (13). However, studies exploring the differential effects of these dosages remain incomplete. While elevated serum levels of vitamin D can confer significant benefits, especially in preterm infants—akin to the effects of vitamin A—there is also a risk of toxicity associated with excessive doses, which must be avoided (14).

In light of this information, the present study was designed to compare the efficacy of the standard supplementation dose (400 IU) with a higher dose (800 IU) of vitamin D in achieving normal serum levels in premature infants.

2- MATERIALS AND METHODS

The present study was a randomized clinical trial conducted on neonates born between 28 and 34 weeks of gestation, weighing between 1000 and 2000 grams, at Imam Reza Hospital in Mashhad during the years 2019-2020.

Infants within this gestational age range were assigned to two groups using block randomization (with blocks of 6 and 8). One group received 400 units of oral vitamin D drops (1 cc) daily, while the other group received the same dosage along with an additional 400 units (0.4 cc) of vitamin D drops from Vitabiotics Ultra, increasing the total intake to 800 units per day. The administration of the drops was initiated within the first 10 days post-birth, via per os (PG-PO) administration, once the infant had achieved at least 40% of their maximum milk feeding (FULL FEED) and demonstrated no signs of intolerance or necrotizing enterocolitis (NEC). Accordingly, the first group received half a cc of the vitamin D drops every 12 hours, while the second group was prescribed half a cc every 6 hours for a minimum duration of two weeks.

Neonates admitted to the neonatal ward of Imam Reza Hospital who met the criteria of being 28-34 weeks gestational age and weighing between 1000 and 2000 grams, while having attained at least 40% of maximum milk supply and showing no signs of intolerance or NEC, were included in the study. Exclusion criteria encompassed neonates with genetic abnormalities, congenital conditions, severe asphyxia, adverse pregnancy events, failure to initiate feeding within the first 10 days post-birth, parental withdrawal of consent, evidence of intolerance, vomiting or nausea lasting over 24 hours, and signs of NEC.

Utilizing a block randomization method, the neonates were divided into two groups, with block sizes of 6 and 8. Based on variations in average vitamin D levels across different groups, and employing a formula for mean comparison with a test power of 80% and a 95% confidence interval, the required sample size was determined to be 72 per group, totaling 144 participants.

Following the acquisition of written informed consent from the parents, a checklist was developed comprising two components. The first part collected data regarding maternal factors, including maternal age, underlying health conditions (such as kidney, neurological, or musculoskeletal disorders), medications (particularly those influencing calcium metabolism, such as phenobarbital), substance use (including smoking and alcohol consumption during pregnancy), calcium and vitamin D supplement intake during pregnancy, parity, and sun exposure, along with skin type. The second part gathered information concerning fetal-neonatal characteristics, including gestational age, sex, time of birth, and physical measurements at birth (such as birth weight, height, and head circumference). Additional neonatal examination outcomes—such as Apgar scores, need for resuscitation, and requirement for mechanical ventilation, presence of asphyxia, respiratory distress,

neonatal transient tachypnea, and respiratory distress syndrome—were also documented in the checklist.

Statistical Analysis

Data analysis was conducted utilizing SPSS software version 22. The normality of the data distribution was evaluated employing the Shapiro-Wilk test. For the description of quantitative data, means and standard deviations were reported, while qualitative data were expressed in terms of frequencies and percentages.

In the analytical phase, Chi-square tests, independent t-tests, and ANOVA were employed to examine the relationships among qualitative variables. Additionally, repeated measures analysis was utilized to compare data across different time points according to the per-protocol analysis. A significance threshold of 0.05 was established for all statistical tests.

3- RESULTS

This study aimed to compare the effects of two distinct doses of vitamin D in preterm infants. A total of 144 neonates were enrolled, with 72 receiving a dose of 400 units and 72 receiving 800 units (see Fig. 1).

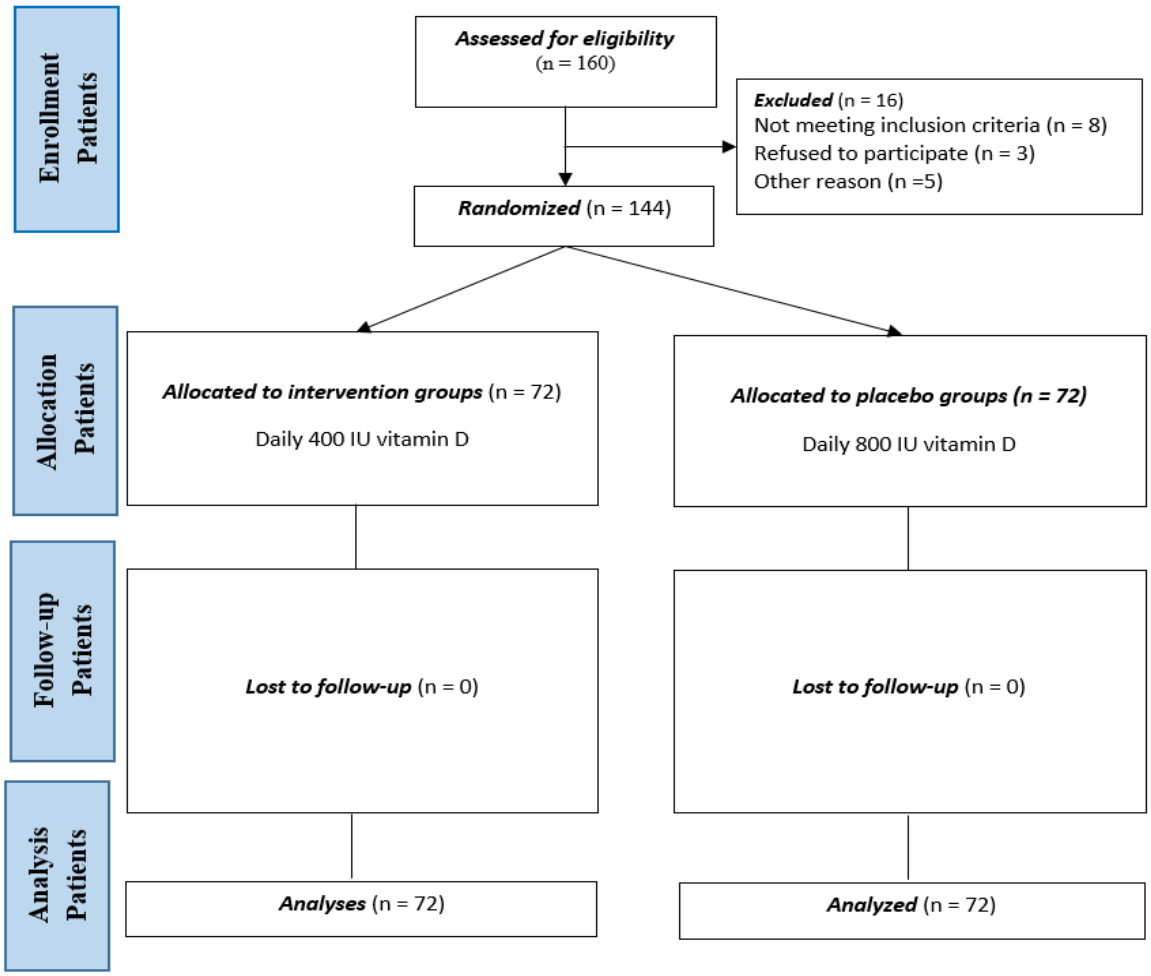

Fig. 1: Consort flow diagram for the trial

The mean gestational age of the participants was 31.25 weeks (SD = 1.95, range 28-34 weeks). Among the 144 neonates, 79 (54.9%) were male and 65 (45.1%) were female. A significant correlation was observed between the

administered doses and the vitamin D levels in the second and third follow-up assessments. Specifically, the mean vitamin D level in the third follow-up for the 400-unit dose group was 18.90 (SD = 8.95), while for the 800-unit dose group, it was 37.45 (SD = 21.59), indicating nearly a twofold difference in vitamin D levels. Notably, there was no significant difference in vitamin D levels between the two groups at baseline, with mean levels of 14.50 (SD = 9.02) for the 400-unit group and 15.19 (SD = 8.68) for the 800-unit group (see Tables 1 and 2).

Table-1: Mean and standard deviation of vitamin D levels in neonates of the two study groups

Variable name	Groups	N	Mean	SD	P-value
Gestational age (weeks)	400 IU	72	31.28	1.80	0.866
	800 IU	72	31.22	2.81	
Weight (g)	400 IU	72	1549.00	242.90	0.821
	800 IU	72	1539.17	275.33	

Table-2: Mean and standard deviation of vitamin D levels in neonates of the two study groups during 3 follow-up

Time	groups	N	Mean (ng/mL)	SD	P-value
F1	400 IU	72	14.50	9.023	0.639
	800 IU	72	15.19	8.682	
F2	400 IU	72	16.49	5.294	<0.001
	800 IU	72	24.11	8.288	
F3	400 IU	72	18.90	8.950	<0.001
	800 IU	72	37.46	21.599	

To account for potential confounding variables, the relationship between gestational age, sex, birth weight, and vitamin D levels was analyzed during follow-up assessments. No significant differences were identified concerning gender or gestational age across the two groups. However, a significant association was observed between birth weight and vitamin D levels. Specifically, the mean vitamin D level for infants weighing less than 1500 g in the third follow-up receiving the 800-unit dose was 33.00 (SD = 14.99), whereas for those weighing over 1500 g, the mean level was 41.23 (SD=25.50) (see Table 3).

Table-3: Relationship between gestational age, gender and birth weight with vitamin D levels during 3 follow-up in both groups

Variable name		Vit.D						P-value
		Dose 400			Dose 400			
		F_1	F_2	F_3	F_1	F_2	F_3	
Gender	Male	15.79(9.38)	17.23(5.76)	19.79(9.87)	15.45(7.49)	23.87(7.20)	37.27(22.50)	0.16
	Female	12.96(8.46)	15.60(4.60)	17.84(7.74)	14.87(10.08)	24.40(9.58)	37.67(20.76)	
GA	>30	15.79(9.38)	17.23(5.76)	19.79(9.87)	15.45(7.49)	23.87(7.20)	37.27(22.50)	0.27
	<30	12.96(8.46)	12.96(8.46)	17.84(7.74)	14.87(10.08)	24.80(9.58)	37.68(20.76)	
B.W	>1500	11.45(5.93)	14.63(3.97)	16.57(7.31)	14.63(7.71)	24.21(8.15)	33(14.99)	0.01
	<1500	17.07(10.37)	18.05(5.79)	20.87(9.80)	15.66(9.49)	24.02(8.50)	41.23(25.50)	

Trend analysis, depicted in the accompanying graphs, illustrates an increase in vitamin D levels across the various follow-ups. The mean vitamin D levels for infants receiving the 800-unit dose consistently outperformed those in the 400-unit group, with this difference reaching statistical significance (p-value = 0.001) (see Figures 2 and 3).

4- DISCUSSION

In Iran, approximately one million infants are born annually, with around 10% classified as premature. These infants often require higher doses of nutritional supplements and specialized care due to the severity of their prematurity, with micronutrient and vitamin deficiencies being a significant concern. This study aimed to compare two different doses of vitamin D in preterm infants.

A total of 144 neonates participated in the study, with 72 assigned to the 400-unit dose group and 72 to the 800-unit dose group. The findings indicated that while changes in calcium and alkaline phosphatase (ALP) levels were not statistically significant, the mean phosphorus levels in the first 24 hours and the second week were significantly lower in the 800-unit group compared to the 400-unit group ($P < 0.05$). However, by the fourth week, no statistically significant difference was observed between the two groups ($P > 0.05$). Furthermore, repeated measures ANOVA revealed that the changes in phosphorus levels were not significant, suggesting that the differences observed at 24 hours and two weeks were attributable to baseline variances between the groups. Additionally, it was noted that vitamin D levels in the second and fourth weeks were significantly higher in infants receiving the 800-unit dose compared to those receiving the 400-unit dose ($P < 0.001$).

Vitamin D deficiency is prevalent among premature infants, primarily due to inadequate intestinal absorption and limited sunlight exposure during hospitalization (15). Furthermore, very low birth weight (VLBW) infants often have reduced opportunities to store vitamin D from maternal sources due to diminished placental transfer, which may heighten their vitamin D requirements (15). Jobe et al. emphasized the critical benefits of vitamin D treatment for various developmental disorders, highlighting the high prevalence of premature infants with blood vitamin D levels below 20 ng/mL (1, 16). However, consensus regarding vitamin D deficiency specifically in preterm infants remains elusive, as limited data are available on the rates of bone mineralization in utero. Current European guidelines recommend daily vitamin D supplementation of 800 to 1,000 IU for premature infants, while recommendations in Western countries typically suggest 400 units per day(8).

The incidence of vitamin D deficiency in preterm infants exhibits considerable variability depending on geographic location. Reported mean serum levels of 25-hydroxyvitamin D (25(OH)D) during the first three days postnatally in preterm infants range from 9.5 to 25 ng/mL across Europe and Western countries(17-19). Given the high prevalence of vitamin D deficiency in this population, immediate supplementation may be necessary to achieve adequate vitamin D levels. While breastfeeding is recommended as the primary source of nutrition for both full-term and preterm infants, breast milk alone typically does not provide sufficient vitamin D. The definition of adequate vitamin D levels in premature infants remains a contentious issue. For numerous health outcomes in adults, an optimal vitamin D status is defined by serum concentrations exceeding 30 ng/mL (20).

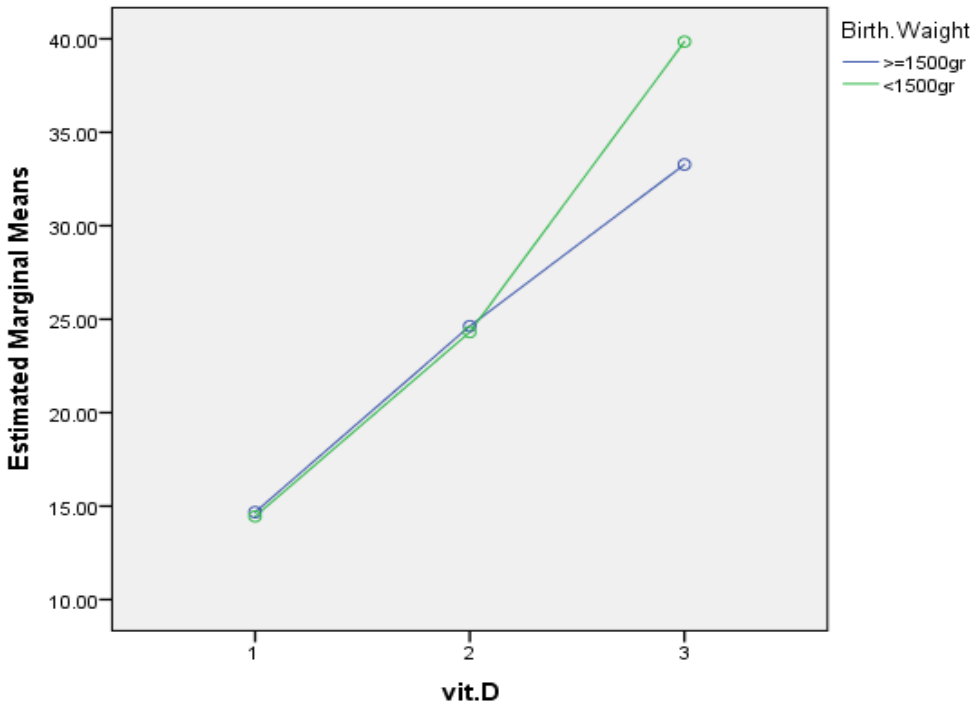

Fig. 2: The mean level of vitamin D in the neonates of the two study groups during 3 follow-ups at a dose of 800 units

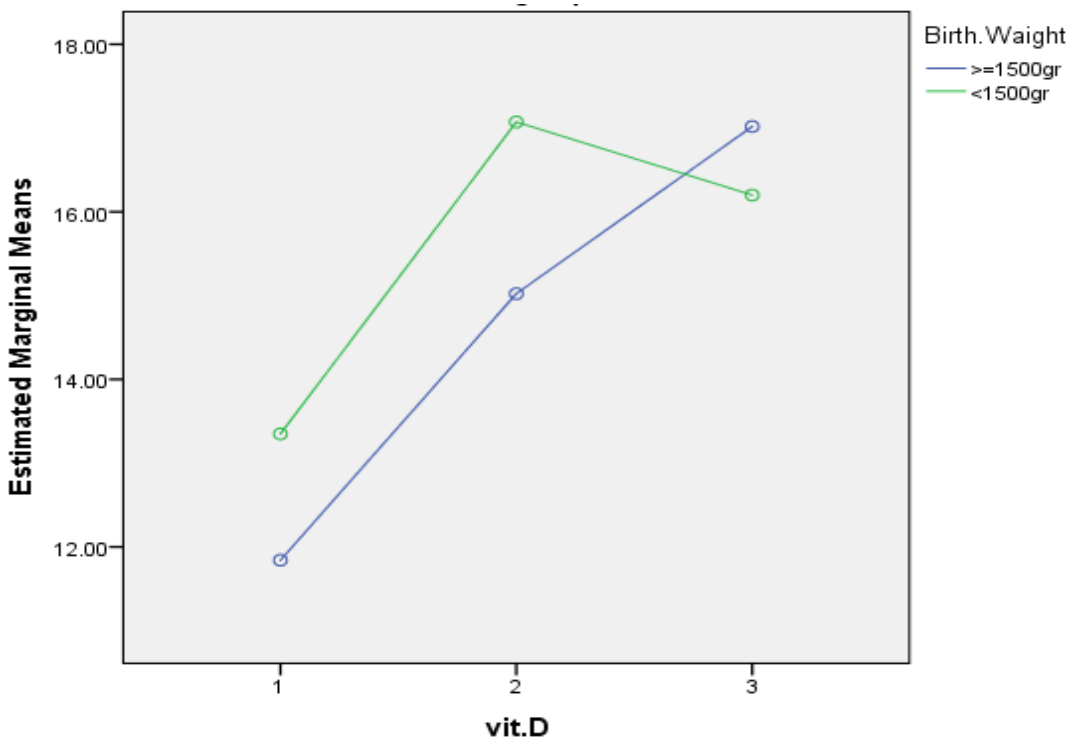

Fig. 3: The mean level of vitamin D in the neonates of the two study groups during 3 follow-ups at a dose of 400 units

Vitamin D is crucial for several physiological processes, including bone mineralization, immune modulation, and early lung development. Recent studies indicate that low vitamin D levels are associated with an increased risk of rickets, immune dysfunction, asthma, type 1 diabetes, and viral respiratory infections during infancy (21-25).

Furthermore, insufficient vitamin D levels in cord blood have been linked to compromised immune status and a higher prevalence of severe respiratory infections during the first year of life, as well as reduced bone density in childhood (26-28).

Employing serial measurements of 25 (OH) to assess vitamin D status during hospitalization may facilitate the identification of premature infants at risk for vitamin D deficiency. Additionally, given the high prevalence of vitamin D deficiency among pregnant women, an adequate supply of vitamin D for preterm infants is critical for the rapid correction of low plasma levels in the fetus (8).Current recommendations suggest that a daily intake of 800 to 1,000 IU of vitamin D can improve serum 25(OH) D levels, enhance calcium absorption, and help prevent osteoporosis in preterm infants (7).

However, the precise timing and efficacy of vitamin D-mediated calcium uptake in this population is not yet fully understood. Premature infants exhibiting radiological signs of elevated alkaline phosphatase levels (greater than 800 IU/L) are generally administered high doses of vitamin D at 800 IU per day. Nonetheless, there is limited evidence-based data to support vitamin D supplementation aimed at achieving optimal serum 25(OH) D levels in accordance with birth status in preterm infants. This gap in evidence has resulted in ongoing discussions among neonatal specialists regarding the thresholds and strategies for administering vitamin D at 800 IU per day to preterm infants in the early stages of life.

According to prior studies examining the dose-response relationship of vitamin D supplementation, an initial administration of 800 IU of vitamin D is likely to safely achieve adequate vitamin D levels in approximately 90% of preterm infants (13, 16). Although the present study observed a significant reduction in vitamin D deficiency following supplementation with a dose of 400 IU, it appears that this lower dosage may be insufficient to attain optimal vitamin D levels in premature infants who are deficient from birth. Notably, supplementation at the 800 IU dosage led to a marked improvement, with no cases of deficiency reported during the second and fourth weeks. Variability in responses to vitamin D supplementation can be attributed to polymorphisms in the vitamin D receptor (VDR) gene, which may contribute to ongoing vitamin D deficiency in some infants despite supplementation (29).

Recent research has indicated that circulating levels of 25-hydroxyvitamin D (25(OH) D) are associated with specific genetic factors, including VDR, CYP2R1, and vitamin D-binding protein (VDBP) (30,31). However, optimal oral vitamin D supplementation regimens for achieving sufficient serum 25(OH) D concentrations in very low birth weight (VLBW) infants with initial low vitamin D levels remain unidentified from birth.

A recent study by Natarajan et al. reported that daily supplementation of vitamin D at a dosage of 800 IU compared to 400 IU significantly reduced the prevalence of vitamin D deficiency after 40 weeks postmenstrual age in preterm infants gestated between 28 to 34 weeks(13).Furthermore, a randomized controlled trial involving 100 infants born between 23 and 27 weeks of gestation demonstrated that supplementation with 800 IU of vitamin D effectively prevented deficiency and was well tolerated by day 28 postpartum (the fourth week)(16).

Grant et al. showed that a dose of 800 IU of vitamin D caused 81% of the neonates at the age of 3 months to have levels higher than 30 ng / ml, while the dose of 400 IU of vitamin D showed an increase in vitamin D levels of more than 30 ng / ml in 55% at 3 months of age (21). In a prospective, randomized, controlled trial of term neonates, Cameron C. et al. showed that serum 25 (OH) D concentrations were higher in the 800-IU/day dose group than in the 400- IU/day dose group. Daily intake of vitamin D supplement for mother (2000 IU) and infant (800 IU) up to 6 months of age in 80% of neonates at 4 months of age reached serum level of 25 (OH) D> 30 ng / ml(24). The findings of the mentioned studies are completely in line with the findings of our study. In our study, it was found that administration of 800 units of vitamin D significantly increases the level of vitamin D in the short term, and compared to the dose of 400 units, vitamin D deficiency was not observed in the second and fourth weeks.

In a study conducted by Sang Yeun Cho et al., the safety of administering an 800 IU daily dosage of vitamin D to preterm infants was evaluated. The study involved 66 infants admitted to the neonatal intensive care unit, each weighing less than 1,500 grams. Out of these, 52 eligible infants received daily supplementation of 800 IU of vitamin D starting at 2 weeks of age. Serum levels of 25-hydroxyvitamin D (25(OH) D) were measured at birth and subsequently at 32 and 36 weeks of gestational age. For the purposes of the study, the neonates were categorized based on their 25(OH) D levels at birth: 20 infants had levels below 10 ng/mL, while 29 exhibited levels of 10 ng/mL or greater.The findings indicated that daily supplementation of 800 IU of vitamin D is likely to be 88% effective in achieving adequate vitamin D levels (≥ 10 ng/mL) in very low birth weight (VLBW) infants by 36 weeks. The authors concluded that given the demonstrated efficacy and safety of vitamin D supplementation in this cohort, the administration of 800 IU daily may significantly enhance vitamin D status in VLBW infants presenting with 25(OH) D levels below 10 ng/mL at birth (31).

The clinical importance of achieving optimal vitamin D intake in very low birth weight (VLBW) neonates warrants further investigation through larger clinical trials. Although the current study did not evaluate a dosage of 400 IU, it did demonstrate that 100% of premature infants who received an 800 IU dose in the initial weeks after birth achieved serum levels exceeding 10 ng/mL. Notably, by the fourth week, six infants within this group exhibited levels greater than 80 ng/mL.

During the course of vitamin D supplementation, it is crucial to closely monitor preterm infants for calcium and phosphorus levels, urinary calcium and phosphorus excretion, as well as potential renal calcification, which is commonly identified via ultrasound. A daily intake of 800 international units may lead to elevated serum concentrations of 25-hydroxyvitamin D (25(OH) D), potentially resulting in increased serum calcium levels and heightened urinary calcium excretion. Premature infants, particularly those with delayed renal maturation and impaired mineralization, are particularly susceptible to hypercalciuria and nephrocalcinosis attributable to renal excretion processes. It is important to note that nephrocalcinosis in this population has a multifactorial etiology, often influenced by factors such as gestational age, low birth weight, and associated conditions like severe respiratory distress, leading to an imbalance between tonic and inhibitory mechanisms affecting mineral metabolism(32).

5- CONCLUSION

The findings of the present study demonstrate that at both the second and fourth weeks, infants receiving a daily dosage of 800 IU of vitamin D exhibited significantly higher serum levels compared to those receiving 400 IU. Notably, in the second week, there were no instances of severe vitamin D deficiency among the infants in the 800 IU group. While six infants in this group presented with serum levels exceeding 80 ng/mL by the end of the fourth week, no specific adverse effects were observed.

Consequently, given the effectiveness and safety of vitamin D supplementation evidenced in this study, the administration of 800 IU per day is likely to facilitate a more rapid attainment of normal vitamin D levels in preterm infants.

6- ACKNOWLEDGMENTS

This research was supported by Mashhad University of Medical Sciences. The funding body had no role in designing the study and did not take part in data collection, data analysis, interpretation of the data, or writing of the manuscript. R.S. and A.A. carried out the concept, design, and drafting of this study. R.S. and A.A. performed data analysis. S.F. and Mh.S. preparate the manuscript and performed critical review manuscript R.S, Mh.S., and S.F. critically revised the manuscript. All authors approved the final version of the manuscript.

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