Effect of vitamin D supplementation as a single dose on the nutritional status of vitamin D

Efecto de la suplementación con vitamina D en dosis única sobre el estado nutricional de vitamina D

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What do we know about the subject matter of this study?

Children under one year of age are known to be at risk of vitamin D (VD) deficiency, so they are supplemented at daily doses of 400 IU of VD for the entire first year of life; without 100% adherence.

What does this study contribute to what is already known?

This study provides an alternative for vitamin D supplementation during the first year of life, at a single dose of 100,000 IU orally, which can be administered in a medical center, improving adherence.

Abstract

Infants are a group at risk of vitamin D (VD) deficiency. The administration of 400 IU of VD per day during the first year of life does not achieve 100% adherence. A single dose of 100,000 IU of oral VD is safe in newborns. **Objective**: To compare the effect of oral administration of VD between a single dose of 100,000 IU at one month of age vs daily doses of 400 IU on serum concentrations of VD, at 6 months of age. **Subjects and Method:** Randomized clinical trial, without masking. 84 healthy infants were included at 1 month of age, randomized to the study group (SG) receiving a single oral dose of 100,000 IU or to the control group (CG), who received daily oral doses of VD of 400 IU from the 1st to the 6th month of life. At 6 months of life, the serum concentration of VD was determined. **Results:** 65 infants completed the study, 36 in SG and 29 in CG. No VD deficiency was found. VD insufficient was 5.5% and 6.8% in the SG and CG, respectively. The serum concentration of VD at six months of age was 38.8 ± 5.2 ng/ml and 39.7 ± 6.3 ng/ml for the SG and CG, respectively (NS). **Conclusions:** Supplementation of 100,000 IU of VD at one month age achieves serum concentrations of VD at 6 months of life similar to the administration of daily doses of 400 IU of VD from the 1st to the 6th month.

Keywords:
Vitamin D;
Infant;
Deficiency;
Rickets;
Nutrition

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Introduction

Vitamin D (VD) is involved in multiple functions in the body. In addition to bone health and the prevention of rickets in children, it plays a role in innate and acquired immunity with the possible decrease in the risk of respiratory infections, some cancers, and some autoimmune diseases such as type I diabetes[1,2].

Factors influencing VD deficiency include general nutritional status (undernutrition or obesity), early life, aging, dark skin color, insufficient VD intake, reduced sun exposure, and prolonged breastfeeding[3,4]. The first year of life is a period of risk for VD deficiency due to the lack of reserves that the mother can provide during pregnancy[5], the low quantity of VD in breast milk, and the low exposure to sunlight of children at this age, and thus it must be supplemented during this period[6].

Reports of infant VD deficiency are variable since they will depend on the geographic location of the study site, the mother's VD nutritional status, the type of feeding the child receives, and the administration of VD supplementation during the first year. The prevalence of VD deficit in the first year of life in breastfed children receiving oral VD supplementation at a dose of 400 IU per day ranges from 15% to 33%[7,8]. When considering the type of feeding and administration of VD supplementation, the deficit can range from 64% in children exclusively breastfed without supplementation to 6% in those receiving only milk formula and supplementation[7].

In Chile, there is no information about the prevalence of VD deficits during pregnancy or the first year of life.

VD supplementation in Chile started in the 1990s, initially by administering at a single oral dose of 600,000 IU (15 mg cholecalciferol) in the first and sixth months of life. This was associated with adverse effects related to calcium metabolism[9], length alterations, and increased blood pressure[10], which was later changed at a dose of 300,000 IU[11]. Subsequently, according to the recommendations of the American Academy of Pediatrics, supplementation begins at an oral dose of 400 IU of VD per day, throughout the first year of life[12].

The problem that daily supplementation implies is the adherence of both mothers to administer medication for an entire year, and health personnel in the delivery and reminder at each checkup. Given this difficulty, new studies of supplementation in newborns have emerged, at single doses of VD of 50,000 to 150,000 IU, which have proven to be safe without side effects or toxic concentration ranges of 25 hydroxyvitamin D (25OHVD) after administration[13,14] as well as studies in other pediatric age groups[15-17].

There are no studies on costs between the two forms of supplementation (daily vs. single) in the first year of life.

The objective was to compare the effect of oral VD supplementation at a single dose of 100,000 IU at the month of age vs. at daily doses of 400 IU, on serum VD concentrations at 6 months of age in healthy infants in Santiago, Chile.

Subjects and Method

A randomized clinical trial was conducted, without blinding, which included 84 healthy infants (42 per group) between August 15, 2015, and July 15, 2016, who attend well-baby checkups at the Padre Vicente Irarrázaval Family Health Center (CESFAM), Santiago (Latitude 33ºS). We included full-term newborns between 25 and 45 days of age, fed with exclusive or mainly breast milk, with the written informed consent of their parents or representative of legal age.

Children with chronic underlying diseases, skin phototype VI (African-American descent), and twin pregnancy were excluded, in addition to those who during the study start the intake of adapted milk formula greater than 150 ml/day in infants under 3 months or 300 ml/day in infants between 3 and 6 months.

Participants were randomly assigned to each group. The study group (SG) included infants who received VD at a single oral dose of 100,000 IU on admission by their physician and the control group (CG) included infants who were prescribed VD at daily oral doses of 400 IU.

The sample size calculated for each group was 35 infants, considering a 20% of VD deficiency in the control group vs. 0% in the study group with an alpha error of 0.05 and a power of 80%. We expected a 20% loss of participants during the study, therefore, we recruited 42 participants per group.

There were three face-to-face meetings, at the time of study entry, at 3 and 6 months of age. At 2, 4, and 5 months, parents or caregivers were contacted by telephone. Only one data collection form was used for each participant. At the age of 6 months, it was collected a blood sample, on an empty stomach for 4 hours, to determine the serum concentration of 25OHVD by radio-immunoassay (DiaSorin, Saluggia, Italy), which was processed at the Micronutrient Laboratory of the Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago.

From the age of 6 months, after blood sampling, SG children were given VD at daily doses of 400 IU, as well as the CG until one year of age.

The VD nutritional status was defined through the serum concentrations of 25OHVD, defined as deficien-

cy concentrations below 20 ng/mL (< 50 nmol/L), insufficiency between 20 and 30 ng/mL (50-75 nmol/L), and sufficiency above 30 ng/mL (> 75 nmol/L)[3].

The collected data were tabulated in a database in an Excel spreadsheet and later analyzed in the STATA 13 software. The database was managed only by the principal investigator. The distribution of the variables was analyzed with the Shapiro-Wilk test and according to their distribution, the corresponding statistical tests were used. So the normal variables were expressed as mean and standard deviation and those with asymmetric distribution as medians and interquartile ranges. For comparison, Student's t-test, Fisher's Chi-square test, and Fisher's exact test were used.
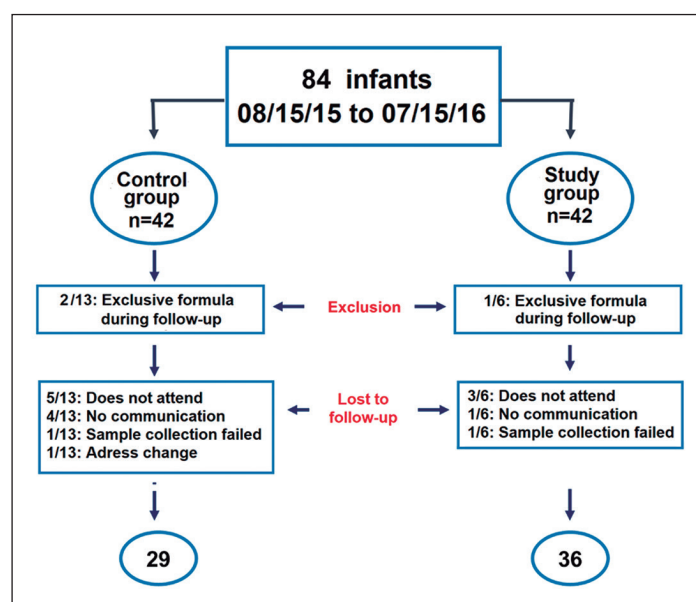

Figure 1. Flowchart of the infants studied.

This study was presented and approved by the Scientific Ethical Committee of the Central Metropolitan Health Service, Santiago.

Results

The study was completed by 65 infants, 29 from the CG, and 36 from the SG, with a loss of participants of 31% (13/42) in the CG and 14% (6/42) in the SG. Despite the loss being higher than 20% in the CG, there were no differences in the characteristics of the children lost in follow-up and those who finished. Figure 1 shows the causes of loss.

Of the 65 infants, 31 were male, 10/29 in the CG and 21/36 in the SG. The mean gestational age was 38.9 ± 0.9 weeks and at birth, the infants were 3,464 ± 445 g in weight and 50.1 ± 1.9 cm in length. The mean maternal age was 28.2 ± 6.4 years and the mean age of the infants at study entry was 33 ± 4 days of age. When comparing the general characteristics of the infants and their mothers, there were no differences between the SG and the CG (Table 1).

The prevalence of exclusive breastfeeding at 6 months of age in all infants was 55.3%, with the CG at 68.9% and the SG at 44.4% (NS). The percentages of exclusive breastfeeding at 3 months of age were 86% and 64% in CG and SG, respectively (NS).

There were no differences when comparing 25OHVD concentrations between infants who were exclusively breastfed up to 6 months of age and those who were not (38.7 ± 6.2 ng/ml and 39.9 ± 5.0 ng/ml, respectively).

The concentration of 25OHVD at 6 months of age was 39.7 ± 6.3 ng/ml and 38.8 ± 5.2 ng/ml for CG and SG respectively, with no statistical difference bet-

Variable	Control group n: 29	Study group n: 36	p* value
Sex male (n)	10	21	
Gestational age, weeks (SD)	38.7 (1.0)	39 (0.9)	NS
Age at admission, days (SD)	32.8 (4.4)	33.3 (4.7)	NS
Birth weight, g (SD)	3394.4 (485.4)	3520.9 (408)	NS
Length at birth, cm (SD)	50.1 (2.1)	50.1 (1.7)	NS
Exclusive breastfeeding at 3 months	25/29	23/36	NS
Exclusive breastfeeding at 6 months	20/29	16/36	NS
Mother age, years (SD)	28.7 (6.5)	27.9 (6.3)	NS
VD intake in pregnancy	4/29	0/29	-

Table 1. General characteristics of the population

*Fisher Test.

Table 2. Comparison of serum 25OHVD concentrations between both groups			
Concentration de 25OH VD	Control group n: 29	Study group n: 36	p* value
Mean ng/ml (SD)	39.7 (6.3)	38.8 (5.2)	NS
Minimum-maximum value (ng/ml)	23.2 - 50.1	25.1 - 48.5	
≥ 30 ng/ml (sufficiency)	27/29	34/36	
20 - < 30 ng/ml (insufficiency)	2/29	2/36	
< 20 ng/ml (deficiency)	0	0	
*Student t test.			

ween them (Figure 2). No VD deficiency was found at 6 months of age in either group. 6.8% (2/29) of the CG reported VD deficiency and in the SG was 5.5% (2/36), with no difference between them. In none of the groups, there were concentrations of 25OHVD above the toxicity ranges. The maximum concentration in each group was 50.1 ng/mL and 48.5 ng/mL in CG and SG, respectively (Table 2).

Of the 29 infants in the CG, 76% achieved ≥ 90% in the administration of VD throughout the study.

When comparing the nutritional status between the CG and the SG, there were no differences between them.

Discussion

In Chile, there is a lack of data on the nutritional status of VD in infants. There are some studies conducted in other pediatric ages, where deficiency and insufficiency are high. In preschool children in Coyhaique (45ºS), there was a deficiency of 65.5% and insufficiency of 17.3%[18]. In school children in Santiago (33ºS), it was reported a deficiency of 19.7% and insufficiency of 49%; and in Punta Arenas (53ºS) 96.3% of deficiency and 3.7% of insufficiency[19,20].

In this study, we found that most of the supplemented infants achieve sufficient VD concentrations. The single dose of 100,000 IU of VD in the first month of life is effective in supplementing the necessary amount of VD for the first 6 months of life and achieving sufficient 25OHVD concentrations at that age. No VD deficiency was found at 6 months of age with this dose and the insufficiency was only 5.5%, both better results than those reported by studies that have used single doses of 50,000 IU in the first month of life. This result was expected by the researchers since it was used a double dose. In Tijuana, Mexico (32ºN), at doses of 50,000 IU in newborns, they found no deficit of VD at six months of life, although they had 36% of insufficiency[13]. When the same 50,000 IU dose was used in newborns in Me-
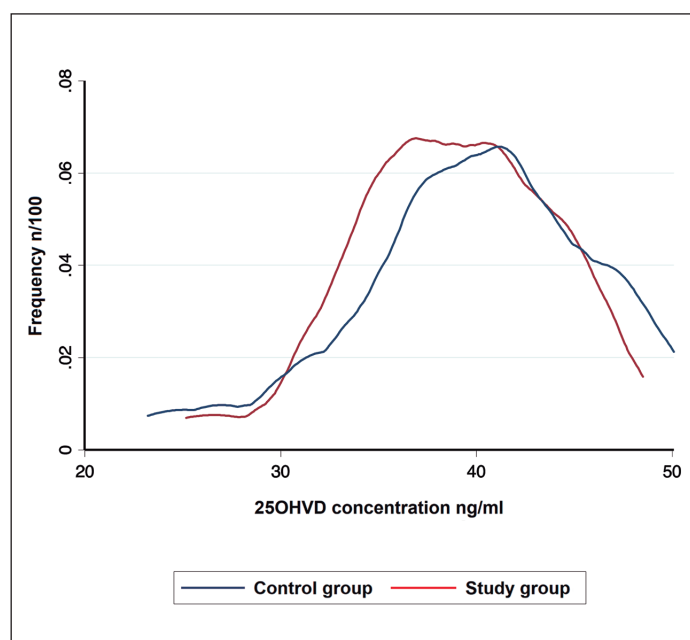
Figure 2. Comparison of the serum 25OHVD concentration between both groups.

lbourne, Australia (37°S), they found a VD deficit of 11% at 4 months of age; data on insufficiency were not reported in such paper[14]. The difference in the results between these two studies using the same dose may be due to the difference in latitudes, suggesting that doses of 100,000 IU may not only be sufficient to prevent VD deficit and insufficiency in infants at latitudes near 33 degrees but also higher latitudes.

Due to the importance of VD in the human body, and especially in stages of accelerated growth such as the first year of life, the goal is to achieve complete coverage and 100% adherence to the administration of VD doses.

The studies report adherence to VD formulation between 36% and 89%[12,21] by health personnel and administration by parents between 8.5%[22] and 60%[23].

The effectiveness of daily doses of 400 IU has again proven in this study as well as difficulties in obtaining complete adherence.

During the study, we emphasized the daily administration of the vitamins by the mothers through meetings or telephone calls; however, the adherence observed was 76%. In a study also conducted in Santiago, in CESFAMs where there was previous education on VD supplementation, the adherence was 68.9%[24], which is similar to this study. This suggests that if these are the reports amid research interventions, under usual conditions the adherence may be much lower.

Bearing in mind this problem of adherence to daily doses, some countries such as New Zealand offer the option of supplementation at a single dose of 150,000 IU of VD in the first year of life, in case adherence to the administration of daily doses of 400 IU is low[26].

Therefore, this study could be the first approach to a future public health intervention, thus allowing future effectiveness studies to compare the effect of daily administration of vitamin D under usual conditions of administration versus single high dose administration in healthy infants.

On the other hand, in the infants of this study, there were no serum concentrations of 25OHVD > 100 ng/mL (250 nmol/L), which have been associated with some adverse effects such as hypercalcemia[25]. The maximum concentration of 25OHVD reported in this study in single-dose infants was 48.5 ng/mL, which is consistent with other studies, where VD doses of 100,000 IU fall into the safety range. However, while all indications are that VD doses of 100,000 IU are safe, more studies are needed to assess possible side effects of this dose in infants. In this study, serial blood samples of 25OHVD concentrations and bone metabolism were not collected, considering the difficulty of collecting samples in healthy newborns, which would have allowed us to know the maximum peak concentration of 25OHVD and to evaluate side effects.

So far, studies do not allow us to know the effect duration of the single dose of 100,000 IU of vitamin D since the cut-off has been made at 4 or 6 months of life, as we did, so it is unknown whether more than one single dose is required during the first year to ensure optimal concentrations of 25OHVD up to one year of life.

Among the weaknesses of this study is the loss of participants of more than 20% in the control group, which is reduced by finding no difference in the characteristics of infants lost in the follow-up and those who completed the study.

Also, baseline measurements of serum concentrations of 25OHVD were not available due to the difficulty of taking blood samples in the first month of life from healthy infants. However, an attempt was made to reduce this fact by not having differences between the groups in the measured variables and by excluding children who were at risk of having lower concentrations from birth, such as African-American descendant (skin phototype VI), premature, twins, or those with underlying disease.

In conclusion, it can be stated that the VD dose of 100,000 IU in the first month of life is a good option at different latitudes, not only to prevent VD deficiency but also insufficiency, mainly when there are difficulties in adherence, since the single-dose, when administered directly in the CESFAM, ensures 100% adherence.

This is an initial study after which further studies could consider evaluating side effects at higher doses of VD and the cost-effectiveness of both types of supplementation.

References

1. Bikle D. Nonclassic Actions of Vitamin D. J Clin Endocrinol Metab 2009;94:26-34.

2. Zepeda J, Centeno D, Fuentes C, Bustos R. Vitamina D y enfermedades respiratorias pediátricas. Rev Chil Pediatr 2019;90:94-101.

3. Saggese G, Vierucci F, Prodam F, et al. Vitamin D in pediatric age: consensus of the Italian Pediatric Society and the Italian Society of Preventive and Social Pediatrics, jointly with the Italian Federation of Pediatricians. Ital J Pediatr. 2018;44:51.

4. Michel H, Olabopo F, Wang L, Nucci A, Greenspan SL, Rajakumar K. Determinants of 25-Hydroxyvitamin D Concentrations in Infants and Toddlers. Curr Nutr Food Sci 2015;11:124-30.

5. Grant CC, Stewart AW, Scragg R, et al. Vitamin D during pregnancy and infancy and infant serum 25-Hydroxyvitamin D concentrations. Pediatrics 2014;133:e143-53.

6. Cediel G, Pacheco-Acosta J, Castillo-Durán C. Deficiencia de vitamina D en la práctica clínica pediátrica. Arch Argent Pediatr 2018;116:e75-e81.

7. Gordon C, Feldman H, Sinclair L, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med 2008;162:505-12.

8. Mansbach J, Ginde A, Camargo C. Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: Do children need more vitamin D? Pediatrics 2009;124:1404-10.

9. Zeghoud F, Ben-Mekhbi H, Djeghri N, Garabedian M. Vitamin D prophylaxis during infancy: comparison of the long-term effects of three intermittent doses (1 5, 5, or 2.5 mg) on 25-hydroxyvitamin D concentrations. Am J Clin Nutr 1994;60:393-6.

10. Lagomarsino E, Arnaiz P, Vial P, et al. Efecto de dos formas de suplementación de vitamina D en el crecimiento y metabolismo óseo del lactante. Rev Chil Pediatr 1996;67:219-23.

11. Harnot J, Verma S, Singhi S, Sankhyan N, Sachdeva N, Bharti B. Comparison of 300,000 and 600,000 IU oral vitamin-D bolus for vitamin-D deficiency in young children. Indian J Pediatr. 2017;84:111-16.

12. Perrine C, Sharma A, Jefferds M, Serdula M, Scanlon K: Adherence to vitamin D recommendations among US infants. Pediatrics 2010;125:627-32.

13. Moodley A, Spector S. Single high-dose vitamin D at birth corrects vitamin D deficiency in infants in Mexico. Int J Food Sci Nutr 2015;66:336-41.

14. Huynh J, Lu T, Liew D, et al. Vitamin D in newborns. A randomised controlled trial comparing daily and single oral bolus vitamin D in infants. Paediatr Child Health 2017;53:163-69.

15. Tau C, Ciriani V, Scaiola E, Acuña M. Twice single doses of 100,000 IU of vitamin D in winter is adequate and safe for prevention of vitamin D deficiency in healthy children from Ushuaia, Tierra Del Fuego, Argentina. J Steroid Biochem Mol Biol 2007;103:651-4.

16. Oliveri B, Cassinelli H, Mautalen C, Ayala M. Vitamin D prophylaxis in children with a single dose of 150000 IU of vitamin D. Eur J ClinNutr. 1996;50:807-10.

17. Le Roy C, Meierc M, Wittingd S, Pérez-Bravo F, Solanog C, Castillo-Durán C. Efecto de la suplementación con vitamina D en monodosis en niños con parálisis cerebral. Estudio preliminar controlado y aleatorizado. Rev Chil Pediatr. 2015;86:393-8.

18. Le Roy C, González J, Pérez-Bravo F, Castillo-Durán C. Estado nutricional de vitamina D en preescolares chilenos de zonas australes. Rev Med Chile 2013;141:435-41.

19. López T, García D, Ángel B, et al. Asociación del polimorfismo Fok I del gen del receptor de vitamina D (VDR) con concentraciones plasmáticas del factortransformador de crecimiento e interferón gamma en la diabetes mellitus tipo 1. Med Clin (Barc) 2008;130:81-4.

20. Brinkmann K, Le Roy C, Iñiguez G, Borzutzky A. Deficiencia severa de vitamina D en niños de Punta Arenas, Chile: influencia de estado nutricional en la respuesta a suplementación. Rev Chil Pediatr 2015;86:182-8.

21. Sherman E, Svec R. Barriers to vitamin D supplementation among military physicians. Mil Med 2009;174:302-7.

22. Taylor J, Geyer L, Feldman K. Use of supplemental vitamin D among infants breastfed for prolonged periods. Pediatrics 2010;125:105-11.

23. Pludowski P, Socha P, Karczmarewicz E, et al. Vitamin D supplementation and status in infants: A prospective cohort observational study. J Pediatr Gastroenterol Nutr. 2011;53:93-9.

24. Arancibia M, Reyes ML, Cerda J. Adherencia a la suplementación con vitamina D y factores determinantes de ella, durante el primer año de vida. Rev Chil Pediatr 2014;85:428-36.

25. Holmlund-Suila E, Viljakainen H, Hytinantti T, Lamberg-Allardt C, Andersson S, Mäkitie O. High-dosevitamin D intervention in infants-effects on vitamin D status, calcium homeostasis, and bone strength. J Clin Endocrinol Metab 2012;97:4139-47.

26. Munns C, Zacharin M, Rodda C, et al. Prevention and treatment of infant and childhood vitamin D deficiency in Australia and New Zealand: a consensus statement. Med J Aust. 2006;185:268-72.