

# Vitamin D levels of the healthy infants using oral spray or drop form of vitamin D supplement in the first year of life

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## ABSTRACT

**OBJECTIVE:** Vitamin D (VD) deficiency is a common problem worldwide, especially in pregnant women and newborns. Regular administration of VD supplements has been recommended worldwide since 2010. Recently, a new formulation providing VD supplementation in the form of a spray which is absorbed through the buccal mucosa has been introduced, but there is very little information in the literature about the effectiveness of it, especially in children. Therefore, in our study, we aim to investigate whether there was a difference in VD levels at one year of age infants who have started oral vitamin D supplements (400 IU/day) as spray or drop form in the neonatal period and have used it regularly during the first year of life.

**METHODS:** In our retrospective study, the medical records of 243 healthy infants at one year of age who were followed up regularly in the first year of life in our well-child follow-up clinic were evaluated. The infants who had congenital anomalies, chronic diseases, and those using irregular vitamin D supplements were excluded from this study.

**RESULTS:** The findings showed that the spray form of VD was used in 136 babies (56.0%) in the study group and the drop form was used in 107 (44.0%) of them. VD deficiency (defined as 25 [OH] D level <20 ng/ml) was 33.3% (n=81). VD levels were 24 ng/ml (8–109 ng/ml) and 21 ng/ml (7–65 ng/ml) in the infants using spray and drop form, respectively. The difference between the two forms of VD supplementation regarding 25 (OH) D levels was significant ( $p=0.010$ ); VD levels were higher in the infants using the spray form.

**CONCLUSION:** Our study findings suggest that the infants using oral spray form have higher VD levels compared to oral drop form. Concerning VD levels, the spray form may be preferred as a suitable alternative to the drop form, and the spray form may provide regular and easy use in children.

*Keywords:* Oral spray; supplement; vitamin D.

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Vitamin D (VD) is one of the basic structural elements that play an important role in various metabolic pathways that provide many functions that are vital for the organism both directly and indirectly in addition to regulating calcium and phosphorus metabolism [1–3]. It is a fat-soluble prohormone and a secosteroid produced in the skin after exposure to sunlight. VD deficiency is related to some factors, such as less sunlight

exposure, insufficient intake of VD and absorption problems [4, 5]. VD deficiency is a common problem all over the world, especially in newborns, the prevention of VD deficiency continues to be the priority of health services [6, 7]. It has been recommended in guidelines published since 2010 worldwide to apply VD supplements regularly [8]. In 2008, the American Academy of Pediatrics (AAP), to prevent rickets, increased their recommended



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intake of VD for infants to 400 IU/daily [9]. Specifically, they recommend supplementing the infants who are exclusively or partially breastfed with VD of 400 IU/day and for nonbreastfeeding infants consuming <1 L a day of formula, AAP recommended to supplement with the same dose of VD as well [9, 10].

The initiation of vitamin D (400 IU/day) supplementation in the neonatal period in our country is a regular application made by the Ministry of Health. There are preparations that have been used as drop form in our country for a long time but using as a spray form has become more popular in recent years. Apart from supplementation frequency, it has been suggested that the mode of supplementary VD delivery affects bioavailability, release and absorption and unstable compounds decomposition [11, 12]. There is little information in both international and national literature about the effectiveness of spray form VD supplements, especially in children, which are used orally and absorb from the buccal and sublingual mucosa. Therefore, in our study, we aim to investigate whether there is a difference between VD levels of one year aged infants who have been started oral VD supplements (400 IU/day) as spray or drop form in the neonatal period and used regularly in the first year of life. Thus, it will be possible to obtain data about the effectiveness of spray form of VD which provides ease of use especially in children.

## MATERIALS AND METHODS

In our retrospective study, 243 medical records of one year-old, healthy infants who were followed up in our well-child outpatient clinic during the first year of life were evaluated.

The records of the infants who were born at our hospital between 2018 January and 2019 January and have started VD supplementation (400 IU/day) as drop or spray form in the neonatal period and who used regularly VD during the first year of their life were included in this study. The infants with missing information on hospital records, those had congenital anomalies, chronic disease and who used irregularly VD were excluded from this study.

The birth weight of the infants and their weight at one year old, their feeding type of (exclusively breast milk, exclusively formula and mixed) during the first six months, the VD supplement they used whether drops or sprays, and VD levels when they were one year old were recorded. In the newborn period VD supplement was started at the end of first week of life.

### Highlight key points

- Vitamin D (VD) deficiency is a common problem throughout the world, especially in pregnant women and newborns.
- VD deficiency rate was 33.3% (n=81) based on 25(OH)D levels <20 ng/ml in this study.
- The median VD level of the infants using spray form it was 24 ng/ml (8–109 ng/ml), while the median of those using VD drops form it was 21 ng/ml (7–65 ng/ml).
- In the mixed-fed (formula fed and breastfeed group) infants using the spray form had higher VD levels than the drop form.
- The infants using oral spray form vitamin D supplements have higher VD levels compared to oral drop form.

VD deficiency is defined according to serum Calcidiol (25-hydroxyvitamin D 25(OH)D) level which is storage form of VD and assess VD status in the body. 25(OH)D level <20 ng/mL is defined as VD deficiency, 20–30 ng/mL is defined VD insufficiency and  $\geq 30$  ng/mL shows VD adequacy [13, 14]. In all participants VD levels were measured when the infants were at age of one year so we ruled out the seasonal difference of VD levels.

This study was approved ethically by the Ethics and Research Committee of Acibadem University (05.11.2020/2020-23/04).

SPSS (v20) program was used for data analysis. The Shapiro-Wilk test was used to evaluate the compliance with normal distribution. In the display of continuous data, median, lowest and highest values (min–max) or mean  $\pm$  standard deviation were preferred compared to normal distribution. Mann-Whitney U or Student's t-test was used according to normal distribution in comparison of continuous data. Pearson Chi-Square test was used for comparison of categorical data,  $p < 0.05$  value was accepted as the limit of significance.

## RESULTS

The mean birth weight of the infants was  $3180 \pm 486$  grams, and the mean weight was  $10007 \pm 1060$  grams when they were one year old. In the study group, 21 (8.64%) infants had only formula, 115 (47.325%) had exclusively breast milk and 107 (44.03%) of them were fed mixed (both breast milk and formula) during the first six months. The spray form of VD was used in 136 infants (56.0%) of the study group, and the drop form of VD was used in 107 (44.0%) of them (Table 1).

**TABLE 1.** Comparison of some properties according to the type of vitamin D supplement

	Spray form of vitamin D	Drop form of vitamin D	p
Vitamin D levels,	24 (8–109)	21 (7–65)	<b>0.010<sup>a</sup></b>
Weight gain, gram	6874±1126	6765±953	0.424 <sup>b</sup>
Feeding type (%)			
Only formula	47.6	52.4	
Only breast milk	65.2	34.8	<b>0.023<sup>c</sup></b>
Mixed (formula+breast milk)	47.7	52.3	

a: Mann-Whitney U test was used, median (min–max) values were given; b: Student's t-test was used, average±standard deviation values were given; c: Chi-square test was used ( $p < 0.05$  statistically significant).

The findings showed that VD deficiency rate was 33.3% ( $n=81$ ) based on 25(OH)D levels  $< 20$  ng/ml in this study. When VD levels were compared according to the type of VD supplements, the median of level of those using spray form it was 24 ng/ml (8–109 ng/ml), while the median of those using VD drops form it was 21 ng/ml (7–65 ng/ml). The difference between the two forms of the supplement concerning 25(OH)D level was significant ( $p=0.010$ ) (Table 1). The levels of VD were higher in the infants who used the spray form than the drop form.

While the average weight gain of the infants who used the spray form of VD until the age of one year was 6874±1126 gram and in the infants who used the VD drops, it was 6765±953 gram. No significant difference was found between the form of VD supplements used and weight gained up to the age of one ( $p=0.424$ ) (Table 1).

The median level of vitamin D (25(OH)D) was 26 ng/ml (13–65 ng/ml) in the infants fed with formula, 23 ng/ml (7–109 ng/ml) in those fed with breast milk and 22 ng/ml (8–59 ng/ml) was in those who had a mixed diet (both breast milk and formula). There was no significant difference between the feeding type and vitamin D levels, weight gain up to one year old ( $p=0.354$ ,  $p=0.833$ , respectively).

In the infants using the spray form and fed with the only formula the median VD level was 28 ng/ml (16–44 ng/ml) and it was 21 ng/ml (13–65 ng/ml) in those who used the drop form. The median VD level was 23 ng/ml (8–109 ng/ml) for only breast-fed infants using the spray form and for those using the drop form it was 21

**TABLE 2.** Comparison of Vitamin D levels of infants according to the type of feeding and vitamin D supplements

Feeding type	Spray form of vitamin D median (min–max)	Drop form of vitamin D median (min–max)	p
Only formula	28 (16–44)	21 (13–65)	0.573
Only breast milk	23 (8–109)	21 (7–48)	0.208
Mixed (formula+breast milk)	24 (16–59)	20 (8–44)	<b>0.016</b>

\*: Mann-Whitney U test was used.

ng/ml (7–48 ng/ml). In the mixed-fed infants, the median VD levels using the spray and the drop form of the VD supplement were 24 ng/ml (16–59 ng/ml), 20 ng/ml (8–44 ng/ml), respectively. The findings showed that in the mixed-fed group using the spray form had higher VD levels than the drop form ( $p=0.016$ ) (Table 2).

## DISCUSSION

VD deficiency is still a public health problem all over the world. In the United States, the overall prevalence of VD deficiency (25[OH]D  $< 20$  ng/ml) is reported as 15% in pediatric populations [15]. Between 30% and 50% of children in many countries in Africa, Asia, Europe, and North America, including geographic areas with very sunny and heterogeneous economic resources, have 25(OH)D less than 20 ng/ml (16).

In a study from Turkey performed with 2346 children, the VD deficiency rate was 42.33% (25[OH]D  $< 20$  ng/ml) [17]. In another study from Turkey, 76.25% of the participants had a serum 25(OH)D level less than 20 ng/ml [18]. A total of 2551 healthy individuals aged one to 17 years enrolled in a study, only 39% of the subjects had sufficient VD levels ( $> 20$  ng/ml), while the rest had poor VD status in Turkey [19]. In our study, we found a VD deficiency rate of 33.3% in infants at the age of one. Because of the high rates of VD deficiency, it is very important to supplement VD, especially in the risk groups like children.

Advances in combination genetics, chemistry and biology have led to the development of various VD supplements [20]. Recently, a new formulation has become available, delivering VD through the buccal mucosa by a spray. The spray form is supposed to be rapidly and

completely absorbed by the oral mucosa bypassing problems linked to dysphagia, malabsorption or difficulties in using drop form by the children [21, 22]. Vitamin D is known to be fat-soluble, and its relative bioavailability can be limited due to the rate of absorption when administered in solid form (like capsules) and the bioavailability is related not only to the pharmaceutically active molecules but also to the formulation. Oral VD (oral delivery) is absorbed in the gastrointestinal tract where is watery. Therefore, for VD (lipid-soluble) to be absorbed, it must be made soluble in the intestine. This is accomplished in two steps: the first step is the emulsification of VD in the intestinal lumen, VD is turned into small micelles with the interaction of free fatty acids, monoglycerides and bile salts, then micelles is sufficiently soluble in water and the content of VD in the intestinal mucosa is released and absorbed. When sprayed inside the mouth, the fine micro-sized droplets of VD are believed to be quickly and completely absorbed through the buccal mucosa into the numerous capillaries and veins close to the surface [23].

According to our retrospective study findings, it has been revealed that VD supplied in oral spray form is more effective at raising a total of 25(OH)D concentrations in one year old infants when compared with oral drop form ( $p=0.010$ ) (Table 1). Therefore, our findings suggest that oral spray VD should be used as a suitable alternative to the drop form due to its ease of use in the infant group. Similarly to our study, in a study performed with adult subjects, Satia et al. [23] demonstrated a superior effect of the buccal spray form compared to the oral drop form. In the other studies, contrary to this finding, there was no significant difference between the two methods concerning VD levels in healthy adults using capsule and oral spray VD forms [24, 25]. In contrast to our study, these three studies mentioned above were adult subjects' studies and buccal spray form was compared to oral capsule and two forms of supplementations were equally effective in the short-term treatment of VD deficiency. In our study, our subjects were one year old healthy infants and they have used long-term VD supplements to prevent from vitamin D deficiency for a year.

Lastly, to our knowledge, there is one study in children with neurodisabilities [26]. VD supplementation with oral spray and drops was equally effective in neurodisabled -children in the short-term treatment of VD deficiency; however, oral spray form has been more usable by the patients. According to this study, using the easier way may be important when it comes to long-term VD treatment especially in children.

The infants of mothers with low VD storage, who are exclusively breastfed, who have limited sunlight in the first few months of life or who take irregular vitamin D supplements are particularly vulnerable to vitamin D deficiency. Consumption of breast milk alone does not ordinarily enable infants to meet vitamin D requirements because it provides less than 0.6 to 2.0 mcg/L (25 to 78 IU/L) VD levels [27]. The VD content of human milk is related to the mother's vitamin D status; various studies show that the mothers who take daily supplements containing at least 50 mcg (2,000 IU) of VD have a higher nutritional level of breast milk [28]. There is an increased risk of VD deficiency in mixed-fed or formula-fed infants until they are weaned and consume at least 1,000 mL/day VD fortified- formula or whole milk. AAP recommends 10 mcg (400 IU)/day VD supplements for infants who are breastfed only or partially to start shortly after birth and to last until they are weaned and consume at least 1,000 mL/day VD fortified -formula or whole milk. AAP also recommends an additional VD of 10 mcg (400 IU)/day for all infants fed without breast milk [9]. The analysis of NHANES 2009–2016 data showed that only 20.5% of breastfed infants and 31.1% of infants not breastfed intake this recommended amount [29].

In infants feeding with fortified formulas, VD levels are higher than the breast-milk [30–32]. In our study, although VD level was higher (26 ng/ml) in infants fed with formula than in those fed with breast milk (23 ng/ml) and in those who had mixed diet (both breast milk and formula) (22 ng/ml), there was no statistically difference between the groups ( $p=0.354$ ). The reason for this finding may be contributed that the mothers may have the VD supplementation during the lactation period; in our retrospective study we could not determine this situation. According to their feeding type when the VD levels of the infants using oral spray form and drop form compared, the findings showed that VD levels in the mixed-fed group using the spray form had higher VD levels than the drop form ( $p=0.016$ ) (Table 2).

Although many studies showed that VD deficiency was inversely associated with weight gain in children [33, 34], there is little knowledge according to the form of VD supplements used in children [26]. In our study, no significant difference was found between the form of VD supplements used (oral or spray form) in the infants and weight gained up to the age of one.

Our study was a retrospective study, so it had some limitations. Firstly, we could only determine the levels of VD of the infants; we could not determine the mother's VD levels or whether they have used VD supplements during the lactation period. Also, we could not investigate the ease of use, the cost and tolerability of the spray form. To recommend the use of the oral spray form VD routinely according to the limitations mentioned in our study, it would be appropriate to conduct a prospective study in a larger sample group.

## Conclusion

Although there are some limitations in our study, our study suggested important data on oral spray formulation of VD supplements. This study showed that in the healthy infants using oral spray form regularly in their first year of life had higher VD levels compared to oral drop form. In other words, it has been demonstrated superiority of spray form over oral drop form concerning VD levels in healthy infants, and the spray form may provide regular and easy use in children.

**Ethics Committee Approval:** The Acibadem University Clinical Research Ethics Committee granted approval for this study (date: 05.11.2020, number: 2020-23/04).

**Conflict of Interest:** No conflict of interest was declared by the authors.

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