

Ceasing Vitamin D Replacement in Infants with Premature Closure of Front Fontanelle: True or False?

Ön Fontaneli Erken Kapanan Bebeklerde D Vitamini Replasmanının Durdurulması: Doğru Mu? Yanlış Mı?

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Abstract

Objective: The purpose of this study was to determine whether fontanelle closure in neonatal and early infancy periods was related to vitamin D levels and the prophylaxis of vitamin D intake. Moreover, our analysis was structured in a retrospective, controlled manner to evaluate our hypothesis.

Materials and Methods: We considered 50 individuals who applied to our child endocrinology polyclinic with infants suffering from premature anterior closure. Further, 35 healthy infants of the same age and gender having open anterior fontanelles were taken as the control group.

Results: The serum vitamin D level was found to be lower, and the parathormone level was significantly higher in the group with premature closure of the anterior fontanelle. In addition, there was a significant difference in serum calcium, alkaline phosphatase and parathormone levels in patients who had ceased vitamin D support compared with regular vitamin D users. While there was no significant difference in serum vitamin D levels, the level was lower in patients who had withdrawn vitamin D support.

Conclusion: In our study, many infants have much lower vitamin D levels than normal levels, even though their anterior fontanelle is prematurely closed. Thus, physicians and other health workers are also warned of the continuity of vitamin D prophylaxis and that it is wrong to cease vitamin D support for reasons such as the premature closing of the anterior fontanelle.

Öz

Amaç: Biz çalışmamızda yenidoğan ve erken süt çocukluğu döneminde fontanel kapanmasının D vitamini düzeyi ve aldığı D vitamini profilaksisinin miktarı ile ilişkili olup olmadığını araştırmak istedik.

Gereç ve Yöntemler: Çocuk endokrin polikliniğimize ön fontaneli 6. aydan erken kapanma şikayetiyle başvuran veya rutin muayene esnasında ön fontanelin 6. aydan önce kapandığı saptanan 50 hastanın çalışmaya alınması planlandı. Aynı yaş ve cinsiyetten ön fontaneli açık 35 sağlıklı çocuk kontrol grubu olarak alındı.

Bulgular: Çalışmamızda, ön fontaneli erken kapanan grupta serum D vitamini düzeyi daha düşük saptanmasına karşın kontrol grubu ile arasında anlamlı bir fark

saptanamadı. Serum parathormon düzeyi ise fontaneli erken kapanan hasta grubunda anlamlı olarak yükselmişti. D vitamini desteği kesilen hastalar ile düzenli D vitamini desteği alan hastalar karşılaştırıldığında serum kalsiyum, alkalin fosfataz ve parathormon düzeyleri arasında anlamlı fark saptandı. Serum D vitamini düzeyleri arasındaki fark anlamlı olmasa da D vitamini desteği kesilen hastalarda daha düşüktü.

Sonuç: Çalışmamızda da gördüğümüz gibi ön fontaneli erken kapansa dahi vitamin D düzeyi normal hatta normalin altında birçok infant bulunmaktadır. Bu nedenle hem hekimlerin hem de diğer sağlık çalışanlarının D vitamini profilaksisinin devamlılığı konusunda uyarılması ve ön fontaneli erken kapanması gibi sebeplerle D vitamini desteğinin kesilmesinin yanlış olduğu vurgulanmalıdır.

Introduction

Nutritional rickets and vitamin D deficiency are two common serious yet preventable problems, and they are frequently treated by ceasing the support of vitamin D due to associating the premature closure of anterior fontanelle in neonatal and infancy periods with vitamin D excess. As the deficiency of vitamin D is known to delay the closure of anterior fontanelle, infants with premature closure of anterior fontanelle are thought to have vitamin D excess and the cease of vitamin D prophylaxis is the first thing that comes to mind. This is a treatment which increases the risks of vitamin D deficiency and rickets in neonates and infants. When we had an emergency patient who applied to us with the clinical findings of hypocalcemic convulsion and rickets due to early cease of vitamin D support by the infant's doctor on the grounds that the infant had premature closure of anterior fontanelle, we felt the need of carrying out a study on the issue.

Vitamin D is a prohormone that is closely associated with the calcium phosphorus metabolism in our body. Calcium absorption from gastrointestinal system and its mineralization in the bone with phosphorus can only occur in the presence of vitamin D. In the study, vitamin D was found in various types of cells among which the immune system, skin, pancreas and the bone are the foremost (1-4).

As stated by Hollick (1), 25-hydroxyvitamin D [25(OH)D] is the best indicator of the nutritional state. When serum 25(OH)D level is below 20 ng/mL, this is called vitamin D deficiency, when it is between 20-36 ng/mL, this is called vitamin D insufficiency. If serum vitamin D is between 10-20 ng/mL, this is low level deficiency; between 5-10 ng/mL, this is medium level deficiency; <5 ng/mL, this is serious deficiency (5,6). In the published Endocrine Society's Practice Guidelines on vitamin D, vitamin D deficiency was defined as a 25(OH)D<20 ng/mL, insufficiency as 21-29 ng/mL and sufficiency as at least 30 ng/mL for

maximum musculoskeletal health (7). The vitamin D deficiency seen in neonatal and infancy periods is closely related to pregnancy and postpartum vitamin D levels. Sufficient 25(OH)D level shall be between 40-60 ng/mL, which corresponds to a daily intake of 4,000 IU vitamin D (1). Classical rickets symptoms due to vitamin D deficiency is more common in kids between 6 months old-2.5 years old. It may be asymptomatic in early periods; or it may be accompanied by a sensitivity in skeleton-muscle system, craniotabes, widening in wrists, breaks, frontal bossing, delay of anterior fontanelle, Harrison's Groove, rachitic rosary, short stature and growth retardation. There may be teething retardation or defects in tooth enamel (8,9).

Anterior fontanelle has a significant role in the clinical evaluation of infants. In their 1st postnatal days, the size of a normal anterior fontanelle is between 0.6 cm-3.6 cm (2.1 cm on average) (10). When the premature infants reach their normal birth terms, the size of their fontanelles show parallelism with term infants. The anterior fontanelle, which is detected to close in 13.8 months on average, may show widening in the first months of life (11). Many studies were made on their sizes and closure times. In 1%, anterior fontanelle closure was seen in the first 3 months; in 38%, closure was seen within 12 months; and 96% was seen to close by 24 months. While the anterior fontanelle closed earlier in boys than girls, there wasn't any pre-estimation about the size and closure time of the fontanelle (12). It was also found in these studies that; anterior fontanelle closure had no significant relationship with head circumference and bone age, anterior fontanelle gap didn't reflect the infant's calcium level, either (13).

To get protected from rickets and vitamin D deficiency, all neonates feeding on breast milk shall be started with a support of 400 units of vitamin D since the first days of life. This support shall be continued until the baby starts to take at least 1 litre of formula milk containing vitamin D (14,15).

We wanted to inquire whether fontanelle closure in neonatal and early infancy periods was related to vitamin D level and the prophylaxis amount of the vitamin D intake, and even to show that infants with premature closure of anterior fontanelle could also have vitamin D deficiency.

Materials and Methods

We planned our study in a retrospective, controlled way to evaluate our hypothesis. The study was approved by Non-invasive Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (protocol no: 2020-227). Before the study, retrospective procedures were explained and all subjects gave consent for study. For our study, we considered 50 patients who applied to our pediatric endocrinology polyclinic with the suffering of premature anterior closure (closure before the 6th month) or whose anterior fontanelles were found to have closed before the 6th month. Patients with accompanying syndromic hypothyroid, hypoparathyroid, macrocephaly or hydrocephaly were excluded from the study. Thirty five healthy infants of the same age and gender who had open anterior fontanelles were taken as the control group. Average age of the patients whose anterior fontanelles closed prematurely was found to be 2.75 ± 1.52 months old. On the other hand, average age of the infants in the control groups was 3.04 ± 1.51 months old ($p=0.398$). While 52% of the group with premature anterior fontanelle closure consisted of male patients, the rate of males in the control group was found to be 54.3% ($p=0.835$). All patients included in the study were terms with respect to their gestational age, premature ones were excluded. Gestational weeks, delivery ways, birth weights and head circumferences of the patients, and their weights and head circumferences on the date of application were all recorded. The vitamin D dose they had been using on application, mother's vitamin D intake background during pregnancy and the infant's nutritional background were noted down. Serum pre-prandial calcium, phosphorus, alkaline phosphates, vitamin D and parathormone levels of all patients were noted from the patient's files.

Statistical Analysis

Statistical analysis of data were performed with Statistical Package for Social Science 17.0 packaged software. Definitive and frequency analysis were

performed. Distribution and homogeneity of the data were assessed with Sample K-S and One-Way ANOVA tests. Chi-square, parametric independent samples, t-test and nonparametric Mann-Whitney U tests were used to compare the two groups.

Results

Twenty eight of the patients with premature closure of anterior fontanelle were delivered by regular spontaneous vaginal way while the remaining 22 were delivered by caesarean operation. On the other hand; 21 of the patients in control group were delivered by regular spontaneous way while the 14 were delivered by caesarean operation ($p=0.713$). While the average birth weights of the patients with closed anterior fontanelles were between 3280 ± 360.3 grams, the ones in the control group had an average birth weight between 3115 ± 452.1 grams ($p=0.327$). While the infants who had premature closure of anterior fontanelle had an average head circumference of 35.8 ± 0.71 cm at birth, average head circumference of the control group was measured as 36.6 ± 0.90 cm, which was considered to be statistically significant ($p<0.001$). However; there was no significant statistical difference between the group with premature closure of anterior fontanelle and the control group with respect to the head circumference on the date of application (40.2 ± 2.1 cm and 41.1 ± 2.63 cm respectively) ($p=0.272$). While 19 of the infants with premature closure of anterior fontanelle were feeding on breast milk only, 31 of them were taking formula milk support. On the other hand; the number of infants feeding on breast milk only was 17 whereas the number of the ones also taking formula milk support was 18 ($p=0.481$). There was no significant statistical difference between the two groups with respect to average serum calcium, phosphorus, alkaline phosphatase and vitamin D levels. But serum parathormone level was significantly high in the patient group with premature closure of anterior fontanelle ($p=0.001$). Comparison of the laboratory findings of the two groups are given in Table 1.

Twenty six of the infants who had premature closure of anterior fontanelle had been ceased of vitamin D support upon doctor's advice. On the other hand, the patients in the control group were using three drops of vitamin D daily. There was a statistically

significant difference between the two groups with respect to the vitamin D usage background ($p < 0.001$). When the patients who had been ceased of vitamin D support were compared with the regular vitamin D takers in the control group, a significant difference was observed considering serum calcium, alkaline phosphatase and parathormone levels ($p = 0.016$ and $p = 0.03$ and $p = 0.0001$ respectively). Even though there was no significant difference considering serum vitamin D levels, the level was lower in the patients who had been ceased of vitamin D support ($p = 0.076$) (Table 2).

While 30 of the mothers who had infants with premature closure of anterior fontanelle reported to have taken vitamin D support during their pregnancy, this number was 15 in the control group ($p = 0.119$). Birth weight and head circumference of the infants in the control group whose mothers had taken vitamin D support were significantly higher than the babies in the control group whose mothers hadn't taken

vitamin D support ($p = 0.04$ and 0.026 respectively). Even though the infants whose mothers had taken vitamin D support during their pregnancy had higher levels of serum vitamin D and calcium levels, there was no significant difference between them ($p = 0.061$ and 0.804 respectively) (Table 3).

Discussion

Nutritional rickets and vitamin D deficiency are common yet preventable problems today in our country as all around the world. World Health Organization publishes regularly updated leaflets emphasizing the significance and necessity of vitamin D support in neonates and adolescents (14,15). Despite that; there is a common treatment of the cease of vitamin D support due to associating the premature closure of anterior fontanelle in neonates with vitamin D excess. This treatment increases the risk of vitamin D deficiency and rickets in neonates and infants.

Table 1. Comparison of the average laboratory values of the two groups

Average	Patients with premature closure of anterior fontanelle	Control group	p*
n	50	35	-
Age (months)	2.75±1.52	3.04±1.51	0.398
Serum calcium level (mg/dL)	9.31±0.87	9.28±0.45	0.519
Serum phosphorus level (mg/dL)	5.10±0.61	4.93±0.69	0.227
Serum alkaline phosphatase Level (u/L)	241±67.7	217±56.9	0.097
Serum vitamin D level (ng/mL)	24.7±11.5	27.7±14.01	0.304
Serum parathormone level (pg/mL)	43.97±18.79	29.85±17.3	0.001

*Mann-Whitney U test was used for serum vitamin D and calcium levels and t-test was used for the other data, $p < 0.05$ was considered to be significant

Table 2. Comparison of the patients who had been ceased of vitamin D support upon doctor's advice with the regular vitamin D takers in the control group

Average	Patients who had been ceased of vitamin D support	Control group taking vitamin D support	p*
n	26	35	-
Age (months)	2.65±1.17	3.04±1.51	0.286
Serum calcium level (mg/dL)	8.97±0.78	9.28±0.45	0.016
Serum phosphorus level (mg/dL)	5.04±0.66	4.83±0.86	0.303
Serum alkaline phosphatase level (u/L)	263±61	217±56.9	0.003
Serum vitamin D level (ng/mL)	21.45±9.89	27.7±14.01	0.076
Serum parathormone level (pg/mL)	51.27±19	29.85±17.3	0.001

*Mann-Whitney U test was used for serum vitamin D and calcium levels and t-test was used for the other data, $p < 0.05$ was considered to be significant

Though in our study, serum vitamin D level was observed to be lower in the group with premature closure of anterior fontanelle, there was no significant difference from the control group. Wang J et al. (13) found in their study that, serum calcium and vitamin D levels of infants did not reflect the size of fontanelles and emphasized that closure of anterior fontanelle was independent from serum vitamin D and calcium levels. Thus; it was not an appropriate approach to cease vitamin D support in infants on the grounds that they had premature closure of anterior fontanelle without looking at their serum vitamin D levels. As can be seen in our study, patients who had premature closure of anterior fontanelle did not have high vitamin D levels, this level could even be lower. When the doctors also cease vitamin D support in countries like Turkey where vitamin D deficiency is widely seen, nutritional rickets incidence rate gets even higher. Apart from these, there was no significant statistical difference between the two groups considering calcium, phosphorus and alkaline phosphatase levels. However; patients with premature closure of anterior fontanelle had significantly higher level of serum parathormone levels compared to the control group ($p=0.001$). When infants with already low vitamin D level at the limits were ceased of vitamin D support, their serum parathormone levels increased. Even though the organism tries to warn us at the early stage by increasing parathormone levels that it is wrong to cease vitamin D support, we usually ignore this warning.

In our study, 26 of the infants with premature closure of anterior fontanelle had been ceased of vitamin D upon doctor's advice. On the other hand; all patients in control group were taking three drops of (400 units) vitamin D daily. There was a statistically significant difference between the two groups considering the vitamin D intake background ($p<0.001$). This difference, which we presumed while planning this study, further increases the nutritional rickets incidence in countries where there is a high rate of vitamin D deficiency. As no similar studies are found in literature, we wanted to emphasize this issue to raise awareness both in patients and in doctors.

While infants with premature closure of anterior fontanelle had 35.8 ± 0.71 cm head circumference at birth, members of the control group were measured to have a head circumference of 36.6 ± 0.90 cm and the difference was considered to be statistically significant ($p<0.001$). The birth head circumference of the infants with premature closure of anterior fontanelle was significantly smaller than that of the control group, and this brought the following question in minds; "Do neonates with small birth head circumference are riskier considering the possibility of premature closure of anterior fontanelle?" We need further studies on this issue.

While serum calcium levels of the patients who were ceased of vitamin D support were significantly lower than the regular vitamin D takers in the control group; their serum alkaline phosphatase and serum parathormone levels were significantly higher than

Table 3. Comparison of the infants whose mothers had taken vitamin D support during their pregnancy with the control group with respect to laboratory and anthropometric measurements

Average	Infants whose mothers had taken vitamin D support during their pregnancy	Control group who had not taken vitamin D support during their pregnancy	p*
n	30	20	-
Age (months)	3.01 ± 1.53	3.00 ± 1.61	0.971
Serum calcium level (mg/dL)	9.34 ± 0.75	9.23 ± 0.50	0.804
Birth weight (gr)	3.35 ± 355.38	3.02 ± 408.89	0.004
Birth head circumference (cm)	36.11 ± 0.71	36.61 ± 0.77	0.026
Serum phosphorus level (mg/dL)	5.64 ± 0.93	4.75 ± 0.85	0.001
Serum alkaline phosphatase level (u/L)	234 ± 71.75	217 ± 52.95	0.370
Serum vitamin D level (ng/mL)	28.58 ± 10.63	22.89 ± 12.66	0.061
Serum parathormone level (pg/mL)	39.47 ± 15.99	31.94 ± 19.37	0.141

*Mann-Whitney U test was used for serum vitamin D and calcium levels and t-test was used for the other data, $p<0.05$ was considered to be significant

those of the control group ($p=0.016$ and $p=0.03$ and $p=0.0001$ respectively). Though there was no significant difference between the two groups considering serum vitamin D levels, the level was lower in patients who had been ceased of vitamin D support ($p=0.076$). When oral 400 units of vitamin D replacement was given regularly, serum level increased above 20 ng/mL. The ones with darker skin, winter babies, veiled mothers' babies had higher daily need (16,17). In literature, no vitamin D intoxication was seen with 400 units vitamin D prophylaxis, even 1427 units/day vitamin D replacement did not cause any intoxication (18). In our study, the group who were younger than 3 months old and had been ceased of vitamin D support developed vitamin D deficiency in such a short time and metabolic changes came up to compensate for this state. This shows how wrong it is to cease vitamin D support due to premature closure of anterior fontanelle or the risk of intoxication.

62% of the infants ($n=32$) in the group with premature closure of anterior fontanelle were feeding on formula milk. Vitamin D level of the infants feeding on formula milk was found to be higher than the vitamin D level of the infants feeding on breast milk only ($p=0.039$). This was directly related to the insufficiency of vitamin D amount in mother's milk (19).

Birth weights and head circumference of the neonates whose mothers had taken vitamin D support during their pregnancy were significantly higher than those of the neonates whose mothers had not taken vitamin D support during their pregnancy. Though serum D vitamin and calcium levels of the infants whose mothers had taken vitamin D support during their pregnancy were higher than the control group, there was no significant difference between them. In their study, Kalra et al. (20) compared the infants whose mothers had received 1.500 units of vitamin D in second trimester and 3.000 units of vitamin D in second and third trimesters with the infants whose mothers had taken no vitamin D support during their pregnancy. Anterior fontanelle sizes of the infants whose mothers had received vitamin D support were found to have smaller size of anterior fontanelle. But, no infants with premature closure of anterior fontanelle were reported. In our study, 30 of the mothers of the infants with premature closure of anterior fontanelle had received vitamin D support

during their pregnancy and in parallel to the studies of Kalra et al. (20), they had higher birth weight and larger head circumference. As Kalra et al. (20) found that these infants had smaller anterior fontanelles, and we found in our study that 30 of the mothers of the infants with premature closure of anterior fontanelle had received vitamin D support during their pregnancy, the following question comes to minds; "Do vitamin intake during pregnancy cause premature closure of anterior fontanelle?" Though we need more patient covering studies on the issue, as in our study the average serum vitamin D level of the infants whose mothers were in this group was below 30 ng/mL, and Wang J et al. (13) showed that there was no relation between vitamin D replacements and anterior fontanelle size; we move away from this hypothesis.

Another frequently faced problem in our country which we did not dealt with in this study is that, patients whose families think that their children have growth retardation, bone weakness, teething retardation have these children take overdose vitamin D support upon a doctor's or another health officer's advise. These patients have normal level of vitamin D and they don't need high dose prophylaxis.

Results

As a result we may face vitamin D intoxication or nephrocalcinosis and these may reach up to health threatening levels. Here we wanted to emphasize that, states like growth retardation, teething retardation or bone weakness did not indicate that high dose of vitamin D support was required without the need of measuring vitamin D levels first. Again further controlled studies covering more patient groups are needed.

Conclusion

Vitamin D support shall be received in an appropriate dose and for an appropriate period in order to prevent a significant health problem which is vitamin D deficiency and rickets. As also shown in our study, there are many infants who have normal even lower than normal vitamin D levels even though their anterior fontanelle gets closed prematurely. Thus; both the doctors and other health personnel shall be warned about the continuity of vitamin D

prophylaxis and that it is wrong to cease vitamin D support for reasons such as premature closure of anterior fontanelle.

Ethics

Ethics Committee Approval: The study was approved by Non-invasive Clinical Research Ethics Committee of Aydın Adnan Menderes University Faculty of Medicine (protocol no: 2020-227).

Informed Consent: Before the study, retrospective procedures were explained and all subjects gave consent for study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: T.Ü., T.U.Ş., E.A., Design: T.Ü., T.U.Ş., E.A., Supervision: T.Ü., T.U.Ş., E.A., Fundings: T.Ü., Materials: T.U.Ş., Data Collection or Processing: T.Ü., Analysis or Interpretation: T.Ü., T.U.Ş., E.A., Literature Search: T.Ü., Writing: T.Ü., T.U.Ş., Critical Review: T.Ü., T.U.Ş., E.A.

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