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Evaluation of the relationship between vitamin D levels and emerge delirium in children who had tonsillectomy and/or adenoidectomy

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Abstract

Background: Pediatric emergence delirium is a general complication of anesthesia with an incidence of 2-80%. Although its etiology is not clearly known, it has been shown that anesthesia method, surgical procedure, and child and parent anxiety may cause the emergence delirium. The relationship between vitamin D levels and emerge delirium in children who underwent tonsillectomy and/or adenoidectomy has not been investigated before

Aim: In this context, this study was carried out to evaluate the relationship between vitamin D levels and emerge delirium in children who underwent tonsillectomy and/or adenoidectomy.

Material and methods: The study population consisted of children between the ages of 2 and 10, ASA I-II and were scheduled to have elective adenoidectomy and/or tonsillectomy under general anesthesia. All children (n=97) were evaluated for anxiety with the modified Yale Preoperative Anxiety Scale (m-YPAS) before surgery. Children with serum 25(OH)D levels<12 ng/ml and ≥12 ng/ml were categorized as group 1 (n=50) and group 2 (n=47). All children were evaluated for delirium with the Pediatric Anesthesia Emergence Delirium (PAED) scale. The face, legs, activity, cry, consolability (FLACC) scale was used in the evaluation of postoperative pain in children who could not express themselves verbally.

Results: The mean serum 1.25(OH)2D3 level was higher, albeit insignificantly, in group 1 than in group 2. There was no significant difference between the two groups in terms of emerge delirium, preoperative anxiety, postoperative pain and analgesia.

Conclusion: Vitamin D deficiency does not affect the incidence of emergence delirium in children. Vitamin D level does not relate to preoperative anxiety and postoperative pain.

Key words: child, delirium, adenoidectomy, vitamin D

Introduction

Pediatric emergence delirium is a general anesthesia complication with an incidence of 2-80%, in which behaviors such as shouting, crying, inability to make eye contact with parents, and agitation are observed during the recovery period [1]. Although its etiology is not clearly known, it has been shown that anesthesia method, surgical procedure, and child and parent anxiety may cause the emergence delirium [2]. In delirium, which usually occurs within the first 30 minutes of recovery, the patient may remove their catheter and injure him/herself and the site of surgery [2]. Hence, delirium causes an increase in the need for sedative and analgesic drugs, prolongation of the discharge time, and parental dissatisfaction [1].

Vitamin D deficiency is an important health problem in developed and developing countries. There are different threshold values used to define vitamin D deficiency in children [3]. High vitamin D levels are considered to protect cognitive functions, thereby preventing delirium [3]. Active vitamin D ($1.25(OH)_2D_3$) regulates intracellular calcium (Ca) balance and expresses neurotrophic factors necessary for nerve cell function. It is known that acetylcholine deficiency causes delirium, and the enzyme which synthesizes acetylcholine is regulated by vitamin D [3]. In order to determine the vitamin D level in the body, both 25(OH)D and $1,25(OH)_2D_3$ can be measured from the serum. Serum 25(OH)D has a longer half-life and its level is 1000 times higher than serum $1,25(OH)_2D_3$. Therefore, 25(OH)D measurement gives more accurate results in determining the vitamin D level. There are studies showing that vitamin D deficiency is associated with the development of emerge delirium in adult patients [4-6], however, a thorough review of the literature did not reveal any study that addressed emergence delirium in the pediatric patient population. In this context, this study was carried out to evaluate the relationship between vitamin D levels and emerge delirium in children who underwent tonsillectomy and/or adenoidectomy.

Material and methods

Study design and setting

This prospective, double-blind study was carried out between February 2019 and February 2020 (NCT05076162). The study protocol was approved by the ethics committee of Aydın Adnan Menderes University **(Approval No: 2019/11).** The study population consisted of children between the ages of 2 and 10, whose health statuses were classified as I or II according to American Society of Anesthesiologists (ASA) classification and were scheduled to have elective adenoidectomy and/or tonsillectomy under general anesthesia. Informed, verbal, and written consent was obtained from the legal guardians of all patients.

Children with previous anesthesia and/or surgery history, kidney-heart and liver failure, whose health statuses were classified as ASA III or IV, who had a neuromuscular disease, craniofacial anomaly, and rickets, and who have been using vitamin D and antipsychotic drugs were not included in the study.

ASA (American Society of Anesthesiologists) CLASSIFICATION

ASA 1. A healthy person with no disease or systemic problem other than normal, surgical pathology that does not cause a systemic disorder.

ASA 2. Person with a mild systemic disorder due to a cause requiring surgery or another disease.

ASA 3. Person with a disease that limits his or her activity but is not debilitating.

ASA 4. A person who has a disease that causes him to lose his strength completely and poses a permanent threat to his life.

ASA 5. A dying person who is not expected to live more than 24 hours, with or without surgery, and for whom surgery is the last hope.

ASA 6. It includes patients with advanced brain death.

Study procedures

The demographic data (age, weight, height, and comorbidities) of all cases were recorded within the scope of the preoperative evaluation. Children were not premedicated. All children were evaluated for anxiety with the modified Yale Preoperative Anxiety Scale (m-YPAS) before surgery [7,8]. The m-YPAS consists of five subscales: activity, vocalizations, emotional expressivity, state of apparent arousal, and use of parents. The scale consists of a total of 22 items. Six of these items are in the vocalizations subscale, whereas all other four subscales include four items each. The total scale score is calculated using the following formula: [(activity subscale score/4)+(emotional expressivity subscale score/4)+(state of apparent arousal subscale score/4)+(use of parents subscale score/4)+(vocalizations subscale score/6) x 100/total number of categories] [8].

Standard monitoring procedures, including the monitoring of heart rate, oxygen saturation, and non-invasive blood pressure, were implemented for all patients who were taken to the operating room for the surgical procedure. In all patients, anesthesia induction was achieved with 6 L/min flow and 100% oxygen and 8% sevoflurane concentration using appropriate face masks. When the adequate depth of anesthesia was achieved, peripheral venous cannulation was performed.

Blood samples were taken to measure serum 25(OH)D, $1.25(OH)_2D_3$, and calcium levels. Serum 25(OH)D levels were measured with the human enzyme-linked immunosorbent assay (ELISA) kit (catalog no: E1546Hu, #1008 Junjiang Inter. Bldg 228 Ningguo Rd, Yangpu Dist Shanghai 200090, China). The study groups were determined according to serum 25(OH)D levels. Accordingly, children with serum 25(OH)D levels<12 ng/ml and ≥12 ng/ml were categorized as group 1 and group 2, respectively [9].

Following the anesthesia, 1 mg/kg lidocaine, 1 µg/kg fentanyl, and 0.6 mg/kg rocuronium were administered intravenously. After 60-90 seconds had elapsed, endotracheal intubation was performed. Anesthesia was maintained with 3 L/min flow and 50% N_2O-O_2 and 2-3% sevoflurane concentration. In order to provide postoperative analgesia, 10 mg/kg of paracetamol was administered to all children intravenously. Details of the surgical procedure were recorded in the anesthesia follow-up form. At the end of the operation, 3 mg/kg sugammadex was administered intravenously for neuromuscular agent antagonism. After observing that spontaneous breathing was sufficient and protective reflexes returned, extubation was performed. Patients with spontaneous eye-opening and extremity movement were taken to the recovery room.

All children included in the study were evaluated for delirium with the Pediatric Anesthesia Emergence Delirium (PAED) scale at 10-min intervals from the time they were taken to the recovery room. PAED scale consists of five criteria. Accordingly, it assesses the child's eye contact with his/her caregiver, whether his/her actions are purposeful, whether he/she is aware of his/her surroundings, whether he/she is restless, and whether he/she is inconsolable. There are five choices to choose from in each criterion: “not at all”, “just a little”, “quite a bit”, “very much”, and “extremely”, which are awarded between 4 and 0 points in the descending order in the case of first three criteria and the ascending order in the case of the last two criteria. A PAED score of 10 or more is considered to indicate pediatric emergence delirium [10].

The face, legs, activity, cry, consolability (FLACC) scale was used in the evaluation of postoperative pain in children who could not express themselves verbally [11]. FLACC scale consists of five categories of face, legs, activity, cry, and consolability, each of which is assigned a score between 0-2 points. Hence, the overall FLACC scale score ranges between 0-10 points. Each category is assessed in 10-minute periods, totaling 50 minutes for the overall scale [12]. Patients who obtained a total score of ≥ 4 from the postoperative FLACC scale were considered to have postoperative pain and thus administered 0.5 mg/kg meperidine intravenously for analgesia.

All patients included in the study were followed up intraoperatively and postoperatively in terms of possible complications such as nausea-vomiting, laryngospasm, bronchospasm, and bleeding. The anesthetist, who performed the intraoperative follow-up of all the patients and made the postoperative PAED and FLACC evaluations, was blinded to the patients' groups.

Statistical analysis

The Kolmogorov-Smirnov test was used to determine whether the quantitative variables conform to the normal distribution. In the comparisons of two independent groups, the two-sample independent t-test was used in the case of normally distributed variables, and the Mann-Whitney U test was used in the case of non-normally distributed variables. Descriptive statistics pertaining to quantitative variables were expressed as mean±standard deviation (SD) values in the case of normally distributed variables and as median (25th-75th percentiles) in the case of non-normally distributed variables. Spearman correlation analysis was used to determine whether there was a linear relationship between quantitative variables. Pearson's chi-squared test was used to test the assumption of independence between categorical variables. Descriptive statistics pertaining to categorical variables were expressed as frequency (n) and percentage (%). Probability (p) values of <0.05 were deemed to indicate statistical significance.

Results

A total of 97 children aged 2-10 years (mean age: 5.6±2.1 years), of whom 61 (62.9%) were boys, were included in the study. Cases (n=50) with serum 25(OH)D levels<12 ng/ml were included in group 1, and cases (n=47) with serum 25(OH) D levels≥12 ng/ml were included in group 2. Thus, the rate of vitamin D deficiency [25(OH)D<12 ng/ml] was determined to be 51.5% (50/97). The distribution of the demographic, clinical, and laboratory characteristics by the patient groups is shown in Table 1. There was no significant difference between the groups in terms of demographic characteristics, surgical procedures, duration of surgery, comorbidities, serum calcium levels, and m-YPAS scale scores (p>0.05).

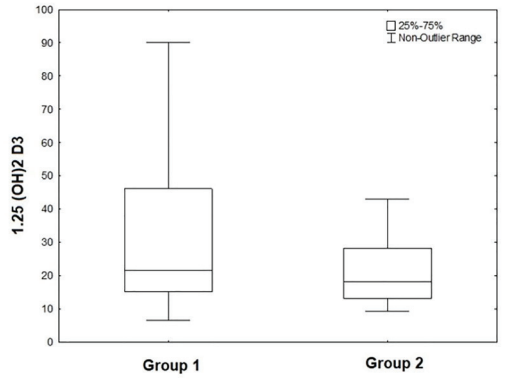

Figure 1 - Comparison of the patient groups by 1.25(OH)2D3 levels

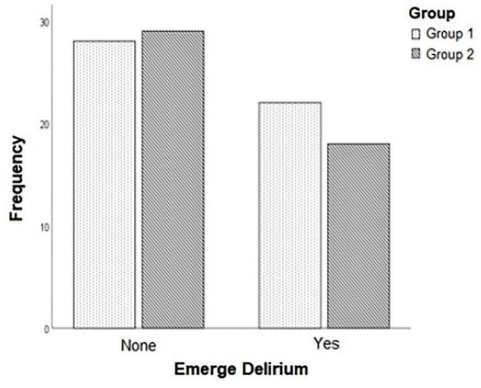

Figure 2 - Comparison of the patient groups by the presence of emergence delirium

The mean serum $1.25(OH)_2D3$ level was higher, albeit insignificantly, in group 1 than in group 2[34.4 (min.15.1, max. 46.6) pg/mL vs. 25.9 (min.13.1, max.28.2) pg/mL, p= 0.177] (Figure 1). The blood samples for serum vitamin D level measurements were taken in winter in 66% (64/97) of the children; however, no significant difference was found between the groups in terms of the season of taking the blood sample (p=0.337).

Table 1 Distribution of the demographic, clinical, and laboratory characteristics by the patient groups

	Group 1 (n=50) 25(OH)D <12 ng/ml	Group 2 (n=47) 25(OH)D ≥12 ng/ml	p
Gender (M/F)(n)	33/17	28/19	0.657
Age (year)	6 (4.7-8)	5.2 (4-7)	0.094
Body mass (kg)	22.7 (18-24.2)	19.8 (16-23)	0.151
Height (cm)	116.8±14.5	111.2±13.1	0.05
Comorbidty (Yes/No)	10/40	8/39	0.908
Comorbid Diseases			
Asthma n (%)	5(10)	4(8.6)	
Drug Allergy n (%)	2(4)	1(2.1)	
Allergic Rhinitis n (%)	1(2)	1(2.1)	
Epilepsy n (%)	1(2)	1(2.1)	
Hydronephrosis n (%)	1(2)	0(0)	
Chronic Bronchitis	0 (0)	1(2.1)	
Operation time (min)	38.3 (29.2-45)	39.7(30-47)	0.677
Surgical procedures			
Adenoidectomy n (%)	33(66)	32(68)	0.792
Tonsillectomy n (%)	4(8)	2(4.2)	
Adenotonsillectomy n (%)	13(26)	13(27.6)	
Serum Calcium (mg/dl)	9.5(9.3-9.8)	9.5 (9.2-9.8)	0.873
m-YPAS score	40.4 (28.3-51.6)	39 (28.3-46.6)	0.780

Data are given as median (25th-75th percentiles), mean±SD, or n (%) values.

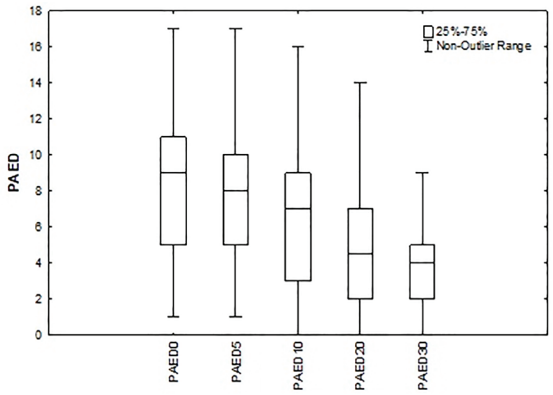

Figure 3a - PAED (0-30 min) score graph of group 1

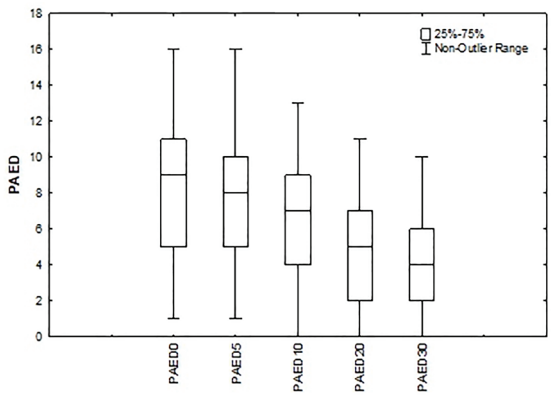

Figure 3b - PAED (0-30 min) score graph of group 2

Delirium was identified in 41.2% (40/97) of the children included in the study. 55% of the 40 children with emergency delirium were in group 1; however, there was no significant difference between the groups in terms of the number of children with emergence delirium (p=0.716) (Figure 2). There was also no significant difference between the groups in the 0-30 min PAED scores (p>0.05) (Figure 3a-3b).

Postoperative pain was detected in 37.1% (36/97) of children. There was no significant difference between the two groups in terms of postoperative pain and analgesia (p=0.692) (Table 2). At least one complication (postoperative nausea, vomiting, bleeding and broncholaryngospasm) developed in 38.1% of the children included in the study. Although there were more children with complications in group 1 (46%) than in group 2 (29.7%), the difference between the groups was not statistically significant (p >0.05).

Table 2 Comparison of the patient groups by postoperative pain

Postoperative pain	Groups		p
	Group 1 25(OH)D<12 ng/ml (n=50)	Group 2 25(OH)D≥12 ng/ml (n=47)	
Yes (n) (%)	20(40)	16(34)	0.692
No (n) (%)	30(60)	31(66)	

In group 1, there was no correlation between 25(OH)D and 1.25(OH)2D3 levels and emergence delirium and postoperative pain (p>0.05); however, there was a negative correlation between 1.25(OH)2D3 levels and m-YPAS scores (-r=0.297 p=0.034).

In group 2, there was no correlation between 25(OH)D and 1.25(OH)2D3 levels and emergence delirium, postoperative pain, m-YPAS scores, and serum calcium levels (p>0.05); however, there was a negative correlation between 25(OH)D levels and age (r=-0.378, p=0.01), height (r=-0.378, p=0.008), and weight (r=-0.348, p=0.018).

Discussion

The relationship between vitamin D levels and emergence delirium in children who underwent tonsillectomy and/or adenoidectomy was assessed in this study. Consequentially, no significant difference was found between patients with 25(OH)D deficiency and those without in terms of the presence of delirium. There are many studies on the relationship between vitamin D levels and emerge delirium in the adult patient population in the literature, most of which reported an increase in the incidence of delirium with low vitamin D levels [13,14]. However, a thorough review of the literature did not reveal any study that addressed the relationship between vitamin D deficiency and emergence delirium in the pediatric patient population.

The prevalence of vitamin D deficiency in children and adults is reported to be 30-80% worldwide. In a meta-analysis conducted in Turkey, the prevalence of vitamin D deficiency was found to be 63% [15]. Similarly, the rate of children with vitamin D deficiency [25(OH)D<12 ng/ml] was found to be 51.5% in this study.

Serum vitamin D levels vary with age. The highest and lowest vitamin D levels have been detected in the age groups of 1 to 6 years and 7 to 17 years, respectively [16]. In parallel, a negative correlation was found in this study between serum 25(OH)D levels and age.

There are contradicting results in the literature on the relationship between serum vitamin D levels and gender. In comparison, no significant difference was found between the patients with and without vitamin D deficiency in terms of gender in this study featuring the preadolescent age group.

Serum 25(OH)D levels are deemed a measure of vitamin D levels in the body. As a reason, 25(OH)D has a long plasma half-life and is found in plasma at a concentration 1000 times higher than $1.25(OH)_2D_3$ [17]. In comparison, the mean serum $1.25(OH)_2D_3$ level was found to be higher, albeit insignificantly, in group 1 than in group 2 in this study (34.4 pg/mL vs. 25.9 pg/mL, p= 0.177). Serum $1.25(OH)_2D_3$ levels are affected by serum calcium and phosphorus levels and dietary calcium intake [18]. In this context, the respective finding of this study may be attributed to the parathyroid hormone levels as a factor that might have affected the $1.25(OH)_2D_3$ levels, which, however, were not measured in this study.

High vitamin D levels are considered to protect cognitive functions, thereby preventing delirium [3]. There are many studies that addressed the vitamin D levels and the development of emerge delirium in the adult population in the literature [13,14]; however, to the best of knowledge of this study's authors, there are no comparable studies conducted with the pediatric population. Emerge delirium was identified in 41.2% of the children included in this study. In most of the studies conducted with the adult population available in the literature, a significant relationship was reported between low 25(OH)D levels and the development of delirium. In contrast, no significant relationship was found between low 25(OH)D levels and the development of delirium in this study which was conducted with a pediatric population with a mean age of 5.6 years. This discrepancy between the respective results of this study and the relevant studies in the literature may be attributed to the fact that the population of this study consisted of children aged between 2-10 years, whose brain maturation has not been completed, and that the serum $1,25(OH)_2D_3$ levels were found to be high in both patient groups studied within the scope of this study.

Although the related pathophysiology is not fully known, low vitamin D levels are thought to be associated with anxiety

[19]. As a matter of fact, many studies in the literature have reported a negative correlation between low 25(OH)D levels and anxiety [19,20]. In comparison, no significant difference was found in this study between the patients with low and normal 25(OH)D levels whose preoperative anxiety was assessed with the m-YPAS scale. This discrepancy between the respective results of this study and the relevant studies in the literature may also be attributed to the fact that the serum $1,25(OH)_2D_3$ levels were found to be high in both patient groups studied within the scope of this study.

On the other hand, negative correlations were found between m-YPAS scores and age consistent with the literature. These findings may be attributed to the greater attachment to parents, separation anxiety, and difficulty adapting to the environment experienced by the children in this age group.

Vitamin D is known to have an anti-inflammatory effect by suppressing the expression of the COX-2 enzyme, which is involved in the synthesis of prostaglandins and increasing the expression of enzymes that inactivate prostaglandins [21]. Additionally, it is known that vitamin D exerts an immunomodulatory effect by regulating the cytokines involved in pain perception and the spread of pain [22]. There are only a few studies in the literature that evaluated the relationship between postoperative pain and vitamin D levels. In comparison, no significant relationship was found in this study between the 25(OH)D levels and postoperative pain and postoperative analgesic requirement, which may be due to the fact that lesser postoperative pain is experienced in adenoidectomy and/or tonsillectomy compared to major surgeries, and that the intraoperative local anesthesia administered by the surgeon might have masked any difference that could have otherwise arisen between the groups in terms of pain.

It has been reported that the frequency of emergence delirium decreases with age in pediatric patients [23]. In parallel, in a study, it was reported that the PAED scores were highest in children aged <6 years and lowest in children aged ten years, indicating that age was a risk factor for the development of emergence delirium [24]. Similarly, a negative correlation was found in this study between the children's PAED (0-30 min) scores and their age. This result may be explained by the fact that children have less tolerance to hunger and pain and may also be attributed to the difficulties they experience in adapting to the environment and establishing communication.

Preoperative anxiety in children is thought to be associated with the development of emergence delirium [25]. In a study that included children who underwent adenoidectomy and tonsillectomy and were not premedicated, it was reported that children in the group with high anxiety levels showed more agitation symptoms in the postoperative period [25]. Similarly, a positive correlation was found in this study, which featured unpremedicated children, between preoperative anxiety measured by m-YPAS and PAED scores. This finding, taken together with the relevant findings reported in the literature, indicates that preoperative anxiety is a risk factor for the development of emergence delirium.

Inadequate treatment of pain in pediatric patients leads to the activation of the physiological and biochemical stress response, causing deterioration in many functions in the body [20]. Along these lines, it was reported in many studies conducted in a number of different surgical fields that high FLACC scores were associated with high PAED scores [26,27]. Similarly, a positive correlation was found in this study between the FLACC and PAED scores. Therefore, postoperative pain, as preoperative anxiety, also seems to be a risk factor for the development of emergence delirium.

Limitations of the Study

The prospective design of this study and the fact that it is the first study to assess the relationship between vitamin D deficiency and emergence delirium in the pediatric patient population constituted its strengths. However, there were also some limitations to this study. First, the study sample was relatively small. Secondly, serum parathormone levels could not be measured. Third, the daily calcium intake, nutritional status, clothing style, and socioeconomic status of the families of the children included in the study were not questioned. Finally, parental anxiety, which is thought to be a risk factor for emergence delirium, was not evaluated.

Conclusion

Children with vitamin D deficiency are frequently encountered in anesthesia applications. This study is the first study to evaluate the relationship between 25(OH)D levels and emerge delirium in children. Accordingly, the incidence of emergence delirium in children with 25(OH) vitamin D deficiency was not found to be high. In addition, there was no significant relationship between 25(OH)D levels and preoperative anxiety and postoperative pain. Although postoperative complications (nausea-vomiting, bleeding and broncholaryngospasm) were seen at a higher rate in the group with vitamin D deficiency, they were not significant. This study's findings suggest that using the preoperative m-YPAS scale scores would be beneficial in predicting emerge delirium and that the development of delirium can be reduced by good management of postoperative pain in pediatric patients. Further prospective, large-scale, multicenter studies are needed to be carried out in the pediatric population to corroborate the results of this study.

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