JoCASS
Çukurova Anestezi ve Cerrahi Bilimler Dergisi
2018 Adana

EFFECT OF PROPHYLACTIC VITAMIN D SUPPLEMENTATION ON POSTOPERATIVE PAIN AND SEDATION IN CHILDREN WITH MENTAL MOTOR RETARDED WHO UNDERGOING DENTAL TREATMENT

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Abstract

Aim: The frequency of vitamin D deficiency is higher in children with mental motor retardation (MMR). We aimed to investigate the effect of vitamin D supplementation on postoperative pain in children with MMR who underwent dental treatment under general anesthesia.

Methods: Dental treatment was planned for a total of 62 patients with MMR, aged 7-17 years. Participants were divided into two groups. Children were prescribed vitamin D (600 IU of vitamin D per day) or Saline. Serum vitamin D levels were measured. Participants continued to intake oral vitamin D 600 IU (Group D) or 2ml saline (Group C) throughout 12 weeks. All participants were observed postoperative 1st hour, and Non-communicating Children's Pain Checklist–Postoperative Version (NCCPC-PV), Ramsay sedation scores, length of stay in post-anesthesia care unit, and analgesic requirements were recorded.

Results: The study was completed with fifty children (35 in Group D, 15 in Group C). Serum vitamin D levels were higher in Group D than Group C at 12 weeks($p=0.007$). Vitamin D deficiency was found at 13 patients (37.1%) and 6 (40%), and vitamin D sufficiency was found 18 (51.4%) and 7 (46.7%) in Groups D and C, respectively at first admission. There was statistically significant difference between groups in NCCPC-PV score at 15^{th}, 30^{th} and 60^{th} minutes in PACU($p<0.05$). However, Ramsey scores were similar between two groups at all times.

Conclusions: Serum vitamin D levels were found to be low in MMR children. It was observed that vitamin D supplementation could reduce pain scores in 1st postoperative hour.

Keywords: *Postoperative analgesia, vitamin D, mental motor retardation*

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Received: 08.12.2022, Accepted: 27.02.2023, Available Online Date: 15.03.2023

Cite this article as: Biricik E, Alpay N, Karacaer F, et al. Effect of Prophylactic Vitamin D Supplementation on Postoperative Pain and Sedation in Children with Mental Motor Retarded Who Undergoing Dental Treatment Introduction. J Cukurova Anesth Surg. 2023;6(1):67-74.

doi: 10.36516/jocass.1216326

Introduction

Mental-motor retardation (MMR) is a very important issue for public health. The studies have estimated that the frequency of mental retardation varies between 1% and 3% in developed countries. However, these percentages are highest among children of low socioeconomic status[1]. Despite there being no current statistical data about the frequency of the MMR children population in Turkey, these children need special attention and protection due to their disabilities. Caregivers should do their personal care such as teeth brushing, bathing, and feeding. The majority of this group needs general anesthesia for dental treatment. However, because of surgical complications such as respiratory failure, aspiration, and delayed recovery, postoperative pain management and sedation might be riskier in children with disabilities than in healthy children. As a result, postoperative care and pain management are becoming increasingly crucial in this group.

Vitamin D is essential for the growth of bone and musculoskeletal development in childhood. It helps the absorption of nutritive calcium and phosphate[2]. In the absence of vitamin D, 10-15% of calcium and 60% of phosphorus can be absorbed[3]. Vitamin D precursor 7 dehydrocholesterol should be activated to the form previtamin D3 by ultraviolet B (UVB) in the epidermis. Previtamin D3 is transported to the liver by vitamin D binding protein, where it is hydroxylated to 25-dihydroxy vitamin D. This form is also transported to the kidney with the blood and hydroxylated by 1αhydroxylase to the active form of 1,25(OH)2 D.

There are so many factors that contribute to vitamin D deficiency in children with MMR such as immobility, poor sunlight exposure, inadequate feeding, and medication of antiepileptic drugs[4].

One of the most common factors which contribute to vitamin D deficiency is inadequate exposure to sunlight in children with CP[5]. As it is predictable, exposure to the sunlight is less in children with CP than in healthy children[6]. Most of these children are usually housebound. Therefore, they are more prone to vitamin D deficiency than a healthy child. Another risk factor of vitamin D deficiency is insufficient feeding in MMR children. Vitamin D has anti-inflammatory and immunemodulatory effects; thus it has a possible effect on pain. The relationship between vitamin D deficiency and chronic pain has been shown in several studies[7-10]. However, effect of vitamin D deficiency on acute pain is presented in only a few studies[11-13]. Vitamin D supplementation can reduce postoperative pain[11].

In this study, we aimed to investigate the effect of vitamin D supplementation on postoperative pain and sedation status in MMR children who undergoing dental treatment. The primary outcome of this study is postoperative pain score and secondary outcomes are sedation scores and stay in post-anesthesia care unit (PACU) time.

Materials and Methods

Study Design

Between July 2016 and December 2020, a randomized, prospective, single-blind, controlled study was conducted. The research protocol was submitted to Clinicaltrials.gov (identifier: NCT02664857) in July 2016 and approved by institution's Ethical Committee on December 17, 2015 (decision number: 47/6). After obtaining written informed consent (from parents), 62 patients with American Society of Anesthesiologists (ASA) physical status II to III, ages 7 to 17 years, and mental motor retardation were scheduled for dental treatment under general anesthesia and were included in this study.

The research will involve patients who are scheduled to have a dental checkup, fluoride treatment, cleaning, polishing, tooth extraction, filling application, amputation, and root canal treatment under general anesthesia. Patients with ASA IV and above, sepsis, hepatic

failure, renal failure, and severe bleeding illness were excluded.

Study Protocol

All participants will be evaluated for demographic information, ASA score, and feeding technique (such as oral, nasogastric, percutaneous gastric feeding). A dental specialist will prescribe oral vitamin D drops or saline to participants at their first admission to the dental clinic. Vitamin D supplementation prescription will include 600 IU vitamin D per day. The participants will continue to intake vitamin D 600 IU or 2 ml saline per day for 12th weeks, orally. Vitamin D supplementation dose based on the Vitamin D Supplementation Guidelines[14]. The planning will be made according to the dental surgical operation to take place at the end of 12th weeks to the oral Vitamin D intake.

Monitoring and Measurements

All the patients will be monitored by noninvasive arterial blood pressure, electrocardiogram (ECG), heart rate (HR) and peripheral oxygen saturation (SpO2). Hemodynamic variables Systolic blood pressure (SBP), mean blood pressure (MBP), diastolic blood pressure (DBP) and heart rate will be followed up with 5-min intervals during anesthesia. The duration of anesthesia time was recorded for all patients. Non-communicating Children's Pain Checklist – Postoperative Version (NCCPC-PV)[15], Ramsay sedation scores[16] time of stay in a post-anesthesia care unit (PACU), additional analgesic requirement and complications will record during the postoperative period. The time of achieving to the 9 points of Aldrete score is assumed as recovery time. But all of the patients were observed till the postoperative 1 hour[17]. Recording to the rescue analgesic requirement, NCCPC-PV and Ramsey sedation score continued during the postoperative first hour. The data will record the 15th -30th min and first hour, postoperatively.

Hemoglobin, hematocrit, liver enzymes and blood urea nitrogen (BUN), creatinine, and serum vitamin D levels will measure at the first dental interview and surgery day. When the blood samples were collected, they would store at 4°C before centrifugation. The samples would have been centrifuged for the removal of serum and stored samples at -20°C or -80°C.

The measured serum 25(OH)D levels were considered deficient if 25(OH)D was ≤12 ng/ml. If 25(OH) D was in the range of 12–20 ng/ml, it was assumed as insufficient. The serum 25(OH)D level in the range of 20≤30 ng/ml is defined as sufficient[18].

Serum 25(OH)D levels were measured with liquid chromatography-tandem mass spectrometry (LC-MS) (25 OH Vitamin D3 UBB No: 4260154633417, IMMUCROM GmbH).

Anesthesia Management

Anesthesia was induced with propofol 2mg/kg and rocuronium 0.6 mg/kg combination if vascular access was obtained. If there is no vascular access, anesthesia induction is performed with sevoflurane insufflation. General anesthesia will maintain with sevoflurane %1-2 with an N2O/O2 mixture of %60/40 in all patients. Local anesthetic drugs will not apply to the surgical area by the dental specialist during the operation. Postoperative analgesia will provide with paracetamol 10 mg/kg intravenously at the last 30 minutes of the surgery. At the postoperative first hour, if NCCPC-PV scores more than 10 it indicates a child has moderate to severe pain and tramadol 2 mg/kg will administer as a rescue analgesic, intravenously.

Randomization and Blinding

Patients were randomly allocated into one of two groups Group D and group C, in a 1: 1 ratio by a computer-generated randomization table. On the surgery day, general anesthesia was performed by an anesthesia specialist who was blinded to the study groups. The same anesthesia specialist observed the patient at the PACU.

Blood Sample Collection

Blood samples were collected two times from all participants. The first collection time was at the dental clinic, the second was under general anesthesia during surgery. When the patients were admitted to the dental clinic department, the dental specialist collected the blood samples for assessing hemoglobin, hematocrit, and vitamin D levels, and the same dental specialist prescript to vitamin D or saline to the participants. On the surgery day, after induction of general anesthesia blood samples were collected from participants for hemoglobin, hematocrit, and vitamin D level assessments.

Statistical Analysis

Categorical variables were expressed as numbers and percentages, whereas continuous variables were summarized as mean and standard deviation and as median and IQR: Inter Quartile Range where appropriate. To compare categorical variables between the groups, Pearson Chi-Square Test or Fishers Exact Test was used depending on whether the expected value problem arises or not.

The normality of distribution for continuous variables was confirmed with the Shapiro-Wilk test. For the comparison of continuous variables between two groups, the Student t-test or Mann-Whitney U test was used depending on whether the statistical hypotheses were fulfilled or not. All analyses were performed using IBM SPSS Statistics Version 20.0 statistical software package. The statistical level of significance for all tests was considered to be 0.05.

Results

Sixty-two children were enrolled in the study, but the study was completed with fifty children. Twelve children were excluded during the following. There was no statistically significant difference between the duration of anesthesia and patient demographics such as age, weight, and gender. The patient characteristics were presented in Table 1. We observed that all participants were fed in an oral way none of them used percutaneous gastrostomy tubes in their daily routine.

Table 1. The Patients Demographics

	Group D (n:35)	Group C (n:15)	p
Age (years)	11.37±3.2	11.33±2.4	0.967
Weight (kg)	31.7±16.2	28.3±7.9	0.330
Gender N (%)			
· Male	21 (60)	7 (46.7)	0.384
· Female	14 (40)	8 (53.3)	
Clinical Diagnosis n (%)			
· Cerebral Palsy	8 (22.9)	7 (46.7)	
· Scoliosis	2 (5.7)	2 (13.3)	
· Epilepsy	8 (22.9)	3 (20)	
· Congenital Cardiac Syndrome	2 (5.7)	1 (6.7)	0.462
· Autism	4 (11.4)	0 (0)	
· Down Syndrome	9 (25.7)	2 (13.3)	
· COPD	2 (5.7)	0 (0)	
Duration of anesthesia (min)	53.3 ±24.4	57.3±9.6	0.339
Stay in PACU time (min)	15.3±5	12.3±4.2	0.041
Resque analgesic need n (%)	2 (5.7)	4 (26.7)	0.058

Data presented as mean ±standard deviation, number, and percentages.

Table 2. Postoperative NCCPC and Ramsey Sedation Scores

	Group D (n:35)	Group C (n:15)	p
NCCPC-PV			
· 15. Min	6,71±2.2	8.87±1.8	0.002
· 30. Min	5.94±1.5	7.33±1.3	0.003
· 60. Min	5.74±1.3	7.07±1.2	0.002
NCCPC 15. Min n (%)			
· <10	32 (91.4)	10 (66.7)	0.043
· ≥10	3 (8.6)	5 (33.3)	
NCCPC 30. Min n (%)			
· <10	33 (94.3)	15 (100)	1.0
· ≥10	2 (5.7)	0 (0)	
NCCPC 60. Min n (%)			
· <10	34 (97.1)	15 (100)	1.0
· ≥10	1 (2.9)	0 (0)	
Ramsey Score 15. Min n (%)			
· 1	4 (11.4)	5 (33.3)	0.306
· 2	16 (45.7)	4 (26.7)	
· 3	12 (34.3)	5 (33.3)	
· 4	3 (8.6)	1 (6.7)	
Ramsey Score 30. Min n (%)			
· 1	5 (14.3)	3 (20)	0.914
· 2	20 (57.1)	8 (53.3)	
· 3	10 (28.6)	4 (26.7)	
· 4	0 (0)	0 (0)	
Ramsey Score 60. Min n (%)			
· 1	4 (11.4)	0 (0)	0.514
· 2	27 (77.1)	14 (93.3)	
· 3	4 (11.4)	1 (6.7)	
· 4	0 (0)	0 (0)	

Data presented as mean ±standard deviation, number, and percentages.

Table 3. Serum Vitamin D Levels

Serum Vitamin D level	Group D (n:35)	Group C (n:15)	p
at first admission mean±SD	13.47±5.2	13.31±4.4	0.917
at 12th weeks	20.4±6.4	15.1±4.9	0.007
at first admission n (%)			
· ≤12	13 (37.1)	6 (40)	1.0
· 12-20	18 (51.4)	7 (46.7)	
· >20	4 (11.4)	2 (13.3)	
at 12th weeks			
· ≤12	3 (8.6)	5 (33.3)	0.037
· 12-20	11 (31.4)	6 (40)	
· >20	21 (60)	4 (26.7)	

Data presented as mean ±standard deviation, number, and percentages.

The stay in PACU time was longer in Group D than in Group C. (Table 1) The rescue analgesic requirement was similar between groups. (Table 1) There was a statistically significant difference between groups in NCCPC-PV score at the 15th,30th, and 60th min in PACU (p=0.002, p=0.003, p=0.002, respectively). (Table 2). But Ramsey scores were similar between the two groups at all times. (Table 2)

The serum Vitamin D levels were similar at the first admission to the dental clinic (p=0.917). But serum Vitamin D levels in the 12th week were higher in Group D than in Group C (p=0.007). Vitamin D deficiency was found at 13 patients (37.1%) and 6 (40%), and vitamin D sufficiency was found in 18 (51.4) and 7 (46.7%) in Groups D and C, respectively at the first admission to the dental clinic. The serum Vitamin D levels were sufficient (higher than 20 ng/ml) in 4 children (11.4%) and 2 children (13.3%) in Group D and C at the first examination. (Table 3)

Discussion

In this study, we aimed to present the effect of vitamin D supplementation on postoperative pain and sedation status in MMR children who undergoing dental treatment. We found that Vitamin D deficiency and sufficiency were very high incidences in MMR children. The NCCPC-PV scores were lower in Group D than in Group C in the postoperative first hour. We found that 32 children (91.4%) in Group D and 10 children (66.7%) in Group C have less than 10 points NCCPC-PV score at the first 15th min in PACU (p=0.043). However, stay in PACU time was found higher in the Vitamin D group (15.3 min) than in Group C (12.3 min) (p=0.041). We assumed that the three-minute difference in a stay in PACU has not created clinical importance. Vitamin D supplementation did not affect the postoperative Ramsey scores in the postoperative first hour. However, the rescue analgesic requirement was higher in Group C than in Group D (n=4 %26.7; n=2 %5.7, respectively), but it was not statistically significant (p=0.058).

Vitamin D deficiency is highly related to tooth defects, periodontitis, caries, and oral treatments failure[19]. Bashutski et al presented that Vitamin D deficiency during periodontal surgery can cause poor outcomes after surgery for up to 1 yr[20]. Forty individuals with severe chronic periodontitis were treated with daily calcium and vitamin D supplements, self-administered teriparatide and periodontal surgery, or placebo for 6 weak. They suggested that analysis of the vitamin D status before surgery may be critical for post-surgical healing. We found that vitamin levels were lower than 20 ng/ml in 44 MMR children (%88) at the first admission to the dental clinic. Sufficient levels of Vitamin D were observed only in 4 children (11.4%) and 2 children (13.3%) in Group D and C at the first examination, respectively. These results confirmed to a higher incidence of lower levels of Vitamin D in MMR children and suggested that vitamin D supplementation should be routinely applied in MMR children[4,21].

Schwalfenberg presented a case series report which shows improvements with vitamin D supplementation in back pain and failed back surgery patients[22]. Six patients experienced improvements in pain during 3 to 6 weeks and some patients showed better moods.

Lee et al investigated to the effects of hypovitaminosis D on postoperative pain (0-72 hours) and health-related quality of life after knee arthroplasty[23]. They found that moderate-to-severe hypovitaminosis D was associated with transient higher pain scores at rest but the total morphine consumption and quality of recovery after surgery did not affect it. Also, they observed that regression analysis suggested the risk of moderate-to-severe persistent pain increased 2- to 3-fold with hypovitaminosis.

Hajimohammadebrahim-Ketabforoush et al searched for the effect of preoperative intramuscular Vitamin D supplementation (300,000 IU vitamin D) on post-craniotomy pain in intracranial tumor surgery and found that pain scores were less in the Vitamin D

group but this result was not statistically significant[13].

The study has some limitations. First, we could not measure parathyroid hormone levels in participants. Second, we assessed the pain and sedation scores only during the postoperative first hour.

In conclusion, Vitamin D levels are very low in MMR children and Vitamin D supplementation can improve postoperative pain scores without affecting sedation scores in MMR children under dental treatment.

Conflict of interest
The authors declare that they have no conflict of interest.

Funding
Authors declared no financial support.

Ethical approval
The research protocol was submitted to Clinicaltrials.gov (identifier: NCT02664857) in July 2016 and approved by institution's (Cukurova Universty) Ethical Committee on December 17, 2015 (decision number: 47/6).

Contribution of the authors:
Study design: Ebru Biricik, data collection and statistical analysis: Nilgün Alpay, Feride Karacaer, Murat Ilgınel, Volkan Ciftci, Ozlem Ozturk, editing: Dilek Özcengiz, Nilgün Alpay. All the authors approved the final version of the manuscript.
The manuscript has been read and approved by all the authors.

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