Effect of Vitamin D Supplementation on Postcraniotomy Pain After Brain Tumor Surgery: A Randomized Clinical Trial

Melika Hajimohammadebrahim-Ketabforoush[1], Mohammadreza Shahmohammadi[2], Batoul Khoundabi[3], Zahra Vahdat Shariatpanahi[4]

■ OBJECTIVE: **To determine the effect of vitamin D supplementation on postoperative pain and analgesic requirement in brain tumor surgery.**

■ METHODS: **A total of 60 patients with vitamin D serum levels ≤20 ng/dL were randomly assigned to 2 groups equally. The study group ($n = 30$) received intramuscular injection of 300,000 IU vitamin D before surgery.**

■ RESULTS: **Preoperative serum level of vitamin D was 15.9 ± 3.8 ng/dL and 14.5 ± 3.6 ng/dL in the study and control groups, respectively ($P = 0.13$). Serum level of vitamin D on day 5 of surgery was 22.5 ± 4.3 and 13.7 ± 3.8 in the study and control groups, respectively ($P < 0.001$). A percentage of 50% had pain scores >4 on the first postoperative day, which decreased with time. The median (interquartile range) of the visual analogue scale score during the 3 postoperative days was 3 (5), 3 (5), 1 (3), and 5 (7), 2 (5), 1 (3) in the study and control groups, respectively, with no significant difference. There was no difference in analgesic consumption between the 2 groups. Analysis through the generalized estimating equation model indicated that patients who had received vitamin D for a longer time before the operative time had an insignificantly less pain score.**

■ CONCLUSIONS: **On the basis of the study results, one half of our patients reported moderate-to-severe pain scores on the first day after surgery. The pain in the study group was insignificantly less than that in the control group, but it seems that chronic high level of vitamin D may lead to promising results.**

INTRODUCTION

Pain following craniotomy has been reported in approximately 60% of the patients.[1] Postcraniotomy pain often has been overlooked, and the pain may extend up to the first or second postoperative day.[2] In addition to the distress for patients, pain contributes to postoperative complications and prolonged hospital stay.[3] The severity of postcraniotomy pain is associated with age, sex, preoperative pain, incision size, and position of incision.[2,3] It has been reported that vitamin D, with its anti-inflammatory and immune-modulatory effects, may play a crucial role in pain perception and have a role in chronic pain states.[4] Levels of this vitamin influence the pain pathways by cortical, immunologic, hormonal, and neuronal changes.[4] Serum vitamin D level is reported to be low in certain groups of patients with various pain states, including headache, abdominal pain, inflammatory pain (rheumatoid arthritis and systemic lupus erythematosus), neuropathic pain (diabetic neuropathy, postherpetic neuropathy, and multiple sclerosis), pain associated with ischemia (sickle cell disease and coronary artery disease), persistent musculoskeletal pain and weakness (rickets, osteomalacia, osteopenia, cystic fibrosis, back pain, knee pain, and costochondritic chest pain), fibromyalgia, and cancer.[4]

Clinical trials have shown different results regarding the effect of vitamin D supplementation on improvement of pain scores in patients with chronic pain states.[5-13] Furthermore, the effect of hypovitaminosis D on postoperative pain is not well understood. A few observational studies conducted on patients undergoing bariatric surgery and knee arthroplasty[14,15] and a clinical trial on sickle cell disease showed conflicting results.[16] We conducted a clinical trial study to investigate the effect of vitamin D supplementation on postoperative pain and opioid requirement in patients with brain tumor surgery.

Key words
- 25(OH) D
- Analgesics
- Brain tumor surgery
- Visual analogue scale

Abbreviations and Acronyms
GEE: Generalized estimating equation
IQR: Interquartile range
VAS: Visual analogue scale

From the [1]Student Research Committee, Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, and [2]Department of Neurosurgery, Shohada Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran; [3]Helal-e-Iran Applied Science Higher Education Institute (Red Crescent Society of Iran), Tehran; and [4]Department of Clinical Nutrition and Dietetics, Faculty of Nutrition Sciences and Food Technology, National Nutrition and Food Technology Research Institute, Shahid Beheshti University of Medical Sciences, Tehran, Iran

To whom correspondence should be addressed: Zahra Vahdat Shariatpanahi, M.D., Ph.D. [E-mail: nutritiondata@yahoo.com]

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MATERIALS AND METHODS

The study protocol was approved by the Shahid Beheshti University of Medical Sciences ethics committee and was therefore performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Adult patients who were at least 18 years of age with newly diagnosed brain tumor with serum level of 25 (OH) vitamin D ≤20 ng/dL, from July 2017 to November 2018, were included in this randomized clinical trial study. Informed consent was obtained from the participants. Since we did not find a related study to our objective, a true power calculation was not applicable. Thus, we conducted a small pilot study to obtain the estimates needed to do a proper sample size calculation. The exclusion criteria were patients having another trial participation session, including previous participation in the pilot trial, pregnant or lactating women, hypercalcemia, hyperphosphatemia, tuberculosis, sarcoidosis, history of nephrolithiasis, history of hyperparathyroidism, medications interfering with vitamin D metabolism, renal insufficiency, patients having psychological diseases, abnormal mental function, and unconscious patients.

Serum level of 25(OH) D was measured for all the patients at the admission time, and those having a serum level of ≤20 ng/dL were randomized into 2 groups. The study group received intramuscular injection of 300,000 IU vitamin D 2–14 days (with an average of 5 days) before surgery. The reason for this was that the neurosurgeons' and the hospital's schedule was to be prioritized for planning a patient's surgery. The patients undergoing general anesthesia were induced with thiopental sodium 5–7 mg/kg, fentanyl 5 μg/kg, midazolam 0.02 mg/kg, lidocaine 1 mg/kg, atracurium 0.5 mg/kg, endotracheal intubation, and maintained with propofol 50–150 μg/kg/min in a 3 L/min oxygen/air mixture. Eventually, the patient's awakening was induced with neostigmine and atropine to an extent of 0.07 mg/kg and 0.02 mg/kg, respectively.

The patients received pain medication, including intravenous injection of apotel 1 g, morphine sulfate 3 mg, and oral acetaminophen 500 mg, depending on each patient's need in the intensive care unit and ward. Postoperative pain was recorded for the 3 postoperative days every day using the visual analogue scale (VAS) by the nurse-based, anesthesiologist-led acute pain service team. VAS was presented by a numerical rating horizontal line scale, ranging from 0 (no pain) to 10 (unbearable pain). The patient marks on the line of the point that they feel that it represents their perception of their pain state. We also measured the doses of analgesic medication consumption during this period. Again, 5 days after surgery, the serum level of 25(OH) D was measured for all patients.

Statistical Analysis

The data were analyzed using the statistical package IBM SPSS, version 22.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, New York, USA). The categorical variables are expressed as proportions and frequencies. The quantitative variables with normal distribution are summarized as mean (standard deviation). Non-normal quantitative variables are presented by median (interquartile range [IQR]), where Q1 and Q3 are the first and third quartiles, respectively. The Kolmogorov–Smirnov test was applied to test the normality distribution. To explore the independent nature of some categorical variables, χ^2 test was used. The comparison of the means between the 2 groups was performed by independent or paired t test as well as by nonparametric tests such as Mann–Whitney U test and Wilcoxon signed-rank test. The data were modeled by generalized estimating equation (GEE) owing to their longitudinal and correlated structure. P values less than 0.05 were considered significant.

RESULTS

A total of 71 patients were randomly divided into 2 groups, namely the study and the control groups. Five patients in the study group and 6 patients in the control group were excluded due to missed follow-up. Finally, 30 patients in the study group and 30 patients in the control group completed the study. **Figure 1** shows the disposition of the patients throughout the study.

Table 1 specifies the basic and surgical data. There was no significant difference in any of the basic characteristics and surgical data in the treatment and control groups. Only the preoperative calcium level was significantly different in the 2 groups.

On the fifth day after surgery, the average of 25(OH) D level significantly increased in the intervention group. In addition, serum levels of calcium in the intervention group significantly decreased, phosphorus remained unchanged, and albumin decreased significantly. In the control group, average serum levels of 25(OH) D, calcium, and albumin decreased significantly, and phosphorus remained unchanged on the fifth day after surgery. **Table 2** shows these changes. The increase in 25(OH) D on the fifth postoperative day in study group was statistically significant compared with the control group ($P \leq 0.001$).

Table 3 presents the pain score assessment and doses of the prescribed medications for pain relief during the 3 days after craniotomy. The commonly used analgesics after surgery included apotel, morphine sulfate, and acetaminophen, with the dose administered per patient measured over 3 days after craniotomy. As **Table 3** shows, the median (IQR) dosage of all 3 drugs did not differ significantly between the 2 groups within 3 days after

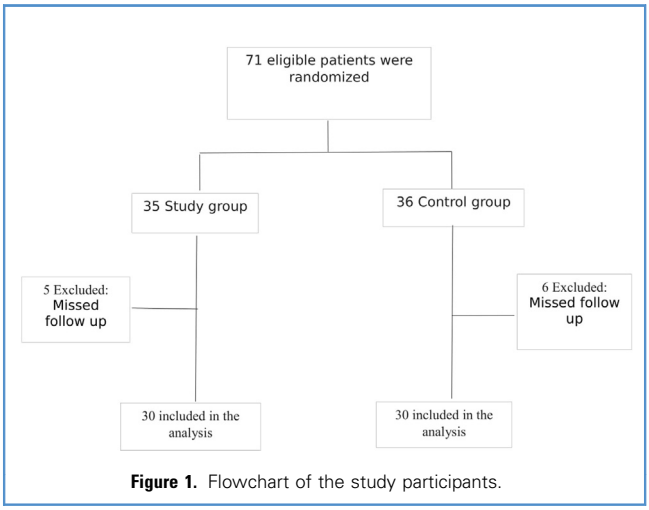

Figure 1. Flowchart of the study participants.

Table 1. Preoperative Basic Characteristics and Surgical Information of Patients

Characteristics	Study Group ($n = 30$)	Control Group ($n = 30$)	*P* Value
Age, years, mean ± SD	48.2 ± 15.3	44.3 ± 15.2	0.327*
Sex, male, *n* (%)	16 (53.3%)	14 (46.7%)	0.331†
Weight, kg, mean ± SD	75.8 ± 14.7	73.1 ± 16.3	0.529*
BMI, kg/m^2, mean ± SD	26.7 ± 4.5	25.8 ± 4.5	0.469*
Previous headache, yes/no	22/8	24/6	0.542†
Chronic headache, *n* (%)	11 (36.7%)	7 (23.3)	0.260†
Hypertension, *n* (%)	4 (13.3%)	3 (10%)	0.688†
Diabetes, *n* (%)	3 (10%)	0 (0%)	0.237†
Smoking, *n* (%)	5 (16.7%)	3 (10%)	0.706†
Surgical position, *n* (%)			0.375†
Supine	23 (76.7%)	27 (90%)	
Prone	4 (13.3%)	1 (3.3%)	
Lateral	3 (10%)	2 (6.7%)	
Craniotomy site, *n* (%)			0.270†
Supratentorial	23 (76.7%)	27 (90%)	
Infratentorial	2 (6.7%)	1 (3.3%)	
Skull base	5 (16.7%)	2 (6.7%)	
Incision size, cm, median (IQR)	7.2 (1)	7 (1)	0.782‡
Operative time, hours, median (IQR)	5.2 (2.1)	5.2 (2.9)	0.976‡
Anesthesia time, hours, median (IQR)	5.7 (2.2)	5.7 (2.4)	0.641‡
Tumor pathology, *n* (%)			0.363†
High-grade glioma	11 (36.7%)	5 (16.7%)	
Low-grade glioma	2 (6.7%)	4 (13.3%)	
Meningioma	8 (26.7%)	8 (26.7%)	
Metastatic	3 (10%)	7 (23.3%)	
Pituitary adenoma	0 (0%)	2 (6.7%)	
Craniopharyngioma	1 (3.3%)	0 (0%)	
Epidermoid cyst	2 (6.7%)	1 (3.3%)	
Lymphoma	0 (0%)	1 (3.3%)	
Schwannoma	1 (3.3%)	0 (0%)	
Other	2 (6.7%)	2 (6.7%)	
Tumor size, cm, mean ± SD	4.1 ± 1.6	4.6 ± 1.7	0.194*
Preop 25-vitamin D3, ng/mL, mean ± SD	15.9 ± 3.8	14.5 ± 3.6	0.133*
Preop calcium, mg/dL, mean ± SD	9.6 ± 0.8	9.1 ± 0.8	0.020*§
Preop phosphorous, mg/dL, mean ± SD	3.4 ± 0.8	3.5 ± 1	0.640*
Preop albumin, g/dL, mean ± SD	4.3 ± 0.5	4.1 ± 0.7	0.176*

SD, standard deviation; BMI, body mass index; Preop, preoperative.
Result from * independent sample *t* test, †χ^2 test, or ‡Mann–Whitney *U* test.
§Significant at the 0.05 level.

craniotomy. We categorized the pain score as mild (0–3), moderate (4–6), and severe (7–10) levels. Fifty percent of our patients had moderate-to-severe pain on the first postoperative day, which decreased to 40% and 26% on the second and third day, respectively (Figure 2). The median (IQR) of VAS score in the intervention and control groups on the first, second and third postoperative day was 3 (5), 3 (5), 1 (3) and 5 (7), 2 (5), 1 (3), respectively.

According to Table 4, in both groups, the pain was significantly decreased with time. However, in the intervention group, the VAS score of the second day was slightly greater than the first day; nonetheless, it was not statistically significant.

GEE modeling was used to compare the pain between the control and treatment groups, evaluating the main effects of some factors or covariates as independent variables. In the GEE modeling, pain in the 3 time periods was used as the dependent variable, and some variables were identified as independent variables. Table 5 shows the results of the GEE modeling.

According to the results, although there was no statistically significant difference between the control and treatment groups in terms of pain, $P = 0.851$, the patients in the control experienced greater pain than those in the treatment group. Over time, pain was reduced in both groups (Figure 3).

Since the patients received vitamin D at a 2- to 14-day interval before surgery, we examined period of our treatment as a separate variable in model to increase the accuracy of the analysis. In our secondary analysis, using the GEE modeling, the results showed that with an increase of 1 day to the number of days before surgery, the pain value was reduced to 0.0997. However, this is not a significant decrease ($P = 0.33$).

DISCUSSION

This study indicated that the pain score in the control group was insignificantly more than that in the intervention group. We found as vitamin D was given for a longer time before the surgical time, the greater its impact was on postoperative pain; however, it was not significant.

Therefore, in our study, vitamin D had no significant effect on pain relief after craniotomy. Furthermore, on the basis of the study findings, serum levels of calcium and albumin decreased in both groups after 5 days postoperatively, phosphorus levels remained unchanged, and 25(OH)D increased in the intervention group and decreased in the control group. Our study demonstrated that headache after craniotomy decreased over time.

Table 2. Changes in Vitamin D, Calcium, Phosphorus, and Albumin Level Before/after Craniotomy

	Preoperative		Postoperative		*P* Value	
Items	**Study**	**Control**	**Study**	**Control**	**Study**	**Control**
25(OH) D, ng/mL	15.9 ± 3.8	14.5 ± 3.5	22.5 ± 4.3	13.7 ± 3.8	0.000*	0.001*
Calcium, mg/dL	9.6 ± 0.8	9.1 ± 0.8	8.8 ± 0.4	8.8 ± 0.7	0.000*	0.005*
Phosphorus, mg/dL	3.4 ± 0.8	3.5 ± 1.0	3.2 ± 0.9	3.5 ± 1.0	0.392	0.535
Albumin, g/dL	4.3 ± 0.5	4.1 ± 0.7	3.7 ± 0.5	3.4 ± 0.8	0.000*	0.000*

The results of paired samples test are shown.
Data are reported as mean (standard deviation).
*Significant at the 0.05 level.

Reports about the incidence and severity of short-term pain after craniotomy are controversial. According to common belief, craniotomy is a painless operation compared with other surgeries,[17] whereas recent studies suggest moderate-to-severe pain after craniotomy.[1,18,19] In our study, approximately 50% of the patients experienced moderate-to-severe pain 24 hours after surgery. Gottschalk et al.[18] studied 187 patients with craniotomy surgery. The findings of their study showed that pain after craniotomy was common, and 69% of the patients experienced moderate-to-severe pain. Furthermore, Mordhorst et al.[19] reported that 55% of the patients experienced moderate-to-severe pain during the first 24 hours after craniotomy.

Our findings confirm the results of these studies. However, one of the possible reasons for discrepancy in these percentages in our study compared with the study conducted by Gottschalk et al. can be found in the large number of their patients treated under the infratentorial procedure. Many studies have demonstrated that postcraniotomy pain after the infratentorial procedure is more intense than supratentorial craniotomy.[17,18] In our study, only 3 patients underwent craniotomy using the infratentorial approach. Consistent with some studies,[18,20,21] we found that postcraniotomy pain reduced with time.

Nevertheless, Suksompong et al.[22] showed increased pain on the second day compared with the first postoperative day; this was probably due to lack of appropriate medical management of

Table 3. Pain Assessment and Medications Data within 3 Postoperative Days

Items	**Study Group (*n* = 30)**	**Control Group (*n* = 30)**	***P* Value**
VAS score			
First day	3 (5)	5 (7)	0.389
Second day	3 (5)	2 (5)	0.578
Third day	1 (3)	1 (3)	0.967
Postoperative apotel dosage consumption, g			
First day	1 (1)	0 (1)	0.114
Second day	0 (1.75)	0 (1)	0.594
Third day	0 (1)	0 (1)	1.000
Postop morphine dosage consumption, mg			
First day	0 (0)	0 (0)	0.212
Second day	0 (0)	0 (0)	0.649
Third day	0 (0)	0 (0)	0.309
Postop acetaminophen dosage consumption, mg			
First day	0 (0)	0 (0)	0.482
Second day	0 (0)	0 (0)	0.483
Third day	0 (0)	0 (0)	0.684

The results of a Mann–Whitney *U* test are shown.
Data are reported as median (interquartile range).
VAS, visual analogue scale; postop, postoperative.

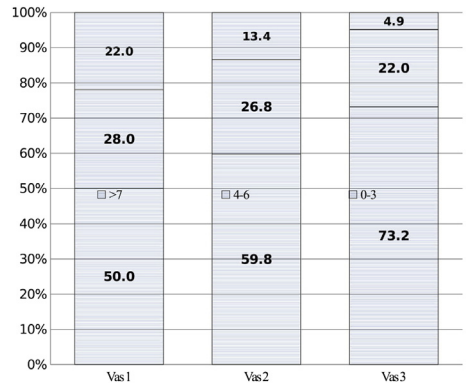

Figure 2. Bar graph that shows the percentage of patients on the y-axis and different levels of pain intensity on the first, second, and third postoperative day on the x-axis. A score of 0–3 indicates mild pain, 4–6 moderate pain, and >7 severe pain.

Table 4. The Change of Pain Score Over Time During the 3 Postoperative Days

Parameter	VAS Score2 – VAS Score 1	VAS Score 3 – VAS Score 2	VAS Score 3 – VAS Score 1
Study			
Z	−0.686	−2.918	−2.570
Asymp. Sig. (2-tailed)	0.493	0.004*	0.010*
Control			
Z	−2.282	−1.849	−2.558
Asymp. Sig. (2-tailed)	0.023*	0.064*	0.011*

The results are from the Wilcoxon signed rank test.
VAS, visual analogue scale.
*Significant at the 0.05 level.

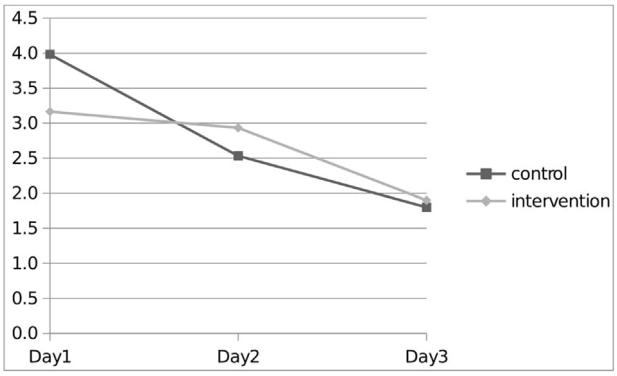

Figure 3. The trend of the pain mean by groups.

postoperative pain in the study. As mentioned previously, this study is the first clinical study examining the effect of vitamin D on postcraniotomy pain. Therefore, we reviewed this effect in other surgeries. Recently, the literature has had a considerable focus on vitamin D and pain. Vitamin D is known as a hormone and a neuroactive steroid in the body that can exert analgesic effects by modulating the excitability of neuronal cells. Types of known mechanisms through which vitamin D disturbs the nociceptive process include inhibition of Cox-2 expression and stimulation of 15-prostaglandin dehydrogenase (15-PGDH) expression, inhibition of synthesis of nitric oxide synthase, upregulation of transforming growth factor beta 1 in astrocytes and microglia and suppression of the tumor necrosis factor alpha and macrophage colony-stimulating factor in astrocytes and microglia.[4,14] Therefore, it is extremely interesting to study whether vitamin D has a relief effect on the short-time pain after surgeries.

Table 5. The Results of GEE Modeling

Parameter	B	SE	95% Wald Confidence Interval Lower	95% Wald Confidence Interval Upper	*P* Value
(Intercept)	4.392	0.6310	3.155	5.628	<0.001†
[Study Groups = 1/2]*	0.106	0.5626	−0.997	1.208	0.851
Time	−0.862	0.2147	−1.283	−0.442	<0.001†

GEE, generalized estimating equation.
*Group 1 were set as the control and group 2 as intervention with vitamin D. The mean pain in the first group was 0.106 greater than the second group, but, overall, the pain difference between the 2 groups was not significant ($P = 0.851$). Time variable was significant ($P < 0.001$). With a time of 1 unit (day), the pain value is reduced to 0.862 units.
†Significant at the 0.05 level.

Some previous observational studies have indicated that hypovitaminosis D is associated with musculoskeletal pain,[13] myalgia,[23] chronic low back pain,[7] and chronic headache.[24] In a case series study, De Torrente la de Jara et al.[11] showed that in 11 female asylum seekers after being supplemented with 2 monthly intramuscular injections of 300,000 IU of cholecalciferol and receiving 1000 mg of calcium and 20 μg of cholecalciferol, their musculoskeletal pain symptoms disappeared in 1–3 months.

In this regard, only 1 patient was treated after 7 months. In addition, in the study conducted by Gloth et al.,[25] 5 patients with unusual pain and resistant to treatment with common analgesics were treated during 5–7 days after receiving different doses of vitamin D in the form of ergocalciferol. However, the total number of articles about vitamin D and postoperative pain is very negligible. Lee et al.[15] found that moderate (12.5–29 nmol/L) to severe (<12.5 nmol/L) hypovitaminosis D before surgery was transient, but it significantly affected the severity of pain score during the early hours after knee arthroplasty. However, Bose et al.,[14] in their cohort study, did not find any correlation between the levels of vitamin D before surgery and the score of postoperative pain as well as the need for analgesics in very obese patients undergoing bariatric surgery. Consistent with previous studies, we also found a slight decrease in pain score in the short time after surgery in the treatment group with vitamin D compared with the control group, but this reduction was not statistically significant. We measured changes in levels of calcium, phosphorus, albumin, and vitamin D after surgery to ensure that the level of vitamin D in the intervention group increased and to check patients for the risk of toxicity. In line with the clinical trials on the effect of vitamin D on critically ill patients admitted to the intensive care unit,[26,27] our study also showed that vitamin D levels in the intervention group increased significantly on the fifth postoperative days. Despite this increase, we did not see any significant effect on pain. It can be attributed to the short interval between prescribing and modifying the serum levels of vitamin D and the onset of surgery.

It may also be significant if the dose of the prescribed vitamin D was greater or if the sample size was larger. In our study, serum levels of vitamin D in the control group decreased on the fifth

postoperative day. Calcium and albumin decreased in both groups and phosphorus was unchanged. Therefore, our intervention was safe in terms of overload of the calcium and phosphorus levels. One of the reasons for these reductions can be attributed to the patients' inflammatory state after surgery. Ardehali et al.[28] found that hypovitaminosis D, hypoalbuminemia, hypocalcemia, and hypophosphatemia were common due to inflammatory conditions in critically ill patients. We found a fascinating finding during the secondary analysis: as vitamin D was given for a longer time before the surgical time, the greater its impact was on postoperative pain.

Although this finding was not statistically significant, it is a clue to understand that if supplementation with vitamin D was used earlier, perhaps we could see a significant effect on pain relief. In the current study, for the first time, we evaluated the effect of vitamin D on postcraniotomy pain in a randomized clinical study design. We measured the levels of calcium and phosphorus before and after surgery to ensure that our intervention was safe. We used the GEE statistical model to precisely study the effect of treatment on pain during 3 days after surgery and the impact of many confounders adjusted. However, our study had some limitations. The sample size of our study was small. It was possible to test more doses of vitamin D in longer time before surgery to observe the maximum effect. Our work would be much more accurate if we measured the pain score in each group several times a day, rather than once a day. Furthermore, pain in movement (dynamic pain) was not assessed.

We recommend designing more clinical studies to evaluate the effect of greater doses of vitamin D in the form of oral or intramuscular injection. Furthermore, designing studies to evaluate the efficacy of oral vitamin D supplementation weekly or several injections for a long time before surgery is suggested.

CONCLUSIONS

Postcraniotomy routine drug therapies for pain relief were inadequate, and moderate-to-severe pain perception in the short term after surgery is common. Although we did not find any significant effect of vitamin D on pain relief, it seems that chronic high level of vitamin D may lead to promising results. In this regard, further clinical studies with greater sample sizes and greater doses of this vitamin are needed.

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