Clinical Nutrition ESPEN 41 (2021) 153–159

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Randomized Controlled Trial

Single high-dose vitamin D3 injection and clinical outcomes in brain tumor resection: A randomized, controlled clinical trial

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ARTICLE INFO

Article history:
Received 23 November 2020
Accepted 24 November 2020

Keywords:
25(OH)D
Craniotomy
Perioperative complications
ICU
Hospitalization

SUMMARY

Background & aims: Vitamin D is known as a neuroprotective hormone with anti-inflammatory and immune-modulatory properties. We evaluated the effect of vitamin D3 injection on vitamin D status and clinical outcomes in patients with low serum levels of 25-hydroxyvitamin D [25(OH)D] undergoing craniotomy for brain tumor resection.

Methods: Patients with benign brain tumors and serum 25(OH)D levels ≤20 ng/mL were randomized to two groups with an equal number of subjects. The study group (n = 30) received intramuscular injection of 300,000 IU vitamin D3 prior to surgery. The control group (n = 30) was left without intervention, and both groups underwent routine therapies.

Results: On day 5 after craniotomy, the serum 25(OH)D levels increased significantly in the study group (P= <0.001). The length of ICU and hospital stay was significantly lower in the study group compared to the control group (P = 0.01 and P = 0.008, respectively). It was true when the age, tumor size, tumor type, Karnofsky Performance Scale (KPS) score, and calcium and albumin levels at baseline entered the logistic regression model (OR = 0.17 (95%CI = 0.04–0.72, P = 0.01), and OR = 0.19 (95%CI = 0.04–0.82, P = 0.02), respectively). With and without the application of logistic regression analysis, there was no significant difference in perioperative complications.

Conclusions: Intramuscular injection of 300,000 IU of vitamin D3 in patients with low serum levels of 25(OH)D undergoing craniotomy, could rise safely the serum 25(OH)D level. This intervention, significantly reduced the length of ICU stay and hospitalization.

Registered under: Clinicaltrials.gov.identifier no: NCT03248544. Date: 8/14/2017.

1. Introduction

Perioperative complications in neurosurgical patients can ensue morbidity, increased length of stay in hospital, higher costs, and even mortality [1]. Factors such as age, Karnofsky Performance Scale (KPS) score, that is an index allows patients to be classified as to their functional impairment and designed to measure the level of patient activity and medical care requirements, medical history, histological type of tumor, tumor location and size, electrophysiological mapping, image guidance, and surgical procedure, affected the perioperative complications [2,3]. Based on the Enhanced Recovery After Surgery (ERAS) protocols, that are multimodal perioperative care pathways designed to achieve early recovery after surgical procedures, it is necessary to account for patient care in order to reduce surgical complications, length of hospitalization, and hospital costs [4]. Vitamin D is known as a neuroprotective hormone regulating a large number of genomic and non-genomic pathways. The role of vitamin D has been studied in various neurological diseases such as Alzheimer's disease [5], depression [6], multiple sclerosis [7], seizure [8], traumatic brain injury [9],

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https://doi.org/10.1016/j.clnesp.2020.11.027
2405-4577/

ischemic stroke [10], as well as cardiovascular events and the subsequent mortality [11,12], and the findings are summarized in the supplementary material,; however, the research on surgical patients is very limited [13–15]. Recently, vitamin D has been recognized as playing a major role regarding critically ill patients. Some observational studies [13–16] and clinical trials [17,18] have shown the possible beneficial effects of vitamin D on infections, cardiovascular events, morbidity and mortality rates, and reduced hospitalization length in surgical or critically ill patients owing to its anti-inflammatory and immune-modulatory properties. Some studies, however, have not reported such effects [19,20]. It is noteworthy that, about cardiovascular events, the findings on vitamin D supplementation have generally found no effect although observational studies do find an inverse correlation between 25(OH)D and cardiovascular events. A probable reason for this may be that serum 25(OH)D act as a biomarker for sunlight exposure through another mechanism, such as the release of nitric oxide, and lowering blood pressure [21]. The role of vitamin D in neurosurgery has not been fully understood; therefore, we evaluated the effect of single high-dose vitamin D3 injection on its serum level status and certain clinical outcomes in patients with low serum levels of 25(OH)D undergoing craniotomy for brain tumor resection.

2. Materials and methods

2.1. Patient selection, inclusion and exclusion criteria

The study protocol was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences and followed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This parallel randomized double blind clinical trial was conducted at Shohada-e-Tajrish Hospital, Tehran, Iran. We included adult patients with minimum 18 years of age and newly diagnosed benign brain tumors with serum levels of 25(OH)D $\leq$ 20 ng/mL, from August 2017 to November 2018. Informed consent was obtained from the participants. The exclusion criteria were previous participation in other trial sessions such as pilot trials, pregnant or lactating women, hypercalcemia (total calcium > 10.6 mg/dL or ionized calcium > 5.4 mg/dL), hyperphosphatemia (>1.45 mmol/L), tuberculosis, sarcoidosis, history of nephrolithiasis, history of hyperparathyroidism, medications interfering with vitamin D metabolism, and renal insufficiency. The patients and researchers remained blinded to the randomization but a nurse was not blinded to the treatment assignment and preparation. Five day before surgery, the patients that met all the study inclusion criteria with none of the exclusion criteria were assigned using computer-generated randomization.

2.2. Blood measurements

Serum levels of 25(OH)D, calcium, phosphorus, and albumin were measured in all patients at the admission time; those with a serum level of 25(OH)D $\leq$ 20 ng/mL and no hypercalcemia and hyperphosphatemia were randomized into two groups. The study group received an intramuscular injection of 300,000 IU vitamin D3 five days before surgery. All patients in the intervention group and neurosurgery ward staff were blinded to the injection content. Five days after surgery, the serum levels of 25(OH)D, calcium, phosphorus, and albumin were once again measured for all patients. The serum levels of 25(OH)D were evaluated by the enzyme-linked immunosorbent assay (Cusabio, USA).

2.3. Pathology results

To confirm the tumor type, tumor tissue was sent to the pathology department. Tumor type and size were determined by a pathologist according to the World Health Organization standards [22].

2.4. Surgical information

The patients undergoing general anesthesia were induced with thiopental sodium 5–7 mg/kg, fentanyl 5 mg/kg, midazolam 0.02 mg/kg, lidocaine 1 mg/kg, atracurium 0.5 mg/kg, endotracheal intubation, and maintained with propofol 50–150 mg/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. Whole the surgical procedures were performed by Dr. MS, that in all of which Dr. MK involved as an assistant.

2.5. Assessment of clinical outcomes and perioperative complications

The primary endpoint was to investigate whether 25(OH)D levels increased in a short time after injection. The secondary endpoint was clinical outcomes, defined as length of ICU stay and hospitalization beside the 1 and 6 months mortality. We also assessed severe hemodynamic complications during anesthesia and surgery, including active intraoperative bleeding, instability of blood pressure (MAP<80 mmHg or MAP>160 mmHg), ventricular fibrillation, severe bradycardia (<40 beats per minute), and cardiac arrest in addition to a wide range of possible post-craniotomy complications, such as intracranial hematoma, cerebral edema, seizure, meningitis, systemic infection, surgical wound infection, deep vein thrombosis, pulmonary embolism, and myocardial infarction. All the basic and medical data were collected via evaluating medical records and interviewing the patients or their surrogates along with consultation with a neurosurgeon. KPS score was specified for each patient ranking runs from 100 to 0, where 100 is “perfect” health and 0 is “death”. Data on intraoperative complications were assessed by cardiovascular monitoring in an operating room and active bleeding according to the estimation of anesthesiologists based on the amount of blood in suction pump and gauzes. Post-craniotomy complications during hospitalization were examined based on patients’ medical records, imaging, and diagnosis by a neurosurgeon. Each patient referred to the neurosurgery clinic at least two times after discharge within one month of the surgery. The length of stay in the ICU and hospital was further recorded. Mortality was determined by telephone interviews.

2.6. Statistical considerations

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). Subjects' characteristics were reported as mean ± SD and median (Q1-Q3) for continuous variables and in frequencies and percentages for categorical ones. Differences between variables were evaluated with the t test, Mann–Whitney U-test, the chi-square test, and Fisher's exact test. Ionized calcium was calculated by [0.9 + (0.55 × total calcium − 0.3 × albumin)]. Regression analysis was used to estimate the relationship between serum 25(OH)D and clinical outcomes. P-values lower than 0.05 were considered significant. We did not find a study with similar

objectives for calculating the sample size. We conducted a small pilot study in order to get the required estimates and perform a proper sample size calculation. The minimum sample size estimation for each group was 30 at a power (1-β) of 80% and $\alpha = 0.05$ for a 2-arm parallel study to detect a difference of 4 ng/mL in 25(OH)D serum level, obtained from the pilot study.

3. Results

A total of 77 patients participated in the study. They were randomly divided into the control and study groups. After excluding 17 patients, 30 were allocated to each group and completed the study (Fig. 1). Table 1 presents the basal characteristics of patients.

3.1. Serum levels of 25(OH)D, calcium, phosphorus, and albumin

As shown in Table 2, on the fifth day after surgery, the mean ± SD of 25(OH)D level in the intervention group increased to 21.69 ± 4.46 ($P < 0.001$). The mean ± SD of total calcium and albumin levels decreased to 8.78 ± 0.40 ($P < 0.001$) and 3.44 ± 0.74 ($P < 0.001$), respectively. In the control group, mean ± SD of 25(OH)D, total calcium, and albumin decreased to 14.14 ± 3.48 ($P = 0.004$), 8.70 ± 0.61 ($P < 0.001$), and 3.21 ± 0.83 ($P < 0.001$), respectively. However, ionized calcium in the study group significantly increased in its normal range on the fifth postoperative day ($P = 0.001$) compared with the control group ($P < 0.001$). Phosphorus remained unchanged in both groups. In the study group, the increase in 25(OH)D on the fifth postoperative day was statistically significant compared to the control group ($P < 0.001$). Our intervention had no adverse events such as hypercalcemia and hyperphosphatemia.

3.2. Clinical outcomes

Median (Q1-Q3) duration of both ICU stay and the entire hospitalization was significantly longer in the control than in the study group (2(1–4.25) vs. 1(0–1.25), $P = 0.01$ and 8(5–9.25) vs. 5(4–6.25), $P = 0.008$, respectively). In the logistic regression model, the length of ICU stay and hospitalization were categorized into two groups by their median (1 (1–2.75) and 6 (4.25–8.75), respectively). After entering the confounding variables of age, tumor size and type, KPS score, and baseline calcium and albumin levels into the model, the differences between the two groups concerning length of ICU and hospital stay remained statistically significant (Table 3). In this regard, the patients in the study group had approximately 83% and 81% lower chances of prolonged ICU and hospital stay, respectively (Table 3). No deaths were reported within six months of craniotomy.

3.3. Perioperative complications

Table 4 shows the occurrence of perioperative complications in two groups. Severe and fatal complications were very rare, and with no significant difference between the two groups.

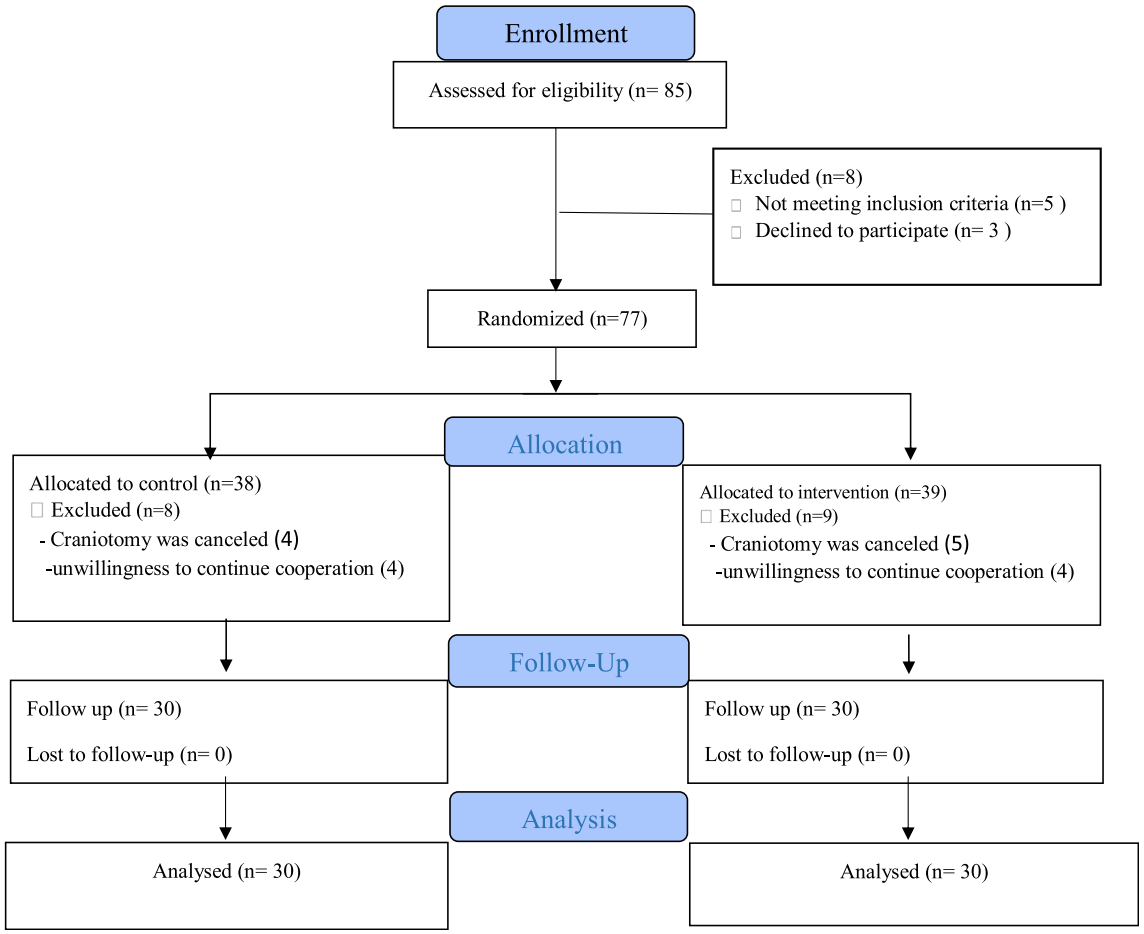

Fig. 1. CONSORT flow diagram.

Table 1
Basic, medical and surgical characteristics of patients.

Items	Study group (n = 30)	Control group (n = 30)	P value
Age (year), (mean. SD)	48.63 ± 15.06	46.33 ± 17.07	0.58[a]
Sex (male) (n. %)	21 (70.00)	17 (56.66)	0.28[b]
Weight (Kg), (mean. SD)	76.60 ± 13.47	76.29 ± 14.58	1.00[a]
BMI (Kg/m2), (mean. SD)	27.03 ± 4.13	27.21 ± 4.68	0.87[a]
Hypertension (n. %)	6 (20.00)	8 (26.66)	0.54[b]
Diabetes (n. %)	3 (10.00)	2 (6.66)	1.00[c]
Smoking (n. %)	4 (13.33)	6 (20.00)	0.48[b]
Immune disorder (n. %)	1 (3.33)	0 (0)	1.00[c]
Coagulopathy (n. %)	3 (10.00)	1 (3.33)	0.61[c]
IHD (n. %)	2 (6.66)	1 (3.33)	1.00[c]
History of Seizure (n. %)	8 (26.66)	13 (43.33)	0.17[b]
Preoperative brain edema (n. %)	10 (33.33)	12 (40.00)	0.59[b]
Surgical position (n. %)			0.50[c]
Supine	25 (83.33)	28 (93.33)	
Prone	3 (10.00)	1 (3.33)	
Lateral	2 (6.66)	1 (3.33)	
Craniotomy site (n. %)			0.46[c]
Supratentorial	25 (83.33)	22 (73.33)	
Infratentorial	2 (6.66)	1 (3.33)	
Skull base	3 (10.00)	7 (23.33)	
Incision size (Cm), (median. Q1-Q3)	8 (7–8.25)	7.25 (7–8.62)	0.55[d]
Operative time (hours), (mean. SD)	5 ± 1.38	4.89 ± 1.48	0.75[a]
Anesthesia time (hours), (mean. SD)	5.56 ± 1.43	5.42 ± 1.47	0.70[a]
Tumor pathology (n. %)			0.11[c]
Low grade glioma	13 (43.33)	9 (30.00)	
Meningioma	11 (36.66)	15 (50.00)	
Pituitary adenoma	0 (0)	3 (10.00)	
Craniopharyngioma	1 (3.33)	2 (6.66)	
Epidermoid cyst	5 (16.66)	1 (3.33)	
Tumor size (Cm), (mean. SD)	3.85 ± 1.71	4.33 ± 1.88	0.30[a]
KPS, (median. Q1-Q3)	90 (80–100)	100 (90–100)	0.35[d]

Abbreviations: BMI, body mass index; IHD, ischemic heart disease.
[a] Independent sample T-test.
[b] Chi-square test.
[c] Fisher's Exact Test.
[d] Mann–Whitney U- test.

Table 2
Changes in serum levels of 25(OH)D, calcium, phosphorus, and albumin level before/5th post-operative day.

Variable	Study group (n = 30)	Control group (n = 30)	P value[a]
25(OH) D, ng/mL			
Pre-op	16.22 ± 3.43	15.62 ± 3.48	0.50
Post-op	21.69 ± 4.46	14.14 ± 3.48	<0.001
P value[b]	<0.001	0.004	
Total calcium, mg/dL			
Pre-op	9.53 ± 0.71	9.17 ± 0.85	0.08
Post-op	8.78 ± 0.40	8.70 ± 0.61	0.56
P value[b]	<0.001	<0.001	
Ionized calcium, mg/dL			
Pre-op	4.85 ± 0.43	4.73 ± 0.40	0.27
Post-op	5.23 ± 0.29	4.72 ± 0.31	<0.001
P value[b]	0.001	0.82	
Phosphorus, mg/dL			
Pre-op	3.55 ± 1.02	3.67 ± 0.83	0.62
Post-op	3.48 ± 1.01	3.59 ± 1.03	0.31
P value[b]	0.46	0.74	
Albumin, g/dL			
Pre-op	4.29 ± 0.56	4.04 ± 0.75	0.14
Post-op	3.44 ± 0.74	3.21 ± 0.83	0.26
P value[b]	<0.001	<0.001	

Abbreviations: Pre-op, preoperative; Post-op, postoperative.
[a] Independent sample T-test.
[b] Paired samples test, data are reported as mean (SD).

Table 3
Logistic regression analysis for length of ICU and hospital stay.

Parameter	95% Wald Confidence Interval		OR	P value
	Lower	Upper		
Dependent variable: length of ICU stay				
Control group compared with intervention	0.04	0.72	0.17	**0.01**[a]
Age				0.81
Pre-op KPS				0.60
Tumor type				0.75
Tumor size				0.25
Pre-op calcium				0.56
Pre-op albumin				0.30
Dependent variable: length of hospital stay				
Control group compared with intervention	0.04	0.82	0.19	**0.02**[a]
Age				0.29
Pre-op KPS				0.13
Tumor type				0.63
Tumor size				0.35
Pre-op calcium				0.50
Pre-op albumin				0.30

Abbreviations: Pre-op, pre-operative; KPS, karnofsky performance scale.
[a] Significant at the 0.05 level.

Table 4
Perioperative complications in study and control group patients.

Item	Study group (n = 30)	Control group (n = 30)	P value
Intraoperative			
VF (n. %)	0 (0)	2 (6.66)	0.49[a]
Severe bradycardia (n. %)	0 (0)	2 (6.66)	0.49[a]
Cardiac arrest (n. %)	0 (0)	2 (6.66)	0.49[a]
Hypotension (n. %)	10 (33.33)	9 (30.00)	0.78[b]
Hypertension (n. %)	4 (13.33)	7 (23.33)	0.31[b]
Bleeding (mL), (median. Q1-Q3)	400 (300–525)	400 (300–412.50)	0.94[c]
Postoperative			
Hematoma (n. %)	1 (3.33)	2 (6.66)	1.00[a]
Brain edema (n. %)	6 (20.00)	7 (23.33)	0.75[b]
Seizure (n. %)	4 (13.33)	3 (10.00)	1.00[a]
Meningitis (n. %)	1 (3.33)	2 (6.66)	1.00[a]
MI (n. %)	1 (3.33)	0 (0)	1.00[a]
DVT (n. %)	1 (3.33)	0 (0)	1.00[a]
PE (n. %)	0 (0)	0 (0)	
Wound infection (n. %)	0 (0)	1 (3.33)	1.00[a]
Sepsis (n. %)	0 (0)	0 (0)	

[a] Fisher's Exact Test.
[b] Chi-square test.
[c] Mann–Whitney *U*- test.

4. Discussion

4.1. Serum levels of 25(OH)D, calcium, phosphorus, and albumin

Intervention with vitamin D3 increased the serum levels over a short period, which is in line with some of the previous research on critically ill patients [17–20]. Nevertheless, in some studies, most patients did not achieve desirable serum levels of 25(OH)D after single high-dose vitamin D3 administration over a short period [23–25]. A number of studies did not measure 25(OH)D levels after a short period of high-dose vitamin D3 administration time, but reported the beneficial effects of vitamin D3 on certain clinical outcomes [26]. Furthermore, we observed a reduction in the serum levels of total calcium and albumin in patients of both groups and a decrease in 25(OH)D levels in the control group. Our findings on post-surgery 25(OH)D depletion in the control group are consistent with study by Parekh et al. [27], and Silva et al. [28]. A possible explanation for 25(OH)D depletion is the inflammatory condition after surgery [28–31]. On the other hand, hemorrhage during surgery can result in electrolyte imbalance [30]. Some studies did not report a significant change in total serum calcium level in a short time after vitamin D3 administration [17,19]; others, however, reported that ionized serum calcium levels significantly increased [20]. In the present study, ionized calcium increased significantly a short time after 300,000 IU vitamin D3 intramuscular injection, which is consistent with Nair et al. [20]. According to our findings, because albumin decreased shortly after surgery and during the inflammatory status, the total calcium was reduced due to binding with albumin, however the ionized calcium increased in its normal range in the study group. Serum levels of phosphate remained unchanged in our study, hence as safe as previous studies [17–20,23–25].

4.2. Clinical outcomes

Vitamin D3 intervention was found to significantly reduce the length of stay in ICU and hospital. Some clinical trials [9,17,18] and observational studies [13,16] have recently shown the beneficial effects of vitamin D3 on the length of ICU and hospital stay and/or mortality rates. On the contrary, Amrein et al. [19] showed that high-dose vitamin D3 did not reduce the length of ICU and hospital stay, hospital mortality, or death after six months in critically ill patients. This difference might be attributed to the fact that our study population included patients with benign cranial tumors, not severe or critically ill patients; also, high dose vitamin D3 was administrated prior surgery and ICU admission. Anti-inflammatory and immunomodulatory properties might be the mechanisms underlying the effectiveness of high-dose vitamin D3 administration in reducing the hospitalization time [18].

4.3. Perioperative complications

The possible mechanisms for the effect of vitamin D3 on the cardiovascular system include the regulation of renin-angiotensin system, reduced expression of collagen and fibronectin, enhanced systolic and diastolic functions, and increased expression of klotho protein [32]. A number of observational [13,15] and clinical studies [33] have suggested the beneficial role of vitamin D in post-operative cardiovascular complications in other surgeries, which is inconsistent with some others [14,34]. These literature findings encouraged us to assess cardiovascular events in our patients. However, in agreement with previous studies [3], intraoperative cardiovascular events were extremely rare and vitamin D3 did not impact any of the intraoperative cardiovascular events. This was also true for certain potential post-craniotomy complications examined in the present study. Some clinical trials [8,18,26], animal studies [35,36], and observational studies [37,38] reported that vitamin D had anti-inflammatory and immune-modulatory activities, reduced the expression of pro-convulsant cytokines, maintained the integrity of the blood–brain barrier, upregulated the thrombomodulin, downregulated the tissue factor, and regulated heart contraction and anti-hypertrophic function. However, some other studies revealed inconsistent findings [39–41]. There is no definitive evidence as to the effects of vitamin D3, and the research on surgical settings is extremely rare. It seems that more treatment dose and/or time is required for such vitamin D3 effect.

4.4. Strengths and weaknesses

This study, for the first time, examined the effect of single high-dose vitamin D3 injection on the vitamin's status, clinical outcomes, and some potential perioperative complications after craniotomy. The intramuscular injection of vitamin D3 was considered for a more rapid replacement. This injection was not accompanied by any side effects in our patients. The patients were followed up to investigate the post-craniotomy complications

within one month and mortality from one to six months after surgery. However, the present study has some weaknesses. First, due to the lack of facilities and time, we were unable to measure 24-h urine calcium, serum PTH, and serum levels of vitamin D-binding protein. Second, the patients were not investigated in terms of the American Society of Anesthesiologists (ASA) physical status classification system, is a subjective assessment of a patient's overall health that is based on five classes (I to V). Although certain comorbidities were examined and their effects were adjusted, some confounders might have remained unknown. Third, this study was carried out in one center, hence the small sample size. Fourth, we could administer higher doses of vitamin D3 to see faster effects, but we only used a single dose and did not include placebo due to the nature of intramuscular injection. Fifth, the serum levels of 25(OH)D $\leq$ 20 ng/mL were considered as low vitamin D levels, and we did not consider categorization into different subgroups such as deficiency (25(OH)D < 12 ng/mL).

5. Conclusion

Intramuscular injection of 300,000 IU of vitamin D3 resulted in a safe increase in serum 25(OH)D level in patients undergoing craniotomy surgery with low serum 25(OH)D levels. This intervention significantly reduced the length of ICU and hospital stay. We recommend that more clinical trials be conducted with larger sample sizes, higher vitamin D3 doses, and different forms of administration (oral or injection) over longer times before the perioperative period.

Ethics approval and consent to participate

This prospective study was performed in accordance with the guidelines of the Declaration of Helsinki. In the beginning of the study, written informed consent was obtained from patients. The study was approved by the Shahid Beheshti University of Medical Sciences ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The study adheres to CONSORT guidelines.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during this study are available from the corresponding author on reasonable request.

Funding

None.

Authors' contributions

The authors' contributions are as follows: M.H. and Z.V. conceptualized and designed the study and wrote the manuscript; M.H, G.E and M.K. analyzed data; M.H. and M.S. collected data; M.H. and Z.V. interpreted the data, provided professional comments; M.S. and M.K. critically revised the manuscript for intellectual content and data accuracy; and M.H. and Z.V. had responsibility for final content. All of the authors read and approved the final manuscript.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgements

We convey our gratitude to the National Nutrition and Food Technology Research Institute, Tehran, Iran and the ICU staff of Shohada Tajrish Hospital.

Abbreviations

KPS	Karnofsky Performance Scale
ERAS	Enhanced Recovery After Surgery

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2020.11.027.

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