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Therapeutic Effects of Vitamin D3 Supplementation in Hypovitaminosis-D Patients Undergoing Neurosurgery at High Altitudes of Kashmir

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Abstract

Background: Vitamin D deficiency is ubiquitous among the people living at high altitudes of Kashmir, Ladakh and hilly regions of Jammu, primarily due to geographical location, dietary habits, skin color and regional lifestyles. Hypovitaminosis-D affects over 83% of the local population in kashmir. Neurosurgery on the other hand is responsible for inflammatory and metabolic processes with occasional long-term progression. Screening of vitamin D status is a reasonable first step, given that adequate vitamin D levels prior to brain surgery have been shown to exert neuroprotective actions and slow the adverse pathological changes after surgery. To date, most of the research on neurosurgery and vitamin D has been carried out on animal models, and translating these models into clinical trials has proven to be challenging. The scarcity of human studies on the neuroprotective effects of vitamin D on neurosurgery related outcomes, confirms that there is a dire need in this area.

Setting & Design: A prospective, observational study, comprising 100 patients with low serum Vitamin D levels, who were distributed into Group A and Group B based on whether preoperative Vitamin D supplementation was given or with-held respectively, with 50 patients in each group.

Materials & Methods: The participants were divided into two groups, those who received Vitamin D (Group A) and those who did not (Group B). These groups were then compared for various primary and secondary outcomes both intra-operatively and in postoperative periods.

Statistical Analysis: Statistical analysis was performed with statistical software SPSS and Microsoft excel. Discrete variables were as expressed as counts (percentage) and continuous variables as mean ± standard deviation (SD). P value of <0.05 was considered significant.

Results: The baseline characteristics of the patients were similar between the two groups. The average intraoperative Mean Arterial Pressure (MAP) and heart rate were better maintained in group A than in group B. The patients in group A displayed a significant normalization of vitamin D levels following supplementation of vitamin D, and the optimal levels were sustained postoperatively, whereas, group B patients had a further drop in their vitamin D levels during postoperative period. Occurrence of postoperative complications e.g. sepsis, seizures and, neuromuscular weakness was low in our study and comparable between the groups. However, the mean duration of hospital stay was significantly more in group B compared to group A patients.

Conclusion: Preoperative Supplemental Vitamin D has a favorable effect on intra-operative hemodynamic parameters and length of hospital stay. Since vitamin D levels tend to decrease further during postoperative period, preoperative supplementation may offer better recovery after neurological surgery, particularly in populations inhabiting Vitamin D deficient regions such as high altitudes.

Keywords: Vitamin D, neurosurgery, craniotomy, general anesthesia, high altitudes, hypovitaminosis, 25(OH)D

Introduction

Vitamin D is a fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, magnesium and phosphate, with multiple other biological effects.[1] Two important compounds in this group are vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol).[2] Humans get vitamin D (cholecalciferol and ergocalciferol) from sunlight exposure, diet and dietary supplements.[2,3] Sunlight plays a vital role in the maintenance of body's vitamin D stores. Solar ultraviolet B radiation (wavelength, 290 to 315 nm) converts 7-dehydrocholesterol to previtamin D3 in skin, which is converted to vitamin D3.[4,5]Any excess previtamin D3 or vitamin D3 is destroyed by sunlight[4,5], preventing Vitamin D intoxication due to excess sun exposure. Vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, and vitamin D3 through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Vitamin D from the skin and diet being biologically inactive is hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D][4,5], which is used to determine a patient's vitamin D status.[4,6,7] 25-hydroxyvitamin D (calcifediol) is further metabolized in the kidneys by the enzyme 25-hydroxyvitamin D-1α- hydroxylase to its biologically active form, 1,25-dihydroxyvitamin D (calcitriol).[4,7]Calcitriol exerts its effects via a nuclear receptor , regulating the concentration of calcium and phosphate, promoting cell growth and remodeling of bones, regulating neuromuscular and immune functions, and reducing inflammatory responses.[8] 1,25-dihydroxyvitamin D increases efficiency of absorption of renal calcium, intestinal calcium and phosphorus.[5,6,9] The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), located in the nuclei of target cells.[10]

Kashmir valley is situated at an altitude of 1574–5425 feet above the sea level at latitudes 320 20'–340 50' N and longitude 730 45'–750 35'E in the Northern mountainous regions of India. Various studies have revealed that vitamin D levels fluctuate with changing seasons especially at high altitudes. During the winter season, levels of serum 25(OH)D are decreased, however, these levels tend to be on a higher side during the summer months.[11] A prior tertiary care hospital based study in Kashmir, revealed the presence of vitamin D deficiency among 83% of the study subjects. The prevalence of vitamin D deficiency ranged from 69.6% in the employed group to 100% in the household group, with no variation between subjects from rural and urban areas. Which led to the conclusion that despite abundant sunlight, healthy individuals in Kashmir valley are vitamin D deficient.[12] Another hospital based cross sectional study conducted at a Tertiary Care Unit of Jammu and Kashmir enlisting 250 post-menopausal women between age group of 45 years to 70 years, vitamin D deficiency was found among 80% of study subjects, 14.8% had insufficient levels and 5% had optimum vitamin D level.[13]

The presence of vitamin D3 receptor (VDR) in brain and spinal cord neurons suggests its possible role in neurogenesis. Vitamin D3 increases the amount of transcripts coding for its own receptor, VDR and also for NGF, further confirming a role in neurogenesis and neuroprotection. Other mechanisms imply that vitamin D3 has a role in neuroprotection by modulating glutathione, used for intracellular redox control and is dependent on intracellular cystine concentrations.[14]

Vitamin D deficiency is common in patients with epilepsy since they are usually on polytherapy with antiepileptic medications. Studies have indicated that administration of vitamin D3 in patients with resistant epilepsy, and with low (< 30 ng/ml) serum 25(OH)D level, resulted in a median seizure number reduction of 40%. Vitamin D tends to increase the electroconvulsive threshold for seizures, decrease the severity of seizures and enhance the action of conventional anticonvulsant agents.[15]

Deleterious effects of vitamin D deficiency on medical and surgical critical care outcomes have been reviewed and documented, and improvements in intensive care mortality after vitamin D therapy have been reported primarily owing to its effects of decreasing nosocomial infections.[16,17] Vitamin D also regulates innate immunity via antimicrobial peptide gene expression and its receptors are found on macrophages, lymphocytes, and neutrophils. As might therefore be expected, vitamin D deficiency is associated with infectious complications. Low vitamin D concentrations are also associated with excessive inflammatory responses, and is a common finding in approximately 80% of all sudden cardiac deaths in post-surgical patients.[18,19]

Material And Methods

This study was undertaken in the Departments of Anesthesiology and Neurosurgery, SKIMS Srinagar, a tertiary care hospital in north india. This prospective, observational cross sectional study was conducted in adult patients planned for major elective neurosurgical procedures under general anesthesia from july 2016 to july 2018. Approval from institutional ethics committee was taken prior to the conduct of this study, and a written informed consent was obtained from all the patients whose data were collected for the study.

In our study 100 adult patients of either gender, age 18 to 65 years, with ASA status I to III and serum 25(OH)D levels of <20ng/ml, diagnosed with brain tumor and planned for major elective neurosurgeries were included. Patients with ASA status > III or with severe cardiopulmonary disease, those on vitamin D3 supplements and pregnant ladies were excluded from the study as were those with severe psychiatric disease and renal or gastrointestinal dysfunction. The patients were subsequently divided into two groups with 50 patients in each.

Group A i.e. Treated hypovitaminosis D patients, and

Group B i.e. Untreated hypovitaminosis D patients.

The eligible subjects underwent a detailed preoperative assessment according to a pre formulated proforma.. Hypovitaminosis D was defined as per guidelines laid down by IOM (Institute Of Medicine, USA) as 25(OH)D levels less than 20ng/ml and vitamin D insufficiency as, levels between 21ng/ml to 29 ng/ml.

Patients with Vitamin D deficiency(<20ng/ml) to be included in group A, were given vitamin D supplementation of 3 lakh IU by the attending neurosurgeon in outpatient clinic. The loading dose of 3, 00,000 IU was used to restore 25(OH) D levels in a reasonable time frame followed by 2000 IU weekly. The dosage was justified, based on safety findings of previous studies using similar vitamin D dosing regimens. Around 3ml of venous blood was also drawn pre operatively and 3 ml post operatively for determining vitamin D and calcium levels. Blood was drawn after fasting for at least 8 hours 1 to 2 weeks before surgery, preoperatively and post operatively 1 to 2 weeks after surgery, or on discharge. Serum 25(OH)D levels were measured by chemiluminescence immunoassay method on Beckman Coulter DXI 800 analyzer as per the protocol provided along with the reagent.

Anesthesia management was standardized for all the patients. Routine invasive and non-invasive monitoring specific for neurosurgical patients was used. Patients were managed on a standard pathway, with targeted sedation and analgesia protocols, ventilation and weaning, standing orders on vasopressors and fluids to achieve patient specific targets in operating room and ICU, using institutional guidelines. Adverse events were recorded (hypercalcemia; renal failure etc.). Patients were evaluated for occurrence of any perioperative complications and clinical outcomes immediately after surgery until discharge from ICU and hospital.

Primary outcome consisted of vitamin D levels measured as 25(OH) D, Ca^{2+}, and length of hospital stay. While secondary outcomes comprised of changes in vitamin D and calcium levels during perioperative period, seizures, muscle strength, effect on hemodynamics, infection, pain and postoperative ICU outcomes. Comorbidities and risk factors were measured by "Charlson comorbidity index".

Statistical analysis

Descriptive statistics were computed for all study variables. Discrete variables were expressed as counts (percentage) and continuous variables as mean ± standard deviation (SD). Two sample independent t-test and paired t-test were used for continuous variables. Chi square & Fischer's exact test were applied for categorized variables. Laboratory variables and intraoperative parameters were measured by using ANOVA. Demographics, nutritional health status, geographic location and seasons were measured by multivariate analysis. P value of <0.05 was considered significant.

Results

The total number of patients included in the study was 100 (n=100). They were distributed equally between group A (n=50) and group B (n=50). All the patients had a low serum 25(OH)D levels (<20ng/ml), scheduled for craniotomy under general anesthesia. The baseline characteristics i.e. age, gender, weight ASA class, comorbidities as defined by Charlson Comorbidity Index (CCI), activity type, preoperative diagnosis, pre-treatment vitamin D levels (before supplementation),post-treatment vitamin D levels, preoperative Ca^{++} levels, Preoperative GCS, timing of operation (winter/summer) are summarized in Table 1.

Table 1: Baseline characteristics of patients

Parameters	Group A	Group B
Age (years)	41.88±14.5	41.92±10.87
Gender (M/F)	48%(24)/ 52%(26)	46%(23)/54%(27)
Weight (Kg)	68.2±9.87	71.62±8.87
ASA (I/II)	74%(37)/26%(13)	80%(40)/20%(10)
Charlson Comorbidity Index (CCI) 0/1/2/3	60%(30)/20%(10)/16%(8)/4%(2)	72%(36)/10%(5)/12%(6)/6%(3)
Activity level (indoor/ outdoor)	46%(23)/54%(27)	42%(21)/58%(29)
Pre-op diagnosis	Meningioma(20%),glioma(22%), schwanoma(12%), medulloblastoma(12%), ependymoma(10%), Pineal tumors(12%), GCT*(12%)	Meningioma(18%), glioma(22%), schwanoma(14%), medulloblastoma(12%), ependymoma(12%), pinealtumors(12%), GCT*(10%)
Initial vit D levels (ng/ml)	10.01	10.56
Post-supplement vit D levels (ng/ml)	23.9340	-
Pre-op Ca^{++} levels (mg/dl)	8.32	8.43
Pre-op GCS 15/14/13	90%(45)/8%(4)/2%(1)	86%(43)/10%(5)/4%(2)
Time of surgery (winter /summer)	48%(24)/52%(26)	44%(22)/56%(28)

***Germ cell tumor**

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The intraoperative parameters of the patients are summarized in Table 2. The mean duration of surgery in group A and group B was 5.44 hours and 5.41 hours, respectively(p=0.880). The average mean arterial pressure (MAP) of the patients in group A was 81.27±4.42 mmHg whereas for group B it was 77.98± 3.81 mmHg (p<0.0001), and mean heart rate (HR) was 81.05±7.52 bpm and 86.01± 7.23 bpm in group A and group B, respectively (p=0.001). The mean intraoperative IV fluids received by patients in group A were 4.04 ± 0.72 liters compared to 4.1 ± 0.58 liters in group B (p=0.648). Single blood transfusion was received by 4(8%) and 7(14%) patients in group A and group B, respectively (p=0.52), whereas, two blood transfusions were received by 1(2%) patient each in group A and group B (p=1.00).

Table 2: Operative parameters

Parameter	Group A	Group B	P-value
Mean duration of surgery (hours)	5.44	5.41	>0.05
MAP (mmhg)	81.27±4.42	77.98±3.81	<0.05
HR (/min)	81.05±7.52	86.01±7.23	<0.05
Intra-operative fluids (litres)	4.04±0.72	4.10±0.58	>0.05
No of Patients receiving intra-operative blood transfusion (single/two)	8%(4)/2%(1)	14%(7)/2%(1)	>0.05

Pretreatment Vitamin D levels were comparable in group A(10.01ng/ml) and group B(10.56ng/ml)(p=0.587). The patients in group A showed a significant normalization of Vitamin D levels after receiving vitamin D supplements (23.94ng/ml), compared to the patients in group B who displayed a further decrease in the levels post-surgery. The mean post-operative vitamin D level of the patients in group A was 23.73ng/ml, whereas for group B it was 8.14ng/ml (p<0.0001). However, the calcium levels exhibited little variation, preoperative and postoperative calcium levels in group A were 8.32mg/dl and 8.47 mg/dl respectively (p=0.086), and in group B they were 8.43mg/dl and 8.26mg/dl respectively (p=0.241). The mean ICU stay in group A and group B was 2.78 days and 2.760 days, respectively (p=0.923), whereas the mean hospital stay in group A and group B was 16.60 days and 18.60 days, respectively (p=0.001). The mean analgesia requirement in group A and group B was 4.94 ± 2.57 grams and 5.44 ± 2.63 grams of paracetamol (PCM), respectively (p=0.343). In group B 1(2%) patient developed sepsis postoperatively and none of the patients in group A developed sepsis (p value >0.05). In group A 2(4%) patients and in group B 1(2%) patient developed seizures (p=0.51). Adequate neuromuscular strength was maintained in all the patients in group A as observed during the post-operative period compared to group B in whom 1(2%) patient developed decrease in the neuromuscular strength post-operatively (p=1.00).

Table 3: Postoperative observations

Parameter	Group A	Group B	P-value
Postoperative vit.D level (ng/ml)	23.73	8.14	<<0.05

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Postoperative Ca^{++} (mg/dl)	8.47	8.26	>0.05
Mean ICU stay (days)	2.78	2.76	>0.05
Mean hospital stay (days)	16.60	18.60	<0.05
Postoperative analgesia (gms of PCM)	4.94±2.57	5.44±2.63	>0.05
Complications:			
Seizures	4%(2)	2%(1)	>0.05
Sepsis	0	2%(1)	>0.05
Neuromuscular weakness	0	2%(1)	>0.05

Discussion

Vitamin D deficiency is rampant among the people residing at high altitudes of Kashmir affecting over 83% of the population.[12] The reasons for this widespread vitamin D deficiency can be linked to dietary habits, melanin content of the skin, seasonal variations, sun exposure and local lifestyles. On the other hand vitamin D3 receptors (VDR) have been identified in brain and spinal cord, and their possible role in neurogenesis and neuroprotection via multiple mechanisms has been suggested.[14] Vitamin D deficiency has been associated with development of seizures especially in neonates, and augmentation of anticonvulsant effect of certain medications has been reported following administration of vitamin D.[15]

Since, neurosurgery may result in profound inflammatory and metabolic changes with occasional long-term progression.[20] This novel prospective observational study was conducted to evaluate the effect of vitamin D on clinical course of patients undergoing major brain surgeries. A sample size of 100 was selected. Patients with vitamin D levels <20ng/ml, undergoing major craniotomy procedures for brain tumors, admitted from july 2016 to july 2018 at our institute were enrolled. They were divided into group A (pre-op vitamin D supplementation received) and group B (no pre-op vitamin D supplementation received), with 50 patients in each group.

The demographic parameters were controlled by including individuals from kashmiri ethnicity, who are largely known to have lower vitamin D levels than individuals from hotter regions of India (**Zargar et al. 2007)**[12]. Although, members of both the groups in our study had similar ethnic and racial makeups, however, vitamin D levels evaluated during spring and winter months have been shown to be significantly lower than the samples taken during autumn and summer months **(Heidari B et al. 2012)**[21], which is likely to be related to different levels of seasonal outdoor activity and quality of sunlight at high altitudes. There was no significant seasonal difference of blood sampling between the groups. The groups were similar in terms of baseline characterics, like, age, weight, gender, occupation and GCS. Similar age cohort was studied by **Azim et al. (2013)**[22] and **Ardehali et al. (2018)**[23].

It was observed that, post-surgery Vitamin D levels tend to decrease, unless supplemented. We found that 85% of patients had vitamin D deficiency and hypovitaminosis D was an independent risk factor for longer duration of hospital stay. A study conducted in neurocritical care patients, revealed that vitamin D deficiency was associated with higher in-hospital mortality in a subset of patients admitted on an emergency basis **(Guan J et al. 2017)**[24]. Multiple factors may contribute to vitamin D deficiency in neurosurgical patients with prolonged hospitalization, including lack of exposure to sunlight, malnutrition, decreased renal hydroxylation and increased tissue conversion of 25(OH) D3 to $1,25(OH)_2D3$. However, reduction in serum albumin and vitamin D binding proteins, or volume resuscitation may be implicated in reduced vitamin D levels on first postoperative day.

The mean duration of ICU stay in group A and group B was 2.78 days and 2.76 days, respectively (p-value >0.05), which implies that Vitamin D levels had no

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effect over duration of ICU stay. Similar observations were made by **Amrein K et al. (2014)**[17]with median ICU stay of 9.7 days and 9.1 days in controls and cases. Study by **Guan J et al. (2017)**[24] also did not show any difference in neuro-ICU stay of Vitamin D deficient and non-deficient patients (3.5 ± 2.1 and 3.3 ± 2.2 days respectively). However, a study by **Ardehali et al. (2018)**[23] reported significantly prolonged ICU stays associated with vitamin D deficiency (17.5days Vs 3 days), whereas a study by **Amrein K et al. (2011)**[25] demonstrated a mean ICU stay of 6 days and 10 days in controls and cases, respectively.

Mild hypocalcaemia was observed in 20% patients, with no correlation between baseline serum calcium level and clinical outcomes. It has been reported that mild hypocalcaemia has a protective effect in critically ill patients and its correction is not recommended (**Zhang Z et al. 2014)**[26]. Results of some other studies using multivariate methods are consistent with our findings as they did not find any association between hypocalcaemia and clinical outcomes **(Collage RD et al. 2013**[27]and **Hastbacka J et al. 2003)**[28]**.**

The average mean arterial pressure (MAP) of patients in the group A and group B was 81 mmHg and 77 mmHg respectively ($p<0.0001$). The mean of heart rate (HR) of the patients in the group A and group B was 81bpm and 86 bpm respectively , indicating that the patients with adequate vitamin D levels are more likely to maintain a normal blood pressure and heart rate during surgery. However, **Turan A et al. (2014)**[19] observed no significant difference between Vitamin D deficient group (MAP 83±13) and normal patients (MAP 84±11) with respect to intraoperative blood pressure, but observations made regarding heart rate between the two groups were consistent with our study. Vasopressor support was required by 19(38%) patients in group A and 32(64%) patients in group B (p= 0.016). Hence, vitamin D deficient patients appear to experience significant hypotensive episodes and are more likely to require vasopressor support during the course of surgery. Similar observations were made by **TuranA et al. (2014)**[19] where in 59% of Vitamin D deficient patients and 48% of normal cases needed vasopressor support. A study by **Amrein K et al. (2011)**[25] observed that the mean duration of vasopressor support was 146 hours and 65 hours in vitamin D deficient group and normal patients, respectively(p=0.56). Similarly, **McNally JD et al. (2015)**[29] reported 53% and 22% patients in Vitamin D deficient and non-deficient group, respectively required intraoperative inotropic support. However, a study by **Amrein K et al. (2014)**[17] failed to show any such association of vitamin D levels with requirement and duration of inotropic support needed.

The mean analgesia requirement in group A and group B was 4.94 grams and 5.44grams of Paracetamol, respectively and the difference was statistically non significant(p=0.343), refuting any possible influence of vitamin D levels on postoperative pain and analgesia requirements. Similar observations were made by **Lee P et al. (2015)**[30]with cumulative morphine dose requirement of 38 and 30 grams in Vitamin D deficient and non-deficient patients respectively (p=0.18). In a retrospective review of medical records from 185 patients undergoing laparoscopic bariatric surgery, there was no association between Vitamin D deficiency and opioid requirement**(Bose S et al. 2015)**[31]**.** In our study the average MAC of isoflurane for Group A and Group B was 1.0480 ± 0.17407 and 1.0240±0.15980, respectively (p=0.470), hence MAC does not appear to be affected by a patient's vitamin D status.

Vitamin D deficiency can influence the sepsis cascade through several mechanisms like immunemodulation, suppression of exaggerated inflammatory response, enhanced phagocytosis, chemotaxis, increased production of antimicrobial peptide cathelicidin and calcium and glucose homeostasis (**Lee P et al. 2009**[30]and **HewisonM et al. 2010**[32]). However, in our study one patient from group B and none of the patients in group A developed sepsis (p=0.51). A study by **Turan A et al. (2014)**[19] suggested that Vitamin D deficiency was associated with serious infections and a study by **Quraishi SA et al. (2013)**[33] suggested increased odds of hospital acquired blood stream infections with low vitamin D levels. Postoperative seizure episodes on the other hand, are common in neurosurgical patients, but our study did not imply any protective role of vitamin D against postoperative seizures in these patients.

All the patients included in our study were discharged from the hospital, and none of these

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patients from either group died during the course of hospital stay. A study by **Amrein K et al. (2011)**[25] and **Amrein K et al. (2014)**[17] did not show any difference in mortality between cases and controls. **Azim et al. (2013)**[22] also failed to show any causal association between Vitamin D deficiency and mortality in critically ill patients. However a study by **Turan A et al (2014)**[19] indicated that higher Vitamin D concentrations were associated with decreased odds of in hospital mortality (p=0.003).

Conclusion

Based on the analysis of recorded data it can be concluded that Vitamin D has an effect on intraoperative hemodynamic parameters and length of hospital stay. Postoperative Vitamin D levels are further decreased if not supplemented. This study arguments further investigation regarding the potential protective effect of vitamin D optimization on recovery from neurological surgery, particularly in populations residing at higher northern regions of india.

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