



A Study on the Effect of Preoperative and Postoperative Administration of Oral Vitamin D on Intraoperative Bleeding and Postoperative Recurrence in Patients with Nasal Polyposis

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Abstract

Background: Chronic rhinosinusitis is inflammation of the mucosa of nose and paranasal sinuses which lasts for more than 12 weeks and may lead to polyp formation. Endoscopic sinus surgery is the most effective management for Sino-nasal polyposis. Vitamin D is found to have properties of inhibiting angiogenesis, inhibiting cellular proliferation and anti-inflammatory role. **Objective:** To assess the role of Vitamin D in minimising intraoperative bleeding and prevent postoperative recurrence in patients undergoing surgical management for Nasal polyposis. **Materials and Methods:** A randomized prospective study was conducted in the Department of otorhinolaryngology, in tertiary health centre, Tamil Nadu, India from June 2020 to October 2021. Sixty consecutive patients were enrolled in two categories, A (n=30) & B (n=30). All the patients underwent detailed history, clinical examination, nasal endoscopy and Computed tomography of nose and paranasal sinuses. Group A in addition to routine medications, also received oral Vitamin D 1000 IU per day for 2 weeks preoperatively and 6 weeks postoperatively. Patients were followed up at 1 month, 3 months and 6 months. **Results:** Most of the patients fell under the age group of 30-40 years. No difference was noted between the groups based on symptomatology. The mean intraoperative blood loss in Group A (345.33 ±42.24) and group B (347.33 ±36.95) with no significant mean difference. There is significant mean difference between Group A and Group B when compared with SNOT 22 score and Meltzer Endoscopic staging at 6 months post-operative. 4 out of 30 patients belonging to Group B reported recurrence of nasal polyposis when compared to Group A with no recurrence. No adverse effects were observed. **Conclusion:** This study shows the efficacy and safety of Vitamin D supplementation in reducing the recurrence rate significantly, but its role in controlling intraoperative bleeding is minimal.

Strength and Limitations:

- Vitamin D supplementation is efficacious and cost effective.

- It is widely available and at therapeutic dose will not cause any serious adverse effects.
- It can prevent patients going in for revision surgery for recurrence.
- Intraoperative bleeding, which is troublesome for surgeons can be controlled.
- Follow-up of 6 months is required.

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Introduction

Chronic rhinosinusitis (CRS) is an inflammatory condition that affects the mucosa of the nasal and paranasal sinuses and lasts longer than 12 weeks. Mucosal changes can range from inflammatory remodelling to the development of nasal polyps. The nasal polyp architecture is provided with extracellular matrix protein by the fibroblasts created during remodelling. Epithelial cell dysfunction, eosinophilic inflammation, angiogenesis and profibrotic functions of the fibroblasts produced from nasal polyps promote the growth of the polyp [1]. The incidence and prevalence of CRS is increasing as a serious health issue, with a prevalence range within 12-15% in various studies. In many circumstances, CRS is still challenging to cure and places a significant economic cost on society and is one of the most common chronic diseases in the world [2,3]. The aetiology and pathophysiologic underpinnings of chronic rhinosinusitis are unknown. Anatomical reasons, viral and fungal aetiology, biofilms, allergies, immunological problems, and genetic causes are some of the hypothesised aetiologies for this illness [4]. However, the immunological barrier and super antigen hypotheses, which describe a balance of interactions between the host, commensal flora, prospective pathogens, and exogenous stimuli, are currently accepted theories of the aetiology of CRS [5]. The available data supports two immunological phenotypes that predominate in CRS and are caused by a skewing of the T helper (Th) cells. In contrast to CRS with nasal polyposis (CRSwNP), CRS without nasal polyposis (CRSsNP) is Th1-skewed. According to recent studies, chronic rhinosinusitis with nasal polyps is characterised by dramatically increased levels of IL-5, IL-13, eotaxin, and eosinophil cationic protein (ECP) [6]. Lack of 25-hydroxyl vitamin D is recently identified variables, which may contribute to the pathophysiology of CRS [3]. 25-hydroxyvitamin D's active form affects both innate and adaptive immunity. It affects T cells and antigen-presenting cells to encourage peripheral tolerance by reducing inflammatory reactions and inducing T-regs. Cellular proliferation, differentiation, apoptosis, and angiogenesis are all crucial regulatory processes of vitamin D. Active form may be therapeutic for chronic inflammatory illnesses like polyposis due to its immunomodulatory function in the human body. New therapeutic challenges are created by the synthetic production of vitamin D compounds with comparable immunological and anti-proliferative properties without side effects. Derivatives of vitamin D have been used effectively to treat psoriasis and other hyperkeratotic skin conditions [7,8]. The main medical treatment for nasal polyposis is the administration of oral and topical nasal steroids. The benefits of antihistamines, decongestants, and cromolyn sodium are minimal. Although immunotherapy does not frequently remove pre-existing polyps, it may be helpful in the treatment of allergic rhinitis. Surgery may be required in severe cases to remove the polyps and restore sinus ventilation [9]. In addition to their traditional function as regulators of calcium and phosphorus homeostasis, vitamin D and its various analogues have developed into a significant family of antiproliferative medicines. These characteristics indicated the possibility of Vitamin D as a treatment for chronic inflammatory disorders [10]. When conservative treatment failed, Endoscopic Sinus Surgery eventually became the preferred

course of treatment in CRSwNP. In terms of the effectiveness of surgery in CRSwNP, research have shown that sinus surgery in those with nasal polyps can lead to a long-lasting improvement in nasal symptoms [11]. However, a good majority of patients will eventually present with recurrent CRSwNP illness regardless of the surgery. In CRSwNP, the prevalence of disease recurrence varied from 4 to 60%, with a median of 20% across all studies analysed over a maximum 2-year period. The rate of revision surgery ranges from 4 to 27%, and the length of the follow-up period ranges from 12 to 60 months [12,13]. Many studies have reported about the etiopathogenesis of vitamin D deficiency in Nasal Polyposis patients but very few studies have been conducted about the role of treatment with Vitamin D. A study by Hashemian et al. demonstrated the effectiveness and safety of vitamin D administration in patients with CRSwNP in minimizing the recurrence rate following endoscopic sinus surgery. But in their study, they supplemented Vitamin D for those patients with insufficiency or deficiency. In our study we included patients with normal Vitamin D level and low dose supplementation was given for a period of 8 weeks. Hence this present study was to investigate the effects of oral Vitamin D3 on Intraoperative bleeding and Postoperative recurrence in patients with Nasal polyposis refractory to medical treatment and planned for Functional Endoscopic Sinus Surgery.

Materials and Methods

A Randomized Control Trial was conducted in the Department of Otorhinolaryngology, in a tertiary health care centre, Tamil Nadu, India for a duration of 18 Months (June 2021- Nov 2022). 60 consecutive patients were selected and were divided into two groups A (n=30) & B (n=30) based on block randomisation method.

Inclusion Criteria: Being more than 18 years and less than 60 years of age. Patients not responding to standard medical treatment and planned for surgical management. Those with recurrent nasal polyposis. Having Normal Vitamin D levels.

Exclusion Criteria: Being less than 18 years and more than 60 years of age. Those who are sensitive to Vitamin D3. Smoker or Alcoholic. Pregnant women. Having a known history of chronic kidney disease and gastrointestinal diseases. Under medications such as estrogen, thiazide diuretics, digoxin, antacids, isoniazid and immunosuppressive drugs.

A detailed history was noted. All patients received standardized treatment. Group A in addition, received oral Vitamin D 1000 IU for 2 weeks prior to surgery and 6 weeks postoperatively.

Pre-operative clinical assessment:

- Sinonasal outcome test (SNOT 22)

Space for Table 1 Sino-nasal outcome test (SNOT 22) : Answer choices for each domain is presented from 1 to 5 for a total of 22 domains, therefore the score ranges from 0-110, with higher scores indicating most severity.

- Meltzer endoscopic grading score

Space for Table 2 Meltzer endoscopic grading score: Scoring is done corresponding to the endoscopic findings with score ranging from 0-4

- Lund-Mckay scoring system.

Space for Table 3 Lund-Mackay scoring system: Scoring is done separately corresponding to the CT findings and score ranges from 0 to 10 on each side.

Investigations:

- Serum Vitamin D level,
- Diagnostic nasal endoscopy,

Space for Figure 1 Diagnostic nasal endoscopy- Nasal endoscopic findings. (A) Normal right nasal cavity (B) Greyish pale polyps seen in the right middle meatus, Note the inferior turbinate (*single asterisk*), nasal septum (*double asterisk*), middle turbinate (*arrow*).

- CT Paranasal sinuses

Space for Figure 2 CT Paranasal sinuses- Coronal cuts from sinus computed tomography scans. (A) Normal scan showing well-aerated (*black area*) sinuses. (B) Scan showing opacification (*gray area*) of the paranasal sinuses, which is consistent with chronic rhinosinusitis. Ethmoid sinus (Black arrow) and maxillary sinuses (x) are marked for orientation

Surgical procedure: Under General Anaesthesia, Orotracheal intubation. Nasal packing was done with 2 % Xylocaine with 1:1,00,000 adrenaline. Using zero-degree endoscope, nasal cavity visualized. Septal correction is done if indicated. Uncinectomy was done. Polyps were removed from the middle meatus using microdebrider. Middle meatal antrostomy was done. Anterior and Posterior ethmoidectomy was done. Sphenoidotomy done. Frontal sinus is addressed wherever it is indicated.

Space for Figure 3 Intraoperative findings (A) Showing debridement using microdebrider. (B) Post operative picture of nasal cavity.

Intraoperative assessment: The amount of normal saline used for nasal irrigation intraoperatively was noted. The amount of blood in the drain jar was noted. The number of soaked nasal packs were noted. Preoperative and Postoperative hemoglobin levels will be checked. The mean arterial pressure was noted which might indicate blood loss. Surgical field grading was done according to Fromme-Boezaart grading. Post operative assessment: Patients will be discharged and followed up at the end of 1month, 3 months and 6 months from the date of surgery. Sinonasal outcome test (SNOT 22) scoring according to the symptoms and social/ emotional consequences and Meltzer endoscopic grading according to nasal endoscopic findings was done at the end of 1 month, 3 month and 6 months.

Space for Table 4 Fromme-Boezaart surgical field grading

Results

Most of the patients in Group A fell under the age group of 31-40 years. Group B patients fell under the age group of 40-60 years. Gender wise, Male preponderance was noted in this study. On comparison based on symptomatology, there was no statistical significance noted. The mean intraoperative blood loss in group A was 345 ml and 347 ml in group B with no statistical significance. When compared with SNOT 22 score, there was significant mean difference on post operative follow-up after 3 month and 6 months. There is a significant mean difference between Group A and B when compared with Meltzer Endoscopic staging at 6 months post operatively with p-value<0.05. Thus, Group A had better symptomatic improvement when compared to Group B. 13.3% of patients belonging to Group B reported with recurrence of nasal polyposis when compared to Group A with no recurrence. There is a significant mean difference between the groups with p value <0.05. No adverse effects were observed in any of the patients.

Space for Table 5 Baseline characteristics

Space for Table 6 Estimation of blood loss

Space for Table 7 SNOT-22 Scoring

Space for Table 8 Recurrence

Space for Table 9 Meltzer endoscopic grading

Space for Table 10 Lund Mackay Scoring

Table 1 Sino-nasal outcome test (SNOT 22):

S No	Symptoms	Severity					
		No Problem (0)	Very mild (1)	Mild (2)	Moderate (3)	Severe (4)	Worse (5)
1	Need to blow nose						
2	Nasal Blockage						
3	Sneezing						
4	Runny nose						
5	Cough						
6	Post-nasal discharge						
7	Thick nasal discharge						
8	Ear fullness						
9	Dizziness						
10	Ear pain						
11	Facial pain						
12	Decreased sense of smell/ Taste						
13	Difficulty in falling asleep						
14	Wake up tired						
15	Fatigue						
16	Reduced productivity						
17	Reduced concentration						
18	Frustrated/ Restless/ Irritable						
19	Sad						
20	Embarrassed						

Table 2 Meltzer endoscopic grading score:

Location	Score
Absence of polyp	0
Small polyps in the middle meatus	1
Polyps obstructing the middle meatus	2
Polyps extending into the nasal cavity without complete obstruction	3
Polyps involving the Sinuses and nasal cavity with complete obstruction	4

Table 3 Lund-Mackay scoring system

Paranasal sinus involved	Right	Left
Maxillary (0,1,2)		
Anterior ethmoid (0,1,2)		
Posterior ethmoid (0,1,2)		
Sphenoid (0,1,2)		
Frontal (0,1,2)		
Osteomeatal complex (0,2)		

Table 4: Fromme-Boezaart surgical field grading

Grade	Surgical field
0	No bleeding
1	Slight bleeding. No suctioning of blood required
2	Slight bleeding. Occasional suctioning required. Bleeding does not threaten surgical field
3	Slight bleeding. Frequent suctioning required. Bleeding threatens surgical field a few seconds after suction is removed.
4	Moderate bleeding. Frequent suctioning required. Bleeding threatens surgical field immediately after suction is removed.
5	Severe bleeding. Constant suctioning required. Bleeding appears faster than it can be suctioned. Surgical field threatened and surgery is not possible.

Table 5: Baseline characteristics

		Group		P value
		Group A	Group B	
Age group	<30	7 (23.3%)	5 (16.7%)	0.683
	31-40	8 (26.7%)	7 (23.3%)	
	41-50	6 (20.0%)	8 (26.7%)	
	51-60	6 (20.0%)	9 (30.0%)	
	>61	3 (10.0%)	1 (3.3%)	
Gender	Female	16 (53.3%)	12 (40.0%)	0.301
	Male	14 (46.7%)	18 (60.0%)	
Vitamin D		36.8 ±4.43	35.26 ±3.51	0.143

Table 6: Estimation of blood loss

	Group		P value
	Group A	Group B	
	Mean ±Sd	Mean ±Sd	
Duration of procedure (Minutes)	155.00 ±22.40	151.00 ±20.06	0.469
Intraoperative blood loss (millilitre)	345.33 ±42.24	347.33 ±36.95	0.345
Mean arterial pressure (mm/hg)	99.30 ±3.70	94.30 ±9.80	0.12
Fromme-Bozaart Surgical field grading	2.30 ±0.47	2.33 ±0.48	0.786

Table 7: Snot-22 scoring.

SNOT 22 score		Group				P value
		Group A		Group B		
Preop	3	23	76.7%	22	73.3%	0.187
	4	7	23.3%	5	16.7%	
	5	0	0.0%	3	10.0%	
1 month Postop	2	29	96.7%	27	76.7%	0.301
	3	1	3.3%	3	23.3%	
3 months Postop	1	18	60.0%	10	33.3%	0.038
	2	12	40.0%	20	66.7%	
6 months Postop	1	25	83.3%	18	60.0%	0.045
	2	5	16.7%	12	40.0%	

Table 8: Recurrence

			Group		Total	P value
			Group A	Group B		
Recurrence	No	Count	30	26	56	0.038
		% within Group	100.0%	86.7%	95.0%	
	Yes	Count	0	4	4	
		% within Group	0.0%	13.3%	5.0%	
Total		Count	30	30	60	
		% within Group	100.0%	100.0%	100.0%	

Table 9: Meltzer endoscopic grading

Meltzer staging	Endoscopic	Group				P value
		Group A		Group B		
Preop	2	4	13.3%	3	10.0%	0.432
	3	13	43.3%	18	60.0%	
	4	13	43.3%	9	30.0%	
6 months Postop	0	30	100.0%	26	86.7%	0.042
	2	0	0.0%	3	10.0%	
	3	0	0.0%	1	3.3%	

Table 10: Lund Mackay score

	Group		P value
	Group A	Group B	
	Mean ±Sd	Mean ±Sd	
Lund-Mackay Radiology scoring - Preoperative	7.75 ±2.55	7.43 ±1.83	0.582
Lund-Mackay Radiology scoring - Post operative 6 months	1.24 ±1.23	2.85 ± 2.05	0.034

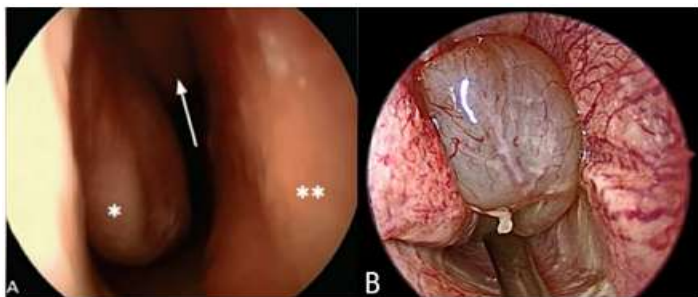


Figure 1: Diagnostic Nasal Endoscopy

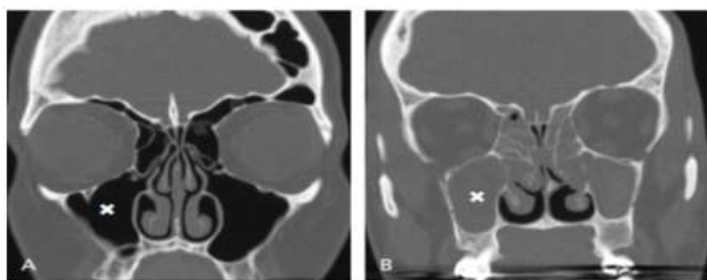


Figure 2: Computed Tomography of Nose And PNS

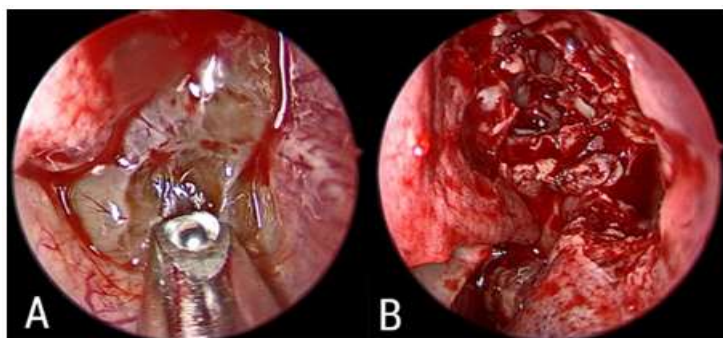


Figure 3: Intraoperative Findings

Discussion

Nasal polyps are the most common non-neoplastic mass of the nasal cavity which results from chronic inflammation of the mucosa of nose and paranasal sinuses [14]. It has a strong association with allergy, infection, asthma, and aspirin sensitivity. Most common presenting symptom is unilateral or bilateral nasal obstruction. Topical and systemic steroids being an option for medical management, Endoscopic sinus surgery remains the mainstay surgical management for Sino-nasal polyposis [15]. Lack of 25-hydroxyl vitamin D was recently found to be in correlation with the formation of polyp in patients with chronic rhinosinusitis [16]. Inhibition of cellular proliferation, Downregulation of proinflammatory markers and IgE-mediated mast cell degranulation, Anti-microbial properties, and Augmenting effect on steroids of Vitamin D [17] suggested its use in chronic rhinosinusitis with nasal polyposis.

In this study, when the two groups were studied in terms of age, most of them in group A belonged to 31 to 40 years whereas in the latter most were of 51 to 60 years. In our study, we male preponderance was noted. Hashemian et al [18] found Patients in the placebo group were reported to have a mean age of 42.5 ± 13.79 years old, while those in the Vitamin D group had a mean age of 41 ± 13.58 years old. Bavi et al [19] in their study found mean age was 41.04 years. Chandrakar et al [7] reported mean age of 37.20 ± 10.89 years. Collins et al [20] in their study of determining various environmental risk factors and gender in nasal polyposis concluded that most of them (52%) were smokers, environmental exposure to allergens such as dusts and chemicals was seen in half of them. Bronchial asthma and allergic rhinitis were more frequently associated with women than men in this study. Likewise, exposure to dust and chemicals was seen predominantly in men.

The study compared the two groups' occurrences of a variety of nasal symptoms, such as nasal obstruction, anosmia, hyposmia, mouth breathing, rhinorrhoea, sneezing, epiphora, frequent throat clearing, and facial heaviness. In both groups, bilateral nasal obstruction was more common than unilateral, but the incidence of obstruction was particularly high in Group A. Roughly 67% of those in group B and 50% of those in group A reported having abnormalities in their sense of smell. Most of them (85%) admitted to either snoring or mouth breathing. A similar number of people were in each group. Around 65% of participants reported having rhinorrhoea, with 40% of those reporting a serous nasal discharge. One of the symptoms was sneezing, which was present in 53% of the sample. Just a few of them experienced symptoms like watery eyes (epiphora) or frequent throat clearing. Majority of them had no history of bronchial asthma. Nearly a third of people reported facial heaviness or tenderness in their sinuses. There was no statistically significant difference between Group A and Group B when all these factors were compared. Faruk et al [6] reported Patients in their study who had nasal polyps prior to taking VD reported facial pain, headache, nasal blockage, nasal discharge, post-nasal drip, and olfactory disturbance on a visual analogue scale (VAS), and polyps, oedema, and discharge were seen on endoscopy. This was consistent with previous reports by Gevaert et al [21] and Newton et al [14] that nasal polyps are benign oedematous masses in the nasal cavities. It was previously reported that histological appearance is characterised by respiratory epithelium with a range of mucosal alterations, such as ulceration, thickening, and TLR-9 overexpression [22,23]. In a study by Zaravinos et al [24] it is reported that the histopathologic feature of a nasal polyp is contributed by the reparative process of the tissue following epithelial damage, which includes hyperplasia of surface epithelium and goblet cells (remodelling).

Out of 60 study participants, the most common diagnosis was Bilateral Sino nasal polyposis. 86.7% percent underwent FESS, 6.7 percent proceeded with FESS with septoplasty and 7 percent needed Revision FESS. Also, there was no significant mean difference in duration of procedure between both the groups. Mean intraoperative blood loss in group A was 345 ml

and 347 ml in group B (no statistical significance) which was justified by comparing the Fromme-Boazaart Surgical field grading which was also found to be insignificant.

When the participants were followed up for recurrence, 5 percent reported with recurrence of nasal polyposis and all other belonged to group B. Group A which consisted of participants treated with vitamin D didn't have recurrence. Hashemian et al [18] concluded their study by quoting Vitamin D supplementation is efficacious in minimizing the recurrence rate of polyposis following surgery. Preoperative Lund and Mackay radiological scoring showed no significance on comparison. There was no significant mean difference between Group A and Group B, preoperatively when compared with SNOT 22 score but there is a significant difference seen in post operative follow-up after 3 weeks and 3 months in current study. There was significant mean difference with Meltzer score among two groups. Hashemian et al [18] quoted no difference between SNOT22 score and Meltzer scoring before intervention. However, following intervention there was statistical difference in SNOT22 scores at 3- and 6-months following surgery. This shows there was better improvement of symptoms in patients who received Vitamin D. SNOT22 score in Bavi et al [19] was 89. Spearman's correlation analysis revealed a negative correlation between the Lund-Mackay score, Lund-Kennedy grading score, and the mean serum vitamin D level. Chandrakar et al [7] reported median SNOT scoring was 48 among patients with polyposis. Patient with polyps had a median Lund and Mackay radiological staging of 11.

In group A, the mean vitamin D levels was 28 and in group B was 25. There is no significant mean difference between groups. Hashemian et al [18], reported vitamin D levels preoperative in the placebo group 17.61 and 17.81 in the placebo group with no statistical significance between them preoperatively. Reduced vitamin D levels were reported in many studies. The group which received Vitamin D also had significantly lower Meltzer endoscopic grading scores compared to the placebo group three and six months after surgery, but there was no difference in the first month. This observation may be attributable to the level-correcting effect of vitamin D and the subsequent regulation of fibroblast growth factor. However, at 3 and 6 months, the recurrence rate was minimized significantly which was evident by lower SNOT-22 scores and endoscopic grading scores. Mostafa et al [25] in their study 74 patients with AFRS, CRS, and CRSwNP had their serum levels of Vitamin D3 compared. The levels were found to be significantly lower in patients with CRSwNP and AFRS, as demonstrated in a forementioned study. Therefore, they concluded that Vitamin D3 supplementation provides therapeutic control of CRSwNP and AFRS. Vitamin D deficiency is associated with the increased proliferation of fibroblasts in CRSwNP, as shown by Carrol and Schlosser [26], who examined the blood and sinus tissue of 15 patients with nasal polyposis. Schlosser et al [27] commented from their study that those with reduced vitamin D levels reported with frequent clinical manifestation. To alleviate the symptoms of the disease and shrink the size of nasal polyps, Faruk et al. [6] analysed the effectiveness of low-dose (1000 IU/day) and high-dose (4000 IU/day) Vitamin D3. In the aforementioned study the group given high dose of 4000IU/day experienced a gross reduction in all symptoms as measured by visual analogue scale and endoscopic scores. As a result, it was determined that high dose of vitamin D supplementation is likely effective in alleviating nasal polyposis symptoms and restoring nasal mucosa after surgery. Bavi et al [19] found that 25-OH vitamin D level is lower in nasal polyposis patients with allergic rhinitis. In a study by Sule et al [28] 60 adult patients with nasal polyposis were evaluated to study the relationship between Th1/Th2 cell balance.

On discussing about levels of vitamin D, in our study we have used therapeutical levels of vitamin D. None of the patients reported symptoms related to vitamin D toxicity, unlike other studies where few cases of toxicity symptoms were reported by the study participants.

Hypervitaminosis D may lead to hypercalcemia. The mean calcium level in group A and B were 9.9 and 8.9 respectively which is within normal range.

Conclusion

This study showed that, supplementation of Vitamin D in patients with Sino nasal polyposis leads to significant improvement in recurrence rate. On comparing its role in controlling intraoperative bleeding, there was no statistically significant difference implying that its role in controlling intraoperative blood loss is minimal. Thus, from our study we propose that, the use of Vitamin D in patients with Sino nasal polyposis produce good surgical outcomes in patients undergoing FESS.

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