

The Effect of Vitamin D Supplement on the Relapsing Incidence of Rhinosinusitis with Nasal Polyposis after Fuctional Endoscopic Sinus Surgery

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Abstract

Background: Nasal polyp (NP) is the most common benign tumor that can cause nasal obstruction and more annoying problems in patients. Recently, investigators have been focusing on complementary therapies alone or in conjunction with endoscopic nasal and sinus surgery. However, given the association of Vitamin D (VD) deficiency and chronic rhinosinusitis with nasal polyposis (CRSwNP) in previous studies, it may be possible to prevent the recurrence of NP and the development of rhinosinusitis by controlling serum levels of VD and maintaining it at a normal level. The current study aimed to investigate the efficacy of VD supplementation in preventing CRSwNP recurrence after endoscopic surgery.

Materials and Methods: This clinical trial composed of vitamin D deficient patients with CRSwNP who were candidates for endoscopic sinus surgery in two groups of cases and controls. After endoscopic sinus surgery for all patients, we administered VD supplementation (50,000 IU) once a week for 8 weeks for cases and no further intervention for controls. The severity of symptoms was assessed using Sino-nasal outcome test (SNOT-22) and NP recurrence and recorded pre- and postintervention.

Results: The findings indicated a higher mean change of SNOT-22 in the case group compared to that of the control group (36.03 ± 10.71 vs. 29.90 ± 11.99 ; $P = 0.041$). Moreover, the percentage of NP recurrence in cases was lower than controls; so that receiving VD supplementation has significantly reduced the chance of NP recurrence (odds ratio [95% confidence interval]: 0.298 [0.099–0.900]; $P = 0.032$).

Conclusion: According to the result of the study, the administration of VD supplementation after endoscopic sinus surgery can reduce the severity of CRSwNP symptoms and NP recurrence significantly.

Keywords: Endoscopy, nasal polyp, rhinosinusitis, Vitamin D

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INTRODUCTION

Chronic rhinosinusitis (CR) as a chronic inflammatory disorder affects nasal airways and paranasal sinuses. CR is one of the most common chronic respiratory diseases that has a significant impact on quality of life and health-care costs.^[1]

CR with nasal polyposis (CRSwNP) or without nasal polyposis (CRSsNP) is a chronic multifactorial inflammatory

disease in which symptoms of sinusitis vary with inflammatory changes ranging from increased mucosal thickness to diffuse polyposis (at least for three months).^[2]

The presence of various inflammatory cells, epithelial damage, and expression of cytokines in this disease are similar to the pathologic features of asthma. From this perspective, nasal polyp (NP) can be seen as a pattern of chronic airway inflammation.^[3]

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CRSsNP is characterized by increased T-helper 1 and T-helper 2 (Th2) cytokines and by infiltration of neutrophils and eosinophils. In fact, CRSwNP exhibits an immunoreactivity toward Th2-cells and an increase in mast cells and eosinophils.^[4,5] Increased eosinophils are among the hallmarks of CRSwNP, and mucosal levels of eosinophils are also associated with many sinus diseases and a lower likelihood of surgical success.^[6,7]

Although topical steroids may be used in the treatment of CRSwNP, they are sometimes unsatisfactory and result in recurrence and therefore often require surgical interventions.^[8] Even with successful treatment of rhinosinusitis and NP with endoscopic surgery, the risk of recurrence is high. The rate of recurrence of NP after endoscopy was 36%.^[9]

Vitamin D3 (VD3) is a steroid hormone that regulates calcium and bone homeostasis and has an immunological regulatory effect on monocytes, macrophages, and T-cells.^[10] VD3 also has anti-proliferative and anti-inflammatory effects and plays an essential role in respiratory health.^[11,12] In addition, VD derivatives inhibit the proliferation of NP-derived fibroblasts.^[13] On the other hand, VD3 deficiency has an inverse relationship with upper respiratory tract infections, and higher VD3 levels are associated with reduced risk of asthma complications and reduced anti-inflammatory drug use.^[14]

Therefore, the ability of VD3 to enhance the innate and adaptive immune response has led to different views on its protective role in allergy.^[2]

Many previous studies found that patients with CR (especially those with CRSwNP and allergic rhinosinusitis) had lower VD levels than normal and there was a significant association between low VD3 and CRSwNP levels.^[15,16]

On the other hand, the use of VD at high therapeutic doses has been known to reduce the size of the NPs, relieve the symptoms of NPs, and restore nasal mucosa to its normal state.^[16-18] Therefore, these findings may be useful in two ways, first to allow more effective types of NP treatment, especially in patients with poor conditions or in patients who refuse surgery, and secondly to prescribe VD as a posttreatment supplement after surgery to prevent NP recurrence. However, given the uncertainty in this area, further studies seem to be necessary. Hence, this study aims to evaluate the effect of VD supplementation in preventing the recurrence of CRSwNP after endoscopic surgery.

MATERIALS AND METHODS

The present study is a clinical trial. The study population included all patients undergoing endoscopic sinus surgery due to rhinosinusitis with NP, presented at Kashani and Alzahra hospitals in Isfahan from April 2019 to December 2019. The sample size was determined at 95% confidence level, 80% test power, polyp recurrence ratio in patients with VD deficiency of 0.3 and error rate of 0.3, 35 patients in each group (70 patients in total) using simple random sampling.

Inclusion criteria included patients aged 18–64 years who were candidates for endoscopic sinus surgery due to CRSwNP. And if patients have samter's syndrome, nasal mass (such as inverted papilloma, antrochoanal polyp, carcinoma, sarcoma, encephalocele, pyogenic granuloma, and angiofibroma) or have a history of receiving VD as a treatment, Smoking, a history of rickets, osteoporosis, osteomalacia, and other metabolic bone diseases were not included in the study. Subjects who refused to cooperate with the study were excluded.

After obtaining the code of ethics from the Ethics Committee of Isfahan University of Medical Sciences and obtaining written consent from eligible patients, the selected patients were first examined by an ENT specialist and the diagnosis confirmed by an endoscopy and PNS CT scan. Then, the patients were divided into two groups (receiving VD and placebo) using random allocation software

At baseline, age, sex, level of VD₃, and disease status (by Sino-nasal outcome test 22 [SNOT-22]) were recorded. Serum VD3 levels were measured and recorded in two groups using spectrophotometric or chemiluminescence method and OCHE HITACHI COBASE E 601. According to Endocrine Society guidelines, serum VD levels below 20 ng/mL were considered deficient, 21–29 ng/mL as inadequate, and levels >30 ng/mL as normal. It should be noted that in this study, patients with normal levels of VD were not included in the study.

The SNOT-22 is a 22-item questionnaire that assesses the severity of symptoms in each question from zero (asymptomatic) to five (most severe). In this questionnaire, patients described their health status in the last 2 weeks by showing the severity of symptoms and their quality of life by indicating the importance of different domains (including physical problems, functional limitations, and emotional consequences of rhinosinusitis). This questionnaire has also been validated and confirmed in Iran.^[19,20]

After endoscopic sinus surgery (antrostomy, uncinectomy, anterior ethmoidectomy, posterior ethmoidectomy, sphenoidectomy), all patients in the study received fluticasone spray and serum normal saline for irrigation. Then, on an outpatient basis, they were monitored and underwent endoscopically at regular intervals and, if necessary, under debridement. The case was given VD supplementation according to the protocol as well.

A Pearl (capsule) of VD (50,000 IU) once a week for 8 weeks was administered for the patients. The second group as the control group received placebo. After 6 months and completion of the study, VD supplementation was also administered for these patients. It should be noted that 4 participants in the control group and 6 participants in the case group were excluded due to lack of follow-up [Figure 1].

After completion of treatment (6 months), the SNOT-22 score was again evaluated for the patients. Nasal Endoscopy was also performed for all patients and recurrence of the polyp was evaluated and recorded after 6 months of intervention.

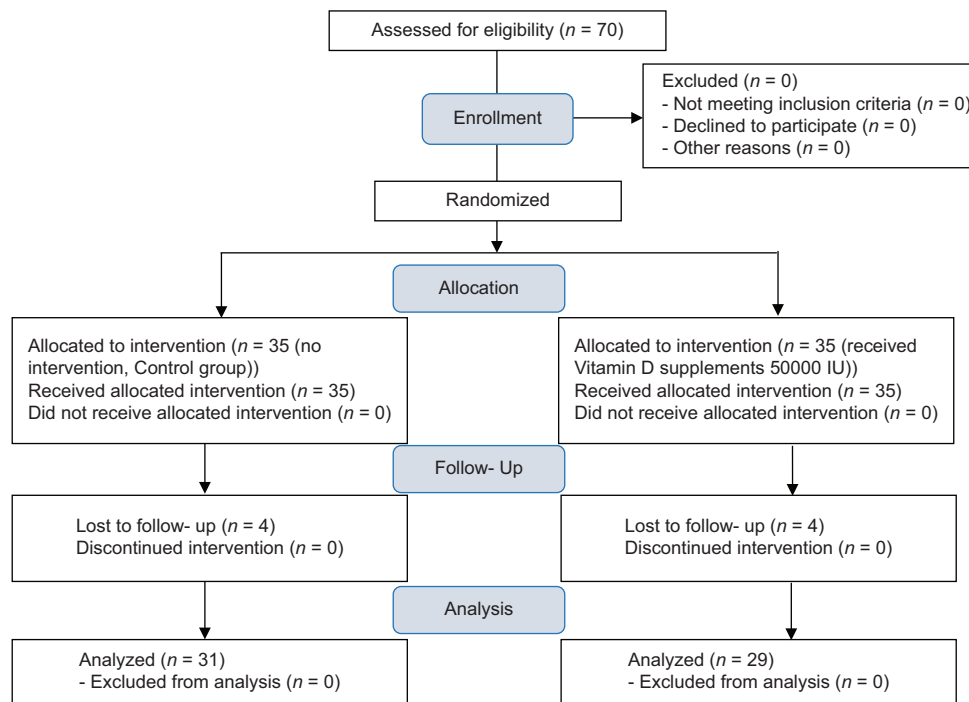


Figure 1: Consort patient flow diagram

Finally, the collected data were analyzed using SPSS software (version 22; SPSS Inc., Chicago, Ill., USA). So the variables were expressed as mean, standard deviation, frequency, and percentage. In addition, according to the results of Kolmogorov–Smirnov test for normality of data distribution, independent *t*-test was used for comparing the mean of quantitative variables between the two groups and paired *t*-test for comparing the mean of quantitative variables pre- and postintervention in each group. Chi-square test was also used to compare the sex distribution and NP recurrence of patients between the two groups. In addition, logistic regression test was used to evaluate the factors affecting NP recurrence and odds ratio (OR) was reported. In all analyzes, the significance level was considered <0.05.

RESULTS

The present study included 17 (58.6%) men and 12 (41.4%) women with a mean age of 45.07 ± 14.79 years in the case group and 15 (48.4%) men and 16 (51.6%) women with a mean age of 40.61 ± 9.71 years in the control group ($P > 0.05$). In addition, the mean serum level of VD_3 was not significantly different between the two study groups [Table 1].

On the other hand, the SNOT-22 score was not significantly different between the two groups preintervention ($P > 0.05$). Although both groups had experienced a significant decrease in SNOT-22 score, this score was significantly lower in the case group (mean score = 18.34 ± 8.30) than in the control group (mean score = 25.19 ± 12.93) postintervention ($P = 0.019$).

Table 1: Age, sex, and serum Vitamin D3 level of the patients

Characteristics	Case group (n=29, n (%))	Control group (n=31, n (%))	P
Sex			
Male	17 (58.6)	15 (48.4)	0.427*
Female	12 (41.4)	16 (51.6)	
Age (years)	45.07 ± 14.79	40.61 ± 9.71	0.170**
VD_3	19.21 ± 5.45	18.67 ± 5.13	0.691**
Deficiency	16 (57.1)	17 (56.7)	0.971*
Insufficiency	12 (42.9)	13 (43.3)	

*Used of Chi-square test, **Used of Independent sample *t*-test. Data are expressed as mean±SD or n (%). SD: Standard deviation, VD_3 : Vitamin D3

Thereby, based on SNOT-22 score the reduction in symptom severity was significantly higher in the case group (mean score = 36.03 ± 10.71) than the control group (mean score = 29.90 ± 11.99) ($P = 0.041$) [Table 2].

NP recurrence after 6 months of intervention was significantly lower in the case group (24.1%) than in the control group (51.6%) ($P = 0.036$) [Figure 2].

Finally, evaluation of the factors affecting NP recurrence using logistic regression analysis indicated that although the chance of NP recurrence would be lower in men (compared to women) at older ages and at higher VD_3 levels, they were not statistically significant ($P > 0.05$). However, VD supplementation (as the intervention of this study) can significantly decrease the chance of NP recurrence (OR [95% confidence interval]: 0.298 [0.099–0.900]; $P = 0.032$) [Table 3].

Table 2: Determination and comparison of mean Sino-Nasal outcome test-22 score pre- and post-intervention in two groups

SNOT-22	Case group (n=29)	Control group (n=31)	P
Before	54.38±16.26	55.10±15.62	0.862*
After	18.34±8.30	25.19±12.93	0.019*
Change	36.03±10.71	29.90±11.99	0.041

*Used of Independent sample *t*-test. Data are shown mean±SD. SD: Standard deviation, SNOT-22: Sino-Nasal outcome test-22

Table 3: Results from logistic regression analysis to identify factors affecting nasal polyp recurrence

Factors	β	SE	OR (95% CI)	P
Sex (male)	-0.378	0.582	0.685 (0.219-2.142)	0.515
Age	-0.024	0.024	0.976 (0.930-1.024)	0.323
VD3	-0.066	0.055	0.936 (0.840-1.042)	0.226
Vitamin D supplements	-1.210	0.563	0.298 (0.099-0.900)	0.032

VD3: Vitamin D3, SE: Standard error, OR: Odds ratio, CI: Confidence interval

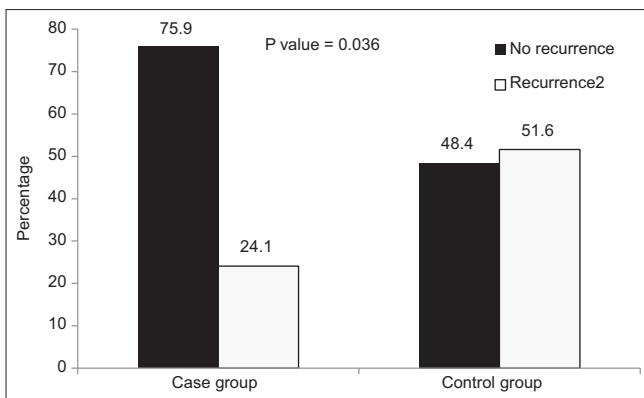


Figure 2: The frequency (%) of nasal polyp recurrence in the two groups

DISCUSSION

NP management has been controversial issue for decades.^[3] Surgical or medical therapy or both is recommended as the selective treatment.^[21]

Despite up-to-date medical therapies results in most cases are not satisfactory and recurrences require surgery. Currently, long-term use of topical and oral steroids is the main treatment for NP. Because of the known side effects of steroids, this treatment option is often rejected. All of these factors indicate the need for research into new agents suitable for the treatment of NP.^[22] The VD active hormone metabolite performs a wide range of biological actions.^[23] The discovery of the systemic role of VD has created a new field of research on the role of this vitamin in modulating physiological and pathological processes as well as the prevention and treatment of many diseases such as CR, cancer, diabetes, or sclerosis.^[24] On the other hand, contradictory results have been obtained regarding inadequate or insufficient levels of this vitamin in CR patients compared to healthy individuals.^[15,25,26]

In this respect, all patients with CRSwNP in this study had deficiency and insufficiency levels of VD. This confirms the results of previous studies suggesting that the blood levels of people with CR (especially in patients with allergic rhinosinusitis or with CRSwNP) have lower VD levels than healthy individuals.^[15,27] The level of VD in healthy individuals has not been addressed, but low levels of VD in all samples indicate a deficiency in this group of patients. Therefore, it seems that VD may play an important role in the prevention and treatment of CR or NP.^[16,17] but the exact explanations are still unclear.

Therefore, the present study aimed at administering VD supplementation (50,000 IU) once a week for 8 weeks (up to 6 months) in patients undergoing endoscopic sinus surgery. The results showed that although both groups had experienced a significant decrease in SNOT-22 score, this score was significantly lower in the case group than in the control group postintervention. Based on the SNOT-22 score the reduction in symptom severity was significantly higher in the case group than in the control group.

In addition, the recurrence rate of NP in the control group was approximately twice that of the VD supplemented group. Furthermore, with a different view of risk factors affecting NP recurrence, it was found that only VD supplementation could significantly decrease the chance of recurrence of NP. Therefore, this conclusion points to the importance and effectiveness of VD in further improving the disease and preventing recurrence of NP.

McCarty *et al.* suggested that VD3 inhibits NP fibroblast proliferation, which may confirm its anti-inflammatory effect.^[28] In addition, VD3 may provide a new, safe, and inexpensive drug to treat CR, especially with NPs.^[26]

In many other studies, the use of daily VD supplementation with doses ranging from 1000 to 4000 IU in patients with prostate cancer, respiratory tract infections, and multiple sclerosis has been suggested as a daily physiological requirement.^[29-31]

Consistent with the present study, Faruk *et al.* investigated the efficacy of low-dose (1000 IU/day) and high-dose (4000 IU/day) VD₃ in relieving symptoms and reducing NP size. They showed that the high-dose VD group received a significant decrease in all Visual Analogue Scale symptoms and endoscopic scores (based on the Lund-Mackey score [polypi, edema, and discharge]). Therefore, it was concluded that high-dose VD₃ supplementation may be more effective in the clinical improvement, relief of NP symptoms, and postoperative nasal mucosa repair due to its anti-inflammatory role in the body.^[18]

Although in our study the disease status was not assessed by this criterion, however, the recurrence of NP in the case group (VD supplementation) was significantly lower than in the control group and according to the SNOT-22 score, the severity of the disease symptoms in case group has been remarkably reduced compared to the control group.

A systematic study by Stokes and Rimmer has also indicated a strong association between VD₃ deficiency and the phenotype of CR with NPs. They have suggested that controlling the serum level of VD and maintaining it at a normal level may prevent the development or progression of rhinosinusitis or recurrence of NP.^[16]

Moreover, several other studies have attempted to investigate the possible relationship between serum VD₃ levels and symptoms of patients with Allergic Fungal Rhinosinusitis (AFRS) and CRSwNP. For example, the results of the study by Mostafa *et al.* showed that the level of VD₃ in patients with CRSwNP and AFRS was significantly lower than in patients in CRSsNP and control groups. Thus, in line with the results of the present study, they concluded that the use of VD₃ supplementation (as a postoperative enhancement therapy) may be an inexpensive and cost-effective prophylactic approach in AFRS and CRSwNP therapeutic control.^[15]

In another study, Carroll *et al.* evaluated blood and tissue sinuses in 15 patients with CRSwNP and found that VD deficiency was associated with a large increase in human sinus fibroblasts in CRSwNP. In addition, when patients were treated with calcitriol tablets, a significant decrease in fibroblast proliferation index was reported in patients with CRSwNP.^[32]

Hashemian also showed the efficacy and safety of using VD supplements in reducing polyp recurrence after endoscopic sinus surgery in patients with CRSwNP and also reported that SNOT-22 score at 1, 3, and 6 months after surgery in the VD supplement recipient group was significantly lower than the control group.^[2]

Therefore, it can be concluded from the present study and other studies that VD supplementation could have a significant role in reducing the severity of symptoms and improving the patient's condition and could potentially prevent polyp recurrence. The strengths of the present study were first attention to patients with CRSwNP and second administration of the VD supplementation for 6 months and the follow-up 6 months later for recurrence of NP. However, failure to evaluate the relapse status of NP (polypi, edema, and discharge) using the Lund-Mackey score criterion and failure to evaluate the VD level of patients after the intervention may be the limitation of the present study. Therefore, it is suggested that researchers in future study should pay more attention to NP in patients with recurrence and to re-evaluate the level of VD at the recurrence of NP.

CONCLUSION

According to the results of the present study, administration of VD supplementation after endoscopic sinus surgery can significantly reduce the severity of symptoms and the chance of recurrence of NP in these patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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