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COMPARATIVE STUDY ON OUTCOMES OF VITAMIN-D SUPPLEMENTATION VS PLACEBO IN PATIENTS OF ALLERGIC RHINITIS

Otorhinolaryngology

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KEYWORDS

INTRODUCTION

The disorder known as allergic rhinitis causes inflammation in the nasal mucosa.[1] AR is now thought to be a factor in disorders affecting the entire respiratory tract, despite the fact that it primarily affects the nose. AR affects 500 million people worldwide, or roughly 10–20% of the world's population.[2] But the disease's prevalence varies from nation to nation and is influenced by climatic, geographic, genetic, and allergen kinds in that area.[3]

Less than 12% of allergy patients consult a doctor, which means that allergic rhinitis is often underdiagnosed, mistreated, and goes untreated despite recent epidemiologic evidence showing the incidence of the condition is rising globally.[4]

Common symptoms of Allergic rhinitis include redness, watering, and itching of the eyes in addition to nasal congestion, sneezing, rhinorrhea, and nose itching. At least four months out of the year, symptoms are experienced by nearly 50% of those with allergic rhinitis. Despite data indicating that allergic rhinitis can have both long- and short-term health repercussions, no longer serious illness that poses a threat to life.[5]Due to the co-occurrence of asthma and allergic rhinitis, the economic burden has also increased. More than 85% of people with asthma also have allergic rhinitis, and upto 40% of those with rhinitis also have asthma.[6,7]

Among the drugs utilized as treatment alternatives are antihistamines, leukotriene antagonists, decongestants, nasal and oral steroids, and, immunotherapy. Low vitamin D levels have been linked to this increase in occurrences. Because of the way people live now, they spend more time indoors, which results in less time spent in the sun and less synthesis of vitamin D. Although the results of many research have linked vitamin D to the treatment of asthma and other allergic illnesses, the findings are still up for debate.[8]There is less generation of vitamin D due to this indoor lifestyle. The population's levels of vitamin D have decreased as a result of this.[9] Recent research has also indicated a possible link between low vitamin D levels and the global rise in allergy-related illnesses. It has also been demonstrated that there is a link between a rise in immunological illnesses and low serum vitamin D levels.[10] According to Schauber et al.[10], there is a causal relationship between the rise in immunological illnesses and blood levels of low vitamin D.

However, a great deal of study has looked at how vitamin D affects asthma treatment. This study evaluated the vitamin D levels and the effect of vitamin D supplementation on the severity of allergic rhinorrhea patients compared to placebo controls.

Aim & Objectives

Aim:

A Comparison of The Effects of Vitamin D Supplementation and a placebo on Individuals with Allergic Rhinitis.

Objectives:

- To assess the outcome of Vitamin D Supplementation in patients of allergic rhinitis.
- To assess the outcome of Placebo supplementation in patients of allergic rhinitis.
- To assess how vitamin D supplementation affects allergic rhinitis patients differently from placebo.

MATERIAL AND METHODS

- **Design Of Study:** Randomized controlled trial research conducted with single blind.
- **Study Area:** Department of ENT at Rajshree Medical College, Bareilly.
- **Study Period:** An 18-month research project was carried out between August 2022 and March 2024. The work plan is shown below.

Table 1: Study Work Plan Showing Percentage Of Study Time Allotted And Length In Months

Work plan	% of allocation of study time	Duration in months
Recognizing the issue and creating the questionnaire.	5-10%	August 2022 to October 2022
Preliminary investigation, validation of the survey, gathering and processing of data	Upto 80%	November 2022-September 2023
Interpretation and analysis	5-10%	October 2023-December 2023
Writing and submitting the dissertation	5-10%	January 2024-March 2024

Sample Size: 100 cases

A sample of 100 patients with allergic rhinitis. Two groups were made GROUP A / GROUP B. GROUP A was given vitamin D supplementation and GROUP B was given placebo.

Inclusion Criteria:

1. All patients of Allergic rhinitis coming to ENT OPD of Rajshree Medical Research Institute.
2. Age Group sixteen years to sixty years.

Exclusion Criteria:

1. Non-Allergic Rhinitis
2. Nasal Associated conditions - Nasal Polyps, Deviated Nasal Septum, Sinusitis.
3. Associated Systemic conditions which affect level of vit D - Rickets, JIA, Crohn's disease, Ulcerative Colitis, Cystic Fibrosis, Thyroid dysfunction, Celiac disease.
4. Patients who had taken drugs including Omega-3 fatty acids, barbiturates, corticosteroids and vitamin-D.

Patient Criteria

100 patients with allergic rhinitis were randomly divided into 2 groups of 50 patients each, designated as Group A and Group B, after the patients gave their informed written agreement in their native easily understood language. The patient was assigned by lottery to a certain group.

- Group A: N=50: Vitamin D supplementation 60000 IU per week for 8 weeks
- Group B: N=50: Placebo for 8 weeks

Method of Data Collection

Before the study began, the Institute Ethics Committee's clearance was acquired. Patients with allergic rhinitis who met all inclusion and exclusion criteria, regardless of gender, and were between the ages of 16 and 60, were included in the study.

All Patients attending ENT OPD in Rajshree medical and research institute with signs and symptoms of allergic rhinitis were evaluated with- History taking, General examination, Systemic examinations, Otorhinolaryngological examination and investigations like CBC and Serum Vitamin D level. The patient's informed agreement was then obtained for the research following the diagnosis of allergic rhino rhinitis.

Following that, using a lottery, all AR patients were split into 2 equal groups: A GROUP and B GROUP. TNSS for these patients were calculated and then recorded. TNSS - addition of scores for symptoms like RHINORRHEA, SNEEZING, NASAL CONGESTION, and NASAL ITCHING, at start and after 8 weeks, using scale of four-point (0 to 3). TNSS was calculated by summing up the rating for every symptom score to total out of 12.

During the screening and NAC visits, participants report the following symptoms: rhinorrhea, congestion, itching, and sneezing, on a scale of 0 to 3.

TABLE 2: TNSS Scoring

	Grading	Indications
0	Not present	Nil symptoms present
1	Mild	symptoms + but readily tolerated; no symptoms are seen
2	Moderate	definite knowledge of the symptom; uncomfortable but bearable
3	Severe	Intolerable symptom that gets in the way of everyday activities

After TNSS calculation and measurement of serum vit-D level, supplement of vit-D as Cholecalciferol in the form of sachets in doses of 60000 IU per week for 8 weeks was given to Group-A, at the same time group B was supplemented with placebo. After 8 weeks, we evaluated both vitamin-D level as well as TNSS score in both Group-A as well as Group-B and then we compared both groups on the basis of severity of symptoms.

RESULTS

The present RCT was done in the department of ENT at Rajashree medical research institute, Bareilly to compare the outcomes of vit D supplementation vs placebo in patients of allergic rhinitis.

The trial had a total of 100 patients, including 50 in either group.

- Group A: Interventional group with Vitamin D supplementation.
- Group B: Placebo group.

Total Nasal Symptom Score (TNSS) for these patients was calculated and recorded. TNSS is addition of cores for symptoms like Rhinorrhea, sneezing, nasal itching, and congestion at start and at follow up, using scale of four-point (0 to 3).

Vitamin-D as Cholecalciferol in the form of sachets in doses of 60000 IU per week for 8 weeks were given to Group-A and at the same time supplementing placebo to Group-B. After 8 weeks again evaluated for both vitamin-D level as well as TNSS score in both Group-A as well as Group-B and then compared both groups on the basis of severity of symptoms.

Following are The Results of the Study:

Age Comparison In Study Groups

Majority of the patients in both A Group (62%) and B Group (54%) belonged to < 30 years of age. Mean age in the A Group was 30.8±11.5 years and in the B Group was 31.8 ±10.05 years. The fact that there was no significant difference between the groups suggests that they are comparable (p>0.05)

Table 3: Age Comparisons Between The Groupings.

Age (in years)	A Group	B Group	p value
<30	31 (62%)	27 (54%)	>0.05
31-40	9 (18%)	17 (34%)	
41-50	7 (14%)	3 (6%)	
51-60	3 (6%)	3 (6%)	
Total	50 (100%)	50 (100%)	

Gender Comparison In Study Groups

Majority of the pts in the A Group were females (56%) and most of the patients in the Group B were males (58%). The fact that there was no significant difference between the groups suggests that they are comparable (p>0.05).

Table 4: Gender Comparison Between Groups.

Gender	A Group	B Group	p value
Female	28 (56%)	21 (42%)	>0.05
Male	22 (44%)	29 (58%)	
Total	50 (100%)	50 (100%)	

Seasonality Comparison In Study Groups

Seasonal allergic rhinitis affected the majority of Groups A patients (78%) and B (66%) respectively. Merely 22% of Group A and 34% of Group B individuals exhibited a persistent allergic rhinitis. The fact that there was no significant difference between the groups suggests that they are comparable (p>0.05).

Table 5: Seasonality Comparison Between Groups.

Seasonality	A Group	B Group	p value
Seasonal	39 (78%)	33 (66%)	>0.05
Perennial	11 (22%)	17 (34%)	
Total	50 (100%)	50 (100%)	

Season Wise Comparison In Study Groups

Max no of the pts in the A Group had rhinitis in the winter season (32%) and most of the patients in the Group B had no seasonal variation (34%). The difference in the groups was not significant demonstrating that the groups are comparable (p>0.05).

Table 6: Season Wise Comparison In Study Groups.

Season	Group A	Group B	p value
Summer	13 (26%)	6 (12%)	>0.05
Winter	16 (32%)	14 (28%)	
Monsoon	10 (20%)	13 (26%)	
No variation	11 (22%)	17 (34%)	
Total	50 (100%)	50 (100%)	

Family History Comparison In Study Groups

About 46% of the pts in the A Group and 52% of the pts in the Group B had family history of allergic rhinitis. The difference in the groups was not significant demonstrating that the groups are comparable (p>0.05).

Table 7: Comparison Of Family History Between Groups.

Family history	A Group	B Group	p value
Present	23 (46%)	26 (52%)	>0.05
Absent	27 (54%)	24 (48%)	
Total	50 (100%)	50 (100%)	

TNSS Scoring Comparison In Study Groups

In the pretest, the mean in A Group was 8.2±1.1 and in the B Group was 8.4±1.1. After Vit D supplementation, the mean in A Group improved to 4.8±1.5 while the mean in Group B remained similar at 8.0±1.1. The difference in the groups was significant after the intervention when independent 't' test was applied (p<0.05).

Table 8: TNSS Comparison Scoring Between Groups.

TNSS scoring (Mean ± SD)	A Group	B Group	p value
Pretest score	8.2±1.1	8.4±1.1	>0.05
Post test score	4.8±1.5	8.0±1.1	<0.001

TNSS Grades Comparison In Study Groups

Majority of the pts in both A Group (98%) and B Group (98%) had TNSS score between 7-10. The fact that there was no significant difference between the groups suggests that they are comparable (p>0.05).

Table 9: TNSS Comparison Grades Before Intervention Between Groups.

TNSS grades	A Group	B Group	p value
3-6	0	1 (2%)	>0.05
7-10	49 (98%)	49 (98%)	
>11	1 (2%)	0	
Total	50 (100%)	50 (100%)	

Majority of the patients in the Group A had scores between 7-10 (70%)

and 30% of the patients had between 3-6 and most of the patients in Group B had scores between 7-10 (96%). The difference in the groups was highly important when applied chi-square test (p<0.001)

Table 10: Comparison of TNSS Grades After Intervention Between Groups.

TNSS grades	Group A	Group B	p value
3-6	15 (30%)	0	<0.001
7-10	35 (70%)	48 (96%)	
>11	0	2 (4%)	
Total	50 (100%)	50 (100%)	

Absolute Eosinophil Count Comparison In Study Groups

Pre intervention, the mean eosinophil count in A Group was 127.2±19.4 and in the B Group was 128.2±20.9. After supplementation with Vitamin D, the mean in the Group A was improved to 93.2±14.4 and the mean in the Group B was similar at 124.4±22 and the difference in the mean after intervention was highly significant when applied independent 't' test (p<0.001).

Table 11: Eosinophil Comparison Count In Study Groups.

Eosinophil count (Mean ± SD)	A Group	B Group	p value
Pre intervention	127.2±19.4	128.2±20.9	>0.05
Post intervention	93.2±14.4	124.4±22	<0.001

Vitamin D Comparison In Study Groups

Pre intervention, the mean vitamin D levels in A Group was 44.2±14.9 and in the B Group was 43.5±15.8. After supplementation with Vitamin D, the mean in the Group A was improved to 50.5±14.6 and the mean in the Group B was similar at 43.5±15.8 and the difference in the mean after intervention was significant when applied independent 't' test (p<0.05)

Table 12: Comparing Vitamin D Levels Between Groups.

Vitamin D (µg)	A Group	B Group	p value
Pre intervention	44.2±14.9	43.5±15.8	>0.05
Post intervention	50.5±14.6	43.5±15.8	<0.05

Vitamin D Status Comparison In Study Groups

Max no of the pts in the Group A had sufficient vit D levels (78%) and 18% had insufficient levels and only 4% had deficient levels. Most of the patients in the Group B had sufficient vitamin D levels (76%) and 18% had insufficient levels and only 6% had deficient levels. The fact that there was no significant difference between the groups suggests that they are comparable (p>0.05).

Table 13: Comparing Vitamin D Status Before Intervention Between Groups

Vitamin D status	A Group	B Group	p value
Sufficient (30-100)	39 (78%)	38 (76%)	>0.05
Insufficient (20-29)	9 (18%)	9 (18%)	
Deficient (<20)	2 (4%)	3 (6%)	
Total	50 (100%)	50 (100%)	

After the intervention, 96% of the patients in the Group A had sufficient vit D levels and only 4% had insufficient vit D levels. In the Group B, 22% of the patients had insufficient levels and 2% had deficient vit D-levels. The difference in the groups after the intervention was significant when applied chi-square test (p<0.05).

Table 14: Comparison Of Vitamin D Status After Intervention Between Groups.

Vitamin D status	Group A	Group B	p value
Sufficient (30-100)	48 (96%)	38 (76%)	<0.05
Insufficient (20-29)	2 (4%)	11 (22%)	
Deficient (<20)	0	1 (2%)	
Total	50 (100%)	50 (100%)	

Statistical Analysis

The data was entered into the Microsoft excel and the statistical analysis was performed by statistical software SPSS 25.0 software (SPSS, Inc., Chicago, IL, USA). The Qualitative (Categorical values) were present in the form of frequency and percentage while the quantitative (Numerical values) were present as mean and standard Deviation.

The student t-test was used for comparing the mean values between the 2 groups whereas chi-square test was applied for comparing the frequency. The p-value was considered to be significant when less than 0.05.

DISCUSSION

The most prevalent immunologic illness and the most frequent chronic illness affecting people is allergic rhinitis. According to the ARIA 2008 study, allergic rhinitis is a major systemic allergy condition that contributes significantly to serious morbidity and disability globally, along with asthma. As nations adjust to western lifestyles, the prevalence of allergy illnesses including asthma and allergic rhinitis is rising noticeably to epidemic proportions. 3.5% of people in India are allergic rhinitis sufferers. Although benign, allergic rhinitis is a prevalent condition that significantly lowers quality of life and costs a lot of money in medical care. The course of treatment is continued until the symptoms subside, as per the guidelines about allergic rhinitis and how it affects asthma. To ascertain the ideal length of treatment for a persistent remission of the symptoms, there are no predetermined guidelines or predictive indicators, though.

India has abundant amount of sunlight and still vit- D def still continues to be an imp health problem in the country affecting the children and adult population. The relationship between vit D and the immune system has been established by the presence of VDRs in immune system cells and the various modulatory effects that arise from stimulating these receptors. The identification of vitamin D receptors in numerous bodily tissues has prompted researchers to carry out fresh investigations into the roles and associations of vitamin D, which is crucial for the metabolism of minerals in bone, with a range of medical conditions. It has been shown that immune system cells such as dendritic cells, B lymphocytes, T lymphocytes, NK cells, and monocytes include the receptor. The biological effects of vit D's active form are mediated by the activation of vit D receptors, which control target gene transcription. 1,25 (Oh)D. 21, 25 (OH) D was shown by Gombart et al. to promote the synthesis of cathelicidin peptides. Previous investigations have shown these peptides to have a protective role against URTIs.

Age Comparison

Today, allergic rhinitis, along with its associated problems, is a prevalent ailment that affects people of all ages, with younger people being more susceptible until their third decade. Three hundred and eighty-eight in Group A and thirty-eight in Group B, respectively, were the participants' mean ages. According to the research of Charles Freche et al. [32 years], the incidence of mean age is in line. The maximum number of cases in both group A (62%) and group B (54%), was between <30 years of age. The lifestyle and activities of this age group may contribute to this, since they are more likely than older age groups to be active, increasing their exposure to a greater variety of allergens. The age distribution results of our investigation align with Animesh et al.'s (2010, Kolkata) clinic-based cross-sectional study on the characteristics of allergic rhinitis patients. According to that study, individuals with allergic rhinitis were mostly between the ages of 30 and 39 (33.3%), with 30.5% coming from the 20 to 29 age range.

Gender Comparison

In this study, 49% of participants were female and 51% were male. According to research by William E. Berger et al. M-38%, F-62% and C. Bachert et al. M-43%, F-57%, respectively, there is a sex occurrence. However, males and females do not experience allergic rhinitis in the same ways or at different stages of the condition. As such, the gender difference has no bearing on the comparison of the groups that were selected after randomization. The percentage of women was slightly more than the percentage of men (57.1% vs. 42.9%). According to ARIA's Asia-Pacific Workshop in Korea, females are more likely than males to have allergic rhinitis.

TNSS Score In Allergic Rhinitis

In the pretest, the mean TNSS in A Group was 8.2±1.1 and in the Group B was 8.4±1.1. After Vit D supplementation, the mean in A Group improved to 4.8±1.5 while the mean in Group B showed slight improvement at 8.0±1.1. (p<0.05). Significant improvements were noted in the TNSS scores for both the Test and Control groups, according to Balakrishna Menon et al. The placebo effect is suggested by the statistically substantial improvement in the individuals' symptom scores while on placebo. The positive outcome that a placebo treatment or medication produces that cannot be ascribed to the placebo's inherent qualities and must instead be the result of the patient's faith in the treatment is known as the placebo effect. In numerous settings, the placebo effect has been thoroughly investigated. Two basic forms of experimental research provide evidence for placebo effects: controlled, randomized clinical trials of

medications and treatments, and laboratory studies designed expressly to assess the placebo effect. Patients in the placebo arm of randomized clinical studies often show considerably superior results with regard to symptoms of their condition when compared to their pretreatment baseline. A placebo effect, however, cannot be demonstrated without contrasting a group receiving a placebo with a group receiving no treatment. It is therefore possible to credit the placebo effect for the improvement seen in the TNSS scores of the Control group.

Bakhshaee et al. showed that in individuals with AR and vitamin D deficiency, weekly supplementation with 50,000 IU cholecalciferol for two months produced a significant difference between the baseline and final nasal symptom severity ratings determined by TNSS (P=0.007). In further trials that included a placebo, cholecalciferol was administered for shorter durations (21 and 30 days) at lower dosages (1000 IU daily), and the total nasal symptom score dropped (P<0.05).

Vit D in Allergic Rhinitis:

Pre intervention, the mean vit D levels in A Group was 44.2±14.9 and in the B Group was 43.5±15.8. After supplementation with Vit D, the mean in the Group A was improved to 50.5±14.6 and the mean in the Group B was similar at 43.5±15.8 (p<0.05) Majority of the patients in the Group A had sufficient vit D levels (78%) and 18% had insufficient levels and only 4% had deficient levels. Most of the patients in the Group B had sufficient vit D levels (76%) and 18% had insufficient levels and only 6% had deficient levels. After the intervention, 96% of the patients in the Group A had sufficient vit D levels and only 4% had insufficient vit D levels. In the Group B, 22% of the patients had insufficient levels and 2% had deficient levels. (p<0.05).

Similar to our findings, a study conducted in Thailand by Krobtrakulchai et al. found that 64% of participants had vit D deficiency or insufficiency. Vitamin D deficiency or insufficiency is highly prevalent in otherwise healthy newborns, kids, and teenagers, as well as in a variety of international nations, including India This could be brought on by lifestyle choices like wearing sunscreen, spending less time outside, and eating a diet low in vit D. But using questions regarding some exposure or vit D-enriched food intake, we were unable to predict vit D statuses in our study. A well-designed questionnaire with a larger sample size will be necessary to ascertain the association between vit D levels and sun exposure or consumption of foods fortified with the vitamin-D.

Vitamin D deficiency was determined for the population under examination (levels of 30 ng/ml), in line with other research by Brehm et al., Krobtrackulchai et al., and Chinellato et al. For the Deficient, Insufficient, and Sufficient groups, the corresponding mean ± standard deviation of vitamin D levels were 14.38 ±3.8, 25.2 ±2.6, and 32.53 ±4.02, respectively.

Vitamin D deficiency was indicated by mean vitamin D levels in test group (17.32+8.26 ng/ml) and control group (18.19+4.66 ng/ml) in patients with allergic rhinitis, according to research by Balakrishna Menon et al. In addition to conventional medications, the test group's blood vitamin D levels and overall nasal symptom score were dramatically improved after receiving 1000 IU of cholecalciferol. There was a statistically significant difference in the improvement of TNSS scores between the Control group (which was given only conventional medications and a placebo) and Test group. The immunomodulatory properties of vitamin D may be the cause of this improvement.

Numerous other research indicates that people with allergic rhinitis have a significantly higher vit -D insufficiency than the general population, suggesting a possible causative relationship. According to a study by Moradzadeh et al., there is a correlation between blood vit D levels and AR status. Patients with AR had a considerably higher prevalence of severe vit D deficiency (30% vs. 5.1%; P = 0.03) than the general population. Similar findings were found in research by Arshi S et al., which found that patients with allergic rhinitis had a considerably greater frequency of severe vit D deficiency (30%) compared to the general population (5.1%; p = 0.03). Vit D levels were also decreased in women with allergic rhinitis. Vit D supplementation may play a theoretical role in improving allergic rhinitis symptoms in those who are low in the vit. Significant clinical improvement in symptom scores was demonstrated by Datt Modh et al. when compared to the control group, which did not receive Vit D supplementation.

In their individual investigations, Yenigun et al., Vatankhah et al., and Sudiro et al. demonstrated a correlation between the classification of allergic rhinitis and vit D deficit, with a notable percentage of patients with allergic rhinitis exhibiting a severe vit D deficiency. According to the findings of several additional studies, Vit-D administration changes the normal course of allergic rhinitis and leads to a notable clinical improvement in patients.

CONCLUSION

Ultimately, the results of this randomized, single-blind, placebo-controlled study indicate that Vit D3 supplementation might be a secure and useful adjuvant treatment for allergic rhinitis. The improvement in nasal obstruction scores indicates Vitamin D3 may help reduce nasal congestion and inflammation. The mechanism by which Vitamin D3 exerts immunomodulatory effects in allergic rhinitis needs further investigation.

There is strong evidence linking low levels of vit D in the serum to allergic rhinitis. This study backs up this conclusion as well. It has been demonstrated that giving these patients vit D supplements helps better regulate their AR symptoms. This finding highlights the value of measuring vit D levels in allergic rhinitis patients and highlights the role of vit D supplementation therapy in deficient individuals in addition to initial anti-allergy treatment

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