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The Impact of Vitamin D in Ulcerative Colitis Patients Among a Tertiary Care Centre

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Abstract

Ulcerative colitis (UC) is a chronic idiopathic disease characterized by an inflammatory response largely limited to the colonic mucosa. Being a lifelong condition, ulcerative colitis has a significant psychological and social impact on patients. Vitamin D can restore the gut mucosal barrier in addition to regulating immunological responses. Vitamin D may improve a patient's quality of life and reduce the symptoms of ulcerative colitis by having an anti-inflammatory impact on the intestines and being instrumental in mucosal repair. The purpose of this study was to assess and contrast the safety and effectiveness of vitamin D adjuvant conventional treatment and to assess its effect on the quality of life in patients with ulcerative colitis. We randomized newly diagnosed patients of ulcerative colitis either to receive standard therapy or oral 4000 IU vitamin D3 in addition to standard therapy for 12 weeks in this prospective, parallel-group, randomized, comparative clinical research. Group I showed a reduction from 7.20 ± 0.29 at baseline and 6.17± 0.29 at 12 weeks in Mayo score with standard therapy at week 12 in comparison with Vitamin D adjuvant standard therapy which showed a reduction from 6.67 ± 0.37 at baseline and 5.37 ± 0.32 at 12 weeks in Mayo score, indicating Vitamin D adjuvant therapy to be better in reducing disease activity. Quality of life was evaluated using the Short Inflammatory Bowel Disease Quality of Life Questionnaire (SIBD-QOL) at weeks 0, 4, 8, and 12. After completion of therapy at 12 weeks Group I SIBDQOL score increased to 44.50 ± 2.01 and Group II increased to 51.27 ± 2.13), with the difference being statistically significant.

Keywords: Ulcerative colitis, Vitamin D, Hepcidin, Quality of life (QoL)

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Introduction

Ulcerative colitis is one type of inflammatory bowel disease that produces inflammation in the large intestines [1]. In developed, western countries it is rather common with the highest prevalence estimates of 505 per 100,000 in Europe, whereas in India its prevalence is 6.02/100,000 [2]. Between ages 30 and 40 years, a peak of ulcerative colitis onset is seen. Eight to 14% of patients with UC have a family history of inflammatory bowel disease (IBD) [3]. Various environmental risk factors, including antibiotics, drinking, breastfeeding, smoking, appendectomy, food, oral contraceptives, infections/vaccinations, and childhood hygiene, have been investigated; nevertheless, the outcomes have been mixed [2]. Apart from controlling the metabolism of calcium and phosphate, vitamin D additionally can regulate immunological responses by influencing T cells, dendritic cells, and macrophages either directly or indirectly. This helps prevent excessive

immune responses. The gut mucosal barrier can be repaired by vitamin D as well. Vitamin D has the potential to mitigate ulcerative colitis symptoms using both its mucosal healing properties and its anti-inflammatory effect on the intestines [4]. The purpose of this study was to assess and contrast the safety and effectiveness of vitamin D adjuvant conventional treatment and to assess its effect on the quality of life in patients with ulcerative colitis.

Materials and Methods

Study design

We conducted an open-label, parallel-group, randomized, comparative clinical study at PGIMS, Rohtak, an Indian tertiary care facility, for 14 months (August 1, 2021, to October 3, 2022). The University of Health Sciences, Rohtak's ethics committee examined and approved the research protocol (BREC/Th/20/Pharma03), and on July 26, 2021, the clinical study was registered with the Clinical Trials Registry of India (CTRI/2021/07/035128). There is no conflict of interest between any of the researchers and the pharmaceutical companies that produced the vitamin D tablets.

Study population, consent, and eligibility

At the study site, patients with ulcerative colitis (UC) who had been newly diagnosed by a gastrointestinal specialist were enrolled and monitored. The patients listed below qualified: Patients that meet the requirements listed below: A minimum of eighteen years of age, irrespective of gender;(2) the ability to provide written, informed consent;(3) a verified diagnosis of ulcerative colitis with anemia;(4) a Mayo score of less than ten; and(5) hemoglobin levels ranging from 8.0 to 11.0 g/dL. The exclusion criteria were as follows: (1) All systemic diseases; (2) Other disorders that mimic the symptoms of ulcerative colitis (UC); (3) Patients with UC who received parenteral iron therapy or blood transfusions within 120 days of study participation; (4) Women who were pregnant or nursing; (5) Patients with a history of gastrointestinal surgery or underlying cancer; (6) Adverse reactions related to study medication. Written informed consent was acquired from each subject.

Study sample

After screening 78 patients were included in the study who met all the inclusion criteria. The eligible patients were divided into two, Group 1 and Group 2, using computer-generated random numbers. Thirty participants from each trial group who completed the study according to protocol were included in the statistical analysis.

Statistical analysis

With a Microsoft Excel Sheet, data was captured and added to a master chart. Version 23 of the Statistical Package for Social Sciences (SPSS) was utilized for all analytical and descriptive analyses. The data were presented as number (%), mean ± SEM. Depending on the type of data, a p-value of less than 0.05 was considered significant, while a p-value of less than 0.0001 was considered extremely significant. The paired "t" test was used to collect and analyze the intra-group results of the SIBDQOL scale and Mayo score. The aforementioned parameters were the subject of an independent unpaired "t" test analysis and compilation of an intergroup analysis between the two groups. In both groups, the frequency of ADRs was expressed as a percentage.

Results and Discussion

Baseline characteristics

The patients' initial values for each parameter in both treatment groups were within the normal range, as **Table 1** illustrates. Before starting treatment, all of the patients in both groups had baseline examinations such as erythrocyte sedimentation rate (ESR) and complete blood count (CBC).

None of the baseline parameters showed a statistically significant difference (P-value > 0.05) between the two groups, indicating that none of the factors had an impact on the study's conclusions. At baseline, both groups were similar in terms of gender, age, primary and secondary endpoints, and marital status and there was no statistically significant difference between them.

Table 1. Baseline Characteristics of the Study Population

Variables	Group I	Group II	P-value
Age (years)	37.13	35.13	0.40
Sex - Male	46.67%	43.33%	0.27
Female	53.3%	56.67%	0.31
Family History	3.33%	6.67%	
Vegetarian	86.67%	93.33%	
Mayo score	7.20 ± 0.29	6.67 ± 0.28	0.27
SIBDQOL	38.67 ± 1.97	38.10 ± 1.78	0.31

Group I- Standard therapy [Mesalamine 2.4-3.6 g/day + prednisolone 40 mg/day reduced by 5 mg every 2 weeks] for 12 weeks.

Group II- Standard therapy [Mesalamine 2.4-3.6 g/day + prednisolone 40 mg/day reduced by 5 mg every 2 weeks] + oral vitamin D3 4000 IU OD for 12 weeks.

Mayo score

Mayo Score was utilized to assess the level of UC illness. Sub-scores for the following areas are included in the validated Mayo Score for UC disease activity: rectal

bleeding, stool frequency, endoscopic features, and the doctor's opinion of the patient's overall well-being. The range of the sub-scores is 0 to 3. The severity of the ailment is indicated by a higher score, while improvement is shown by a lower score. At the beginning and completion of the therapy, the Mayo score was evaluated.

Intragroup analysis

The baseline score in Group I, **Table 2** and **Figure 1** was 7.20 ± 0.29 (Mean ± SEM), and after 12 weeks, it dropped to 6.17 ± 0.29 (Mean ± SEM). The Mayo score decreased in a very statistically significant (P-value < 0.0001) way as compared to the Baseline. Likewise, at 12 weeks, the Mayo score reduction in Group II, **Table 2** was significantly statistically significant (P-value < 0.0001) about the initial score of 6.67 ± 0.37 (Mean ± SEM). The Mayo score dropped to 5.37 ± 0.32 (Mean ± SEM) after 12 weeks. The fact that both groups' Mayo scores significantly decreased suggests that conventional therapy and standard therapy combined with vitamin D were successful in reducing the severity of the condition.

Intergroup analysis

The simultaneous intergroup analysis revealed that the baseline readings for both treatment groups were similar, as indicated in **Table 2 and Figure 1**. After receiving additional therapy, Group II's Mayo score decreased more than Group I's, while the differences between the two groups' outcomes were not quite statistically significant (P-value = 0.09).

Overall, the findings listed above suggest improvements in the following areas: the frequency of stools, rectal bleeding, intestinal inflammation, the doctor's overall assessment of the patient's health, and a decrease in the severity of the illness when conventional medication and Vitamin D administered as an adjuvant with standard therapy are used.

Table 2. Comparison of Mayo Score

MAYO SCORE	Group I	Group II	P-valueβ	95% CI
	Mean ± SEM	Mean ± SEM		
0 week	7.20 ± 0.29	6.67 ± 0.38	0.27	-0.427 to 1.487
12 week	6.17 ± 0.29	5.37 ± 0.38	0.09	-0.157 to 1.757
P-valueα	< 0.0001	< 0.0001		

Intragroup analysis

Comparison of values at the end of week 12 with baseline values was statistically significant (P-value < 0.0001) for both groups.

Intergroup analysis

After week 12, a comparison of Group I and II's data was determined to be statistically significant.

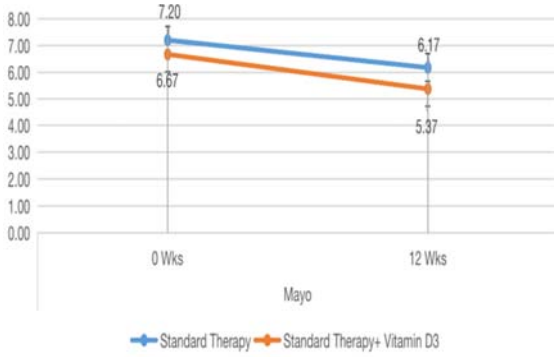

Figure 1. Comparison of changes in Mayo score.

The greater improvement in Group II is to expect that vitamin D can prevent excessive immunological responses via directly or indirectly affecting macrophages, dendritic cells, and T lymphocytes. The gut mucosal barrier can be repaired by vitamin D as well. Vitamin D has the potential to mitigate ulcerative colitis symptoms using both its mucosal healing properties and its anti-inflammatory effect on the intestines [5].

Additionally, by controlling proteins linked to gap junctions between epithelial cells, vitamin D seems to be essential for maintaining the integrity of the gastrointestinal barrier [6]. The effect of vitamin D on the gastrointestinal microbiota is similarly connected to its barrier function; in humans, alterations in bacterial genera linked to inflammatory immune responses in the gastrointestinal tract are correlated with changes in blood 25-OH-D status.

Mathur *et al*. [7] enrolled study subjects with UC with a blood 25(OH)D level < 30 ng/ml in a prospective double-blind, randomized study. For ninety days, enrolled patients were randomized to receive oral vitamin D3 at a dose of 2,000 IU or 4,000 IU per day. In both treatment dose groups, assessments of UC disease activity decreased after ninety days of vitamin D3. For the group receiving 2,000 IU of vitamin D3 daily, the mean drop in the Partial Mayo Score was 0.5 ± 1.5, whereas for the group receiving 4,000 IU, it was 1.3 ± 2.9 [7].

In a randomized controlled experiment performed by Ben Horin *et al.* [8] in 149 patients, 73 got corticosteroids with mesalamine, and 76 received corticosteroids alone, 53 of 73 patients (72.6%) who received corticosteroids together with mesalamine responded to the main outcome, compared to 58 of 76 patients (76.3%) who received corticosteroids alone. Acne, weight gain, nausea, and headaches were the most typical adverse reactions [8].

The improvement in Mayo score following treatment for 12 weeks with normal adjuvant vitamin D therapy and also in the standard therapy group, is quite comparable to the results of the previously mentioned studies.

SIBD quality of life (SIBD-QoL)

Before starting medication (baseline), as well as at 4, 8, and 12 weeks, all patients in both groups showed improvements in their quality of life scores. The questionnaire is scored with a minimum of 10 and the maximum score obtained is 70. The increase in quality of life score from baseline stated improvement in the patient's health and quality of life.

Intragroup analysis

In Group I, **Table 3** and **Figure 2**, the baseline score was 38.67 ± 2.01 (Mean ± SEM) which increased to 40.43 ± 2.01 (Mean ± SEM) at 4 weeks, 42.57 ± 2.01 (Mean ± SEM) at 8 weeks and 44.50 ± 2.01 (Mean ± SEM) at 12 weeks. At 4, 8, and 12 weeks, the quality of life score increased significantly (P-value < 0.0001) in comparison to the baseline.

Comparing Group II, **Table 3** to the baseline score (38.10 ± 1.79) (Mean ± SEM), the rise in the quality of life score seen in **Figure 2** was also highly statistically significant (P-value < 0.0001) at 4, 8, and 12 weeks. The SIBD-QOL score increased to 41.10 ± 1.80 (Mean ± SEM) at 4 weeks, 45.27 ± 1.93 (Mean ± SEM) at 8 weeks, and 51.27 ± 2.13 (Mean ± SEM) at 12 weeks.

Intergroup analysis

As **Table 3** and **Figure 2** show, both medication treatments were similar at the start of therapy based on simultaneous intergroup analysis. At 12 weeks, there was a statistical difference (P-value < 0.05) between the two groups.

Table 3. Comparison of Sibd Quality of Life Score

SIBDQOL	Group I	Group II	P-valueβ	95% CI
	Mean ± SEM	Mean ± SEM		
Week 0	38.67 ± 2.01	38.10 ± 1.79	0.83	-4..817 to 5.957
Week 4	40.43 ± 2.01	41.10 ± 1.80	0.80	-6.056 to 4.717
Week 8	42.57 ± 2.01	45.27 ± 1.93	0.32	-8.087 to 2.687
Week 12	44.50 ± 2.01	51.27 ± 2.13	0.024	-12.633 to -0.907
P-valueα	< 0.0001	< 0.0001		

Intragroup analysis

When readings at the end of weeks 4, 8, and 12 were compared to baseline levels, there was a significant statistical difference (P-value < 0.0001).

Intergroup analysis

After week 12, there was a statistically significant difference in the results between Group I and II (P-value < 0.05).

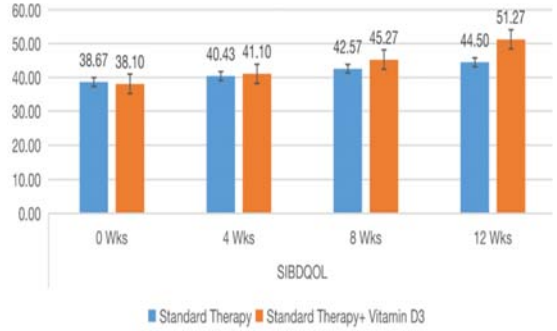

Figure 2. Comparison of changes in SIBD quality of Life

The SIBD-QOL [9] consists of 10 items, each with a seven-point response scale. The ten-item, validated SIBDQOL consists of questions with scores ranging from 1 to 7, rising in sequence, depending on the emotional, social, systemic, and gastrointestinal domains. The sum of the points earned on each of the 10 elements determines the overall SIBDQOL score.

A prospective double-blind, randomized experiment included patients with UC whose blood 25(OH)D level was less than 30 ng/ml. For a total of 90 days, eight UC patients received 2,000 IU of vitamin D3 daily, and ten received 4,000 IU. The group receiving 4,000 IU of vitamin D3 per day showed a significant increase in quality of life scores (SIBDQ) (P-value = 0.017), but the group receiving 2,000 IU did not (P-value = 0.87) [7].

Vitamin D was administered at 1000 or 2000 IU/day for 12 weeks to fifty patients with mild to severe UC who met the requirements for the double-blind, randomized clinical trial (the low dosage group received 2000 IU/day, while the high dose group received 1000 IU/day). The high-dose group's serum 25-OHD levels increased significantly (P-value < 0.001), and this increase was significantly greater than that of the low-dose group (P-value < 0.001). Furthermore, the IBDQ-9 mean score, which measures the quality of life, showed a substantial rise (P-value = 0.001) in the high-dosage group [10].

The results of the current study are quite similar to those of the previously mentioned research since, at the end of the trial, there was a statistically significant rise in the quality of life score following 12 weeks of vitamin D adjuvant standard therapy.

Safety assessment

Safety assessment was carried out by active adverse drug events (ADE) monitoring with the help of a predefined ADR form based on the known spectrum of adverse drug reactions with the study drugs with the provision to record

any other ADR as and when it happened. All the patients were subjected to ADR monitoring as and when these happened during the study specifically at 4, 8, and 12 weeks after starting the drug treatment.

Table 4. Comparison of Adverse Events in Both Groups

	Adverse events	GROUP I (n=30)	GROUP II (n=30)	P-value
Week 0	Bloating	1 (3.3%)	0 (0.0%)	1.00
	Flatulence	0 (0.0%)	1 (3.3%)	
	Nausea	2 (6.7%)	0 (0.0%)	
	Headache	0 (0.0%)	1 (3.3%)	
Week 4	Bloating	1 (3.3%)	0 (0.0%)	0.019
	Diarrhea	0 (0.0%)	1 (3.3%)	
	Abdominal pain	0 (0.0%)	1 (3.3%)	
	Acne	1 (3.3%)	0 (0.0%)	
Week 8	Bloating	1 (3.3%)	0 (0.0%)	1.00
	Acne	0 (0.0%)	1 (3.3%)	
Week 12	None	0 (0.0%)	0 (0.0%)	
Total no.		6	5	0.20

Adverse drug events

Side symptoms such as dizziness, flatulence, anxiety, chest discomfort, constipation, epigastric pain, myalgia, vomiting, and stomach pain were monitored in the patients. Patients were also enquired about any other side effects.

As shown in, **Table 4**, a total of 11 patients out of 60 showed some ADEs. In Group I, 20% of patients (n = 6) showed ADEs. The ADEs seen were nausea, headache, bloating, acne, anxiety, and drowsiness.

In Group II, 16.67% of patients (n = 5) showed any adverse event. Bloating, headache, diarrhea, and nausea were the most common ADEs in patients of Group II.

Overall, according to the aforementioned findings, adverse occurrences were similar in both groups (P-value = 0.20). In all groups, no patient stopped taking the study medicine because of a negative pharmacological event.

In this study, no serious ADEs were observed in any patient of the groups, and no intervention to prevent permanent impairment/damage was required.

Conclusion

Mayo Score decreased significantly in both groups at 12 weeks. On comparing both the groups, reduction in disease activity fell just short of being statistically significant with patients receiving Vitamin D as an adjuvant with standard therapy at 12 weeks in comparison to standard therapy alone. Both groups showed significant improvement in SIBD- Quality Of Life Score (SIBD-QoL) at 4, 8, and 12 weeks from the baseline score. On comparing both the groups, statistically significant improvement was observed in overall quality of life with the patients receiving Vitamin D as an adjuvant to standard therapy, at 12 weeks in comparison to standard therapy alone. In the present study, a total of 6 (20%), and 5 (16.67%) patients in the standard therapy group, and Vitamin D as an adjuvant with the standard therapy group, respectively, reported some ADEs. All the ADEs were of mild grade and none of them warranted any discontinuation of treatment. The most common ADEs observed were nausea and headache in group 1, and bloating and nausea in group 2. Other AEs reported were flatulence, acne, anxiety, and rashes.

Vitamin D adjuvant standard therapy and standard therapy were both found to be safe and effective in patients with ulcerative colitis. However, Vitamin D as an adjuvant with standard therapy was found to be superior to standard therapy in reducing pain parameters and improving quality of life.

The present study shows the beneficial role of Vitamin D supplementation with standard therapy as an adjuvant in reducing disease activity, ameliorating pain, and improving the quality of life in ulcerative colitis patients therefore Vitamin D can be used as an adjuvant in ulcerative colitis patients.

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Conflict of interest: None.

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Ethics statement: The study protocol was reviewed and approved by the ethics committee of the University of Health Sciences, Rohtak (BREC/Th/20/Pharma03).

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