Original Research Article

The effect of vitamin D on haemoglobin, patient assessed disease activity and endoscopic assessment in ulcerative colitis patients with anaemia

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ABSTRACT

Background: Anemia has a dramatic impact on patient's quality of life, yet anemia in patients with UC is still underdiagnosed and undertreated. Hepcidin has been identified to be a central regulator of iron absorption from the intestines and of plasma iron levels. In this study we evaluated the effect of vitamin D supplementation on haemoglobin levels, patient assessed disease activity and endoscopic assessment in ulcerative colitis (UC).
Methods: In this prospective, open-labeled, parallel-group, randomized, comparative clinical study, we assigned newly diagnosed cases of UC with haemoglobin levels between 8-11 gm/dL to receive either standard therapy for 12 weeks or to receive oral 4000IU vitamin D3 along with standard therapy for 12 weeks.
Results: Data from 60 patients were analyzed after 12 weeks. Supplementation with vitamin D3 significantly raised haemoglobin level in treatment group from (9.09±0.20) (Mean ± SEM) at baseline to 9.62±0.22 (Mean ± SEM) at 12 weeks. On assessment of abdominal pain with NRS scale at the end of treatment at 12 weeks the reduction in NRS score was to 3.47±0.29 in group I and to 2.23±0.21 in group II (p=0.0012) which was highly significant. There was also a statistically significant reduction in the Likert scale at the end of 4, 8 and 12 weeks in both groups. At week 12, there was no statistical difference between the two groups in improving the endoscopy score.
Conclusions: Daily high dose vitamin D supplementation is beneficial in ameliorating UC symptoms like abdominal pain and has a positive effect on haemoglobin levels.

Keywords: Anemia, Vitamin D, Haemoglobin

INTRODUCTION

Ulcerative colitis (UC) is a form of inflammatory bowel disease that causes inflammation in the large intestines.[1] Patients with UC predominantly complain of rectal bleeding, frequent stools, mucous discharge from the rectum, occasional tenesmus, and lower abdominal pain. Anaemia is often associated with inflammation in patients with UC and is one of the commonest complications associated with it.[2] One-third of patients with UC have hemoglobin levels <12 g/dL.[3]

The therapy of choice for anemia, the most common complication associated with UC, has been oral iron supplementation for many years.[5] However, in some studies it has been observed that exacerbation of UC occurs when receiving oral iron supplementation through the generation of reactive oxygen species (Fenton reaction) and changes in intestinal microbiota. This leads to worsening of symptoms in the patient and decreased quality of life.[6]

In addition to regulating calcium and phosphate metabolism, vitamin D can also modulate immune responses by directly or indirectly affecting T lymphocytes, dendritic cells, and macrophages, avoiding excessive immune responses. Vitamin D also has the function of repairing the intestinal mucosal barrier. Some

studies have shed light on the therapeutic lowering of hepcidin levels using vitamin D to correct anemia and intestinal inflammation in chronic inflammatory conditions.[7] Hepcidin, which regulates the rates of iron absorption and also influences plasma iron levels and distribution, increases manifold in UC patients due to intestinal inflammation. Through these mechanisms, vitamin D may help in the amelioration of UC symptoms via its anti-inflammatory effect on intestines and mucosal healing.[8]

With this background, the present study was conducted to evaluate the effect of Vitamin D adjuvant standard therapy in patients with UC with anemia by assessing the improvement hemoglobin level, endoscopic level and abdominal pain parameters as assessed by the patients.

METHODS

Study design

We conducted a prospective, open-labeled, parallel-group, randomized, comparative clinical study at PGIMS, Rohtak a tertiary care centre in India over a 14 month period (from Aug 1, 2021 to Oct 3, 2022). The study protocol was reviewed and approved by the ethics committee of university of health sciences, Rohtak (BREC/Th/20/Pharma03) and the trial was registered under Clinical Trials Registry of India on 26 July 2021 (CTRI/2021/07/035128). None of the authors has a conflict of interest with the pharmaceutical company that made the vitamin D supplements.

Study population, eligibility, and consent

Patients with UC diagnosed by a gastrointestinal specialist were recruited and followed-up at PGIMS, Rohtak. The following patients were eligible: (1) Patients of either gender aged ≥18 years; (2) Patients willing to provide written informed consent; (3) Patients with a confirmed diagnosis of UC with anemia; (4) Patients with Mayo score <10; (5) Patients with hemoglobin levels between 8-11 g/dL. The exclusion criteria were as follows: (1) Any systemic disease; (2) Other disorders which mimic UC symptoms e.g., Crohn's disease, internal hemorrhoids, Behcet's disease, ischaemic colitis, colon cancer, etc.; (3) Patients of UC who have undergone blood transfusion/ parenteral iron therapy within 120 days of study enrollment; (4) Pregnant/lactating females; (5) Any previous gastrointestinal surgery/underlying malignancy; (6) Any study drug related allergic reaction and (7) Any known hemoglobinopathies. All participants provided written informed consent.

Study sample

The 78 patients who met the inclusion criteria were screened. The eligible patients were randomly divided into two study groups i.e., group 1 and group 2 with the help of computer-generated random numbers. Each study group had 30 patients who completed the study as per the protocol.

Statistical analysis

Data was recorded and entered into a master chart using Microsoft excel Sheet. For all descriptive and analytical analysis, statistical package for social sciences (SPSS) version 23 was used. Data were expressed as Mean ± SEM, number (%) depending on the nature of the data, a p<0.05 was considered significant and a p<0.0001 was considered highly significant. The intra-group outcomes of NRS, haemoglobin, endoscopic assessment, five-point Likert scale were compiled and analyzed using paired "t" test. Inter-group analysis between 2 groups for the above-mentioned parameters was compiled and analyzed using an independent unpaired "t" test. The frequency of ADRs in the different drugs/ groups was expressed as the percentage.

RESULTS

Baseline characteristics

As shown in Table 1, the baseline values of all the parameters were in the normal range in patients of both treatment groups. At baseline, routine investigations such as complete blood count (CBC), and erythrocyte sedimentation rate (ESR), were recorded in all the patients of either group before drug administration. The baseline values of all the parameters were in the normal range in patients of both treatment groups.

There was no statistically significant difference (p>0.05) in any of the baseline parameters among the two groups thereby showing that the study outcomes were not affected by any of the parameters. Both the groups were also comparable in age, gender, marital status, and primary and secondary endpoints at baseline and the difference was statistically not significant.

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
Smoking (%)	3.33	10	
Family history (%)	3.33	6.67	
Vegetarian (%)	86.67	93.33	
Hemoglobin	8.93±0.19	9.09±0.20	0.56
NRS	5.13±0.29	4.93±0.30	0.07
Likert	2.80±0.14	2.70±0.13	0.60
Endoscopy	2.00±0.09	1.80±0.11	0.16

Changes in haemoglobin level

The level of hemoglobin was recorded in all the patients of both groups before drug administration (baseline) and at the end of 12 weeks.

Intragroup analysis

In group I, baseline score was 8.93±0.19 (Mean ± SEM) which increased to 9.10±0.20 (Mean ± SEM) at 12 weeks. The increase in haemoglobin was highly statistically significant when compared to the baseline at 12 weeks (p<0.0001).

Similarly, in group II increase in haemoglobin was highly statistically significant (p<0.0001) at 12 weeks as compared to the baseline score (9.09±0.20) (Mean ± SEM). Haemoglobin increased to 9.62±0.22 (Mean ± SEM) at 12 weeks.

Intergroup analysis

On intergroup analysis (Table 2) both groups were comparable at the beginning of treatment (p=0.56). On comparing the treatments, at week 12 after treatment, a statistically significant difference in the increase of Hb level was not quite observed between the treatment groups (p>0.05).

Table 2: Comparison of haemoglobin levels intergroup.

Hb	Group I Mean ± SEM	Group II Mean ± SEM	P$^\beta$	95% CI
0 week	8.93±0.19	9.09±0.20	0.56	-0.712 to 0.392
12 weeks	9.10±0.20	9.62±0.22	0.08	-1.115 to 0.075

All values are expressed in Mean ± SEM, β-Inter-group p.

Comparison of values between group I and II at end of week 12 was not quite statistically significant (p=0.08).

Changes in numeric rating scale (NRS)

The NRS score was evaluated at baseline (before drug administration) and then at the end of 4, 8, and 12 weeks after treatment. NRS scale is used to assess the intensity of abdominal pain. An increase in NRS score shows increasing severity of the abdominal pain whereas a decrease shows amelioration of pain.

Intragroup analysis

In group I, the baseline score was 5.13±0.29 (Mean ± SEM) which reduced to 4.63±0.30 (Mean ± SEM) at 4 weeks, 3.80±0.30 (Mean ± SEM) at 8 weeks and

3.47±0.29 (Mean ± SEM) at 12 weeks. Maximum reduction was seen at 12 weeks. The decrease in NRS score was highly statistically significant when compared to baseline at 4, 8, and 12 weeks (p<0.0001).

Similarly, in group II reduction in NRS score was highly statistically significant (p<0.0001) at 4, 8, and 12 weeks as compared to the baseline score (4.93±0.30) (Mean ± SEM). The NRS score reduced to 3.97±0.26 (Mean ± SEM) at 4 weeks, 2.93±0.25 (Mean ± SEM) at 8 weeks and 2.23±0.21 (Mean ± SEM) at 12 weeks.

A significant reduction of NRS score in both groups indicates that both drugs were effective in decreasing abdominal pain associated with UC. The improvement was seen as early as the 4th week which continued till the study ended i.e., 12 weeks.

Intergroup analysis

On simultaneous intergroup analysis as shown in Table 3 and Figure 3, the baseline readings of both the treatment groups were found to be comparable. With further treatment, the reduction in NRS score was more in group II as compared to group I, and the results were statistically significant (p<0.05) at 8 and 12 weeks

Table 3: Comparison of NRS scale intergroup.

Likert scale	Group I Mean ± SEM	Group II Mean ± SEM	P value$^\beta$	95% CI
Week 0	5.13±0.29	4.93±0.30	0.65	-0.645 to 1.02
Week 4	4.63±0.29	3.97±0.27	0.1018	-0.134 to 1.454
Week 8	3.80±0.29	2.93±0.26	0.035	0.062 to 1.677
Week 12	3.47±0.29	2.23±0.22	0.0012	0.511 to 1.968

All values are expressed in Mean ± SEM β-Inter-group p value.

Comparison of values between group I and II at end of weeks 8 and 12 was statistically significant

Changes in Likert scale

The pain associated with bowel movement was evaluated in all the patients of both groups at baseline, 4, 8, and 12 weeks. Increase in the Likert scale from baseline showed relief in pain symptoms associated with bowel movement.

Intragroup analysis

In group I, the baseline score was 2.80±0.14 (Mean ± SEM) which reduced to 2.30±0.16 (Mean ± SEM) at 4

weeks, 2±0.16 (Mean ± SEM) at 8 weeks and 1.73±0.16 (Mean ± SEM) at 12 weeks. The decrease in the Likert score was highly statistically significant when compared to baseline at 4, 8, and 12 weeks (p<0.0001).

Similarly, in group II decrease in the Likert scale was highly statistically significant (p<0.0001) at 4, 8, and 12 weeks as compared to the baseline score (2.70±0.13) (Mean ± SEM). The Likert score decreased to 1.87±0.15 (Mean ± SEM) at 4 weeks, 1.20±0.14 (Mean ± SEM) at 8 weeks and 0.83±0.12 (Mean ± SEM) at 12 weeks. A significant improvement in the two groups was indicative that, both drugs were effective in improving pain associated with bowel movement in UC. The improvement was seen as early as 4 weeks which continued and was maximum at 12 weeks.

Intergroup analysis

On simultaneous intergroup analysis as shown in (Table 4 and Figure 4) both drug treatments were comparable at the beginning of treatment. On comparing the treatments, at weeks 4, 8, and 12, a statistically significant difference in the reduction of the score was observed in group II at 8 and 12 weeks.

Table 4: Comparison of 5- point Likert scale intergroup.

Likert scale	Group I Mean ± SEM	Group II Mean ± SEM	P value[β]	95% CI
Week 0	2.80±0.14	2.70±0.13	0.60	-0.282 to 0.482
Week 4	2.30±0.16	1.87±0.15	0.05	-0.009 to 0.867
Week 8	2.00±0.16	1.20±0.14	0.0004	0.374 to 1.226
Week 12	1.73±0.16	0.83±0.12	<0.0001	0.499 to 1.300

All values are expressed in mean ± SEM, β-Inter-group p

Comparison of values between group I and II at end of weeks 4, 8 and 12 was statistically significant (p<0.05) at week 8 and highly statistically significant (p<0.0001) at week 12.

Changes in endoscopy

Intragroup analysis

In group I, baseline score was 2±0.09 (Mean ± SEM) which decreased to 1.93±0.08 (Mean ± SEM) at 12 weeks. The decrease in endoscopy score was not statistically significant when compared to baseline at 12 weeks (p>0.05).

Similarly, in group II, baseline score (1.80±0.11) (Mean ± SEM) decreased to 1.73±0.10 (Mean ± SEM) at 12 weeks. The decrease in endoscopy score was not statistically significant when compared to baseline at 12 weeks (p>0.05)

Intergroup analysis

On simultaneous intergroup analysis (Table 5) both groups were comparable at the beginning of treatment. At week 12, there was no statistical difference between the two groups in improving the endoscopy score.

Table 5: Comparison of endoscopy score intergroup.

Endoscopy assessment	Group I Mean ± SEM	Group II Mean ± SEM	P value[β]	95% CI
Week 0	2.00±0.09	1.80±0.11	0.16	-0.084 to 0.484
Week 12	1.93±0.08	1.73±0.10	0.12	-0.056 to 0.456

All values are expressed in Mean ± SEM, β-Inter-group p value

The comparison of values between group I and II was not statistically significant (p<0.05) at baseline and 12 weeks.

DISCUSSION

Hemoglobin levels were assessed at baseline and 12 weeks. In the present study, there was a statistically significant increase in hemoglobin levels at the end of 12 weeks compared to baseline values in both, standard therapy and vitamin D adjuvant standard therapy groups. There was increase in haemoglobin from 8.93±0.19 at baseline to 9.10±0.20 at 12 weeks in group I and from 9.09±0.20 at baseline to 9.62±0.22 in group II at the end of week 12. At the end of treatment, there was an increase in hemoglobin levels but the difference in both the groups at end of treatment fell just short of being statistically significant.

Although similar studies were not available in which similar treatment groups were compared for observing improvement in hemoglobin, few studies were found that have assessed improvement in hemoglobin levels with vitamin D, but in other diseases.

The observed improvement is on the expected lines of the relation between hepcidin, vitamin D, and inflammation in IBD. It has been seen in different pre-clinical and clinical studies that vitamin D suppresses hepcidin transcription and decreases pro-inflammatory cytokines which leads to an increase in iron moving from cells into the circulation which increases red cell production. Further, the hepcidin antimicrobial peptide gene (HAMP) has been found to

contain a vitamin D response element, thus lending biological plausibility to the observed association between vitamin D deficiency and anemia.[9]

Ernst et al conducted EVITA (Effect of vitamin D on mortality in heart failure), which is a randomized, placebo-controlled clinical trial in heart failure patients with initial 25OHD levels <75 nmol/l. Participants received either 4000 IU of vitamin D3 daily or a matching placebo for 36 months. A total of 172 patients (vitamin D group: n=85; placebo group: n=87) were investigated. Hemoglobin (Hb) and other hematological parameters were measured at baseline and study termination. In the vitamin D and placebo group, baseline proportions of patients with anemia (Hb <12 g/dL in females and <13 g/dL in males) were 17.2% and 10.6%, respectively (p=0.19). At study termination, the proportion of patients with anemia in the vitamin D and placebo groups was 32.2% and 31.8%, respectively (p>0.99). There was no statistical group difference in change in the Hb concentrations (-0.04 g/dL [95% CI:-0.53 to 0.45 g/dL]; p=0.87).[10]

In a randomized placebo-controlled trial by Smith et al mechanically ventilated critically ill adults (n=30) enrolled in a pilot trial of high-dose vitamin D3. Participants were randomized to receive a placebo, 50,000 IU D3, or 100,000 IU D3 daily for 5 days intramuscularly (totaling 250,000 IU D3, and 500,000 IU D3, respectively). In the 500,000 IU D3 group, hemoglobin concentrations increased significantly over time compared to the placebo but did not change in the 250,000 IU D3 group. Hepcidin concentrations decreased acutely in the 500,000 IU D3 group relative to the placebo after 1 week. Hepcidin did not change significantly in 250,000 IU D3 group. In these critically ill adults, treatment with 500,000 IU D3 was associated with increased hemoglobin concentrations over time and acutely reduced serum hepcidin concentrations.[11]

The findings in the present study are consistent with the above-mentioned studies although not as statistically significant. This may be due to the fact that the present study had a lower dose than the above study as well as a different route of administration.

In a cross-sectional study by Syed et al data was obtained from n=69 IBD patients aged 5 to <19 year. Iron biomarkers, 25-hydroxyvitamin D (25(OH)D), inflammatory biomarkers [C-reactive protein (CRP), α1-acid glycoprotein (AGP)], hepcidin, and hemoglobin were collected. In a linear regression model vitamin D insufficiency was associated with increased hepcidin levels (p=0.01) and decreased hemoglobin although the results were not statistically significant.[12]

The findings in the present study correlate well with the above-mentioned studies with regard to positive association between hemoglobin and vitamin D.

Abdominal pain assessment was done at baseline, 4 weeks, 8 weeks, and 12 weeks.

The clinical improvement was assessed by providing a self-administered form to the patients to monitor their pain intensity during the 12 weeks of the study period. In the present study, both groups showed a highly statistically significant reduction in NRS score for pain intensity over 12 weeks. This statistically significant reduction was observed starting from week 4 which gradually decreased further in the subsequent weeks indicating that the improvement was ongoing throughout the study period.

At the end of week 4, the score reduced from 5.13±0.29 at baseline to 4.63±0.30 in group I and from 4.93±0.30 at baseline to 3.97±0.26 in group II. The reduction by week 8 was to 3.80±0.30 and NRS score reduced to 2.93±0.25 in group I and group II, respectively. At the end of treatment at 12 weeks the reduction in NRS score was to 3.47±0.29 in group I and to 2.23±0.21 in group II. This improvement may be due to the fact that vitamin D can downregulate the inflammatory cascade by decreasing the proliferation of T cells (Th1), inhibiting cytokine production of IL-2 and INF-V, and inducing proliferation of regulatory T cells.[13]

After literature search, no similar study was found where the NRS score was compared after administration of vitamin D adjuvant standard therapy in UC patients but studies where the effect of vitamin D and mesalamine on abdominal pain in UC patients was seen were found.

In a multicenter cross-sectional study, the brief pain inventory (BPI) questionnaire was used to measure pain. Of 407 patients included in the analyses, 229 (56%) had Crohn's disease (CD) and 178 (44%) had UC (UC). vitamin D deficiency was present in half (203/407) of patients. The presence of pain was reported by 76% (309/407). In this study, no statistically significant association between pain severity and vitamin D deficiency was revealed in patients with IBD.[14]

The findings of the present study are quite similar to those of the above-mentioned study as statistically significant improvement in abdominal pain was observed at end of the study at 12 weeks with vitamin D adjuvant standard therapy.

Patients rated the frequency of pain using a five-point Likert scale, as follows: 1-`never or rarely'; 2-`sometimes'; 3-`often'; `4-`most of the time'; 5-`always'.

There was a statistically significant reduction in the Likert scale at the end of 4, 8 and 12 weeks compared to baseline values in both groups. At 4 weeks, group I showed a decrease in Likert score from 2.80±0.14 at baseline to 2.30±0.16. Group II showed a decrease from 2.70±0.13 at baseline to 1.87±0.15. At 8 weeks the reduction in scores was 2.00±0.16 and 1.20±0.14 in group I and group II, respectively. After 12 weeks the score decreased to 1.73±0.16 in group I and to 0.83±0.12 in group II.

On literature search, no similar study was found where the

Likert score was compared after administration of Vitamin D adjuvant standard therapy in UC patients but some relevant studies where the efficacy of mesalamine and vitamin D in ameliorating pain using other scales was observed.

The 1500-4000 IU daily dosage of vitamin D3 was given in a study on 39 IBD patients and 33 healthy controls with most of the UC patients graded severe on the Mayo score. The presence of pain was reported by 76.9% of patients (30/39) at the end of treatment in the supplementation group at 3 weeks. The mean scores for pain severity and frequency decreased in the supplementation group but were not statistically significant in both the CD and UC groups.[15]

The findings of the present study are quite similar to those of the above-mentioned studies as improvement in abdominal pain was observed at end of the study at 12 weeks with standard therapy as well as vitamin D adjuvant standard therapy.

Assessment of intestinal inflammation

It was done at baseline, 4 weeks, 8 weeks, and 12 weeks using the endoscopic parameter of the mayo score and ESR. Endoscopic findings include continuous colonic inflammation characterized by erythema, friability, loss of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations.[16] In the present study, there was a decrease in endoscopy score at the end of 12 weeks compared to baseline values in both, standard therapy and vitamin D adjuvant standard therapy groups. The decrease was from 2.00 ± 0.09 at baseline to 1.93 ± 0.08 in group I and from 1.80 ± 0.11 at baseline to 1.73 ± 0.10 in Group II at the end of week 12.

Garg et al conducted a study in eight patients with active UC, nine with inactive UC, and eight non-IBD controls who received 40000 units of cholecalciferol weekly for 8 weeks. In patients with active UC, markers of intestinal inflammation, platelet count decreased and albumin increased in patients of UC who received Vitamin D. Vitamin D supplementation was associated with reduced intestinal inflammation in patients with active UC.[17]

In a pilot study, 1000 to 10,000 IU of vitamin D3 was given according to serum levels of the 5 patients of mild to moderate UC as an adjuvant to mesalamine and prednisolone standard therapy. Fecal calprotectin and biomarkers of inflammation did not improve. Clinical disease activity (HBI and SSCAI) significantly reduced over 12 weeks in CD (p=0.019), and a trend was seen in UC (p=0.051). The most common adverse effect observed was hypercalciuria.[18]

The findings in the present study are quite consistent with the abovementioned studies as a statistically significant change in intestinal inflammation scores has not been observed with vitamin D as early as 12 weeks.

There are certain limitations to the study such as not analyzing hepcidin levels through S-hep-25 by mass spectrometry periodically, some patients having vitamin D deficiency at baseline, short intervention period and no power calculation performed which may have limited its statistical power.

CONCLUSION

In conclusion, the results of the present study suggest that daily high dose vitamin D supplementation is beneficial in ameliorating UC symptoms like abdominal pain and has a positive effect on haemoglobin levels.

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