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Original Article

Combined therapy with vitamin D, mesalazine, and microecological preparations improves clinical outcome in ulcerative colitis

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Abstract: Objective: To evaluate the clinical efficacy of adjunctive vitamin D to mesalazine combined with microecological preparations in the treatment of ulcerative colitis. Methods: A retrospective analysis was conducted on the clinical data of 103 patients with ulcerative colitis. The conventional treatment group (n=54) received mesalazine plus microecological preparations, while the combined treatment group (n=49) received additional vitamin D. Both groups were treated for one month. The efficacy, safety, and mechanistic indicators were compared between the two groups. Results: After one month of treatment, the combined treatment group showed better results than the conventional treatment group in terms of endoscopic findings, disease activity, inflammatory indicators, intestinal barrier function, oxidative stress levels, and the Inflammatory Bowel Disease Questionnaire (all $P<0.05$). No significant difference was found in the incidence of adverse reactions ($P>0.05$). Conclusion: Vitamin D supplementation on the basis of mesalazine combined with microecological preparations can improve the clinical efficacy, mucosal healing, and related biological indicators in patients with ulcerative colitis, and has good safety.

Keywords: Vitamin D, mesalazine, microecological preparations, ulcerative colitis, inflammatory response

Introduction

Ulcerative colitis is a chronic inflammatory bowel disease that primarily affects the colonic mucosa and submucosa. Common symptoms include diarrhea, abdominal pain, urgency, and tenesmus. The disease is protracted and prone to recurrence. If not effectively controlled, it can lead to a series of serious complications such as intestinal bleeding, perforation, and even cancer, significantly impacting patients' quality of life and placing a considerable economic burden on families and society [1]. Mesalazine, a 5-aminosalicylic acid derivative, can inhibit the COX and LOX pathways, reducing the synthesis of inflammatory mediators like prostaglandins and leukotrienes, thus exhibiting local anti-inflammatory activity [2]. However, clinical practice shows that some patients do not respond well to mesalazine monotherapy and exhibit drug resistance, requiring combination therapy with other drugs to further enhance efficacy [3].

In recent years, with the deepening clinical research on the role of gut microbiota in the pathogenesis of ulcerative colitis, the application of microecological preparations has received increasing attention. Related studies have found that gut microbiota dysbiosis is common in patients with ulcerative colitis. Microecological preparations can improve the intestinal microenvironment through multiple pathways, such as directly supplementing beneficial bacteria in the gut, inhibiting pathogen colonization, modulating host immune respons-

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es, and strengthening the intestinal epithelial barrier function [4, 5].

Furthermore, studies have found that vitamin D receptors are widely expressed in intestinal epithelial cells and immune cells. Vitamin D can not only improve symptoms in patients with ulcerative colitis by modulating the gut microbiota, but also help restore the normal structure of the intestinal epithelium and reduce inflammatory cell infiltration [6]. In recent years, microecological preparations and vitamin D have been frequently used as adjunctive therapy for patients with ulcerative colitis, demonstrating potential application value [7, 8]. Therefore, this study explores the use of vitamin D and microecological preparations as adjunctive therapy with mesalazine for ulcerative colitis, aiming to provide a reference for optimizing clinical treatment plans for ulcerative colitis.

Materials and methods

Clinical materials

Clinical data of 103 patients with ulcerative colitis admitted to Hebei University of Chinese Medicine First Affiliated Hospital and Hebei University of Chinese Medicine Fourth Affiliated Hospital from February to December 2024 were retrospectively collected. Inclusion criteria: meeting the diagnostic criteria for ulcerative colitis [9]; age between 18 and 70 years; mild to moderate disease activity; complete baseline data and laboratory test data; no allergic reaction to mesalazine and other drugs used in the study. Exclusion criteria: recent use of glucocorticoids, immunosuppressants or biological agents; complicated by infectious enteritis, radiation enteritis, Crohn's disease or other types of intestinal diseases; previous gastrointestinal surgery; complicated by colon cancer, intestinal polyps, intestinal perforation and severe intestinal bleeding; pregnant or lactating; complicated with severe heart, liver or kidney dysfunction. The 103 patients with ulcerative colitis were divided into groups based on the treatment regimen. The conventional treatment group (n=54) received mesalazine + microecological preparations, and the combined treatment group (n=49) received mesalazine + microecological preparations + vitamin D. This study was approved by the medical ethics committee of the Hebei University of Chinese Medicine Fourth Affiliated Hospital and was a retrospective study, exempting patients from informed consent.

Methods

The treatment regimen for the conventional treatment group was mesalazine + microecological preparations (Bifidobacterium and Lactobacillus triple live bacteria).

Specific dosage and administration: oral mesalazine enteric-coated tablets (Sunflower Pharmaceutical Group Jiamusi Luling Pharmaceutical Co., Ltd., National Drug Approval number: H19980148), 1.0 g/time, 4 times/day; oral Bifidobacterium and Lactobacillus triple live bacteria tablets (main strains include Bifidobacterium longum, Lactobacillus bulgaricus, and Streptococcus thermophilus; live bacteria count per gram: Bifidobacterium longum: not less than 1.0×10^7 CFU/g, Lactobacillus bulgaricus: not less than 1.0×10^6 CFU/g, Streptococcus thermophilus: not less than 1.0×10^6 CFU/g; store at 2-8°C; protect from light prior to use; Inner Mongolia Shuangqi Pharmaceutical Co., Ltd., approval number S19980004), 1.0 g/dose, 4 times/day.

The combined therapy group received additional vitamin D (calcitriol) treatment on the standard treatment regimen. Specific dosage and administration: oral calcitriol soft capsules (Hunan Yinze Huahao Biotechnology Co., Ltd., National Drug Approval Number H2024-9599), 0.25 μg/dose, once/day. Both groups of patients received treatment for one month.

Outcome measures

(1) Endoscopic findings. Before and 1 month after treatment, all patients underwent colonoscopy assessment using the Baron endoscopic score. This score ranges from 0 to 5 points based on mucosal vascular texture, bleeding tendency, erosion, and ulceration. Higher scores indicate poorer endoscopic findings.

(2) Disease activity. Before and the 1 month after treatment, the Sutherland Disease Activity Index (DAI) was used to quantitatively assess the patients' disease status. The DAI integrates four aspects: frequency of diarrhea, degree of rectal bleeding, mucosal find-

ings, and overall physician evaluation. Its score range is 0-12 points, with higher scores indicating more severe disease activity.

(3) Inflammatory indicators. Five milliliters of fasting venous blood samples were collected from two groups before and 1 month after treatment. The samples were centrifuged at 3000 rpm for 10 minutes for subsequent analysis. The upper serum layer was separated and the levels of interleukin-1β (IL-1β), matrix metalloproteinase-1 (MMP-1), and tumor necrosis factor-α (TNF-α) in both groups were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Wuhan Enkilife Science & Technology Co., Ltd.). The erythrocyte sedimentation rate (ESR) in both groups was measured using the Widmanstätten method.

(4) Intestinal barrier function indicators. Five milliliters of fasting venous blood from both groups was centrifuged at 3000 rpm for 10 minutes before and 1 month after treatment to obtain serum. The levels of D-lactic acid (D-LA), diamine oxidase (DAO), and lipopolysaccharide (LPS) in the serum were measured using ELISA.

(5) Oxidative stress indicators. Using the same serum samples and the same methods outlined above, serum was processed and subsequently analyzed by distinct assays to characterize the oxidative stress status. Superoxide dismutase (SOD) levels in both groups were measured using the thiobarbituric acid colorimetric method, malondialdehyde (MDA) levels in both groups were measured using ELISA, and lipid peroxide (LPO) levels were measured using a colorimetric assay.

(6) Quality of life. The Inflammatory Bowel Disease Questionnaire (IBDQ) was used to assess quality of life before treatment and one month after treatment. The IBDQ included four dimensions: intestinal symptoms, systemic symptoms, emotional function, and social function, with a total of 32 questions. Each question was scored from 1 to 7 points, for a total score of 32 to 224 points. The score was directly proportional to the quality of life.

(7) Clinical efficacy. One month after treatment, a comprehensive evaluation was performed based on patients' clinical symptoms, signs, and colonoscopy results. Significant effect: Symptoms and signs completely or essentially disappear, and colonoscopy shows mucosal healing and near-normal recovery. Effective: Symptoms and signs significantly improve, and colonoscopy shows only mild inflammatory reaction in the mucosa. Ineffective: The above criteria are not met or the condition worsens. The total effective rate is the sum of the significant effect rate and the effective rate.

(8) Adverse reactions. All possible adverse reactions, such as nausea and vomiting, pruritus and fatigue, were closely observed and recorded. The total incidence was calculated to compare the safety of the two treatment regimens.

Statistical analysis

Data analysis was conducted using SPSS 26.0 statistical software (IBM Corp., Armonk, NY, USA). Following normality assessment, normally distributed measured data were presented as mean ± SD, with the t-test used for between-group comparisons. Those not conforming to a normal distribution were expressed as the median (interquartile range), and non-parametric tests were used for inter-group comparisons. Counted data were expressed as n (%), and the χ^2 test was used. $P<0.05$ was considered significant.

Results

Baseline characteristics

There were no significant differences in baseline data between the conventional treatment group and the combined treatment group, making them comparable ($P>0.05$). Key baseline data included gender, age, disease severity (mild/moderate), disease course, body mass index, and lesion location (all $P>0.05$). See **Table 1**.

Endoscopic findings and disease activity

One month after treatment, both groups showed a decrease in Baron endoscopic scores and Sutherland DAI scores, with the combined treatment group showing a lower score than the conventional treatment group (both $P<0.05$).

Figure 1 shows a typical patient with ulcerative colitis. Before treatment, colonoscopy reveal-

Table 1. Comparison of baseline characteristics between the two groups [n (%)/mean ± SD]

Item		Conventional treatment group (n=54)	Combined treatment group (n=49)	$\chi^2/t/Z$	*P*
Sex	Male	24 (44.44)	21 (42.86)	0.026	0.871
	Female	30 (55.56)	28 (57.14)		
Age (y)		37.12±6.50	37.35±5.98	0.186	0.853
Disease severity	Mild	29 (53.70)	24 (48.98)	0.230	0.632
	Moderate	25 (46.30)	25 (51.02)		
Disease course (y)		3.52±1.10	3.68±1.03	0.760	0.449
BMI (kg/m^2)		23.04±4.26	23.21±3.80	0.213	0.832
Disease sites	Left-sides colon	24 (44.44)	21 (42.86)	0.439	0.660
	Rectosigmoid colon	19 (35.19)	15 (30.61)		
	Extensive colitis	11 (20.37)	13 (26.53)		

Note: BMI, Body mass index.

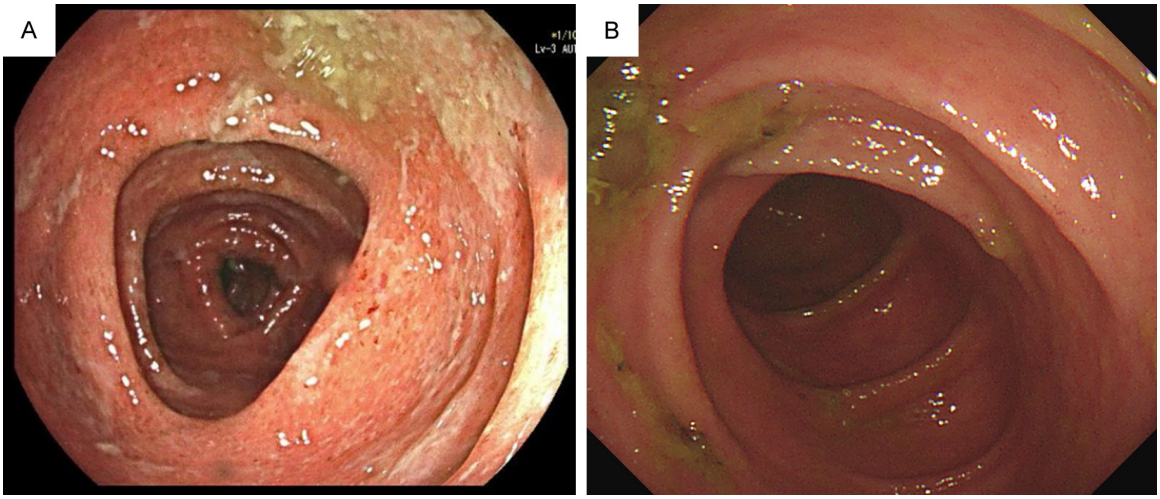

Figure 1. Comparison of endoscopic findings of the diseased intestinal segments before and after treatment (rectosigmoid colon). A. Pre-treatment: Before treatment, the Baron Endoscopic Score was 2 points, with marked mucosal hyperemia, edema, erosion and exudation; B. One month after treatment, the Baron endoscopic score decreased to 1 point, and mucosal inflammation was significantly alleviated, indicating mucosal repair.

ed: a distinct annular narrowing structure in the intestinal lumen, with reduced lumen size, diffuse hyperemia and edema of the surrounding mucosa, a smooth surface with mild exudation, and patchy erosions and punctate hemorrhages. A small channel was visible in the center of the narrowed area, with a darker red mucosa. Local inflammatory stenosis was suspected. Post-treatment colonoscopy revealed significant improvement in the intestinal mucosa, with reduced congestion and edema, and a smoother surface. Previously visible mucosal erosion and exudate were significantly reduced, with only a small amount of residual yellowish-white mucus remaining. The intestinal lumen was patent, without significant annular stenosis, and the lumen was more open than before treatment, with a softer intestinal wall. Overall, this indicated a significant decrease in inflammatory activity and good mucosal repair (**Table 2** and **Figure 1**).

Inflammatory indicators

One month after treatment, the levels of IL-1β, MMP-1, TNF-α, and ESR in both groups were significantly lower than before treatment (all $P<0.05$). The combined treatment group showed a significant advantage in the reduction of all the above inflammatory indicators, with its final levels of IL-1β, MMP-1, TNF-α, and ESR significantly lower than those in the con-

Table 2. Comparison of endoscopic findings and disease activity ($\bar{x}\pm s$, points)

Item		Conventional treatment group (n=54)	Combined treatment group (n=49)	*t*	*P*
Baron endoscopic scores	Before treatment	1.72±0.49	1.74±0.50	0.205	0.838
	After one month of treatment	0.98±0.31*	0.71±0.46*	3.522	0.001
Sutherland DAI	Before treatment	6.11±1.35	6.16±1.21	0.197	0.844
	After one month of treatment	2.85±0.81*	2.41±0.67*	2.987	0.004

Note: DAI, disease activity index. *P<0.05 vs. pre-treatment within the same group.

Table 3. Comparison of inflammatory indicators between the two groups (mean ± SD)

Item		Conventional treatment group (n=54)	Combined treatment group (n=49)	*t*	*P*
IL-1β (μg/L)	Before treatment	11.33±2.67	11.72±3.15	0.680	0.498
	After one month of treatment	7.12±2.22*	4.01±1.39*	8.420	<0.001
MMP-1 (μg/L)	Before treatment	2.89±0.53	2.95±0.58	0.549	0.585
	After one month of treatment	1.62±0.42*	1.03±0.42*	7.120	<0.001
TNF-α (μg/L)	Before treatment	33.70±6.20	34.71±7.13	0.769	0.444
	After one month of treatment	19.33±4.77*	12.72±3.12*	8.231	<0.001
ESR (mm/h)	Before treatment	24.10±4.88	23.72±4.10	0.426	0.671
	After one month of treatment	14.77±3.32*	10.99±2.92*	6.109	<0.001

Note: IL-1β, interleukin-1β; MMP-1, matrix metalloproteinase-1; TNF-α, tumor necrosis factor-α; ESR, erythrocyte sedimentation rate. *P<0.05 vs. pre-treatment within the same group.

Table 4. Comparison of intestinal barrier function indicators between the two groups (mean ± SD)

Item		Conventional treatment group (n=54)	Combined treatment group (n=49)	*t*	*P*
D-LA (U/L)	Before treatment	20.23±4.12	21.06±4.77	0.947	0.346
	After one month of treatment	11.42±3.79*	6.83±2.11*	7.488	<0.001
DAO (mg/L)	Before treatment	28.12±4.32	28.62±3.89	0.615	0.540
	After one month of treatment	22.81±4.56*	16.33±3.12*	6.139	<0.001
LPS (pg/mL)	Before treatment	84.12±12.32	86.21±15.82	0.752	0.454
	After one month of treatment	25.72±7.11*	18.20±5.66*	5.899	<0.001

Note: D-LA, D-lactate; DAO, diamine oxidase; LPS, lipopolysaccharide. *P<0.05 vs. pre-treatment within the same group.

ventional treatment group (all P<0.05) (**Table 3**).

Intestinal barrier function indicators

After one month of treatment, the levels of intestinal barrier function indicators D-LA, DAO, and LPS in both groups decreased significantly, and the combined treatment group showed lower levels of these indicators compared to the conventional treatment group (all P<0.05). See **Table 4**.

Oxidative stress indicators

After one month of treatment, the levels of MDA and LPO in both groups decreased significantly, while the levels of SOD increased significantly (all P<0.05). The combined treatment group showed better improvement in these indicators than the conventional treatment group (all P<0.05). See **Table 5**.

Quality of life

At baseline, there was no significant difference in IBDQ scores between the two groups (P>0.05). After treatment, the scores and total scores in the four dimensions of intestinal symptoms, systemic symptoms, emotional function, and social function in both groups significantly improved compared to before treatment, and the combined treatment group showed

Table 5. Comparison of oxidative stress indicators between the two groups (mean ± SD)

Item		Conventional treatment group (n=54)	Combined treatment group (n=49)	*t*	*P*
MDA (nmol/L)	Before treatment	22.73±4.90	23.26±5.12	0.537	0.593
	After one month of treatment	12.10±3.34*	9.87±2.23*	3.943	<0.001
SOD (IU/mL)	Before treatment	18.12±4.32	18.62±3.89	0.615	0.540
	After one month of treatment	32.81±8.56*	56.33±9.12*	13.500	<0.001
LPO (mmol/L)	Before treatment	9.12±2.30	9.25±1.83	0.315	0.753
	After one month of treatment	5.77±1.56*	4.37±1.32*	4.891	<0.001

Note: SOD, superoxide dismutase; MDA, malondialdehyde; LPO, lipid peroxide. *P<0.05 vs. pre-treatment within the same group.

Table 6. Comparison of IBDQ scores between the two groups (mean ± SD, points)

Item		Conventional treatment group (n=54)	Combined treatment group (n=49)	*t*	*P*
Bowel symptoms	Before treatment	47.63±6.20	46.55±5.82	0.909	0.366
	After one month of treatment	60.12±6.07*	63.17±4.24*	2.928	0.004
Systemic symptoms	Before treatment	25.12±3.39	24.79±4.13	0.445	0.657
	After one month of treatment	29.26±2.16*	31.27±2.04*	4.842	<0.001
Emotional function	Before treatment	62.33±6.20	61.07±5.77	1.065	0.290
	After one month of treatment	67.32±5.24*	71.33±6.80*	3.370	0.001
Social function	Before treatment	25.77±5.12	26.25±4.32	0.512	0.610
	After one month of treatment	28.72±2.99*	30.50±3.55*	2.761	0.007
Total score	Before treatment	160.83±10.14	158.63±10.53	1.080	0.283
	After one month of treatment	185.37±9.36*	196.29±10.06*	5.707	<0.001

Note: IBDQ, inflammatory bowel disease questionnaire. *P<0.05 vs. pre-treatment within the same group.

Table 7. Comparison of clinical efficacy between the two groups [n (%)]

Group	Markedly effective	Effective	Ineffective	Total effective rate
Conventional treatment group (n=54)	16 (29.63)	24 (44.44)	14 (25.93)	40 (74.07)
Combined treatment group (n=49)	32 (65.31)	13 (26.53)	4 (8.16)	45 (91.84)
χ^2				5.620
P				0.018

higher scores in all these dimensions than the conventional treatment group (all P<0.05). See **Table 6**.

Clinical efficacy

The total effective rate in the combined treatment group (91.84%) was significantly higher than that in the conventional treatment group (74.07%) (P<0.05). The results indicate that vitamin D supplementation, in addition to mesalazine and microecological preparations, can more effectively improve the clinical efficacy in patients with ulcerative colitis. See **Table 7**.

Drug safety

Throughout the treatment period, both groups demonstrated good drug safety. All adverse reactions were mild and did not affect the normal progress of treatment. There was no significant difference in the incidence of adverse reactions between the two groups (7.41% vs. 8.16%) (P>0.05). See **Table 8**.

Discussion

Ulcerative colitis is characterized by its chronic, persistent, and recurrent nature, and its incidence rate in China has been increasing year

Table 8. Comparison of adverse reactions between the two groups [n (%)]

Group	Nausea & Vomiting	Pruritus	Fatigue	Total
Conventional treatment group (n=54)	1 (1.85)	1 (1.85)	2 (3.70)	4 (7.41)
Combined treatment group (n=49)	2 (4.08)	1 (2.04)	1 (2.04)	4 (8.16)
χ^2				0.051
P				0.822

by year [10]. At present, drug therapy remains the main treatment option in clinical practice, with the core goal of inducing and maintaining clinical remission, while emphasizing individualized and comprehensive management of treatment [11, 12]. However, there is currently no consensus on which combination therapy regimen can achieve the optimal balance between efficacy and safety. Mesalazine, as a basic treatment for ulcerative colitis, has a mechanism of action involving multiple aspects. On the one hand, this drug can effectively inhibit the biosynthesis of key inflammatory mediators such as prostaglandins and leukotrienes by regulating the cyclooxygenase and lipoxygenase pathways, thereby reducing the inflammatory cascade reaction of the intestinal mucosa [13]. On the other hand, mesalazine has the ability to scavenge oxygen free radicals, which helps to reduce the damage of oxidative stress to intestinal mucosal cells and exert a mucosal protective effect. In addition, mesalazine can effectively inhibit the excessive activation of immune cells such as lymphocytes and macrophages in the mucosa, thereby regulating the local immune inflammatory response [14, 15].

Microecological preparations can not only regulate the gut microbiota by increasing the number of beneficial bacteria in the patient's gut and restoring the balance of the microbiota, but also inhibit the body's inflammatory response by inhibiting multiple inflammatory signaling pathways and regulating immune function. At the same time, these preparations also have pharmacological effects such as protecting the intestinal barrier and regulating metabolism, and have a positive effect on relieving symptoms in patients with ulcerative colitis [16]. Previous studies have confirmed that the efficacy of mesalazine combined with microecological preparations is better than that of mesalazine alone [17]. However, some patients still have poor responses, suggesting that new treatment regimens have important clinical significance.

Vitamin D is a fat-soluble vitamin that plays an important role not only in regulating the body's calcium and phosphorus metabolism and maintaining bone health, but also in cell proliferation, differentiation, apoptosis and regulating adaptive immune responses [18, 19]. This study evaluated the intervention method of vitamin D combined with microecological preparations and mesalazine. This study showed that the total clinical effective rate of the combined treatment group (91.84%) was higher than that of the conventional treatment group (74.07%). One month after treatment, the Baron endoscopic score, Sutherland DAI score, inflammatory indicators (IL-1β, MMP-1, TNF-α, ESR), and intestinal barrier function indicators (D-LA, DAO, LPS) were all lower than those in the conventional treatment group. This indicates that the treatment regimen can further enhance efficacy, alleviate systemic inflammation, and promote the recovery of intestinal barrier function. The reason for this is that mesalazine, microecological preparations, and vitamin D form a multi-target synergistic anti-inflammatory system. Mesalazine mainly blocks the synthesis of inflammatory mediators; microecological preparations enhance immune homeostasis by regulating the gut-immune axis; vitamin D can directionally regulate T lymphocyte subsets and intervene in the activation of key inflammatory signaling pathways such as NF-κB. Mesalazine creates conditions for intestinal mucosal repair by controlling basic inflammation; microecological preparations improve the mucosal microenvironment through mechanisms such as colonization of beneficial bacteria and production of short-chain fatty acids; vitamin D can directly upregulate the expression of tight junction proteins between intestinal epithelial cells and stimulate Paneth cells to produce antimicrobial peptides. The syner-

gistic effect of these three factors can more effectively repair and protect the intestinal barrier.

Clinical studies have identified a close relationship between oxidative stress and ulcerative colitis. Oxidative stress can exacerbate the progression of ulcerative colitis in patients through various mechanisms, including lipid peroxidation damaging cell membranes, amplifying inflammatory signals, and impairing barrier integrity [20, 21]. In our study, after one month of treatment, the combined treatment group showed more significant improvement in oxidative stress indicators (MDA, LPO, SOD) compared to the conventional treatment group, suggesting that combined treatment has an advantage in reducing oxidative stress and indicating that increasing vitamin D is beneficial in alleviating oxidative stress in patients. Vitamin D may alleviate oxidative stress through multiple synergistic pathways. After binding to its receptor, it enhances free radical scavenging capacity by activating the Nrf2 signaling pathway and upregulating the expression of endogenous antioxidant enzymes such as SOD; on the other hand, it reduces the source of reactive oxygen species by inhibiting NADPH oxidase activity. Furthermore, its anti-inflammatory effect also helps reduce oxidative stress.

Regarding quality of life, patients receiving combined treatment for one month showed better results, with significantly higher IBDQ scores than the conventional treatment group. This advantage suggests that the addition of vitamin D may provide additional benefits to patients. From a safety perspective, the incidence of adverse reactions was essentially the same in both groups, indicating good tolerability of the combination therapy. This suggests that increasing vitamin D does not significantly affect treatment safety. This may be due to the high adverse reaction threshold of vitamin D and its multiple protective mechanisms, including immune regulation, intestinal barrier repair, and antioxidation.

However, this study was a single-center retrospective study, and patient grouping was based on previous clinical treatment protocols rather than randomization. Selection bias and potential confounding factors (such as dietary intervention and adherence to non-pharmacologic treatments) may not have been fully controlled. Therefore, the study conclusions still need to be interpreted with caution. Furthermore, only the short-term efficacy after one month of treatment was observed; the recurrence rate, long-term mucosal healing maintenance, and the safety of long-term vitamin D supplementation were not assessed. Future large-sample, multi-center, randomized, double-blind prospective studies with extended follow-up periods are necessary to verify the reliability of these conclusions.

In conclusion, combining mesalazine and microecological preparations with vitamin D supplementation could more effectively improve the clinical efficacy of patients with ulcerative colitis, promote mucosal healing, reduce disease activity, alleviate inflammatory and oxidative stress responses, and improve intestinal barrier function without increasing additional adverse reactions. It is a safe and effective adjunctive treatment option.

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Disclosure of conflict of interest

None.

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