MEDICAL SCIENCE MONITOR

Combined Diosmectite and Mesalazine Treatment for Mild-to-Moderate Ulcerative Colitis: A Randomized, Placebo-Controlled Study

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: The relapse rate of ulcerative colitis (UC) is high. The efficacy of combined diosmectite and mesalazine treatment for active mild-to-moderate UC was investigated.

Material/Methods: A total of 120 patients with UC were enrolled in this randomized, single-blind, placebo-controlled study. Sixty patients were assigned to the Diosmectite group (diosmectite and mesalazine) and 60 were assigned to Placebo group (placebo and mesalazine). In the induction phase, the primary end point was the clinical remission rate at 8 weeks; secondary end points were clinical response, endothelial mucosal healing, Mayo score, erythrocyte sedimentation rate, C-reactive protein levels, and defecation frequency. In the maintenance phase, the primary end point was clinical remission at 52 weeks; secondary end points were clinical response, endothelial mucosal healing, Mayo score, erythrocyte sedimentation rate, and defecation frequency.

Results: At 8 weeks, the Diosmectite group had a significantly higher clinical remission rate (68.3% *vs.* 50%) and mucosal healing rate (66.7% *vs.* 48.3%) compared with the Placebo group. There were no significant differences in clinical response rates, Mayo score, erythrocyte sedimentation rate, C-reactive protein, or defecation frequency. At 52 weeks, the Diosmectite group had a significantly higher clinical remission rate (61.7% *vs.* 40%) and mucosal healing rate (60% *vs.* 38.3%) compared with the Placebo group. Defecation frequency was lower, but this was not significant.

Conclusions: Combined diosmectite and mesalazine treatment successfully induced and maintained the treatment of active mild-to-moderate UC as indicated by higher rates of clinical remission and mucosal healing.

MeSH Keywords: **Colitis, Ulcerative • Inflammatory Bowel Diseases • Mesalamine**

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Background

Ulcerative colitis (UC) is a chronic, non-specific, inflammatory bowel disease (IBD) characterized by ulcerative intestinal mucosa, bloody stools, diarrhea, and abdominal pain. Etiology and pathogenesis of UC remain to be elucidated and current treatment strategies lack specificity. At present, no curative treatment is available, resulting in prolonged disease, recurrences, and long-term diarrhea that affect overall health and quality of life [1,2].

Aminosalicylates are the primary drugs used for the treatment of UC. These drugs are also used for remission induction and maintenance treatment [3,4]. Despite constant administration of 5-aminosalicylate, mesalazine, or sulfasalazine (SASP), the proportion of patients having relapses remains high. A recent Norwegian study reported that the 1-year relapse rate of UC was approximately 50%, even with the administration of SASP or mesalazine [5]. In addition, follow-up visits performed in 1161 patients with UC in Denmark during a 2–2.5 year period revealed that only 50% of the patients being treated with mesalazine had sustained remission [6]. A study in Japan showed that the relapse rate was 30% when using long-term mesalazine (4.0 g/d) treatment compared with 48% when using short-term treatment [7]. Lastly, a study performed in a Korean population showed that 49.6% of patients with UC treated with SASP or mesalazine experienced relapses of the disease [8]. Although mesalazine is well tolerated and its efficacy in maintenance treatment of mild-to-moderate UC is superior to that of placebo [9], the long-term clinical remission rate and endoscopic mucosal healing rate of UC require improvements.

Diosmectite is a natural silicate that has been used widely for the treatment of diarrhea [10,11]. Animal studies have also shown that administration of diosmectite can effectively treat infectious diarrhea [12]. Diosmectite absorbs intestinal bacteria, proteins and toxins, and increases colonic mucin levels. Administration of diosmectite has successfully treated rats with hapten trinitrobenzene sulphonic acid (TNBS)-induced colitis. In these animals, diosmectite treatment alleviated diarrheal symptoms and pathological intestinal injury, and improved biochemical indices.

Clinical studies have also indicated that diosmectite treatment significantly alleviates clinical diarrheal symptoms, as well as endoscopic and pathological damages in pediatric patients with UC [13]. For adult patients with UC whose clinical symptoms failed to be substantially improved following treatment with mesalazine for 4 weeks, the average clinical activity index was lowered by additional administration of diosmectite for 30 days with maintenance mesalazine treatment [14].

Therefore, the objective of the present study was to further investigate the clinical efficacy of diosmectite and mesalazine treatment in patients with UC. The effects of this combination on the prevention of relapses were investigated, introducing a new treatment protocol that could yield higher rates of clinical remission and endoscopic mucosal healing.

Material and Methods

Patients

A total of 120 patients diagnosed with active UC at the Jinan Military General Hospital, Peking University First Hospital and Shandong University between April 2010 and April 2012 were prospectively enrolled. All patients presented the Montreal classification criteria of IBD [15]. Inclusion criteria were: 1) provided a written informed consent; 2) age 18–65 years old; 3) continual or recurrent mucosal bloody stools and abdominal pain, without any pathogenic microorganisms being detected in stool cultures for 2 or more times; 4) discontinuation of any drugs that may influence UC within 1 week prior to the study; 5) diagnosed with active mild-to-moderate UC by enteroscopy and pathological examination 1 week prior to the study; and 6) a Mayo score <10 [16]. Exclusion criteria were: 1) a Mayo score >10; 2) history of allergies to salicylates; 3) alanine aminotransferase (ALT) levels ≥1.5-fold the upper limit of normal (ULN) and/or creatinine levels ≥ULN; 4) co-morbidities such as acute pancreatitis, leukopenia, pericarditis, or myocarditis; 5) concurrent gastrointestinal diseases such as Behçet's disease, intestinal tuberculosis, or any other disease that could influence the implementation of this treatment protocol and/or influence the action and efficacy evaluation of treatment; or 6) patients treated with concomitant azathioprine/6-mercaptopurine. Patients were withdrawn from the study if: 1) they failed to take drugs for 2 consecutive days within a 4-week period; and 2) there was concomitant administration of any other drugs for the treatment of UC or the use of any other drugs and treatments during the study that could affect the clinical observations of the study.

Criteria for study termination were: 1) serious adverse reactions, exacerbations, or complications; 2) development of other diseases for which treatment could affect the clinical observation of the study drugs or concurrent participation in clinical trials with other drugs; or 3) pregnancy (Figure 1).

Study design

This was a prospective, randomized, placebo-controlled, single-blind study. The study was approved by the medical ethics committee of all 3 sites. All patients provided written informed consent. Patients were randomized using a computer-generated random number table and assigned to 1 of 2 groups: the Diosmectite group (diosmectite and mesalazine, n=60) and the Placebo group (placebo and mesalazine, n=60).
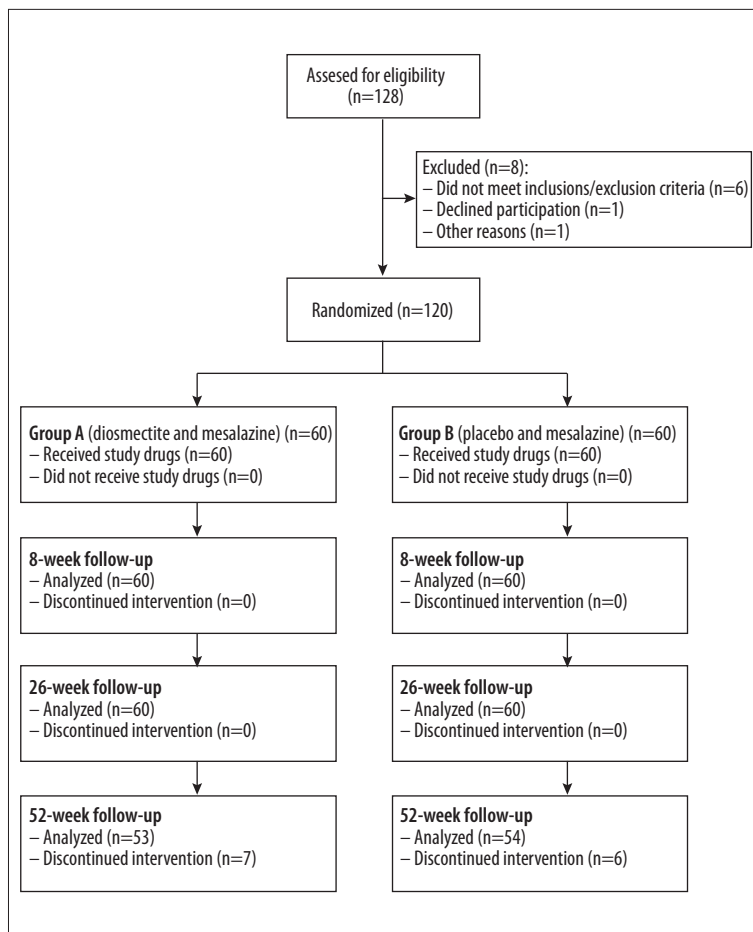
Figure 1. Enrollment, allocation, follow-up, and analysis of patients

Patients in the Diosmectite group received diosmectite (France Beaufour Ipsen Industrie, Tianjin, China) 3 g tid (3 times a day) 1 h before meals, combined with mesalazine (Ethypharm, France, registration certificate number: H20100063) 1 g qid (4 times a day) after meals for 8 weeks, then 0.5 g qid after meals for 44 weeks. Patients in the Placebo group received placebo (Pharmacy School of Shandong University) 3 g tid 1 h before meals, combined with mesalazine 1 g qid after meals for 8 weeks, then 0.5 g qid after meals for 44 weeks.

Study measures

The improved Mayo scoring system was used to evaluate clinical efficacy (Table 1) [16]. Clinical response was defined as a decrease in the Mayo score of at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding of at least 1 point or absolute rectal-bleeding subscore of 0 or 1. Clinical remission was defined as a total Mayo score of ≤2 with no individual subscore >1 point, or an absolute rectal bleeding subscore of 0 or 1. Mucosal healing was defined as an absolute endoscopy Mayo subscore of 0 (normal or inactive disease) or 1 (mild disease: erythema, decreased vascular pattern, mild friability) (Table 1) [17].

In the induction phase (weeks 0–8), the primary end point was clinical remission within 8 weeks after beginning treatment. The secondary end points included clinical responses, endoscopic mucosal healing, Mayo score, erythrocyte sedimentation rate, C-reactive protein (CRP) levels, presence of bloody stools, and defecation frequency. In the maintenance phase (weeks 9–52), the primary end point was clinical remission within 52 weeks after beginning treatment. The secondary end points included clinical responses, endoscopic mucosal healing, Mayo score, erythrocyte sedimentation rate, CRP levels, the presence of bloody stools, and defecation frequency.

The following laboratory tests were performed in all patients of both groups: 1) CRP and erythrocyte sedimentation rate before treatment and at weeks 2, 4, 8, 26, and 52; and 2) serum levels of potassium, sodium, chlorine, creatinine, blood urea nitrogen, ALT, and total bilirubin before treatment and at weeks 8, 26, and 52. Colonoscopy was performed in all patients to observe lesions of the intestinal mucosa including erythema, vascular texture, tissue fragility, erosion, and hemorrhage before treatment and at weeks 8, 26, and 52.

Table 1. The modified Mayo Score*.

Subscore	Mayo score
Stool frequency**	0 = Normal number of stools for this patient 1 = 1 or 2 stools more than normal 2 = 3 or 4 stools more than normal 3 = 5 or more stools more than normal
Rectal bleeding#	0 = No blood seen 1 = Streaks of blood less than half the time 2 = Obvious blood most of the time 3 = Blood alone passes
Findings on endoscopy	0 = Normal or inactive disease 1 = Mild disease (erythema, decreased vascular pattern, mild friability) 2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions) 3 = Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment##	0 = Normal 1 = Mild disease 2 = Moderate disease 3 = Severe disease

* The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease [16,17]; ** Each patient serves as his own control to establish their normal stool frequency; # The daily bleeding score represents the most severe bleeding of the day; ## The physician's global assessment acknowledges the three other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing, and other observations, such as physical findings and the patient's performance status.

The occurrence of adverse events (headaches, nausea, increased stool frequency, abnormal ALT) were recorded during the follow-up visits, including the time elapsed after beginning treatment, severity, duration, and measures taken.

Statistical analysis

SPSS 16.0 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses. All analyses were performed on an intention-to-treat basis. Continuous data are presented as means ± standard deviation (SD), and were analyzed using paired-samples t-tests for before/after treatment analyses, or independent samples t-tests for comparisons between groups (Mayo scores, erythrocyte sedimentation rates, C-reactive protein, and defecation frequencies). Categorical data are presented as absolute counts and proportions, and were analyzed using χ^2 tests between the 2 groups after treatment (clinical response rates, clinical remission rates, and endoscopic mucosal healing rates). P-values <0.05 were considered statistically significant.

Results

A total of 120 patients were prospectively enrolled in this randomized, single-blind, placebo-controlled study (Figure 1). The cohort included 68 males and 52 females aged 18–65 years. Forty patients were newly diagnosed with UC and 80 were patients with chronic relapsing UC. The baseline clinical features of patients in both groups are presented in Table 2.

Disease course ranged from 6 months to 2 years, and the average body weight was 56.5 kg. There were 62 patients with proctitis, 58 of which had left colitis. Seventy patients presented with mild UC and 50 with moderate UC. Sixty patients were randomly assigned to the Diosmectite group (diosmectite and mesalazine) and 60 patients were assigned to the Placebo group (placebo and mesalazine).

After 8 weeks of treatment, a clinical response was observed in 55 of the 60 Diosmectite group patients (91.7%), 41 patients (68.3%) achieved clinical remission, 40 (66.7%) patients achieved endoscopic mucosal healing, and there was no improvement in 5 patients (Table 3). The average Mayo score decreased from 5.1±1.3 before treatment to 1.6±1.1 after treatment (P<0.05); the average erythrocyte sedimentation rate decreased from 30.1±12.3 mm/h before treatment to 11.5±5.7 mm/h (P<0.01); mean CRP levels decreased from 21.6±11.2 mg/l before treatment to 5.2±3.6 mg/l after treatment (P<0.01); and the mean defecation frequency decreased from 4.7±2.3 times per day before treatment to 1.0±1.3 times per day after treatment (P<0.05) (Table 3).

In the Placebo group, 50 of the 60 patients (83.3%) showed a clinical response, 30 achieved clinical remission (50%), 29 achieved endoscopic mucosal healing (48.3%), and there was no improvement in 10. Mean Mayo score decreased from 5.3±1.4 before treatment to 2.2±1.9 after treatment (P<0.05); the average erythrocyte sedimentation rate decreased from 31.7±11.2 mm/h before treatment to 20.4±9.9 mm/h (P<0.05);

Table 2. Baseline characteristics for patients in Diosmectite group and Placebo group.

Basic information	Diosmectite group	Placebo group	P-value
N	60	60	
Gender: Male no (%)	34 (56.7)	33 (55.0)	0.85
Age (years)	33.9±12.7	33.8±15.2	0.97
Course of disease (months)	12.2±2.4	12.4±2.7	0.89
Body weight (kg)	62.7±12.3	63.1±12.4	0.86
Mayo score (points)	5.1±1.3	5.3±1.4	0.82
C-reactive protein (mg/l)	21.6±11.2	22.6±10.8	0.92
Site of disease, n (%)			0.91
Rectum	30 (50.0)	32 (53.3)	
Left side of colon	30 (50.0)	28 (46.7)	
Severity, n (%)			0.89
Mild	34 (56.7)	36 (60.0)	
Moderate	26 (43.3)	24 (40.0)	
Clinical presentation, n (%)			0.96
Newly diagnosed	20 (33.3)	20 (33.3)	
Chronic relapse	40 (66.7)	640 (66.7)	
Pretreatments, n (%)*			0.83
5-Aminosalicylates	40 (66.7)	40 (66.7)	
Corticosteroids	10 (16.7)	9 (15.0)	
Pednisone acetate ≥20 mg/day	6 (10.0)	5 (8.3)	
Defecation frequency (times per day)	4.7±2.3	4.5±1.4	0.85
Erythrocyte sedimentation rate (mm/h)	30.1±12.3	31.7±11.2	0.77

Data are expressed as mean values ±SD. * For chronic relapsing patients only.

mean CRP levels decreased from 22.6±10.8 mg/l before treatment to 9.0±6.9 mg/l (P<0.05); and average defecation frequency decreased from 4.5±1.4 times per day before treatment to 2.0±1.3 times per day (P<0.05) (Table 3). There was no significant difference in clinical responses between the Diosmectite group and the Placebo group (P>0.05). However, rates of clinical remission and endoscopic mucosal healing were significantly higher in the Diosmectite group compared with the Placebo group. There was no significant difference in Mayo scores, erythrocyte sedimentation rate, CRP levels, or defecation frequency between the 2 groups after treatment (Table 3).

After 26 weeks of treatment, 38 (63.3%) patients in the Diosmectite group achieved clinical remission (Figure 2A) and 37 (61.7%) achieved endoscopic mucosal healing (Figure 2B). Defecation frequency was 1.0±0.8 times per day. In the

Placebo group, 26 patients (43.3%) achieved clinical remission (Figure 2A) and 25 (41.7%) achieved endoscopic mucosal healing (Figure 2B). Defecation frequency was 2.0±0.9 times per day. Clinical efficacy comparisons showed that the clinical remission and endoscopic mucosal healing rate of the Diosmectite group were significantly higher than in the Placebo group (P=0.028 and P=0.028, respectively). The defecation frequency of the Diosmectite group was lower than in the Placebo group, but the difference was not significant (P=0.80).

After 52 weeks of treatment, 37 patients (61.7%) in the Diosmectite group achieved clinical remission (Figure 2A), and 36 (60%) achieved endoscopic mucosal healing (Figure 2B). The defecation frequency was 1.0±0.7 times per day. In the Placebo group, 24 patients (40%) achieved clinical remission (Figure 2A) and 23 patients (38.3%) achieved endoscopic mucosal

Table 3. Comparison of clinical efficacy between Diosmectite and Placebo group after eight weeks of treatment.

Item	Diosmectite group	Placebo group	P-value
Mayo score (points)	1.6±1.1	2.2±1.9	0.70
C-reactive protein (mg/l)	5.2±3.6	9.0±6.9	0.60
Erythrocyte sedimentation rate (mm/h)	11.5±5.7	20.4±9.9	0.80
Defecation frequency (times per day)	1.0±1.3	2.0±1.3	0.90
Clinical response, n (%)	55　(91.7)	50　(83.3)	0.168
Clinical remission, n (%)	41　(68.3)	30　(50.0)	0.041
Mucosal healing, n (%)	40　(66.7)	29　(48.3)	0.042

Unless otherwise indicated, data are expressed as mean values ±SD.

	8 w	26 w	52 w
Diosmectite group	41 (68.3%)	38 (63.3%)	37 (61.7%)
Placebo group	30 (50.0%)	26 (43.3%)	24 (40.0%)

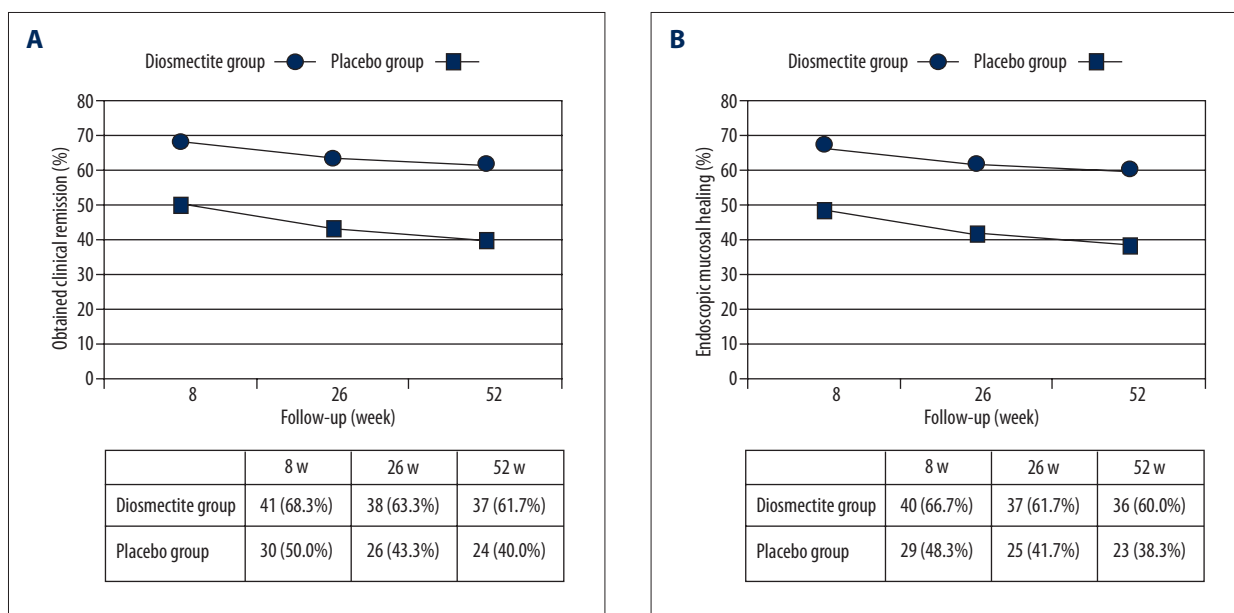|	8 w	26 w	52 w
Diosmectite group	40 (66.7%)	37 (61.7%)	36 (60.0%)
Placebo group	29 (48.3%)	25 (41.7%)	23 (38.3%)

Figure 2. (**A**) Clinical remission of patients in the Diosmectite group and Placebo group at different time points. (**B**) Mucosal healing of patients in both Diosmectite group and Placebo group at different time points.

healing (Figure 2B). The defecation frequency was 2.0±1.2 times per day. The clinical remission rate and endoscopic mucosal healing rate in the Diosmectite group were significantly higher (61.7% and 60%, respectively) than in the Placebo group (40% and 38.3%, respectively, P=0.018 and P=0.018, respectively). The defecation frequency of the Diosmectite group was lower than in the Placebo group, but the difference was not significant (P=0.80).

Both groups showed a decrease in clinical remission rate and mucosal healing (Figure 2A, 2B), but rates of remission and mucosal healing were significantly higher at all time points in the Diosmectite group compared with the Placebo group.

Adverse reactions were recorded for all patients (Table 4). In the Diosmectite group, 1 patient had headaches and 1 patient

had nausea. In the Placebo group, 3 patients had headaches, two patients had nausea, 3 patients had increased defecation frequency of more than 3 times per day, and 1 patient had elevated ALT levels that returned to normal following discontinuation of study drugs (Table 4).

Discussion

The objective of the present study was to investigate the efficacy of combined diosmectite and mesalazine treatment for UC compared with placebo and mesalazine using a randomized, single-blind approach. The combined treatment group showed higher rates of clinical remission and endoscopic mucosal healing as early as 8 weeks after beginning treatment, and these improvements were sustained for 52 weeks.

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Table 4. Adverse events.

Adverse reactions	Diosmectite group	Placebo group
Headaches	1	3
Nausea	1	2
Increased stool frequency	0	3
Abnomal ALT	0	1

Many studies have shown that diosmectite can effectively treat various types of pediatric and adult diarrhea, such as those caused by acute and chronic diseases or bacterial and non-bacterial infections [11]. This effect appears to be related to its pharmacological, structural, and antimicrobial properties [18]. Indeed, diosmectite is a mineral clay with a multi-layer structure consisting of di-tetrahedron silicon oxide and octahedron aluminum oxide. Diosmectite presents an extensive superficial area (approximately 100 m^2/g) that allows it to cover and adhere to the intestinal mucosal surface of the entire enteric cavity. It absorbs bacteria, viruses, and toxins and negatively affects pathogenesis of UC [19]. Diosmectite binds to *Clostridium difficile* toxins A and B, as well as *Clostridium perfringens* toxins and endotoxins [20]. Moreover, it binds to mucosa and mucin, and reinforces the mucosal barrier. In doing so, it protects already damaged intestinal mucosa and prevents further histopathological changes induced by bacterial infections. Diosmectite increases mucosal production and intestinal mucosal thickness, prolongs mucosa half-life, maintains normal intestinal secretions, reduces the loss of water and electrolytes, and reinforces the intestinal mucosa barrier function [21]. Importantly, diosmectite does not enter into the bloodstream, and is therefore safe and well-tolerated, with minimal adverse effects.

Interestingly, a study has shown that diosmectite-zinc oxide modulates the expression of pro-inflammatory cytokines and tight junction protein in early-weaned pigs [21]. Another mineral clay, montmorillonite, relieves diarrhea, improves barrier dysfunction and expression of inflammatory cytokines, and increases tight junction protein expression, and it is possible that diosmectite acts in a similar manner [22]. Another possible mechanism is that it facilitates intestinal barrier repair by reducing inflammatory cell infiltration of the mucous membrane [12]. It has been demonstrated that diosmectite is more efficient in repairing damaged mucosal membranes than SASP, significantly improving the expression of colonic mucin 2 and protecting the mucosal barrier [12].

Previous studies have indicated that diosmectite might be an effective, additional treatment for UC patients. For instance, Olives et al. reported that diosmectite significantly relieves clinical diarrheal symptoms and reduces histopathological

damages in children and adults [13]. In addition, combined mesalazine and diosmectite treatment decreased the inflammatory response in an early-phase study involving 25 patients with active-stage mild-to-moderate UC [14].

In the present study, after 8 weeks, CRP levels and erythrocyte sedimentation rate were significantly decreased. These data suggest that the combined treatment could relieve the inflammatory response in patients with active UC, since these indices are associated with UC disease activity [23,24]. There was also a significant reduction in defecation frequency, and clinical remission and endoscopic mucosal healing rates were significantly higher in the combined treatment group compared with the placebo group. These findings are important because improved mucosal healing can improve quality of life and prevent relapse [25,26]. As such, these improvements were still observed at 26 and 52 weeks of treatment.

It has been proposed that mesalazine prevents 5-aminosalicylate from being absorbed in the upper gastrointestinal tract, and ensures that sufficient 5-aminosalicylate reaches the diseased colon at the distal end, allowing for effective and localized treatment [9]. In turn, 5-aminosalicylate may inhibit prostaglandin synthesis and inflammation of the intestinal mucosa. In contrast, diosmectite acts to absorb endotoxins and antigens in the enteric cavity, partially inhibiting the inflammatory response, increasing permeability, and protecting the intestinal mucosal barrier [12,18–20,27]. It is hypothesize that the combination of diosmectite and mesalazine facilitates and promotes the repair of damaged intestinal mucosa.

In this study, there were no serious adverse reactions induced by the combined diosmectite and mesalazine treatment. This indicates that the combination is safe and well-tolerated.

The present study is not without limitations. This was a single-blind study. A double-blind study, similar to a study previously reported investigating vedolizumab in induction and maintenance therapy of UC [28], may provide more conclusive findings. Other anti-inflammatory drugs exist for the treatment of IBD [29], and other combinations might be tried and compared. These limitations indicate the need for future research.

Conclusions

Combined treatment with diosmectite and mesalazine was successful as both induction (8 weeks) and maintenance (52 weeks) therapies for patients with active-stage mild-to-moderate UC. These patients had higher rates of clinical remission and mucosal healing at 8 weeks and maintenance at 52 weeks of treatment compared with patients who received placebo and mesalazine treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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