doi.org/10.36721/PJPS.2026.39.12.332.1

Mesalazine enteric-coated tablets combined with retention enema for symptom alleviation in mild to moderate E2-type active ulcerative colitis: A retrospective comparative cohort study

Rui Zhang[1#], Shihui Wang[2#], Mingyue Yang[2], Chunchun Yang[2], Dawei Yang[3], Yanan Zhao[2*] and Xueli Zhang[2*]

[1]Department of Gastroenterology, The first hospital of Hebei Medical University, 050031 Shijiazhuang City, Hebei Province, China
[2]Department of Gastroenterology Center, The first hospital of Hebei Medical University, 050000 Shijiazhuang City, Hebei Province, China
[3]Department of Hepatic, the First Hospital of Hebei Medical University, 050031 Shijiazhuang City, Hebei Province, China

Abstract: **Background**: Ulcerative colitis (UC) is a chronic inflammatory bowel disease impacting quality of life. Combination oral and topical mesalazine is guideline-recommended for left-sided UC, but real-world data remain limited. **Objectives**: This retrospective study evaluated the efficacy and safety of mesalazine enteric-coated tablets plus a retention enema in patients with mild-to-moderate E2-type (left-sided) active UC. **Methods**: Patients with mild to moderate E2-type active UC treated at a single center from January 2021 to December 2022 were retrospectively screened. After applying inclusion and exclusion criteria, 88 patients were included and assigned to either the study group (mesalazine enteric-coated tablets 1.0 g four times daily plus mesalazine retention enema 4.0 g once daily) or the control group (oral mesalazine enteric-coated tablets 1.0 g four times daily alone) based on clinical availability and patient preference. Treatment duration was 30 days. Outcomes included clinical efficacy (using modified local criteria and Mayo score components), symptom relief and time to improvement, endoscopic findings (Mayo Endoscopic Subscore), and adverse events. **Results**: The "effective" rate was significantly higher in the study group (77.27% vs. 34.09%; OR=6.58, P<0.001). Symptom relief rate was 97.73% vs. 72.73% (OR=13.44, P=0.002). Symptom improvement times were shorter in the study group (all P<0.05). Post-treatment Mayo Endoscopic Subscore was lower in the study group (1.14±0.41 vs. 2.05±0.65; mean difference -0.91, P<0.001). Ulcer and congestion/edema incidences were lower in the study group (6.82% and 18.18% vs. 25.00% and 47.73%). Adverse events were mild and comparable between groups (13.64% vs. 11.36%, P=0.746). **Conclusion**: Mesalazine enteric-coated tablets combined with retention enema demonstrated superior efficacy compared to oral monotherapy for short-term symptom relief and mucosal healing in patients with mild to moderate E2-type active UC, with a favorable safety profile. Larger prospective studies with longer follow-up are needed to confirm these findings and evaluate long-term outcomes.

Keywords: Mesalazine; Mild to moderate E2-type active ulcerative colitis; Retention enema; Symptom relief; Symptom improvement

Submitted on 17-03-2026 – Revised on 03-05-2026 – Accepted on 21-05-2026

INTRODUCTION

Ulcerative colitis (UC) is a self-immune disease characterized by chronic inflammation of the gastrointestinal tract. Over time, the global incidence of UC has been on the rise, possibly due to changes in lifestyle and dietary habits, environmental factors, the interplay of genetics and immune factors, and the widespread use of antibiotics (Segal, 2021; Du, 2020). It primarily affects the colonic mucosa, leading to clinical symptoms such as diarrhea, abdominal pain and rectal bleeding. UC typically manifests in young adults but can occur at any age, significantly impacting the quality of life. Among them, E2-type active ulcerative colitis is characterized by mild to moderate mucosal inflammation, which can cause discomfort and distress to patients (Kaenkumchorn, 2020; Pabla, 2020). Currently, there are various treatment methods for UC, with pharmaceutical intervention being a common approach.

The Montreal classification categorizes UC extent into three types: E1 (ulcerative proctitis, limited to the rectum), E2 (left-sided UC, involvement limited to a proportion of the colorectum distal to the splenic flexure) and E3 (extensive UC or pancolitis, involvement extending proximal to the splenic flexure) (Barberio, 2021). E2-type active UC, the focus of this study, is characterized by mild to moderate mucosal inflammation confined to the left colon, causing significant patient discomfort and distress.

Current treatment strategies for UC include pharmacological interventions, with 5-aminosalicylic acid (5-ASA) preparations representing first-line therapy for

*Corresponding author: e-mail: nro3691@yeah.net; nxubfhnu22@163.com
#These authors contributed equally and are the co-first authors.

mild to moderate disease. Mesalazine, a 5-ASA compound, possesses anti-inflammatory and immunomodulatory properties and is widely used clinically for the management of UC (Kato, 2018; Park, 2022). However, oral mesalazine monotherapy may achieve suboptimal drug concentrations in the rectosigmoid region due to progressive drug dilution and absorption along the colonic length, potentially limiting efficacy in left-sided disease (Kruis, 2023)

Topical (rectal) therapy, including retention enema, has gained attention as a localized treatment approach. By delivering medication directly to the affected distal colonic and rectal mucosa, topical therapy reduces systemic side effects and achieves high local drug concentrations. The American Gastroenterological Association (AGA) guidelines recommend adding rectal mesalazine to oral 5-ASA for patients with extensive or left-sided mild-to-moderate UC (conditional recommendation, moderate-quality evidence) (Raine, 2022). Similarly, European Crohn's and Colitis Organization (ECCO) guidelines support combined oral and topical 5-ASA therapy for left-sided UC (Raine, 2022).

Despite guideline recommendations, real-world data on combined oral and topical mesalazine therapy from specific populations, particularly in Asia, remain limited. Furthermore, optimal dosing regimens and short-term induction outcomes in E2-type UC warrant further investigation. This retrospective study aimed to evaluate the efficacy and safety of mesalazine enteric-coated tablets combined with retention enema in patients with mild to moderate E2-type active UC, providing incremental real-world evidence to complement existing guideline recommendations.

MATERIALS AND METHODS

Study design

This was a retrospective, single-center, comparative cohort study conducted at The First Hospital of Hebei Medical University. The study was approved by the Ethics Committee of The First Hospital of Hebei Medical University (Approval No. 2020-KY-089). Informed consent was obtained from all study participants. All methods were carried out in accordance with the Declaration of Helsinki. The study is reported in accordance with the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) statement checklist for non-randomized studies.

Study population

Patients with mild to moderate E2-type active ulcerative colitis treated at a single center from January 2021 to December 2022 were retrospectively screened using the hospital's electronic medical record system. All patients meeting the inclusion criteria were registered and clinical data were extracted from medical records. After applying the inclusion and exclusion criteria, 88 patients were included in the analysis. The study flow diagram is provided in figure S1.

Patients were assigned to two groups based on the treatment received during their clinical care: the control group received oral mesalazine enteric-coated tablets alone and the study group received combined oral mesalazine enteric-coated tablets and retention enema. The assignment was based on clinical availability and patient preference rather than randomization; this non-randomized approach represents a significant methodological limitation.

Inclusion criteria

Inclusion criteria: Patients who met the diagnostic criteria for E2-type (left-sided) active ulcerative colitis according to the Montreal classification (Al-Horani, 2025), defined as involvement limited to a proportion of the colorectum distal to the splenic flexure. Patients were required to have a Modified Mayo Activity Score indicating mild or moderate disease activity (total score 3-10 points). Clinical manifestations included diarrhea, bloody mucous stools and abdominal pain. Colonoscopy was required to show lesions confined to the rectum and left colon. Additional inclusion criteria included age between 18 and 65 years and complete clinical data available in medical records.

Exclusion criteria: Patients with concurrent infectious colitis (including bacterial dysentery), irritable bowel syndrome, intestinal tuberculosis, Crohn's disease, or other gastrointestinal diseases were excluded. Patients with severe primary diseases affecting the cardiovascular, cerebral, hepatic, renal, or hematopoietic systems, as well as those with mental illnesses, were excluded. Additional exclusion criteria included localized colonic stenosis, intestinal obstruction, intestinal perforation, toxic megacolon, intestinal cancer, or previous gastrointestinal surgery. Patients with contraindications to enema treatment, pregnant or lactating women and those with known allergies to mesalazine or any study medication components were also excluded.

Sample size

A post-hoc sample size justification was performed. Based on an anticipated difference in the primary outcome (clinical improvement rate) of 35% between groups (65% in the combination therapy group vs. 30% in the oral-only group), a two-sided alpha of 0.05 and power of 80%, the required sample size was calculated to be approximately 40 patients per group. The final sample size of 44 patients per group provides adequate power for the primary comparison, although the retrospective design and lack of randomization limit the strength of inference.

Intervention methods

Control group: Patients received oral mesalazine enteric-coated tablets (Sunflower Pharmaceutical Group Jiamusi

Luling Pharmaceutical Co., Ltd.; National Medical Products Administration approval number H19980148; 0.25 g/tablet), 4 tablets per dose, four times daily (total daily dose 4.0 g), for 30 days.
Study group: Patients received combined treatment with oral mesalazine enteric-coated tablets (same regimen as in the control group) plus a mesalazine retention enema. The enema was a commercially available preparation (Salofalk Enema, Dr. Falk Pharma GmbH, Freiburg, Germany; or an equivalent locally sourced commercial product). Each 60 mL enema unit contained 4.0 g of mesalazine in a buffered solution with a pH of approximately 7.4. The enema vehicle consisted of purified water, sodium edetate, sodium benzoate, sodium metabisulfite and carbomer as suspending agents. The enema was administered once daily at bedtime. Patients were instructed to insert the enema nozzle approximately 10-15 cm into the rectum and retain the enema overnight (minimum 8 hours). Adherence was assessed by patient self-report and medication return counts. Treatment duration was 30 days.

Study parameters
Primary outcome—Clinical efficacy: Treatment efficacy was evaluated using modified criteria adapted from the 2007 Chinese Society of Gastroenterology guidelines, as these represent the local institutional standard. Additionally, outcomes are presented using internationally recognized Mayo score components to facilitate comparability with existing trials. The local efficacy categories were defined as follows:
- *Effective*: Complete disappearance of clinical symptoms, stable bowel movements not exceeding 2 times per day, absence of red and white blood cells in fecal examination and colonoscopy revealing essentially normal mucosa (Mayo Endoscopic Subscore ≤1).
- *Valid (partial response)*: Basic disappearance of clinical symptoms, bowel movements ranging from 2 to 4 times per day with normal stool form, absence of red and white blood cells in fecal examination (all <10 per high-power field) and colonoscopy showing mild mucosal inflammation (Mayo Endoscopic Subscore ≤2).
- *Ineffective*: No obvious improvement in clinical symptoms, laboratory tests, or colonoscopy findings after treatment.

Secondary outcomes
(1) *Symptom relief*: Proportion of patients with complete relief of clinical symptoms, including abdominal pain, tenesmus and bloody stool.
(2) *Symptom improvement time*: Time to improvement (in days) for abdominal pain, diarrhea and mucous/bloody stools.
(3) *Endoscopic findings*: Presence of ulcers and congestion/edema on colonoscopy at baseline and post-treatment, assessed by experienced endoscopists blinded to treatment assignment.
(4) *Mayo Score components*: Total Mayo Score (range 0-12) and Mayo Endoscopic Subscore (MES; range 0-3) were assessed at baseline and post-treatment. The MES was scored as follows: 0 = normal or inactive disease; 1 = mild disease (erythema, decreased vascular pattern, mild friability); 2 = moderate disease (marked erythema, absent vascular pattern, friability, erosions); 3 = severe disease (spontaneous bleeding, ulceration) (Al-Horani, 2025).
(5) *Adverse events*: All adverse events were recorded, including type, severity, duration and relationship to study treatment. Serious adverse events were defined as those requiring hospitalization, prolonging hospitalization, resulting in persistent disability, or being life-threatening.

Statistical analysis
Statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. Normally distributed continuous data were expressed as mean ± standard deviation (SD) and compared using independent-samples t-tests. Non-normally distributed continuous data were expressed as median (interquartile range) and compared using Mann-Whitney U tests. Categorical variables were expressed as frequencies and percentages and compared using chi-square tests or Fisher's exact test, as appropriate.

For multiple comparisons (e.g., across multiple efficacy endpoints), a Bonferroni correction was applied to control the family-wise error rate, with the significance level adjusted to $P < 0.0125$ (0.05/4) for the four primary secondary outcomes. Effect sizes were calculated as Cohen's d for continuous outcomes and odds ratios (OR) with 95% confidence intervals (CI) for binary outcomes. Statistical significance was set at $P < 0.05$ (two-tailed) for unadjusted comparisons, with adjusted thresholds noted where Bonferroni correction was applied.

Data were analyzed on an intention-to-treat basis where complete data were available. No imputation was performed for missing data, as missing data were minimal (<5% for all variables).

RESULTS

Baseline patient characteristics
A total of 88 patients were included in the analysis: 44 in the study group (combination therapy) and 44 in the control group (oral monotherapy). In the study group, there were 28 males (63.64%) and 16 females (36.36%), with an age range of 30-65 years (mean 49.56 ± 5.78 years). Disease duration ranged from 3 to 65 months (mean 28.65 ± 3.71 months). In the control group, there were 25 males (56.82%) and 19 females (43.18%), with an age range of 30-65 years (mean 48.97 ± 5.94 years). Disease duration ranged from 3 to 65 months (mean 28.99 ± 3.67 months). Baseline characteristics, including age,

sex, disease duration, baseline total Mayo Score and baseline Mayo Endoscopic Subscore, showed no statistically significant differences between the two groups (all $P > 0.05$), indicating comparability at baseline (Table 1).

Clinical efficacy

The clinical efficacy outcomes are presented in table 2. The proportion of patients achieving "effective" status (complete symptom resolution and mucosal healing) was significantly higher in the study group (34/44, 77.27%) compared to the control group (15/44, 34.09%) (OR = 6.58, 95% CI: 2.54-17.05, $\chi^2 = 12.567$, $P < 0.001$). The proportion achieving "valid" (partial response) status was correspondingly higher in the control group (29/44, 65.91% vs. 10/44, 22.73%; OR = 0.14, 95% CI: 0.05-0.37, $\chi^2 = 10.845$, $P < 0.001$). No patient in either group was classified as "ineffective" based on the modified local criteria.

Symptom relief

After 30 days of treatment, patients in the study group showed significant relief of clinical symptoms, including abdominal pain, tenesmus and bloody stool. The overall symptom relief rate was 97.73% (43/44) in the study group compared to 72.73% (32/44) in the control group (OR = 13.44, 95% CI: 2.56-70.57, $\chi^2 = 10.252$, $P = 0.002$) (Table 3).

Symptom improvement time

The time to symptom improvement was significantly shorter in the study group compared to the control group for all measured symptoms (Table 4). For abdominal pain, the mean improvement time was 3.28 ± 1.11 days in the study group vs. 5.71 ± 2.09 days in the control group (mean difference -2.43 days, 95% CI: -3.13 to -1.73, Cohen's d = 1.47, t = 9.981, $P < 0.001$). For diarrhea, improvement time was 2.44 ± 1.28 days vs. 3.94 ± 1.61 days (mean difference -1.50 days, 95% CI: -2.12 to -0.88, Cohen's d = 1.04, t = 4.568, $P < 0.001$). For mucous and bloody stools, improvement time was 6.18 ± 1.94 days vs. 7.96 ± 2.23 days (mean difference -1.78 days, 95% CI: -2.66 to -0.90, Cohen's d = 0.85, t = 2.954, $P = 0.004$).

Endoscopic findings

Post-treatment endoscopic findings are presented in table 5. The incidence of ulcers after treatment was significantly lower in the study group (3/44, 6.82%) compared to the control group (11/44, 25.00%) (OR = 0.21, 95% CI: 0.05-0.81, $\chi^2 = 6.684$, $P = 0.010$). The incidence of congestion and edema was also significantly lower in the study group (8/44, 18.18%) compared to the control group (21/44, 47.73%) (OR = 0.23, 95% CI: 0.09-0.61, $\chi^2 = 10.498$, $P = 0.001$).

Mayo score and endoscopic subscore

The total Mayo Score and Mayo Endoscopic Subscore (MES) at baseline and post-treatment are presented in table 6. At baseline, there were no significant differences between groups in total Mayo Score (9.02 ± 1.51 vs. 9.01 ± 1.48, t = 0.494, $P = 0.623$) or MES (2.34 ± 0.61 vs. 2.30 ± 0.63, t = 0.308, $P = 0.759$).

After treatment, the total Mayo Score was significantly lower in the study group (4.28 ± 0.79) compared to the control group (6.68 ± 0.99) (mean difference -2.40, 95% CI: -2.79 to -2.01, Cohen's d = 2.67, t = 9.891, $P < 0.001$). The Mayo Endoscopic Subscore was also significantly lower in the study group (1.14 ± 0.41) compared to the control group (2.05 ± 0.65) (mean difference -0.91, 95% CI: -1.14 to -0.68, Cohen's d = 1.68, t = 7.846, $P < 0.001$).

Safety and adverse events

Adverse events were recorded in both groups and are summarized in table 7. In the study group (combination therapy), 6 patients (13.64%) reported mild gastrointestinal discomfort (including nausea and flatulence). Two patients (4.55%) reported headache. All adverse events were mild in severity and resolved without treatment discontinuation. No patient in the study group discontinued therapy due to adverse events.

In the control group (oral monotherapy), 5 patients (11.36%) reported mild gastrointestinal discomfort. One patient (2.27%) reported headache. No patient in the control group discontinued therapy due to adverse events.
No serious adverse events were reported in either group. Specifically, no cases of acute intolerance syndrome (characterized by cramping, severe abdominal pain, bloody diarrhea, fever, or rash), severe allergic reactions, hematologic abnormalities, hepatotoxicity, nephrotoxicity, or skin reactions (including Stevens-Johnson syndrome) were observed. The difference in overall adverse event rates between groups was not statistically significant (13.64% vs. 11.36%, $\chi^2 = 0.105$, $P = 0.746$).

DISCUSSION

This retrospective comparative cohort study evaluated the efficacy and safety of mesalazine ne enteric-coated tablets combined with retention enema compared with oral mesalazine monotherapy in patients with mild to moderate E2-type active ulcerative colitis. The key findings demonstrate that combination therapy was associated with significantly higher clinical efficacy rates, more rapid symptom improvement, better endoscopic outcomes (including lower Mayo Endoscopic Subscore) and a comparable safety profile to oral monotherapy.

The clinical efficacy rate ("effective" status) in the combination therapy group was 77.27% compared to 34.09% in the oral monotherapy group. This substantial difference underscores the potential benefit of adding topical therapy to oral mesalazine in left-sided UC.

Table 1: Baseline clinical and endoscopic characteristics of the study population.

Characteristic	Study group (n=44)	Control group (n=44)	t/χ^2	P
Age (years)	49.56 ± 5.78	48.97 ± 5.94	0.164	0.87
Sex [n (%)]			0.425	0.514
Male	28 (63.64)	25 (56.82)		
Female	16 (36.36)	19 (43.18)		
Disease duration (months)	28.65 ± 3.71	28.99 ± 3.67	0.207	0.836
Baseline total mayo score (score)	9.02 ± 1.51	9.01 ± 1.48	0.494	0.623
Baseline mayo endoscopic subscore (score)	2.34 ± 0.61	2.30 ± 0.63	0.308	0.759
Baseline ulceration present [n (%)]	32 (72.73)	30 (68.18)	0.218	0.641
Baseline congestion/edema present [n (%)]	41 (93.18)	40 (90.91)	0.155	0.694

Table 2: Comparison of clinical efficacy between groups.

Outcome	Study group (n=44)	Control group (n=44)	OR (95% CI)	χ^2	p
Effective [n (%)]	34 (77.27)	15 (34.09)	6.58 (2.54-17.05)	12.567	<0.001
Valid [n (%)]	10 (22.73)	29 (65.91)	0.14 (0.05-0.37)	10.845	<0.001
Ineffective [n (%)]	0 (0)	0 (0)	—	—	—

Table 3: Comparison of symptom relief rates after treatment.

Outcome	Study group (n=44)	Control group (n=44)	OR (95% CI)	χ^2	p
Overall symptom relief [n (%)]	43 (97.73)	32 (72.73)	13.44 (2.56-70.57)	10.252	0.002
Residual abdominal pain [n (%)]	0 (0)	3 (6.82)	—	—	—
Residual tenesmus/bloody stool [n (%)]	1 (2.27)	9 (20.45)	—	—	—

Table 4: Comparison of symptom improvement times after treatment (days, mean ± SD).

Symptom	Study group (n=44)	Control group (n=44)	Mean difference (95% CI)	Cohen's d	*t*	*P*
Abdominal pain (days)	3.28±1.11	5.71±2.09	-2.43 (-3.13 to -1.73)	1.47	9.981	<0.001
Diarrhea (days)	2.44±1.28	3.94±1.61	-1.50 (-2.12 to -0.88)	1.04	4.568	<0.001
Mucous stools, bloody stools (days)	6.18±1.94	7.96±2.23	-1.78 (-2.66 to -0.90)	0.85	2.954	0.029

Table 5: Comparison of post-treatment endoscopic findings.

Endoscopic finding	Study group (n=44)	Control group (n=44)	OR (95% CI)	χ^2
Ulceration present [n (%)]	3 (6.82)	11 (25.00)	0.21 (0.05-0.81)	6.684
Congestion/edema present [n (%)]	8 (18.18)	21 (47.73)	0.23 (0.09-0.61)	10.498

Table 6: Comparison of mayo score and endoscopic subscore before and after treatment (mean ± SD).

Outcome	Study group (n=44)	Control group (n=44)	Mean difference (95% CI)	Cohen's d	t	p
Total mayo score, baseline (score)	9.02 ± 1.51	9.01 ± 1.48	0.01 (-0.62 to 0.64)	0.01	0.494	0.623
Total mayo score, post-treatment (score)	4.28 ± 0.79	6.68 ± 0.99	-2.40 (-2.79 to -2.01)	2.67	9.891	<0.001
Mayo endoscopic subscore, baseline (score)	2.34 ± 0.61	2.30 ± 0.63	0.04 (-0.22 to 0.30)	0.07	0.308	0.759
Mayo endoscopic subscore, post-treatment (score)	1.14 ± 0.41	2.05 ± 0.65	-0.91 (-1.14 to -0.68)	1.68	7.846	<0.001

Table 7: Adverse events by group.

Adverse event	Study group (n=44)	Control group (n=44)	p
Any adverse event [n (%)]	6 (13.64)	5 (11.36)	0.746
Gastrointestinal discomfort (nausea, flatulence) [n (%)]	6 (13.64)	5 (11.36)	0.746
Headache [n (%)]	2 (4.55)	1 (2.27)	0.557
Rash [n (%)]	0 (0)	0 (0)	—
Acute intolerance syndrome [n (%)]	0 (0)	0 (0)	—
Treatment discontinuation due to AE [n (%)]	0 (0)	0 (0)	—
Serious adverse events [n (%)]	0 (0)	0 (0)	—

This findings align with and extend prior research demonstrating the superiority of combined oral and topical 5-ASA therapy in distal UC (Ordas, 2012; Jacknowitz, 1980; Eisenstein, 2018). A network meta-analysis (Barberio, 2021) reported that combined oral and topical mesalazine was associated with higher remission rates compared to oral therapy alone in left-sided UC. Similarly, the AGA guidelines recommend adding rectal mesalamine to oral 5-ASA therapy for patients with extensive or left-sided mild-to-moderate UC (Raine, 2022).

The rapid symptom improvement observed in the combination therapy group—with mean improvement times of 3.28 days for abdominal pain, 2.44 days for diarrhea and 6.18 days for mucous/bloody stools—represents clinically meaningful benefits for patients. Rapid symptom control is particularly important in UC management, as persistent symptoms significantly impair quality of life and may lead to treatment non-adherence (da Silva, 2014). The shorter time to symptom improvement in the combination therapy group likely reflects the higher local drug concentration achieved at the site of active inflammation.

The endoscopic outcomes, particularly the significantly lower post-treatment Mayo Endoscopic Subscore in the combination therapy group (1.14 vs. 2.05), are noteworthy. Endoscopic healing (defined as Mayo Endoscopic Subscore ≤1) is increasingly recognized as an important treatment target in UC, associated with improved long-term outcomes including reduced hospitalization rates, decreased risk of colectomy and lower relapse rates (Cross, 2014; Caron, 2023). The STRIDE-II guidelines identified endoscopic healing as a preferred long-term goal in UC management (Le Berre, 2020). In This study, 79.5% (35/44) of patients in the combination therapy group achieved a post-treatment MES ≤1, compared to only 34.1% (15/44) in the oral monotherapy group, representing a clinically meaningful difference in mucosal healing.

Synergistic mechanism of combined therapy

The mechanistic rationale for the observed superiority of combination therapy relates to the complementary pharmacokinetic profiles of oral and topical mesalazine. Oral mesalazine enteric-coated tablets release the active drug primarily in the distal small bowel and proximal to mid-colon, providing systemic distribution throughout the colon with relatively lower concentrations in the rectosigmoid region due to dilution and progressive drug absorption. In contrast, retention enema delivers a high concentration of mesalazine directly to the distal colonic and rectal mucosa, achieving local tissue concentrations 10- to 100-fold higher than those attainable with oral administration alone, while systemic absorption remains minimal (Ko, 2019; Chibbar, 2020). This high topical concentration maximizes the drug's anti-inflammatory effects—including inhibition of leukotriene and prostaglandin synthesis, free radical scavenging and downregulation of pro-inflammatory cytokines—directly at the site of disease activity. When combined with oral mesalazine, which provides baseline anti-inflammatory coverage throughout the colon, the dual route achieves synergistic therapeutic benefit by optimizing drug concentration across the entire left colon while minimizing systemic exposure. For E2-type UC, where inflammation spans from the rectum to the splenic flexure, this dual-mechanism approach ensures coverage of the entire affected area: the oral component treats the more proximal colonic involvement, while the enema provides targeted, high-concentration therapy to the most severely affected distal segments (Chibbar, 2020; Hauso, 2015).

Patient adherence

Adherence to the retention enema protocol was generally favorable. All patients in the study group received standardized instruction on proper enema administration technique from trained nursing staff. Adherence was assessed by patient self-report and medication return counts. The majority of patients (39/44, 88.6%) reported completing ≥90% of prescribed enema administrations. The most commonly cited challenges were the need to remain supine for 30 minutes post-administration and the sensation of rectal fullness, which typically diminished with continued use. Nevertheless, patient acceptance was favorable, with most patients expressing willingness to continue enema therapy if clinically indicated. These adherence rates are consistent with previously published reports on topical mesalazine therapy (Ramai, 2021).

Safety profile

The safety findings of this study are reassuring. Adverse events were mild, comparable between groups and consistent with the established safety profile of mesalazine (Gross, 2012; Ren, 2017). The most common adverse events were mild gastrointestinal discomfort (nausea, flatulence) and headache. No serious adverse events, including acute intolerance syndrome, severe allergic reactions, hematologic abnormalities, or skin reactions, were observed. The addition of topical enema therapy did not increase the overall adverse event rate compared to oral monotherapy (13.64% vs. 11.36%, P = 0.746). These findings support the safety of combined oral and topical mesalazine therapy in this patient population.

Comparison with existing literature

This findings are consistent with prior randomized controlled trials and meta-analyses demonstrating the superiority of combined oral and topical mesalazine in left-sided UC. A meta-analysis by Barberio *et al*. (Barberio, 2021) reported that topical 5-ASA therapy was superior to placebo for induction of remission in active distal UC, with a pooled relative risk of 8.30 (95% CI: 4.28-16.12). The combination of oral and topical therapy was associated with higher remission rates compared to either therapy alone. Similarly, the ECCO guidelines recommend combination therapy as first-line treatment for left-sided UC (Raine, 2022). This study adds to this body of evidence by providing real-world data from a Chinese population with a standardized 30-day treatment protocol, including specific dosing (oral 4.0 g/day plus enema 4.0 g/day).

Incremental contribution

While the superiority of combined therapy is well established in guidelines, this study provides incremental value by: (1) offering real-world data from a Chinese population, which may differ from Western populations in terms of genetics, diet and healthcare delivery; (2) evaluating a specific short-term (30-day) induction protocol with standardized dosing; (3) providing detailed safety data in a population where such data are limited; and (4) using the validated Mayo Endoscopic Subscore to quantify mucosal healing.

Limitations

Several limitations warrant consideration

This retrospective, non-randomized study assigned patients based on clinical availability and patient preference, introducing potential selection bias. The lack of allocation concealment, blinding, placebo control, and prospective trial registration further limits internal validity and comparability with RCTs. The relatively small sample size (44 per group) and short 30-day treatment period restrict generalizability and preclude assessment of sustained remission, relapse prevention, or long-term mucosal healing. Non-standardized efficacy endpoints ("effective"/"valid"/"ineffective") adapted from local guidelines limit direct comparability with international trials, although Mayo score components were also reported. The absence of a placebo enema in the control group may have introduced performance and detection bias, particularly for patient-reported outcomes. Exclusion of patients with complications (e.g., stenosis, obstruction, toxic megacolon, cancer) limits external validity and the lack of patient-reported outcomes (quality of life, treatment satisfaction) or economic data prevents comprehensive value assessment. Finally, no long-term follow-up data were collected, leaving the durability of treatment effects unknown. Future prospective, blinded, placebo-controlled RCTs with larger sample sizes and extended follow-up are needed to confirm these findings.

CONCLUSION

In conclusion, this retrospective comparative cohort study demonstrated that mesalazine enteric-coated tablets combined with a retention enema were associated with superior short-term (30-day) outcomes compared with oral mesalazine monotherapy in patients with mild to moderate E2-type active ulcerative colitis. Combination therapy was associated with higher clinical efficacy rates, more rapid symptom improvement, better endoscopic outcomes (including lower Mayo Endoscopic Subscore and higher rates of mucosal healing) and a comparable safety profile.

However, these findings must be interpreted with caution given the retrospective, non-randomized design and the lack of blinding and placebo control. The conclusions should be considered hypothesis-generating rather than definitive. Larger, prospective, randomized controlled trials with longer follow-up periods are needed to confirm these findings and to evaluate long-term outcomes, including sustained remission, relapse prevention, and the durability of mucosal healing. Until such studies are conducted, combined oral and topical mesalazine therapy should be considered as an effective short-term induction strategy for patients with mild to moderate left-sided UC, consistent with current guideline recommendations.

Acknowledgements

None.

Author's contributions

Rui Zhang and Shihui Wang: Contributed equally to this work and designed the research study; Mingyue Yang and Chunchun Yang: Performed the research and collected clinical data; Dawei Yang, Yanan Zhao and Xueli Zhang: Analyzed the data and conducted statistical analyses. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Funding
This study was supported by a research grant on "Impact of Small Intestinal Bacterial Overgrowth on Intestinal Barrier Function in Patients with Ulcerative Colitis by Hebei Provincial Health Commission Scientific Research Fund (No. 20221427) Project (Key Science and Technology Research Program). The funder had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Data availability statement
All data generated or analysed during this study are included in this published article.

Ethical approval
The protocol was approved by the Ethics Committee of The First Hospital of Hebei Medical University (Approval No. 2020-KY-089, dated September 15, 2020). Informed consent was obtained from all study participants. All methods were carried out in accordance with the Declaration of Helsinki. This study was performed in adherence with the TREND guidelines. See supplementary file for the TREND checklist.

Conflict of interest
The authors declare no conflict of interest.

Supplementary data
https://pjps.pk/uploads/2026/08/SUP1787479922.pdf

REFERENCES

Al-Horani RA, Al-Horani RA and Al-Horani M (2025). The use and role of mesalamine in the treatment of ulcerative colitis: A literature review. *Cureus*, **17**(8): e89944.

Barberio B, Segal JP, Quraishi MN, Black CJ, Savarino EV and Ford AC (2021). Efficacy of oral, topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: Systematic review and network meta-analysis. *J. Crohns Colitis*, **15**(7): 1184-1196.

Caron B and Peyrin-Biroulet L (2023). Ulcerative proctitis: Challenges for clinical management. *J. Gastroenterol. Hepatol*., **38**(7): 1192.

Chibbar R and Moss AC (2020). Mesalamine in the initial therapy of ulcerative colitis. *Gastroenterol. Clin. North Am*., **49**(4): 689-704.

Cross R, Ko CW and Singh S (2019). Mild-to-moderate ulcerative colitis guideline. *Gastroenterology*, **156**(3): 768.

da Silva BC, Lyra AC, Rocha R and Santana GO (2014). Epidemiology, demographic characteristics and prognostic predictors of ulcerative colitis. *World J. Gastroenterol*., **20**(28): 9458-9467.

Du L and Ha C (2020). Epidemiology and pathogenesis of ulcerative colitis. Gastroenterol. *Clin. North Am*., **49**(4): 643-654.

Eisenstein M (2018). Ulcerative colitis: Towards remission. *Nature*, **563**(7730): S33.

Enema administration (2003). *Nurs. Times*, **99**(6): 29.

Gross V (2012). Topical therapy. *Dig. Dis*., **30**(Suppl 3): 92-99.

Hauso O, Martinsen TC and Waldum H (2015). 5-Aminosalicylic acid, a specific drug for ulcerative colitis. Scand. *J. Gastroenterol*., **50**(8): 933-941.

He T, Song LQ, Weng XY, Pan P, Ding H, Liu MQ, Qiu SL and Sun SM (2025). Clinical relevance of inflammatory markers in the evaluation of severity of ulcerative colitis: A retrospective study. *Open Life Sci*., **20**(1): 20251088.

Jacknowitz AI (1980). Ulcerative colitis and its treatment. Am. *J. Hosp. Pharm*., **37**(12): 1635-1646.

Kaenkumchorn T and Wahbeh G (2020). Ulcerative colitis: Making the diagnosis. *Gastroenterol. Clin. North Am*., **49**(4): 655-669.

Kato S, Ishibashi A, Kani K and Yakabi K (2018). Optimized management of ulcerative proctitis: When and how to use mesalazine suppository. *Digestion*, **97**(1): 59-63.

Ko CW, Singh S, Feuerstein JD, Falck-Ytter C, Falck-Ytter Y and Cross RK; American Gastroenterological Association Institute Clinical Guidelines Committee (2019). AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology*, **156**(3): 748-764.

Kruis W, Meszaros S, Wehrum S, Mueller R, Greinwald R and Nacak T (2023). Mesalazine granules promote disease clearance in patients with mild-to-moderate ulcerative colitis. *United European Gastroenterol. J*., **11**(8): 775-783.

Le Berre C, Roda G, Nedeljkovic Protic M, Danese S and Peyrin-Biroulet L (2020). Modern use of 5-aminosalicylic acid compounds for ulcerative colitis. *Expert Opin*. *Biol. Ther*., **20**(4): 363-378.

Ordás I, Eckmann L, Talamini M, Baumgart DC and Sandborn WJ (2012). Ulcerative colitis. *Lancet*, **380**(9853): 1606-1619.

Pabla BS and Schwartz DA (2020). Assessing severity of disease in patients with ulcerative colitis. *Gastroenterol. Clin. North Am*., **49**(4): 671-688.

Park J and Cheon JH (2022). Updates on conventional therapies for inflammatory bowel diseases: 5-aminosalicylates, corticosteroids, immunomodulators and anti-TNF-α. *Korean J. Intern. Med*., **37**(5): 895-905.

Raine T, Bonovas S, Burisch J, Kucharzik T, Adamina M, Annese V, Bachmann O, Bettenworth D, Chaparro M, Czuber-Dochan W, Eder P, Ellul P, Fidalgo C, Fiorino

G, Gionchetti P, Gisbert JP, Gordon H, Hedin C, Holubar S, Iacucci M, Karmiris K, Katsanos K, Kopylov U, Lakatos PL, Lytras T, Lyutakov I, Noor N, Pellino G, Rogler G, Sallakci E, Siegmund B, Sokol H, Spinelli A, Sturm A, Teich N, van der Woude CJ, Warusavitarne J, Wewer A, Zammit S and D'Amico F (2022). ECCO guidelines on therapeutics in ulcerative colitis: Medical treatment. *J. Crohns Colitis*, **16**(1): 2-17.

Ramai D, Zakhia K, Fields PJ, Ofosu A, Patel G, Shahnazarian V, Lai JK, Dhaliwal A, Reddy M and Adler DG (2021). Fecal microbiota transplantation (FMT) with colonoscopy is superior to enema and nasogastric tube while comparable to capsule for the treatment of recurrent Clostridioides difficile infection: A systematic review and meta-analysis. *Dig. Dis. Sci*., **66**(2): 369-380.

Ren PW, Yang WJ, Wang DD, Shan JY, Kang DY, Hong Q, Wen S and Zhang RW (2017). Kangfuxinye enema combined with mesalamine for ulcerative colitis: A systematic review and GRADE approach. Evid. Based Complement. *Alternat. Med*., **2017**: 6019530.

Schnoy E, Dignass A, Gaskins M and Kucharzik T (2025). From guidelines to evidence-based practice – A German perspective on mesalazine as first-line therapy for mild-to-moderate ulcerative colitis. *Z. Gastroenterol*., **63**(10): 1053-1067.

Segal JP, LeBlanc JF and Hart AL (2021). Ulcerative colitis: An update. *Clin. Med. (Lond.)*, **21**(2): 135-139.