Efficacy and safety of Fufangkushen colon-coated capsule in the treatment of ulcerative colitis compared with mesalazine: A double-blinded and randomized study

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ABSTRACT

Ethnopharmacological relevance: Fufangkushen colon-coated capsule (FCC) was a newly developed herbal drug for treating ulcerative colitis (UC) patients with traditional Chinese medicine (TCM) pattern of damp-heat accumulating in the interior.

Objective: To explore the efficacy and safety of FCC in the treatment of active UC compared with Huidi (HD, mesalazine enteric-coated tablets) were evaluated in a double-blinded and randomized clinical trial.

Materials and Methods: In the double-blind, double-dummy, multicenter, randomized and controlled study, 320 active UC patients with TCM pattern of damp-heat accumulating in the interior were assigned to two groups: 240 treated with FCC plus HD placebo treatment, 80 with HD plus FCC placebo. The drugs and their corresponding placebos were administrated at advised dosage for 8 weeks. The primary endpoint was a positive clinical response at week 8, and Mayo scoring system was employed for assessment of UC activity.

Results: At the 8th week, 72.50% of patients in FCC group (170 of 234) and 65.00% of patients in HD group (52 of 80) had achieved a clinical response. There was no statistically significance between the 2 groups (P > 0.05). The proportions of patients who had a clinical remission was similar in 2 groups (41.50% in FCC group, 41.25% in HD group, P > 0.05), mucosal healing rate at week 8 in the two groups were also without significant difference (55.13% in FCC group, 55.00% in HD group, P > 0.05). Mayo scores at week 8 showed no statistically difference in the two groups. No significant differences were observed between the safety profiles of the 2 groups (P > 0.05). No severe AEs were reported in either group. The latent class analysis indicated that FCC was superior applicable for the left hemicolon involved patients than HD.

Conclusions: Compared with HD, a mesalamine enteric-coated tablet, FCC is similarly effective and safe in the treatment of active UC with TCM pattern of damp-heat accumulation interior pattern. In addition, FCC indicates superior effect in the treatment of UC with inflamed area of the left hemicolon than HD.

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1. Introduction

Ulcerative colitis (UC) (Buyse et al., 1999; Bernstein et al., 2010; Carter et al., 2004) is one of the two main inflammatory bowel diseases (IBD), characterized by inflamed mucosa limited to the large intestine, and the main symptoms in clinic include diarrhea, mucilage or blood–pus stools and abdominal pain (Bernstein et al., 2010; Carter et al., 2004). Although the etiology has not yet been elucidated, UC has long been considered a disease that affects predominantly a Western population, however, more recent data have shown significantly higher rates in Asians and time trend studies have shown an increase in the incidence (Fujimoto et al., 2007; Goh and Xiao, 2009; Jiang and Cui, 2002).

Drug therapy and surgery are the major therapeutic approaches to UC, and the goal is long-term control of the disease condition in order to improve the patients’ quality of life (QOL) (Carter et al., 2004; Kornbluth and Sachar, 2004). Mesalamine, corticosteroids,
immunosuppressants and biological agents are currently utilized to treat UC, and long-term treatment with oral mesalamine has been the first-line approach to the treatment of patients with UC. However, there are still a large number of patients who do not respond to the treatment or suffer from adverse drug reactions due to variety of causes, thus new treatments, being rapid available, effective and safe for UC are needed (Fiorentini et al., 1990; Fiorino et al., 2010; Marteau et al., 1996).

In China, UC incidence has increased rapidly in the recent decade, and some surveys indicated that compared with in Western countries, UC in China has some differences in clinical characteristics (Wang and Ouyang, 2007). For instance, a lower percent (14%) of UC patients were observed complicated by extraintestinal manifestations in China than in Western studies (40–50%), the rate of intestinal complications was also lower (0.4% vs. 3–5%). Furthermore, only 3% of the patients required colectomy and only 0.6% died as the result of UC. In Western countries, surgical operations have been reported to be performed on 20–25% of patients with UC died as the result of UC. In Western countries, surgical operations have been reported to be performed on 20–25% of patients with UC (Kirsner and Shorter, 1982), and the mortality rate was as high as 19.7% reported (Edwards and Truelove, 1964). This difference might be due to the differences in their racial and geographic conditions. Thus, to develop an effective and specified therapy applying to UC patients in Chinese population is an urgent task.

Traditional Chinese medicine (TCM) has been widely used in the treatment of UC patients. From 1981 to 2000, there reported that over 20% UC patients were treated with pure Chinese herbs, and 59.1% were treated with combined Chinese and western medicine approach, only 18.6% accepted 5-ASA and/or corticosteroid only therapy (Jiang and Cui, 2002). Undoubtedly, Chinese herbal medicine is a huge source for new drug discovery for UC treatment.

Fufangkushen colon-coated capsule (FCC) was a newly developed herbal drug for treating UC patients with Chinese medicine pattern of damp-heat accumulating in the interior, which was composed of Sophorae Flavescentis, Sanguisorba Officinalis L., Indigo Naturalis, Bletilla Striata and Glycyrrhiza Uralensis. Previous studies proved FCC can achieve a satisfactory outcome in the induction of remission in UC patients with a good safety profile (Changhong et al., 2009). Here we report a double-blind, double-dummy, multicenter, randomized, controlled study aimed to clarify the efficacy and safety of FCC, comparing with Huidi, mesalazine enteric-coated tablets (HD) in patients with UC in the active phase.

2. Materials and methods

2.1. Patient selection

We conducted the study in patients with active UC on the basis of the following 3 inclusion criteria: patients who were 18–65 years of age at the time of informed consent; who had active UC defined by a Mayo score (Schroeder et al., 1987) of 6–12 points (scores range from 0 to 12, with higher scores indicating more severe disease activity) as shown in Table 1; and who meet the Chinese pattern diagnosis of damp-heat accumulation interior. The damp-heat accumulation interior pattern diagnosis can be identified based on the co-existence of 3 major symptoms (diarrhea, mucous or bloody purulent stools, abdominal pain) and at least 2 secondary symptoms (tenesmus, burning pain in anus, fever, anorexia, dry or bitter mouth, foul stools) according to New Drug Chinese Treatment of Chronic Non-specific Ulcerative Colitis Research Guidelines (Zheng, 2002).

The patients were excluded according to following criteria: patients had quiescent UC; who were complicated with other severe diseases; female patients in pregnancy or lactation and male patients have desire for procreation; who showed allergic to the drug; who had higher blood creatinine level, or blood alanine transaminase level higher than double of normal; who took any other investigational drugs within 3 months.

<table>
<thead>
<tr>
<th>Stool frequency</th>
<th>0 = Normal number of stools for this patient</th>
<th>1 = 1–2 stools more than normal</th>
<th>2 = 3–4 stools more than normal</th>
<th>3 = 5 or more stools more than normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Findings on endoscopy</td>
<td>0 = Normal or inactive disease</td>
<td>1 = Mild disease (erythema, decreased vascular pattern, mild friability)</td>
<td>2 = Moderate disease (marked erythema, lack of vascular pattern, friability, erosions)</td>
<td>3 = Severe disease (spontaneous bleeding, ulceration)</td>
</tr>
<tr>
<td>Physician’s global assessment</td>
<td>0 = Normal</td>
<td>1 = Mild disease</td>
<td>2 = Moderate disease</td>
<td>3 = Severe disease</td>
</tr>
</tbody>
</table>

The Mayo score ranges from 0 to 12, with higher scores indicating more severe disease. Data are from Schroeder et al. (1987).

1. Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency.

2. The daily bleeding score represents the most severe bleeding of the day.

3. 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.

2.2. Ethical considerations

This study was conducted according to the principles of the Declaration of Helsinki after obtaining approvals from the SFDA (Approval Document No. 2003L30617) and Ethics Committee at each of the participating medical centers. Written informed consent was obtained from all participants.

2.3. Study drugs

Fufangkushen colon-coated capsule (FCC, 0.4 g/capsule, supplied by Zhonghui Pharmaceutical, Beijing, China. Patch No. 20070301), Huidi mesalazine tablet (HD, mesalazine enteric-coated tablets, 0.25 g/tablet, supplied by Luling Pharmaceutical, Jiamusi, China. Patch No. 071006), and two placebos prepared identical in color, taste and consistency to the 2 above drugs respectively (supplied by Zhonghui Pharmaceutical, Beijing, China). FCC was a newly developed drug for treating UC with Chinese medicine pattern of damp-heat accumulation interior, which is composed of extracts of Chinese herbal medicine Radix Sophorae Flavescentis (Kushen), Radix Sanguisorbae (Diyu), Indigo Naturalis (Qingdai), Bletilla hyacinthina reichb (Baiji), Radix Glycyrrhizae (Gancao). All the extracts were coated in a capsule which ensures the medicine to be released in the colon. All the drugs were packed into unified packages with uniform labels, and each package contained 10 bottles (72 capsules per bottle) of FCC and 8 bottles of HD placebo (112 tablets per bottle); or 10 bottles of FCC placebo and 8 bottles of HD. During the study, each patient would take FCC 4 capsules per time, 3 times per day, plus HD placebo 4 tablets per time, 4 times
per day; or FCC placebo 4 capsules per time, 3 times per day, plus HD 4 tablets per time, 4 times per day. The medication course was 8 weeks.

2.4. Study design

This double-blind, double-dummy, randomized, controlled study was conducted at 13 centers in China from December of 2007 to June of 2009. All eligible patients were randomly allocated at a 3:1 ratio into two groups. 240 patients accepted FCC, 80 accepted HD treatment. The central randomization system was adopted for the patient allocation, and the randomization code was sealed until the blind was removed.

At time of the informed consent, investigators evaluated the background characteristics of patients. After an observation period of 0–7 days from the time of informed consent, investigators assessed patients for their eligibility for enrolment according to the criteria. At the assessment for eligibility, the Mayo score was calculated. The area of the inflammation was determined by colonoscopy. Then administration was started for 8 weeks. During the study, for each patient, the condition of the bloody stools, stool frequency, drug compliance, physician’s global assessment, traditional Chinese pattern related symptoms and vital signs were recorded at every visit of the 1, 2, 4, 6, 8 weeks after the administration. Colonoscopy was performed at 8 weeks or at withdrawal from the study. For safety evaluation, clinical laboratory data were checked at the time of informed consent at the 4th and 8th week.

2.5. Outcome assessment

Patients were evaluated at weeks 0 and 8. The Mayo score (Table 1) was determined at weeks 0, 8. A partial Mayo score (Mayo score without endoscopy) was determined at all visits. Clinical response was defined as a decrease from baseline in the total Mayo score at least 3 points and at least 30%, with an accompanying decrease in the subscore for rectal bleeding at least 1 point or absolute subscore for rectal bleeding of 0 or 1. Clinical remission was defined as a total Mayo score of 2 points or lower, with no individual subscore exceeding 1 point. Mucosal healing was defined as absolute subscore for endoscopy of 0 or 1.

Clinical response, clinical remission, and mucosal healing were assessed at weeks 8. Patients who had a clinical response or who were in clinical remission at each time were considered to have a sustained clinical response or to be in sustained clinical remission, respectively. Adverse events and concomitant medications were recorded at each visit.

2.6. Statistical analysis

Sample size was determined based on the calculation of non-inferiority trial design (D’Agostino et al., 2003; Ellenberg, 1989; Fleming, 2008). The effective rate of HD was 77.5% according to previous reports (Andus et al., 2010; Hartmann and Stein, 2010; Ito et al., 2010). In this study, \( \alpha = 0.05, \beta = 0.2, \delta_0 = 0.15 \) were used for the calculation. Concern that there have been abundant data on the effective rate of mesalamine, the eligible patients would be assigned in FCC:HD groups in a 3:1 ratio, and the sample size was 256 in total (192 in FCC group; 64 in HD group). Allowing for a withdrawal rate at 20%, the final sample size was determined as 320 cases, 240 in FCC group and 80 in HD group.

\[
N = \left[ \sigma \times \left( \frac{U_0 + U_0}{\delta_0 - \delta} \right) \right]^2 \times \frac{1}{k} + \frac{1}{(1-k)}
\]

The primary end point was a clinical response at week 8. Patients who took prohibited medication owing to lack of efficacy or loss of response to the study medication, who discontinued the study medication because of lack of efficacy, or who underwent a colectomy or ostomy were not considered to have had a clinical response, to be in clinical remission, or to have had mucosal healing from the time of the event onward, regardless of the Mayo score.

Demographic and baseline characteristics were compared with the use of the chi-square test or Fisher’s exact test for categorical variables and with the use of analysis of variance for van der Waerden normal scores for continuous variables. A two-sided Cochran–Mantel–Haenszel chi-square test, at a significance level of 0.05, stratified according to corticosteroid-refractory status and the location of the study center, was used to compare dichotomous end points (i.e., clinical response, clinical remission, mucosal healing, and clinical remission with discontinuation of corticosteroids) among treatment groups. All efficacy analyses used intention-to-treat methods. Safety analysis set (SS) consisted of patients who accepted at least one visit after randomization and safety comparisons were performed with the use of Fisher’s exact test. \( P < 0.05 \) was considered statistically significant. All data were analyzed on a Statistics Analysis System (Ito et al., 2010) 9.1 (Order No. 195557).

In the subgroup analysis, latent class analysis (LCA) was utilized to categorize UC patients according to the inflamed areas of colon, and to explore the correlation between the patient responses and the subgroups. LCA operation is unavailable in SAS, the Methodology Center of the Pennsylvania State University distributes a suite of programs for LCA as add-on procedures for SAS (http://methodology.psu.edu/index.php/ra/lcalta), and we used this software for LCA analysis.

3. Results

3.1. Characteristics of the patients

Three hundred and twenty patients underwent randomization: 240 were assigned to FCC group, 80 to HD group. The baseline characteristics of the patients were similar. Treatment was discontinued prematurely by 35 patients in FCC group, 18 in HD group, due to adverse events (AE), lack of efficacy, protocol violation, absence in visit, and other reasons (Fig. 1). There are no differences in the baseline, including gender, age, body weight, duration of disease and the Mayo score (Table 2).

3.2. Efficacy

At week 8, there were 72.65% of patients in FCC group (170 of 234) and 65.00% of patients in HD group (52 of 80) who had achieved a clinical response. No statistically significance was detected between the 2 groups (\( P = 0.19 > 0.05 \)). The proportions of patients who had a clinical remission was similar in 2 groups (41.50% in FCC group, 41.25% in HD group, \( P = 0.97 > 0.05 \)), mucosal healing rate at week 8 in the two groups were also without sig-

| Table 2 Baseline characteristics of patients in FCC and HD group. |
|----------------------|----------------------|----------------------|
| Characteristics      | FCC group (n = 234)  | HD group (n = 80)    | \( P \)-value |
| Male sex – no. (%)   | 123 (52.6)           | 38 (47.5)            | 0.43         |
| Age – year           | 43.63 ± 12.01        | 44.51 ± 12.02        | 0.57         |
| Weight – kg          | 59.39 ± 8.87         | 60.17 ± 8.79         | 0.49         |
| Duration of disease – year | 2.99 ± 3.56       | 2.39 ± 3.89          | 0.24         |
| Mayo score           | 7.86 ± 1.59          | 7.95 ± 1.29          | 0.64         |

* Plus–minus values are means ± SD.
\[ \dagger \] \( P \)-values for all categorical variables are based on a two-sided chi-square test. \( P \)-values for continuous variables are based on t-test or adjusted t-test.

The Mayo scores range from 0 to 12, with higher scores indicating more severe disease.
significant difference (55.13% in FCC group, 55.00% in HD group, \( P = 0.98 > 0.05 \)). Mayo scores at week 8 showed no statistically difference in the two groups as indicated in Table 3.

### 3.3. Safety

The incidence of adverse events (AE) was similar between the 2 groups. In FCC group, 38 AEs (15.97%) were reported, and in HD group the number was 10 (12.50). The AEs were described in Table 4. The majority of AEs were recorded as mild or moderate, including nausea, fatigue, abdominal pain, abdominal distension, liver discomfort, pain around the anus, upper respiratory tract infection, indigestion, drug prototype discharge, felt fever. The adverse drug reactions being considered as related to drugs were listed in Table 5. No severe AE was reported in either group.

### 3.4. Specified indication analysis

In order to explore the exact indications of the drugs, latent class analysis (LCA) was employed in the study. The inflamed location involved in UC can be divided into 4 parts: rectum, sigmoid, left hemicolon and other colon. One patient might have single part, or have two or more parts involved. If the 4 parts were all involved, the entire colon was inflamed.

In the LCA model, all the recorded involved locations were divided into 2 latent classes according to the clinical response of FCC and HD. There was obvious difference between the 2 classes. Class 1 showed high distribution probabilities in rectum and sigmoid, whereas class 2 in left hemicolon (Fig. 2). Then multinomial logistic model was employed to explore the correlation between the 2 classes and clinical response to different therapies (FCC or HD). Rho starting values were randomly generated (seed = 175 338 476). The convergence method was maximum absolute deviation. According to clinical response, the odds ratio in each group was estimated. The odds ratio in effective group was 1.088, the 95%CI were from 0.538 to 2.200; the odds ratio in non-effective group was 2.674, the 95%CI was from 1.028 to 6.954 (\( P < 0.05 \)). The response rate of each group in each latent class was listed in Table 6.

The significant odds ratio in non-responsive patients and the responsive rate of each group denoted that HD showed higher probability in non-effective patients in class 2 than FCC (\( P < 0.05 \)), which can be explained as in left hemicolon involved patients, HD

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**Table 3**

Summary of efficacy in FCC and HD group. *P*-values for all categorical variables are based on a two-sided chi-square test. *P*-values for continuous variables are based on t-test or adjusted t-test.

<table>
<thead>
<tr>
<th>Variable</th>
<th>FCC group (n = 234)</th>
<th>HD group (n = 80)</th>
<th>( P )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response – no. (%)</td>
<td>170 (72.65)</td>
<td>52 (65.00)</td>
<td>0.19</td>
</tr>
<tr>
<td>Clinical remission – no. (%)</td>
<td>97 (41.45)</td>
<td>33 (41.25)</td>
<td>0.97</td>
</tr>
<tr>
<td>Mucosal healing – no. (%)</td>
<td>129 (55.13)</td>
<td>44 (55.00)</td>
<td>0.98</td>
</tr>
<tr>
<td>Mayo score</td>
<td>7.86 ± 1.59</td>
<td>7.95 ± 1.29</td>
<td>0.64</td>
</tr>
<tr>
<td>Week 8</td>
<td>3.32 ± 2.52</td>
<td>3.80 ± 2.88</td>
<td>0.16</td>
</tr>
</tbody>
</table>

* Data shown with plus–minus values are means ± SD.

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4. Discussion

HD (mesalamine), patients who received FCC achieved similar proportion in clinical response, clinical remission and mucosal healing at week 8. It is noteworthy that FCC is superior to HD in the treatment of patients with UC involving the left hemicolon, which is a clinically meaningful result.

The FCC formula is an experiential effective recipe which has been successfully applied in TCM clinical practice for many years. According to TCM theory, the Radix Sophorae Flavescentis (Kushen) acts as the sovereign medicine in the formula, which has the function of clearing heat and drying dampness, being specialized in clearing the damp-heat of lower energizer; Radix Sanguisorbae (Kushen) can help remove toxin and promote wound healing, cool the blood aspect and stanch bleeding; Indigo Naturalis (Qingdai) and Blettilla hyacinthina reichb (Baiji) can help remove toxin and promote wound healing, cool the blood aspect and stanch bleeding, so that these two herbal drugs are adjuvant and messenger drugs in chorus; Radix Glycyrrhizae (Gancao) can coordinate the drug actions of the prescription in addition with the function of clearing heat and remove toxin, relax spasm and relieve pain. In combination, the formula has the function to clear heat and dry dampness, remove toxin and promote wound healing, cool the blood aspect and stanch bleeding, which can be used in treating UC with damp-heat accumulation interior pattern.

In TCM, a certain part of UC symptoms belong to damp-heat accumulation interior (a TCM term for conditions with diarrhea, bloody stools, burning pain in anus, tenesmus, fever, anorexia, foul stools, etc.). The damp-heat accumulation interior pattern is one of the most commonly seen patterns in patients with UC, especially in cases of initial onset of UC, there has been reported that 51.9% of UC patients were identified as damp-heat accumulation interior pattern. According to TCM theory, the Radix Sophorae Flavescentis (Kushen) acts as the sovereign medicine in the formula, which has the function of clearing heat and drying dampness, being specialized in clearing the damp-heat of lower energizer; Radix Sanguisorbae (Diyu) is applied as the minister medicinal which can remove toxin and promote wound healing, cool the blood aspect and stanch bleeding; Indigo Naturalis (Qingdai) and Blettilla hyacinthina reichb (Baiji) can help remove toxin and promote wound healing, cool the blood aspect and stanch bleeding, so that these two herbal drugs are adjuvant and messenger drugs in chorus; Radix Glycyrrhizae (Gancao) can coordinate the drug actions of the prescription in addition with the function of clearing heat and remove toxin, relax spasm and relieve pain.

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mechanisms by which some of these modalities may work have become apparent gradually.

There exist some internal relations between TCM patterns and pathological changes in UC. In the damp-heat accumulation interior pattern, mucosal edema was more apparent than congestion, and there was marked swelling around the ulcer with surface covering of yellow purulent secretion (while in cases of spleen-kidney Yang deficiency pattern, mucosal edema was more apparent than congestion, and there was no marked swelling around the ulcer, the surface of which was covered by white secretive material) (Chen et al., 1996). T-cell subsets were also related with the pattern differentiation in UC patients (Chang et al., 2009), in cases of damp-heat accumulation interior pattern, the level of CD4+ cell decreased and CD8+ cell increased significantly, yet these changes were only slight in other pattern types (spleen-kidney Yang deficiency, qi-stagnation with blood stasis and Yin-blood deficiency). Thus, different therapeutic approach based on pattern differentiation is reasonable.

Remedies derived from herbs contain a huge range of compounds, some common to many plants (for example pyrrolizidine alkaloids) and others specific to individual plants (Langmead and Rampton, 2001). Extensive work have suggested that, in vitro at least, individual chemicals derived from a variety of plants may have antibacterial, antioxidant, anticytokine, antispasmodic, cytotoxic and neuromodulatory actions (Langmead and Rampton, 2001). In our previous pharmacological studies, FCC was proved to have the function of protective effect to the UC tissue induced by dinitrochlorobenzene in Guinea pigs and rats, analgesic effect to the pain induced by chemical and physical stimulation, and depressant effect to the increasing capillary permeability induced by acetic acid in mice (unpublished data). Nevertheless, the long-term effect and the mechanism of FCC for UC remain as the important issues.

LCA is employed in the indications exploration, which can facilitate targetting future intervention resources to subgroups that promise to show the maximum treatment response (Bureau et al., 2011; Lanza and Rhoades, 2011). Traditionally, subgroup analysis aims to determine whether individuals respond differently to a treatment based on one or more measured characteristics. LCA provides a way to identify a small set of underlying subgroups characterized by multiple dimensions which could, in turn, be used to examine differential treatment effects. Since the latent variable is discrete and mutually exclusive and exhaustive, in this study, the patients were categorized into 4 subgroups according to the involved location of colon (rectum, sigmoid, left hemicolon and other). The 4 Inflamed areas can be categorized to two latent classes by LCA. Although the mechanism remains unclear, it is documented that FCC shows a superior effect than HD in the patients with UC involving the left hemicolon area, which would be helpful to the clinicians. Yet further studies are still expected to explore the mechanism of this special indication of FCC.

5. Conclusion

FCC has a similar effect and safety in the treatment of active UC with TCM damp-heat accumulation interior pattern at week 8 compared with HD, a mesalamine enteric-coated tablets, in achieving clinical response and remission, mucosal healing. In addition, FCC is superior to HD in treating patients with UC as the inflamed area was the left hemicolon.

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References


Table 6

<table>
<thead>
<tr>
<th>Latent class</th>
<th>Group</th>
<th>N</th>
<th>Responsive N (%)</th>
<th>Statistic value (X²)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 1 (Proctosigmoiditis)</td>
<td>FCC</td>
<td>177</td>
<td>127 (71.75)</td>
<td>0.0387</td>
<td>0.8441</td>
</tr>
<tr>
<td>Class 2 (Left hemicolon)</td>
<td>HD</td>
<td>54</td>
<td>38 (70.37)</td>
<td>0.0387</td>
<td>0.8441</td>
</tr>
<tr>
<td></td>
<td>FCC</td>
<td>57</td>
<td>43 (75.44)</td>
<td>3.8967</td>
<td>0.0492</td>
</tr>
<tr>
<td></td>
<td>HD</td>
<td>26</td>
<td>14 (53.85)</td>
<td>0.0387</td>
<td>0.8441</td>
</tr>
</tbody>
</table>

* The response rate of each group in each latent class indicates there is lower response rate in left hemicolon group of HD (P = 0.05).
of budesonide or mesalazine enemas in active left-sided ulcerative colitis. Alimentary Pharmacology and Therapeutics 32, 368–376.


