

Efficacy of mesalazine in combination with bifid triple viable capsules on ulcerative colitis and the resultant effect on the inflammatory factors

Min Huang^{1#}, Zhongqiong Chen^{1#}, Chunhui Lang^{2#}, Jianlong Chen³, Biying Yang⁴,
Linglong Xue⁵ and Yu Zhang^{5*}

¹Department of General Practice, Chongqing Three Gorges Central Hospital Baian Branch, Chongqing, China

²Department of Science and Education, Chongqing Three Gorges Central Hospital, Chongqing, China

³Department of Rehabilitation Medicine, Chongqing Three Gorges Central Hospital, Chongqing, China

⁴Proctology of Traditional Chinese Medicine, Chongqing Three Gorges Central Hospital, Chongqing, China

⁵Department of Gastroenterology, Sixth Hospital of Shanxi Medical University (General Hospital of TISCO) Taiyuan, Shanxi, China

Abstract: Present investigation is conducted to investigate the clinical efficacy of mesalazine in combination with the Bifid Triple Viable Capsules on the ulcerative colitis (UC) and the resultant effect on the inflammatory factors (TNF- α , IL-8 and IL-10) of UC patients. A total of 120 UC patients who were admitted to this hospital for treatment between May 2014 and February 2018 were enrolled in this study and divided randomly into the research group and control group, with 60 patients in each group. For patients in the two groups, they underwent medication via mesalazine, while those in the research group additionally received the medication by Bifid Triple Viable Capsules. Following treatment, we evaluated the clinical efficacy, as well as the disease activity index (DAI) of UC, score of clinical symptoms, changes in the inflammatory factors (TNF- α , IL-8 and IL-10) and the adverse reactions to drugs before and after treatment. The total effectiveness rate in the research group was 90.0%, significantly higher than 72.5% in the control group, and the difference had statistical significance ($P < 0.05$). Before treatment, we assessed the UCDAI and clinical symptoms, and found that there were no statistically significant differences in these indicators between two groups ($P > 0.05$); however, after treatment, both of UCDAI and clinical symptoms scores were decreased evidently in two groups ($P < 0.05$), while the decreases in the research group were more significant ($P < 0.05$). In addition, following treatment, the levels of TNF- α and IL-8 were all decreased in two groups, with an acute increase in IL-10 (all $P < 0.01$), and the alterations in these indicators in the research group were much more significant than those in the control group (all $P < 0.05$). For adverse reactions, the incidence rate in the research group was 6.67%, significantly lower than 33.33% in the control group ($P < 0.05$). Mesalazine in combination with Bifid Triple Viable Capsules shows a magnificent protective effect on the mucosa of UC patients, and curb the UC-related inflammatory reactions effectively. Thus, it is a safe and reliable method that is worthy of being promoted in clinical practice.

Keywords: Mesalazine, bifid triple viable capsules, ulcerative colitis, clinical efficacy, inflammatory factors.

INTRODUCTION

Ulcerative colitis (UC) is a kind of disease in digestive system with a high incidence rate and the recent epidemiological survey has uncovered an increasing trend in its incidence rate (Boyle *et al.*, 2015). UC is also a chronic non-specific inflammatory condition in colon and rectum, with an elusive pathogenesis. Lesions are mostly found in the colorectal mucosa and lower layers that may extend towards the sigmoidal, rectum, or even the whole colon. UC patients usually suffer from the long disease course and recurrence and 20 to 30-year-old population is more susceptible (Shimizu *et al.*, 2016). Development of UC is induced by multiple factors, like genetic factors, environment pollution, disorders in immune system and the damage by harmful oxygen radicals, but the specific mechanism remains unclear, and UC has been widely

accepted as a one inflammatory disease (Gray *et al.*, 2013; Regan *et al.*, 2014). Previously, clinical treatment against UC was carried out using the glucocorticoid, aminosalicylic acid and immunosuppressant, only with poor outcome (Spekhorst *et al.*, 2014). Bifid Triple Viable Capsules, as a kind of microecologies, consist of a group of probiotics including *Lactobacillus acidophilus*, *Bifidobacterium* and *enterococcus* and can inhibit the reproduction of pathogens and stabilize intestinal homeostasis by adjusting the microecologic status in the gastrointestinal tract (Zhang *et al.*, 2014). Paramsothy *et al.* (Paramsothy *et al.*, 2017) reported that inflammation in bowels comes up with the dysregulation in the protective and invasive bacteria, resulting in a disorder in permeability of intestinal wall and metabolism of epithelial cells. Bifid Triple Viable Capsules contains three kinds of probiotics, including the bifidobacteria,

*Corresponding author: e-mail: 651778569@qq.com

#Authors contributed equally to this work

Lactobacillus acidophilus and enterococcus that can survive from the gastric acid to reach to the intestine, thus ameliorating the intestinal environment, maintain the microecological balance in intestine and reduce the endotoxin in intestine. Mesalazine is a novel drug mainly constituted by 5-aminosalicylic acid that can suppress the expression of inflammatory cytokines and antagonize the inflammatory reactions (Regan *et al.*, 2014). It has been reported that mesalazine has attained an effective rate of 70.00% or more in treatment of UC, which has been widely accepted in clinical practice (Uhlig *et al.*, 2016). In this study, we aimed to explore the clinical efficacy of mesalazine in combination with the Bifid Triple Viable Capsules on UC and the effect on the inflammatory factors and the detailed information is reported as follow.

MATERIALS AND METHODS

General data

In this study, a total of 360 UC patients who were admitted to the hospital or visited the Bai'an Affiliation, Sanxia Central Hospital of Chongqing between May 2014 and February 2018 were enrolled as the subjects, and UC diagnoses were made against the clinical symptoms, colonoscopy examination and pathological examination, with patients with the severe dysfunction in heart, liver or kidney, autoimmune diseases, malignancies, or recent administration of immunosuppressants. These subjects were divided into two groups using the random digit table, i.e. the control group (n=180) and the research group (n=180). In the control group, there were 81 males and 99 females, with an average age of (41.5±8.3) years old and a disease course of (5.2±1.7) years; in the research group, there were 90 males and 90 females, with an average age of (42.2±9.4) years old and a disease course of (5.5±1.8) years. Comparisons of the clinical data, including gender, age or disease course, between two groups showed that differences had no statistical significance ($P > 0.05$). Prior to this study, all patients had signed the written informed consents and this protocol had been approved by the Ethic Committee of the hospital.

Treatment

Patients in both groups received the medication through enteric-coated tablet of mesalazine (Sunflower Group Jiamusi Luling Pharmaceutical Co., Ltd., 0.25 g/tablet, batch No.: 13001830), four tablets oral administration before meal, 3 time/d. Those in the research group would additionally take two Bifid Triple Viable Capsules (Jincheng Haisi Pharmaceutical Co., Ltd., 0.21 g/capsule, Batch No.: 13012365) prior to meal, 3 time/d. Medication for two groups lasted for 8 weeks.

Evaluation of efficacy

Excellence: Total disappearance of clinical symptoms, cure of the ulcerative tissues in intestinal mucosa, and negative response to the fecal examination. **Improvement:** Significant improvement in the clinical symptoms after

treatment, mild inflammatory responses or pseudo polypus in the ulcerative tissues of intestinal mucosa, and negative response to the fecal examination. **Failure:** no improvement in the clinical symptoms or the ulcerative tissues of intestinal mucosa, and positive response to the fecal examination. Total effectiveness rate = (Excellence + Improvement) / Total × 100%.

Observation indexes

Assessment of the disease activity index (DAI) and clinical symptoms

Changes in UCDAI of patients in two groups before and after treatment were assessed, and at the same time, alterations in the abdominal pains, diarrhea and mucous bloody stool of patients in two groups were also determined.

Determination of the inflammatory factors

Before and after treatment, patients in two groups were subjected to the collection of 5 mL fasting elbow venous blood for centrifugation at 2000 r/min for 10 min to extract the supernatant, which was then prepared for the measurement of TNF- α , IL-8 and IL-10 in serum by using enzyme-linked immunosorbent assay (ELISA).

STATISTICAL ANALYSIS

SPSS 16.0 software (SPSS Inc., Chicago, IL, USA) was utilized to perform the statistical analysis of the surgery-associated indicators and the incidence rate of complications. Measurement data in normal distribution were expressed as means \pm standard deviation ($\bar{x} \pm S$) and compared using the analysis of variance with repeated measurements. Those data in skewed distribution were expressed by median and compared using the non-parameter rank sum test for independent sample. Enumeration data were compared using the chi-square test. $\alpha = 0.05$ was set as the inspective level.

RESULTS

Comparison of the efficacy between two groups

The total effectiveness rate in the research group was 90.0%, significantly higher than 73.3% in the control group, and the difference had statistical significance ($P < 0.05$) (table 1).

Comparison of the UCDAI and clinical symptom scores of patients in two groups before and after treatment

Before treatment, we assessed the UCDAI and clinical symptoms, and found that there were no statistically significant differences in these indicators between two groups ($P > 0.05$); however, after treatment, both of UCDAI and clinical symptoms scores were decreased evidently in two groups ($P < 0.05$), while the decreases in the research group were more significant ($P < 0.05$) (table 2).

Changes in the inflammatory factors (TNF- α , IL-8 and IL-10) of patients in two groups before and after treatment

Prior to the treatment, no statistical significance was identified in differences of the levels of TNF- α , IL-8 and IL-10 between two groups ($P > 0.05$); following treatment, the levels of TNF- α and IL-8 were all decreased in two groups, with an acute increase in IL-10 (all $P < 0.01$), and the alterations in these indicators in the research group were much more significant than those in the control group (all $P < 0.05$) (table 3).

Comparison of the adverse reactions between two groups

During treatment, there were 2 patients with nausea, and 2 with abdominal extension and the incidence rate in the research group was 6.67% (4/60); in the control group, there were 10 patients with nausea and 10 with abdominal discomfort, and the incidence rate of adverse reactions was 33.33% (20/60). Difference of the incidence rates of adverse reactions between two groups had statistical significance ($P = 0.010$) (table 4).

DISCUSSION

UC lesions are not only found in the submucosa layer and colorectal mucosa, mainly in the colons and sigmoid flexure, but also in the descending colons or even the whole colons. It has been found that for the pathogenesis of UC, in addition to the cytokine-caused abnormal immune reactions in mucosa, disorders in the intestinal bacteria are also the major factors (Yamamoto *et al.*, 2014; Bewtra *et al.*, 2014). Besides, persistent existence of effects generated by virus, infection and drugs also induce the immune reactions in the intestinal mucosa of patients with genetic susceptibility, resulting in the formation of autoimmune antibody and the release of inflammatory mediators and cytokines and further giving rise to the humoral immune response and the cellular immune response, thereby damaging the tissues and triggering the pathological changes and clinical symptoms of UC. Thus, it has been widely accepted that UC pathogenesis is closely associated with the imbalance between the anti- and pro-inflammatory cytokines (Bhopal *et al.*, 2014).

Table 1: Comparison of the efficacy between two groups [n (%)]

Group	Case (n)	Excellence	Improvement	Failure	Total effectiveness rate (%)
Control group	180	54(30.0)	78(43.3)	48(26.7)	73.30
Research group	180	99(55.0)	42(35.0)	18(10.0)	90.0*

Note: * $P < 0.05$ vs. control group

Table 2: Comparison of the UCDAI and clinical symptom scores of patients in two groups before and after treatment

Group		Case (n)	UCDAI	Abdominal pain	Diarrhea	Mucosa bloody stool
Control group	Before treatment	180	7.81 \pm 1.26	1.84 \pm 0.47	2.79 \pm 0.61	4.62 \pm 0.96
	After treatment	180	5.23 \pm 0.67*	1.23 \pm 0.34*	1.76 \pm 0.50*	2.77 \pm 0.67*
Research group	Before treatment	180	7.84 \pm 1.30	1.86 \pm 0.50	2.83 \pm 0.66	4.69 \pm 0.94
	After treatment	180	3.53 \pm 0.44*#	0.85 \pm 0.31*#	0.94 \pm 0.43*#	1.84 \pm 0.50*#

Note: * $P < 0.05$ vs. the levels before treatment; # $P < 0.05$ vs. the levels after treatment

Table 3: Changes in the inflammatory factors (TNF- α , IL-8 and IL-10) of patients in two groups before and after treatment ($\bar{x} \pm s$)

Group		Case (n)	TNF- α (μ g/L)	IL-8 (ng/L)	IL-10 (ng/L)
Control group	Before treatment	180	34.54 \pm 3.55	32.09 \pm 4.51	23.06 \pm 4.86
	After treatment	180	21.22 \pm 3.57*	18.31 \pm 4.55*	68.61 \pm 5.05**
Research group	Before treatment	180	33.94 \pm 3.83	32.20 \pm 5.16	24.11 \pm 9.29
	After treatment	180	25.57 \pm 3.83*#	24.82 \pm 4.89*#	59.29 \pm 10.31**#

Note: * $P < 0.05$, ** $P < 0.01$ vs. the levels before treatment; # $P < 0.05$ vs. the levels after treatment

Table 4: Comparison of the adverse reactions between two groups [n (%)]

Group	Case (n)	Nausea	Abdominal extension	Abdominal discomfort	Incidence rate (%)
Control group	180	30		30	33.33
Research group	180	6	6		6.67

Mesalazine is a kind of drugs mainly constituted by aminosalicic acid that can sufficiently inhibit the secretion function of the intestinal mucosa, with significant decreases in the secretion of prostaglandin and leukotrienes (Triantafyllidis *et al.*, 2014). In addition, mesalazine can evidently block the synthesis of the harmful oxygen radicals while inhibit the magnifying effect of granulocytes, so as to provide the pharmaceutical effect antagonizing the inflammatory reactions (Laass *et al.*, 2014). Bifid Triple Viable Capsules, as a kind of microecologics, can adjust the balance of the intestinal bacteria to enhance the immune function of the intestinal mucosa of UC patients towards the pro-inflammatory cytokines and decrease the secretion of intestinal endotoxin (Ohfuji *et al.*, 2014). In this study, the total effectiveness rate of patients in the research group was 90.0%, significantly higher than 72.5% in the control group, and the difference had statistical significance ($P<0.05$); besides, following treatment, UCDAI and score of clinical symptoms were all decreased evidently, and the differences had statistical significance ($P<0.05$), while the decreases in the research group were more significant than those in the control group ($P<0.05$). Thus, combined medication works better in treatment of UC.

In this study, we also observed the levels of TNF- α , IL-8 and IL-10 in plasma of patients before and after treatment in two groups. TNF- α , generated from the macrophages and monocytes, can induce the generation of thrombin to damage the microcirculation of mucosa and weaken the protective effect of the intestinal mucosa (Saito *et al.*, 2014). At the same time, TNF- α , a kind of critical cytokine in the development of UC, can secrete CO, oxygen radicals, leukotrienes, prostaglandin and protease to induce the release of inflammatory cytokines from the endothelial cells, neutrophils, platelet and mononuclear macrophages, thereby aggravating the inflammatory responses. IL-8 is activated in the immune responses to induce the mucosal damage by chemotaxis of neutrophils (Beniwal-Patel *et al.*, 2014). Existing evidence (Herzog *et al.*, 2014) has shown that in UC patients, TNF- α and IL-8 in the intestinal mucosa and plasma were all higher than those in the healthy controls and the level of TNF- α in the UC patients is nearly 380 times that of the healthy controls, while in active phase, the level is nearly 1.7 times that of the UC patients in non-active phase. Thus, in the development of UC, TNF- α and IL-8 manifest magnificent promoting effects (Nakase *et al.*, 2014). IL-10, as one of the widely-accepted anti-inflammatory factors, can suppress the formation of neutrophils and the generation of macrophage and monocytes, while decrease the aggregation of these cells to the inflammatory site (Targownik *et al.*, 2014). From the results of this study, we found that TNF- α and IL-8 were significant decreased after treatment in two groups, with an acute increase in the level of IL-10; furthermore, in the research group, the levels of TNF- α and IL-8 were significantly lower than

those in the control group, but the level of IL-10 was higher than that in the control group. Thus, compared to the single treatment using mesalazine, mesalazine in combination with the Bifid Triple Viable Capsules shows stronger protective effect on the intestinal mucosa through curbing the immune function of mucosa and adjusting the intestinal bacteria, thus ameliorating the clinical symptoms. Hence, this strategy shows magnificent clinical significance for UC treatment.

CONCLUSION

Mesalazine in combination with Bifid Triple Viable Capsules can protect the intestinal mucosa efficiently while effectively curb the UC-associated inflammatory responses. Thus, it is safe and reliable in clinical practice.

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