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ABOUT COVER

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Prospective Study

Kuicolong-yu enema decoction retains traditional Chinese medicine enema attenuates inflammatory response ulcerative colitis through TLR4/NF- κ B signaling pathway

Li Han, Kun Tang, Xiao-Li Fang, Jing-Xi Xu, Xi-Yun Mao, Ming Li

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Abstract

BACKGROUND

Ulcer colitis (UC) is a chronic, nonspecific, and noninfectious inflammatory bowel disease. Recently, Toll-like receptors (TLRs) have been found to be closely associated with clinical inflammatory diseases. Achieving complete remission in patients with intermittent periods of activity followed by dormancy is challenging. Moreover, no study has explored the mechanism by which Kuicolong-yu enema decoction retains traditional Chinese medicine enemas to attenuate the inflammatory response in UC.

AIM

To explore the mechanism by which Kuicolong-yu enema decoction retains traditional Chinese medicine enemas to attenuate the inflammatory response in UC.

METHODS

This prospective clinical study included patients who met the exclusion criteria in 2020 and 2021. The patients with UC were divided into two groups (control and experimental). The peripheral blood of the experimental and control groups were collected under aseptic conditions. The expression of TLR4 protein, NF- κ B, IL-6, and IL-17 was detected in the peripheral blood of patients in the experimental group and control group before and 1 month after taking the drug. Linear co-

relation analysis was used to analyze the relationship between the expression level of TLR4 protein and the expression levels of downstream signal NF- κ B and inflammatory factors IL-6 and IL-17, and $P < 0.05$ was considered statistically significant.

RESULTS

There were no significant differences in the patient characteristics between the control and experimental groups. The results showed that the expression levels of TLR4 and NF- κ B in the experimental group were significantly lower than those in the control group ($P < 0.05$). The levels of IL-6 and IL-17 in the experimental group were significantly lower than those in the control group ($P < 0.05$). The TLR4 protein expression in the experimental group was positively correlated with the expression level of downstream signal NF- κ B and was positively correlated with the levels of downstream inflammatory cytokines IL-6 and IL-17 ($r = 0.823$, $P < 0.05$).

CONCLUSION

Kuicolong-yu enema decoction retains traditional Chinese medicine enema attenuates the inflammatory response of UC through the TLR4/NF- κ B signaling pathway.

Key Words: Ulcerative colitis; TLR4; NF- κ B signaling pathway; Kuicolong-yu enema

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Core Tip: Kuicolong-yu enema decoction retains a traditional Chinese medicine enema that can prolong the remission period; however, there is not enough evidence to prove this. This prospective clinical study showed that Kuicolong-yu enema decoction retains traditional Chinese medicine enema attenuates the inflammatory response of ulcerative colitis through the TLR4/NF- κ B signaling pathway.

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INTRODUCTION

Ulcer colitis (UC) is a chronic, non-specific, non-infectious inflammatory bowel disease that mainly affects the colorectal mucosa and submucosa[1]. It is characterized by continuous, diffuse distribution and continuous mucosal ulcers in the rectum and colon, which begin in the rectum, expand to varying degrees, and can spread to the cecum at the longest, and is a common inflammatory bowel disease[2]. Clinical types can be divided into primary and chronic recurrent types. The primary type refers to the first attack without a previous history. The chronic relapsing type refers to the recurrence of symptoms in clinical remission and is the most common type. UC severity varies from person to person, and symptoms can vary over time. The main clinical manifestations of UC are persistent or recurrent diarrhea, mucous, pus, and bloody stools with abdominal pain, posterior tenesmus, fever, and varying degrees of systemic symptoms. The disease course is usually 4-6 wks[3]. It can be related to joints, skin, eyes, mouth, liver, gallbladder, and other external clinical manifestations, including joint pain, joint swelling, oral sores, and inflammatory eye diseases[4].

Toll-like receptors (TLRs) play an important role in anti-inflammatory immunity[5,6]. TLRs recognize bacterial lipopolysaccharide molecules in pathogenic microorganisms. Recently, the role of TLRs in anti-inflammatory immunity has received increasing attention, and TLRs have been found to be closely associated with clinical inflammatory diseases [7]. Among these, TLR4 was the first discovered[8]. After activation, this receptor can activate NF- κ B through signal transduction, and NF- κ B regulates the expression of other genes, including multiple inflammatory mediators and cytokines in the blood, and plays a role in anti-inflammatory immune regulation[9]. Studies have found that NF- κ B can play a role as a messenger in the same systemic inflammatory response syndrome, and in the early stage of its pathogenesis, local inflammation of the organism can mediate inflammatory cytokine activation through NF- κ B. Therefore, the TLRs/NF- κ B pathway plays an extremely important role in inflammation occurrence and development. The signaling of the TLR- NF- κ B pathway mainly focuses on the study of TLR4. TLR activation not only leads to inflammation but also promotes the maturation and differentiation of the antigen-specific immune response of the organism [10]. Some related downregulatory factors in the TLR-NF κ B signaling pathway have been studied. It has been reported to exert a negative regulatory effect on the conduction of TLR-mediated signaling pathways. When cells are stimulated, this protein inhibits IRAK activity to a certain extent, ultimately blocking TLR-mediated signal transduction. In addition, some studies have found that RIP1 can activate TRIF-induced NF- κ B, and RIP3 can play a certain negative role in the TRIF-RIP1-induced NF- κ B signaling pathway.

Although many drugs are available for the clinical treatment of UC, none can definitively cure the condition. These therapies primarily aim to alleviate symptoms. In recent years, studies on the pathogenesis of UC have focused more on molecular mechanisms to find new therapeutic targets; however, no breakthroughs have been made[11-13]. Kuicolong-yu enema decoction retains the traditional Chinese medicine enema is traditional Chinese medicine, which has been used in patients with UC for a long time. However, no study has explored the mechanism by which Kuicolong-yu enema decoction retains traditional Chinese medicine enemas to attenuate the inflammatory response in UC. Hence, we conducted this study to explore the mechanism by which Kuicolong-yu enema decoction retains traditional Chinese medicine enemas to attenuate the inflammatory response in UC.

MATERIALS AND METHODS

This prospective study was approved by Shuguang Hospital Affiliated with the Shanghai University of Traditional Chinese Medicine Anhui Hospital Department. This study was approved by the ethics committee of our hospital. All the patients signed an informed consent form before inclusion in the study.

Patient recruitment and selection criteria

The patients enrolled in the study met the inclusion and exclusion criteria. The inclusion criteria were as follows: (1) Diagnosis of UC; (2) The age of the patient was above 18 years old; (3) All patients were not treated with hormones, immunosuppressants, and other drugs; (4) Signed informed consent to participate in our study; and (5) No other infectious and autoimmune diseases. Exclusion criteria: Cancer patients and recent use of biologics.

Study design

This prospective clinical study included patients who met the exclusion criteria in 2020 and 2021. The patients with UC were divided into two groups (control and experimental). The patients in the control group received only conventional therapy, and the patients in the experimental group received conventional therapy and traditional medicine prescriptions (Baiqi, *Phellodendron phellodendron*, *Matrine*, *Purslane*, *Astragalus*, *Hercules*, and *Xijie powder*). The expression of TLR4 protein, NF- κ B, IL-6, and IL-17 was detected in the peripheral blood of patients in the experimental group and control group before and 1 month after taking the drug.

Specimen collection

The peripheral blood of the experimental and control groups was collected under aseptic conditions (6 mL in the morning was divided into three tubes). One tube was used to detect TLR4 protein expression by flow cytometry, and the other tube was used to detect NF- κ B by double-antibody sandwich ABC-ELISA. Another 2 mL heparin anticoagulant tube was centrifuged for the determination of IL-6 and IL-17 by ELISA.

Inspection methods

TLR4 protein expression was detected by flow cytometry with the kit of Shanghai Sixin Biological Co., Ltd., and NF- κ B was detected by double-antibody sandwich ABC-ELISA with the kit of Shanghai Bogu Biological Technology Co., LTD. Another 2 mL heparin anticoagulant tube was used to detect IL-6 and IL-17 by ELISA, using a kit from Shanghai Hengyuan Biological Co., Ltd.

Statistical analysis

SPSS statistical software package (version 22.0) was used to analyze the data. The counting data of experimental data were presented as χ^2 , and the measurement data were presented as mean \pm SD. The chi-square test was used for comparison of measurement data among multiple groups; the *t*-test was used for pound-wise comparison among groups with homogeneous variance; the TamhanesT2 test was used for groups with uneven variance. Linear correlation analysis was used to analyze the relationship between the TLR4 protein expression level and the expression levels of downstream signal NF- κ B and inflammatory factors IL-6 and IL-17, and $P < 0.05$ was considered statistically significant.

RESULTS

Patient characteristics

This study included 120 patients (60 in the control group and 60 in the experimental group). All the patients successfully completed the experiment without any adverse reactions.

Table 1 outlines the patient characteristics. In summary, there were no significant differences in the patient characteristics between the control and experimental groups.

Comparison of TLR4 and NF- κ B expression in peripheral blood

The NF- κ B expression level between the two groups had statistical significance ($P < 0.05$), and the results of the pair-to-group comparison showed that the expression of TLR4 and NF- κ B in the experimental group was significantly higher than that in the control group, as shown in Table 2.

Table 1 Characteristics of patients with ulcer colitis

Variables	Control group	Experiment group
Sample size	60	60
Male (%)	46	53
Age (yr), mean \pm SD	44.7 \pm 7.7	48.7 \pm 7.7
Duration of illness (yr), mean \pm SD	7.3 \pm 2.3	8.1 \pm 3.2

Table 2 Comparison of TLR4 and NF- κ B expression in peripheral blood

Group	Sample size	Initial stage		One month after	
		TLR4 (%)	NF- κ B (ng/L)	TLR4 (%)	NF- κ B (ng/L)
Experiment group	60	38.35 \pm 7.5	164 \pm 12.2	21.69 \pm 2.79	98.24 \pm 35.64
Control group	60	40.11 \pm 15.3	162.73 \pm 45.23	39.37 \pm 4.35	163.33 \pm 65.45

Comparison of IL-6 and IL-17 expression in peripheral blood

There were statistically significant differences in the IL-6 and IL-17 expression levels ($P < 0.05$), and the IL-6 and IL-17 levels in the experimental group were significantly higher than those in the control group (Table 3).

Correlation analysis

The expression of TLR4 protein in the experimental group was positively correlated with the expression level of downstream signal NF- κ B ($r = 0.823$, $P < 0.05$), and was positively correlated with the levels of downstream inflammatory cytokines IL-6 and IL-17 ($r = 0.675$, $r = 0.690$. $P < 0.05$).

DISCUSSION

UC is a lifelong inflammatory disease that affects the rectum and colon to varying degrees[14]. At present, the main treatment principles of Western medicine are: (1) Control seizures, the main drugs being salazosulapyridine and mesalazine; (2) Improve the symptoms of acute attack, and the main drugs are glucocorticoids; and (3) Mesenteric mucosal repair, mainly by various stem cell transplantations, is still relatively difficult to achieve[15-17]. Others use anti-inflammatory agents, leukocyte isolation, mesenteric artery catheterization, *etc*[18]. UC is an immune disease that is difficult to cure completely; however, there are remission periods, also called intermittent periods, followed by periods of dormancy. In some patients with UC treated with traditional Chinese medicine, the remission period is gradually prolonged; however, there is insufficient evidence to prove that the disease can be cured.

Gastrointestinal cytokines and oxidative stress regulate the occurrence, development, intensification, and recurrence of inflammatory processes in various intestinal inflammatory diseases, both in time and space[19,20]. In recent years, there has been a surge of interest in the role of cytokine adhesion molecules, the role of TLR4 and NF- κ B in the occurrence and development of UC has become a hot topic. NF- κ B, a transcription factor, is an important downstream node of the TLR4/MyD88 signaling pathway, an important immune response and inflammation regulator, and is involved in regulating the expression of important cytokines, inflammatory factors, and adhesion molecules *in vivo*, such as TNF- α , IL-1, and IL-6[21-23].

Zhou M *et al*[24] found that mTOR-dependent autophagy flux damage in colitis mouse models, human intestinal epithelial cells, and active UC patients may be regulated by TLR4-MyD88-MAPK signaling and NF- κ B pathway. Silencing mTOR significantly weakened, whereas inhibiting ATG5 aggravated LPS-induced inflammation and oxidative damage. The pharmacological administration of mTOR inhibitors and autophagy stimulants significantly improved experimental colitis and oxidative stress *in vivo*. In our study, Kuicolong-yu enema decoction retains traditional Chinese medicine enema can significantly decrease the level of TLR4, NF- κ B, IL-6, and IL-17 in peripheral blood. The TLR4 protein expression in the experimental group was positively correlated with the expression level of downstream signal NF- κ B and was positively correlated with the levels of downstream inflammatory cytokines IL-6 and IL-17.

Our study had a number of limitations. First of all, the sample size is not large enough, and a larger sample size study is needed to verify the test results. Second, the study was not a multicenter randomized controlled trial. So our findings should be treated with caution.

CONCLUSION

Kuicolong-yu enema decoction retains traditional Chinese medicine enema attenuates the inflammatory response of UC

Table 3 Comparison of IL-6 and IL-17 expression in peripheral blood

Group	Sample size	Initial stage		One month after	
		IL-6 (ng/L)	IL-17 (ng/L)	IL-6 (ng/L)	IL-17 (ng/L)
Experiment group	60	19.78 ± 12.23	13.56 ± 14.23	8.01 ± 1.02	9.08 ± 2.02
Control group	60	21.89 ± 3.24	11.36 ± 9.00	20.15 ± 2.40	12.25 ± 2.80

through the TLR4/NF-κB signaling pathway.

ARTICLE HIGHLIGHTS

Research background

Ulcer colitis (UC) is difficult to cure completely, with periods of remission, also called intermittent periods, followed by dormancy.

Research motivation

The Kuicolong-yu enema decoction is a traditional Chinese medicine enema that can prolong the remission period of UC, but there is not enough evidence to prove this.

Research objectives

To explore the mechanism by which Kuicolong-yu enema decoction retains traditional Chinese medicine enemas to attenuate the inflammatory response in ulcerative.

Research methods

Under aseptic conditions, peripheral blood samples were collected from both groups before and one month after drug administration. The expression levels of Toll-like receptor 4 (TLR4) protein, NF-κB, IL-6, and IL-17 were measured in the peripheral blood samples.

Research results

The results showed that the TLR4 and NF-κB expression levels in the experimental group were significantly lower than those in the control group. The IL-6 and IL-17 Levels in the experimental group were significantly lower than those in the control group. The expression of TLR4 protein in the experimental group was positively correlated with the expression level of downstream signal NF-κB and was positively correlated with the levels of downstream inflammatory cytokines IL-6 and IL-17.

Research conclusions

Kuicolong-yu enema decoction retains traditional Chinese medicine enema attenuates the inflammatory response of ulcerative colitis through the TLR4/NF-κB signaling pathway.

Research perspectives

Kuicolong-yu enema decoction retains traditional Chinese medicine enemas, which are valuable in the treatment of ulcerative colitis.

FOOTNOTES

Author contributions: Han L and Li M contributed equally to this work; Han L, Tang K, Fang XL, Xu JX, Mao XY and Li M, designed the research study; Han L, Tang K, Fang XL, Xu JX, Mao XY and Li M performed the research; Han L, Tang K and Li M analyzed the data and wrote the manuscript; all authors have read and approve the final manuscript.

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