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Influencing mechanism of cupping moxibustion on gastrointestinal function and immune function in patients with functional diarrhea

Cuiying Yin[1], Ying Fang[2], Dan Yao[1], Xiaojing Zhang[3*]

[1] Department of Critical Medicine, The Third Affiliated Hospital of Zhejiang Chinese Medicine University, Hangzhou, 310005, China
[2] Department of Respiratory, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, 310005, China
[3] Department of Nursing, The Third Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou, 310005, China

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ABSTRACT

It was aimed to investigate the efficacy and safety of cupping moxibustion in patients with functional diarrhea. 51 patients diagnosed with functional diarrhea from January 2021 to December 2021 were selected as the objects, and they were randomly divided into the control group (oral montmorillonite powder) and the experiment group (oral montmorillonite powder combined with cupping moxibustion). The number of diarrheas, Bristol stool, traditional Chinese medicine (TCM) syndromes, clinical efficacy indexes, self-rating anxiety scale (SAS) score, the MOS item short from health survey (SF-36) scale score, peripheral blood cell levels of CD_4^+, CD_8^+, and Th17, gastrin (GAS), motilin (MTL), and cholecystokinin (CCK) levels was assessed before and after treatment. The adverse events were also recorded. Compared with those before treatment, all indexes of both groups were significantly improved ($P<0.05$). Compared with those of the control group, the number of diarrheas, Bristol stool, TCM syndrome score, SAS score, and CD_8^+ cell levels was significantly decreased after treatment in the experiment group ($P<0.05$). The clinical cure rate (48.0% vs. 73.1%), SF-36 score, GAS, MTL, CCK contents, and CD_4^+, and Th17 cell levels were significantly increased ($P<0.05$). No significant difference was in the incidence of adverse events between the two groups ($P>0.05$). It could be suggested that cupping moxibustion could be applied in the treatment of functional diarrhea, improving the clinical symptoms, relieving anxiety, enhancing gastrointestinal and immune functions, and promoting the quality of life of patients significantly.

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Introduction

Functional diarrhea is a type of functional bowel disease that is not accompanied by abdominal pain or discomfort and has persistent or recurrent episodes of loose or watery stools. The disease usually does not show organic changes in the intestinal tract, and there were no positive findings in the examinations (1). Researches have shown that the incidence of functional diarrhea in China is 1.5% (2). Due to the long course of functional diarrhea, it is easy to reoccur, and long-term chronic diarrhea can cause malnutrition, low immune function, etc. It will lead to weight loss, fatigue, depression, and anxiety, bringing huge social and psychological pressure on patients (3). Nowadays, the etiology and pathogenesis of functional diarrhea have not been fully elucidated, so the clinical treatment is mainly to relieve or eliminate symptoms such as diarrhea (4). Montmorillonite powder has been widely used in the treatment of acute or chronic diarrhea in adults and children (5). However, it has been confirmed that montmorillonite powder causes the issues of poor durability and high recurrence in the treatment of functional diarrhea (6).

Traditional Chinese medicine (TCM) believes that functional diarrhea belongs to the category of diarrhea and long-term diarrhea. Exogenous pathogens, unreasonable food, emotional disorders, or physical weakness are the main causes (7). The major pathogenesis of functional diarrhea include the dysfunction of the spleen and stomach, the disturbance of the transportation and transformation of the middle-jiao, and the abnormal rise and fall of the Qi. The main methods of TCM clinical treatment for functional diarrhea are oral administration of traditional medicines and external moxibustion or cupping, and all the treatment methods can greatly improve the symptoms of patients (8). The cupping technique is a traditional technique that has been improved. With the specially designed jar mouth, it enables comprehensive therapies such as massage, scraping, and moxibustion. The heat generated by the burning moxa cones in the cupping jar is a physical factor infrared ray, which can stimulate the body and activate the immune system, thereby achieving the effect of treatment (9). At present, cupping technology has achieved excellent results in the treatment of neuralgia and other diseases (10). However, the clinical efficacy of cupping in the treatment of functional diarrhea remains to be explored.

Therefore, patients with functional diarrhea were taken as the research objects. With oral administration of montmorillonite powder and the combination with cupping moxibustion, the clinical symptoms, anxiety, quality of

* Corresponding author. Email: zhuohao3830535@163.com

life, gastrointestinal function, and immune function of the patients were compared before and after treatment. The clinical advantages of cupping moxibustion in the treatment of functional diarrhea were evaluated, and the basis was provided for finding the best treatment schedule for functional diarrhea.

Materials and Methods

Research objects

51 patients diagnosed with functional diarrhea in The Third Affiliated Hospital of Zhejiang Chinese Medical University from January 2021 to December 2021 were selected as the research objects. According to the random number table method, the patients were randomly divided into the control group with 25 cases and the experiment group with 26 cases. It had been approved by the The Third Affiliated Hospital of Zhejiang Chinese Medical University Medical Ethics Committee.

Diagnostic criteria

The western medicine diagnostic criteria referred to the diagnostic criteria for functional diarrhea in Rome III, which were described as follows. The patients suffered from repeated abdominal pain for more than 3 days per month. The number of diarrheas was more than 3 times per day. The stools were loose or watery, and complicated symptoms had occurred at least 6 months before the diagnosis as well as within 3 months recently.

TCM diagnostic criteria were in accordance with *Diagnosis and Efficacy Criteria of Traditional Chinese Medicine* (ZY/T001, 9~001.9-94) for diarrhea issued by the National Administration of Traditional Chinese Medicine. The stools were watery, and the main symptom was the increased diarrhea frequency accompanied by abdominal distention and pain, etc. Within one year, it mostly occurred in summer and autumn. For acute diarrhea, it went with a sudden episode, a short course of the disease, and was accompanied by symptoms such as aversion to cold and fever. For chronic diarrhea, there was a slow episode, long course, and repeated occurrences; and it was sometimes mild and sometimes severe. Improper diet, being affected by cold, or emotional changes could induce functional diarrhea.

Case selection

The following inclusion criteria were presented. Those patients met the diagnostic criteria of Rome III for functional diarrhea. Patients met the diagnostic criteria for diarrhea in *Diagnosis and Efficacy Criteria of Traditional Chinese Medicine*. They had an aged between 18-70 years old, with no gender restriction. Those who did not take other drugs and external treatment of TCM within 30 days before the participation. All the patients signed the informed consent willingly.

Exclusion criteria were as follows. Patients had organic diseases of the digestive system, systemic diseases affecting gastric motility, or a history of drinking and chronic alcoholism. Patients had long-term use of psychoactive drugs such as opioids once. Patients were complicated with cardiovascular, hepatic, and renal insufficiency or uncontrolled endocrine diseases. Those were allergic to therapeutic drugs or had a history of severe allergies. Pregnant or breastfeeding-period women were excluded.

There were also elimination or dropout criteria. The patients who met the conditions below were out. The disease was not correctly diagnosed. The patients met the above exclusion criteria. Due to other factors, the treatment could not be implemented according to the experimental plan. Clinical diagnosis and treatment records or data were incomplete, which affected the evaluation of efficacy. After receiving certain treatment methods, they were afflicted with serious adverse events and couldn't adhere to the treatment. That self-exited during treatment.

Treatment methods in different groups

The patients in the control group were treated with conventional drugs. 3g montmorillonite powder (manufactured by Zhejiang Hailisheng Pharmaceutical Co., Ltd., the approval number was H19980050, and the specification was 3g×12bags/box) was taken orally every day. 3 times a day and 7 days were considered as a course of treatment.

With the treatment method in the control group, the patients in the experiment group were treated with cupping, and the treatment cycle lasted for 7 days. The appropriate-size cupping jars (record number: Minxia Machinery Equipment No. 20180337) were selected according to the patient's treatment points. The jar mouths were checked to make sure they were intact, and the corresponding-size moxa cones were placed and fully burnt inside the cupping jars. The moxa cones were produced by Hubei Li Shizhen Traditional Chinese Medicine Co., Ltd., with the production license of Hubei 20160105, the approval number of Z32020152. The moxa cones had the specifications of the diameter * height in 55mm * 30mm/ 45mm * 25mm / 25mm * 20mm. When the temperature of the jar mouth was suitable and the temperature of the moxa cones was evenly heated, an appropriate amount of mugwort essential oil was applied to the treatment area, and then the jar was inverted there. The jar was gently slid along the bladder meridian and the governor meridian of the patient's back for 5 minutes. The downward pressure was strengthened after the patient was adapted. The scraping, pulling, and spotting methods were used alternately. After the skin of the treatment site became red, the cupping was operated for 15 minutes. The pulling method and spotting method was performed on the patient's abdominal acupoints, Shenque, Tianshu, Zhongwan, and Guanyuan acupoints. The speed was adjusted on the basis of the temperature in the jar and the patient's reaction, and it was operated for 15 minutes. It was stopped when the patient's skin was ruddy and slightly sweaty with scraping spots, and the essential oil was wiped off. The patient was instructed to drink an appropriate amount of warm water after rest, and air conditioning and exposure to wind were not allowed within 4 hours after treatment.

Observation indexes

For the evaluation of clinical symptoms, the number of diarrheas was recorded before treatment, 14 days, and 30 days after treatment, respectively. The Bristol stool character grading was adopted to classify stool features. It was mainly divided into grades 1 to 7, of which grade 1 was for scattered hard stools (constipation), and grade 7 was for watery stools (diarrhea).

TCM syndrome score refers to the grading and quantitative standards for TCM syndromes in the *Guidelines*

for Clinical Research on New Chinese Medicines. TCM syndromes of patients were scored before treatment, 14 days, and 30 days after the end of treatment. It was scored as none (0 points), mild (1 point), moderate (2 points), and severe (3 points), and then the total score was calculated.

Efficacy index evaluation was in line with the TCM syndrome scores before and after treatment, and the Nimody's assessment method was used to determine the efficacy index. $Efficacy\ index = [(Before\ treatment - After\ treatment)/After\ treatment] \times 100\%$. It was considered as being cured that the clinical symptoms and signs had completely or basically disappeared, and the reduction rate of syndrome points was ≥95%. When the clinical symptoms and signs were significantly improved, and the reduction rate of syndrome points was more than 70%, it was thought as markedly effective. The clinical symptoms and signs were improved, and the reduction rate of syndrome score ≥30%, it was regarded to be effective. If the clinical symptoms and signs were not improved or aggravated, and the reduction rate of syndrome score was less than 30%, it was considered to be ineffective.

Before treatment, 14, and 30 days after treatment, the self-rating anxiety scale (SAS) (11) was adopted to assess the patients' anxiety scores. The scale contained a total of 20 items, and each item was scored on 1-4. The higher the score, the more severe the patient's anxiety. If the total score was below 50 points, it was considered as normal.

Quality of life score was evaluated using the MOS item short from health survey (SF-36) scale (12) before treatment, 14 days after treatment, and 30 days after treatment, respectively.

Evaluation of immune function was performed before and after treatment. Blood samples of patients were collected, treated with heparin anticoagulation, and then centrifuged. Flow cytometry was used to detect the levels of immune cells CD_4^+T, CD_8^+T, and Th17 in the patients' blood.

Detection of gastrointestinal function indexes was carried out before treatment, 14 days, and 30 days after treatment, respectively. The gastrin (GAS), motilin (MTL), and cholecystokinin (CCK) in serum samples were detected through the enzyme-linked immunosorbent assay.

30 days after the end of treatment was taken as a node, and the complications of patients during treatment were recorded. For patients with adverse events, a one-month follow-up was required to ensure patients' safety.

Observation indexes

Statistical analysis of data was performed using SPSS 22.0. Measurement data were expressed as mean ± standard deviation and were analyzed by independent samples t-test. Enumeration data were expressed by frequency (%) and analyzed by a chi-square test. $P<0.05$ expressed the significant statistical differences.

Results

Comparison of general data of patients

The differences in gender ratio, age, course of the disease, and body mass index (BMI) were compared, and it was found with no statistical difference between the two groups of patients in each item ($P>0.05$). Table 1 presents a detailed comparison.

Comparison of the number of diarrheas in patients before and after treatment

The changes in the number of diarrheas in the two groups at different time points before and after treatment were compared. It could be observed that the number of diarrheas 14 days and 30 days after treatment was significantly lower than that before treatment in both groups ($P<0.05$). The diarrhea frequency in the experiment group was significantly lower than that in the control group at 14 days and 30 days after treatment ($P<0.05$), which were shown in Figure 1.

Comparison of Bristol stool scores before and after treatment

It was shown in Figure 2 that the differences in Bristol stool trait scores of patients at different time points before and after treatment were compared between the two groups. The Bristol stool scores 14 days and 30 days after treatment of the control group and the experiment group were significantly lower than those before treatment ($P<0.05$). Those of the experiment group patients were significantly lower than those of the control group at 14 days and 30 days after treatment ($P<0.05$).

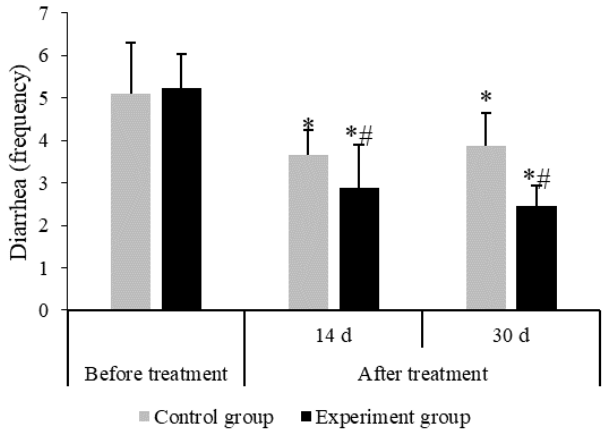

Figure 1. Comparison of the number of diarrheas in the two groups before and after treatment. Note: Compared with the same group before treatment, *$P<0.05$; compared with the control group at the same time point, #$P<0.05$.

Table 1. Comparison of the patients' general data in two groups.

General data	Control group (n=25)	Experiment group (n=26)	t or χ^2 value	*P* value
Male (cases/%)	13/52.0	14/53.8	1.534	0.227
Age (years old)	49.53 ± 5.31	50.15 ± 4.19	0.121	0.108
Course of disease (years)	5.83 ± 1.44	5.92 ± 1.56	0.157	0.095
BMI (kg/m^2)	22.18 ± 2.57	23.09 ± 3.14	0.093	0.203

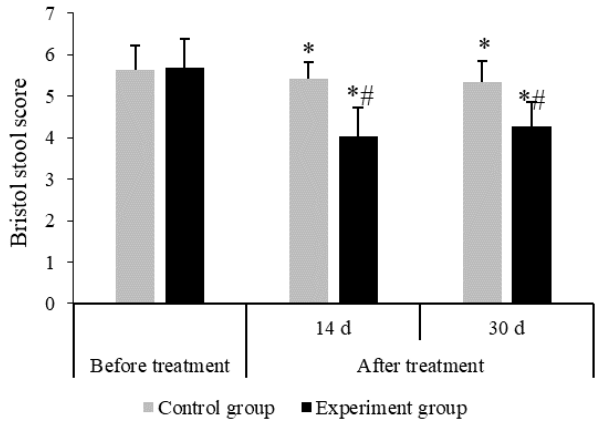

Figure 2. Comparison of Bristol stool scores between the two groups before and after treatment. Note: *P<0.05 and #P<0.05 indicated the differences compared with the same group before treatment and the control group at the same time point, respectively.

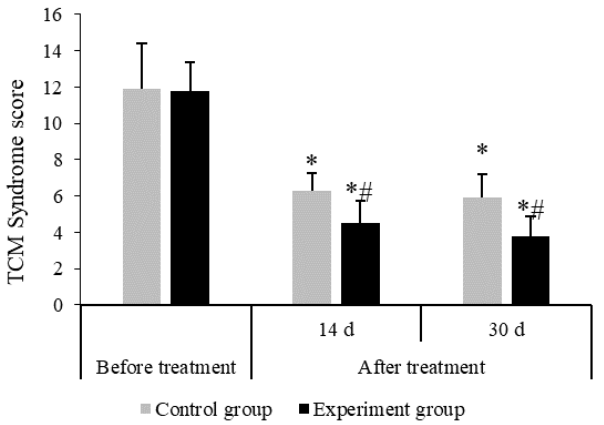

Figure 3. Comparison of TCM syndrome scores between the two groups before and after treatment. Note: It was suggested that *P<0.05 meant the significant differences compared with the same group before treatment, while #P<0.05 showed those compared with the control group at the same time point.

Comparison of TCM syndrome scores and the effective rate before and after treatment

As shown in Figure 3, the TCM syndrome scores of patients were compared between the two groups at different time points before and after treatment. The TCM syndrome scores of the patients 14 and 30 days after treatment were significantly lower than those before treatment in both groups (P<0.05). While those of the patients in the experiment group were significantly lower than those in the control group 14 days after treatment and 30 days after treatment (P<0.05).

It could be observed from Table 2 that the effective rate after treatment was calculated and compared between the two groups using the TCM syndrome score. The total effective rate of patients in the experiment group was 100.0%, and that in the control group was 96.0%, indicating no significant difference between the two groups (P>0.05). But the cure rate of the patients in the experiment group was significantly higher than that in the control group (P<0.05).

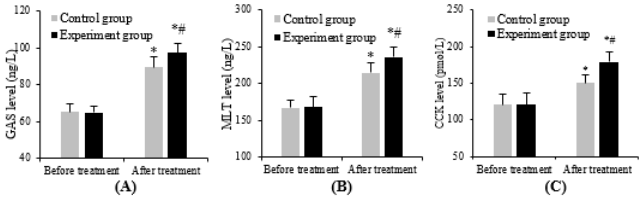

Figure 4. Comparison of the levels of GAS, MLT, and CCK in peripheral blood between the two groups before and after treatment. Notes: Figures (A), (B), and (C) displayed the comparisons of GAS, MLT, and CCK, respectively. It was indicated that there were significant differences as *P<0.05 and #P<0.05, which were compared with the same group before treatment and the control group at the same time point, respectively.

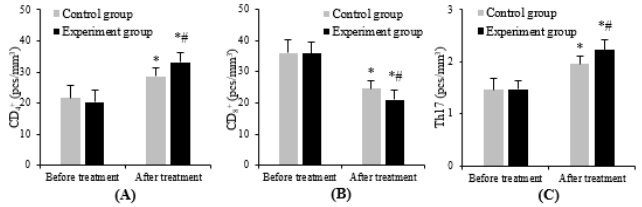

Figure 5. Comparison of the levels of CD_4^+, CD_8^+, and Th17 in peripheral blood in the two groups before and after treatment. Notes: The levels of CD_4^+, CD_8^+, and Th17 immune cells were presented in Figures (A), (B), and (C), respectively. *P<0.05 and #P<0.05 were obtained compared with the same group before treatment and the control group at the same time point, respectively.

Comparison of indexes of peripheral blood gastrointestinal function before and after treatment

The peripheral blood gastrointestinal function evaluation indexes GAS, MLT, and CCK were compared between the two groups before and after treatment. As shown in Figure 4, the levels of GAS, MLT, and CCK in peripheral blood of patients after treatment were significantly higher than those before treatment in both groups (P<0.05). After treatment, the levels of GAS, MLT, and CCK in the experiment group were significantly increased compared with those in the control group (P<0.05).

Comparison of immune cell content in peripheral blood of patients before and after treatment

The levels of CD_4^+, CD_8^+, and Th17 immune cells in peripheral blood were compared between the two groups before and after treatment. It was observed from Figure 5 that the levels of CD_4^+ and Th17 cells in the peripheral blood after treatment were significantly higher than those before treatment in both groups, while the level of CD_8^+

Table 2. Comparison of the effective rates between the two groups.

Groups	Cured (cases/%)	Markedly effective (cases/%)	Effective (cases/%)	Ineffective (cases/%)	Total effective rate (%)
Control group (n=25)	12/48.0	9/36.0	3/12.0	1/4.0	96.0
Experiment group (n=26)	19/73.1	5/19.2	2/7.7	0/0.0	100.0
χ^2 value	6.012	1.339	0.326	0.577	0.418
P value	0.000	0.048	0.225	0.308	0.210

cells was significantly decreased (P<0.05). The levels of CD_4^+ and Th17 were significantly higher than those of the control group, and the level of CD_8^+ was significantly lower in the experiment group (P<0.05).

Comparison of anxiety SAS scores and quality of life SF-36 scores before and after treatment

The SAS scores for anxiety and the SF-36 scores of quality of life were compared at different time points before and after treatment between the two groups. It was displayed in Figure 6 that the SAS scores of anxiety symptoms were significantly decreased after treatment in both the control group and the experiment group, and the quality-of-life SF-36 scores were significantly increased (P<0.05). After treatment, the SAS scores of patients in the experiment group were significantly lower than those of the control group, and the SF-36 scores were also significantly higher than those of the control group (P<0.05).

Comparison of adverse events in patients after treatment

During the treatment, there were no drug allergies, liver and kidney function impairment, abnormal electrocardiograms, and other issues in the two groups. 1 patient in the control group developed constipation, which was significantly relieved after reducing the drug dosage. The incidence of adverse events was 1/4.0% in the control group. None of the patients in the experiment group had any adverse events, so the incidence of adverse events was 0/0.0%. After comparison, no significant difference was found in the incidence of adverse events during the treatment period between the control group and the experiment group (P>0.05).

Discussion

Functional diarrhea refers to functional bowel disease with diarrhea as the main clinical manifestation, caused by non-bacterial, non-infectious, and non-foreign body-induced hyperperistalsis. Patients with functional diarrhea have no organic changes. If the symptoms of patients with functional diarrhea can't be improved, it is not conducive to the absorption of nutrients; and the long course of the disease will also cause malnutrition in patients (13). The etiology of functional diarrhea is not clear now, and it may be related to factors such as intestinal flora imbalance, mental and psychological changes, abnormal gastrointestinal or other organs' sensory function, and unreasonable dietary structure (14,15). Western medicine treatment of functional diarrhea is mainly based on the ground of symptomatic treatment. The drugs commonly used clinically for functional diarrhea include montmorillonite powder, bismuth subcarbonate, and Bifidobacterium viable capsules (16). However, long-term use of western medicine can cause damage to liver and kidney function, and the recurrence rate is also high (17). TCM believes that the main lesions of functional diarrhea are in the spleen, stomach, and intestines. Therefore, the treatment of the spleen and stomach is the key to the treatment of this disease (18). In TCM, traditional Chinese drugs and external cupping or moxibustion are commonly used to treat functional diarrhea, having achieved good results (19). The cupping technology can take advantage of the moxibustion method in the jar to regulate the functions of the immune, nervous,

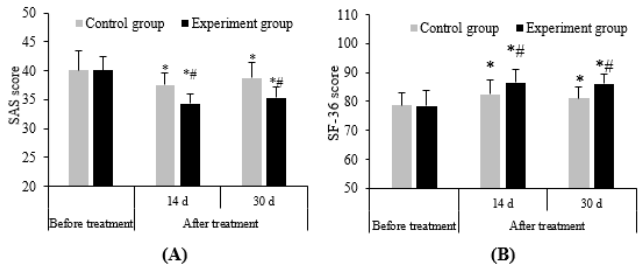

Figure 6. Comparison of SAS and SF-36 scores between the two groups before and after treatment. Note: Figure (A) showed the SAS scores, and Figure (B) showed the SF-36 scale scores. *P<0.05 meant the differences were compared with the same group before treatment, #P<0.05 meant those compared with the control group at the same time point.

and endocrine systems of the body through the chemical effects of electromagnetic waves and photoelectric radiation of near-infrared lights (20).

For the exploration of the clinical efficacy of cupping in the treatment of functional diarrhea, patients with functional diarrhea were taken as the research objects. The curative effect of oral montmorillonite powder and montmorillonite powder combined with cupping were compared. The number of diarrheas in patients exceeded 3 times a day, and the results proved that the combined therapy of montmorillonite powder with cupping could significantly reduce the number of diarrheas and improve the characteristics of patients' stools. The combined therapy had a better improvement effect than that of a single one. While patients with functional diarrhea were treated, attention should also be paid to relieving their mental stress of them (21). It was suggested that montmorillonite powder combined with cupping moxibustion could reduce the SAS scale scores, so it can regulate anxiety in patients effectively. It was shown that cupping moxibustion could relax the patients physiologically and psychologically, thereby relaxing the patients' spirit. Studies have confirmed that patients with long-term diarrhea would suffer from malnutrition and low immunity due to intestinal dysfunction, which seriously affects the quality of life of patients (22). Montmorillonite powder combined with cupping moxibustion could improve the SF-36 scale scores of patients and also improve the quality of life of patients after treatment.

The brain-gut axis is the connecting channel between the gastrointestinal neuroendocrine and the central nervous system, which is closely related to the pathogenesis of functional diarrhea (23). GAS, MLT, and CCK are also in close relation to gastrointestinal function, among which GAS can improve the blood flow of gastric mucosa and enhance gastrointestinal motility (24). MLT can induce the release of pepsin and accelerate gastrointestinal motility and emptying (25-27). CCK can inhibit gastric emptying, promote the contraction of intestinal smooth muscle, and accelerate intestinal peristalsis (28). The GAS, MLT, and CCK in the peripheral blood of the patients were significantly increased after treatment, and the improvement of montmorillonite powder combined with cupping moxibustion was more obvious. It was indicated that the brain-gut axis was involved in the occurrence of functional diarrhea, and montmorillonite powder combined with cupping moxibustion could improve gastrointestinal function

by regulating the levels of GAS MLT, and CCK. Treatment methods such as scraping and cupping will stimulate and improve the state of the body, and adjust the function of the organs, thereby promoting the body's metabolism and enhancing the immune function. The results showed that after treatment, the levels of CD_4^+ and Th17 immune cells in the peripheral blood of patients were significantly increased, and that of CD_8^+ was significantly decreased. The effect was more obvious under the combined therapy, which was suggested could regulate the immune system function of the body. Furthermore, the improvement of immune function could promote the treatment of diarrhea and prevent the recurrence of the disease.

The clinical effect of oral montmorillonite powder combined with cupping moxibustion was significantly better than that of a single drug treatment in the treatment of functional diarrhea. It protected the gastrointestinal function by regulating the function of the brain-gut axis of the body. It could also improve the immune system function, relieve clinical symptoms, and promote the recovery of patients. Due to the small sample size and the short follow-up time, no difference was discovered in the incidence of adverse events in patients. It lacked the in-depth exploration of the interaction mechanism among the indexes as well. In future work, the mechanism of cupping moxibustion in the treatment of functional diarrhea needs to be further explored and verified. The results were expected to provide a reference for the diagnosis and treatment of functional diarrheal diseases.

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