The Effectiveness of Herbal Enema for Irritable Bowel Syndrome: A Meta-Analysis of Randomized, Calcium Channel Blocker-Controlled Trials

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ABSTRACT

Objective: Irritable bowel syndrome (IBS) is a common functional gastrointestinal disorder, and a symptom-based diagnosis. Because of the unclear mechanisms, the treatment available have not acquired the satisfied effect. We performed a meta-analysis to assess the effectiveness and safety of herbal enema in treating IBS compared to the calcium channel blocker administration.

Methods: We searched for randomized controlled trials (RCTs) testing herbal enema in patients with IBS which compared to the calcium channel blocker administration in PubMed, EMMBASE, the Chinese National Knowledge Infrastructure (CNKI), the Wan-fang Database and the VIP Database up to May 2016 with no language restrictions. Primary outcome was the global symptom improvement and secondary outcome was the symptom severity scale score. Safety was also assessed. We used Revman 5.3 to estimate the pooled mean difference (MD) for continuous outcomes and relative risk (RR) for binary outcome measures, with a 95% confidence interval (CI).

Results: Five studies (230 patients in experimental group and 209 patients in control group) were included in the meta-analysis. The results showed that herbal enema as the sole intervention or combined with other treating methods could significantly promote the global symptom improvement and mucous stool scale and has potential to improve abdominal distention compared to the calcium channel blocker administration. But there was no difference between the two groups in abdominal pain. The recurrence rate was lower than the control group.

Conclusions: The study indicated that herbal enema may be an effective assistant means for IBS.

Key words: Herbal enema, Irritable bowel syndrome, Meta-analysis

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Introduction

Irritable bowel syndrome (IBS) is a chronic, relapsing gastrointestinal problem, characterized by abdominal pain and changes in the pattern of bowel movements without any evidence of underlying damage[1]. It has been classified into four subtypes according to the bowel behaviors: IBS-D (diarrhea-predominant), IBS-C (constipation-predominant), IBS-M (mixed), and unspecified IBS (IBS-U)[2]. The prevalence of IBS in children and adolescents in Asia ranges from 2.8% to 25.7%, with a pooled prevalence of 12.41% and the prevalence risk ratio of girl to boy is 1.39[3]. A recent report conducted by experts around the world showed the prevalence of IBS varies in different regions ranging from 1.1% in France and Iran to 35.5% in Mexico, and with 9.5% to 9.8% in Asia[4]. IBS often negatively affects quality of life in patients[5] and may result the increased burden to their families[6].

While the causes of IBS are still unknown, the pathophysiology is reported to be related to the infection and immune activation, serotonin dysregulation, bacterial overgrowth, brain-gut interaction and genetics[7]. A number of methods that aim at improving symptoms and quality of life, such as exercise, diet modification, psychological therapies, antispasmodic and antidepressant medication have been used for IBS. While several agents can help reduce symptoms of IBS, the issues of recurrence and resistance to therapy are difficult to handle[8,9]. Among the clinical applications to IBS, herbal enema employing traditional Chinese medicine formulas is becoming an attractive option for patients[10].

Herbal enema as a component of traditional Chinese medicine remedies is herbal decoction administration by way of rectum. Patients lying on his/her left side are injected herbal decoction (around 39°C, 150 mL, prescribed based on syndrome differentiation and the doctor’s experience), after defecation and urination by disposable perfusion tube or catheter by the way of rectum in order to make the herbal decoction directly contact with rectal mucosa. Patients can switch position lightly after 20-30 minutes, and the residence time of herbal decoction should be more than 2 hours. The rectal mucosa will be highly vascularized without having the medication pass through the entire gastrointestinal tract, which simplifies the delivery of medication to the affected area, limits the gastrointestinal side effects, and thus allows a greater bioavailability[10,11].

Among the multifactorial pathogenesis of IBS, intestinal motility impairment and visceral hypersensitivity are the key factors[12]. There were studies showed that the increased colonic motility in IBS is associated with up-regulation of...
calcium channels in colon\textsuperscript{[13,14]}. Pinaverium bromide and otilonium are L-type calcium channel blockers that act locally in the gastrointestinal tract. Pinaverium bromide can improve motility disorders and consequently reduce stool problems, while otilonium can effectively reduce pain and improve defecation alterations in IBS patients\textsuperscript{[13,14]}. These two agents are recommended for treating IBS\textsuperscript{[21,22]}, but their side-effects and the high recurrence of IBS still cannot be ignored.

Through searching the available clinical studies about herbal enema treatment for IBS compared with orally administration with calcium channel blocker, here we conducted a meta-analysis to assess the effectiveness and the safety of herbal enema on IBS.

**Methods**

**Search Strategy**

We searched in the multiple electronic databases [PubMed, the Chinese National Knowledge Infrastructure (CNKI), the Wan-fang Database and the VIP Database] without imposing any restrictions on language, date or status of publication. The search last ran on May 2016. All potentially relevant articles were investigated as full text.

The search strategy was composed of the following medical terms: "irritable bowel syndrome" or "IBS"; and "Chinese herbs" or "traditional Chinese medicine"; and "enema" or "rectal perfusion" or "rectal administration".

**Study Selection Criteria**

Study selection process was carried out by two independent reviewers respectively, and disagreements were resolved by consensus. Inclusion criteria of the articles were as follows: (a) Participants with IBS irrespective of age, sex, ethnic, conformed to the diagnostic criteria of the Roman II/III, Chinese National criteria and other guidelines; (b) Randomized controlled trials (RCTs) stating "randomization"; (c) The intervention of the experimental group was the enema therapy using traditional Chinese herbs, while the positive control was solely calcium channel blocker (pinaverium bromide or otilonium bromide); (e) The outcomes were the global symptom improvement and/or the symptom severity scale score.

Exclusion criteria of the articles were as follows: (a) Animal experiments; (b) Information of diagnostic criteria, treatment time or outcomes were not defined; (c) The same data was published in different journals; (d) Abstracts, reviews and case reports.

**Data Extraction and Quality Assessment**

Two authors (Chunyan Wang and Li Zhang) independently extracted data about the authors, study characteristics, IBS type, diagnostic criteria, information of intervention, duration of treatment, outcome measures and follow-up. Disagreement between the two authors was resolved by consensus and/or the suggestions from the third reviewer. The quality of each study was assessed by the Cochrane Risk of Bias Tool in Revman\textsuperscript{[18,20]}.

**Statistical analysis**

Revman 5.3 was used to estimate the pooled mean difference (MD) for continuous outcomes and relative risk (RR) for binary outcome measures. 95% confidence interval (95% CI) was used as effective size for the combined analysis. Forest plots were applied to assess the presence of heterogeneity, Chi-squared test ($\chi^2$) and the statistic $I^2$ were used to evaluate and qualify the heterogeneity. When $I^2 < 50\%$ and $P > 0.10$, the results were considered to be homogeneous and the fixed-effect model was used; when 50% $\leq I^2 < 75\%$, the results were considered to be heterogeneous and the random-effect model was used; When $I^2 \geq 75\%$, sensitivity analysis or subgroup analysis were conducted to identify the causes of the heterogeneity, and if $I^2$ remained 75% or greater, we only provided descriptive results without pooling estimates. Statistical significance was set at 0.05 level. A funnel plot was used to evaluate publication bias.

**Results**

**Study Description**

The systematic literature search identified a total number of three hundred and fifty-six studies, twenty-one of which were considered as relevant after screening at title and abstract level. Through screening at full text level, five (all in Chinese)\textsuperscript{[21-25]} of them were in accordance with our inclusion criteria, and found to be eligible (Figure 1). Hence our meta-analysis included five primary studies with 230 patients in experimental group and 209 patients in control group. The characteristics of studies were showed in Table 1. For all the studies included, the baseline information of enrolled patients in each individual study was well balanced between the two groups. Four studies\textsuperscript{[21-24]} used Rome criteria for the diagnosis, while one study\textsuperscript{[25]} used Chinese National criteria. Four studies\textsuperscript{[21,22,24,25]} enrolled patients with IBS-D and one study\textsuperscript{[25]} failed to specify the subtypes of IBS. Two studies\textsuperscript{[21,22]} used the herbal enema as the sole intervention and others compared western medicine with enema\textsuperscript{[23]} or traditional Chinese medicine orally\textsuperscript{[24]}, or acupuncture and moxibustion\textsuperscript{[25]}. Four studies\textsuperscript{[21,23,25]} used pinaverium bromide as positive control and one study\textsuperscript{[22]} used both pinaverium and otilonium bromide. All the studies included evaluated the global symptom improvement; two studies\textsuperscript{[22,24]} reported the symptom severity scale score before and after the treatment; and one study\textsuperscript{[21]} reported the difference of the score based on the clinical guideline of new drugs for traditional Chinese medicine. Two studies\textsuperscript{[21,24]} reported the adverse effects and three\textsuperscript{[22,24,25]} reported the recurrence. The duration of treatment ranged from 2 weeks to 1 month. Two studies\textsuperscript{[22,24]} mentioned the follow-up visit of 6 months, and one study\textsuperscript{[25]} followed up one year.

**Quality assessment**

The quality assessment of included studies showed in Figure 2. The random sequences were decided in various ways. There was one study\textsuperscript{[25]} used random card; two studies\textsuperscript{[24,25]} used random number table to group participants; the other two
Figure 1. Flow diagram of the study selection process.

Table 1. Characteristics of the 5 studies included in the meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>IBS Type</th>
<th>Diagnostic Criteria</th>
<th>Sample size (CHE/CCB)</th>
<th>Sex (male/female)</th>
<th>Age (mean/range)</th>
<th>Intervention of CHE</th>
<th>Intervention of CCB</th>
<th>Duration</th>
<th>Outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Huang[21] 2006</td>
<td>IBS-D</td>
<td>Rome II</td>
<td>52/50</td>
<td>CHE:12/40 CCB:10/40</td>
<td>CHE:17-70 CCB:19-72</td>
<td>Hydrotherapy and Anchang Decoction for enema, qd</td>
<td>Pinaverium Bromide Tablets orally, 50mg, tid</td>
<td>2w</td>
<td>Effective rate; symptom severity scale score</td>
<td>6m</td>
</tr>
<tr>
<td>Kuang[25] 2015</td>
<td>IBS-D</td>
<td>Rome II</td>
<td>48/49</td>
<td>CHE:19/29 CCB:23/26</td>
<td>CHE:38.13 CCB:37.52</td>
<td>Modified Tongxie Yaofang for enema, qd, and acupuncture and moxibustion</td>
<td>Pinaverium Bromide Tablets orally, 50mg, tid</td>
<td>4w</td>
<td>Effective rate</td>
<td>1 year</td>
</tr>
<tr>
<td>Zhao[22] 2014</td>
<td>IBS-D</td>
<td>Chinese National Criteria</td>
<td>60/40</td>
<td>CHE:31/29 CCB:19/21</td>
<td>CHE:16-72 CCB:19-71</td>
<td>Baitongweng Decoction for enema, qd</td>
<td>Otilonium Bromide Tablets orally, 40mg, tid</td>
<td>2w</td>
<td>Effective rate; symptom severity scale score</td>
<td>6m</td>
</tr>
</tbody>
</table>

Notes: IBS: Irritable bowel syndrome; IBS-D: diarrhea-predominant subtype of IBS; CHE: Chinese herbs enema; CCB: Calcium channel blocker; NA: not reported.
studies\(^{[22,23]}\) mentioned “randomization” but without details. Owing to the specificity of Chinese herbal enema, the blinding of participants and personnel is difficult to implement, thereby allocation concealment in all the studies was absent.

**Merging and meta-analysis**

**Primary outcome: global symptom improvement**

All the included studies reported the global symptom improvement of herbal enema for IBS patients. There was no heterogeneity \( (P = 0.84, I^2 = 0\%) \), so we used the fixed effect model to make the meta-analysis. The results indicated that the herbal enema as the sole intervention or combined with other treating methods may increase the global symptom improvement compared with calcium channel blocker treatment in all IBS patients \( (RR = 1.20, 95\% CI 1.10 \text{ to } 1.30, P < 0.0001, \text{Figure 3}) \). Because there were only 5 studies included in our study, we didn’t make the funnel plot to analyze the publication bias.

And there were two studies used the herbal enema as the sole intervention. There was no heterogeneity \( (P = 0.82, I^2 = 0\%) \), so we used the fixed effect model to make the meta-analysis. The results indicated that the herbal enema as the sole intervention may increase the global symptom improvement compared with control group \( (RR = 1.21, 95\% CI 1.06 \text{ to } 1.37, P = 0.005, \text{Figure 4}) \).

**Second outcome: symptom severity scale score**

Two studies\(^{[22,24]}\) reported the symptom severity scale score before and after the treatment including the abdominal pain, abdominal distention, defecation frequency and mucous stool scale, with 90 IBS-D patients and 70 IBS-D patients in treatment group and control group, respectively. One study\(^{[21]}\) reported the difference between the pre-treatment and post-treatment and showed that herbal enema could significantly relieve the discomfort symptoms in IBS-D patients.
The effectiveness of herbal enema on abdominal pain

There was a heterogeneity for abdominal pain with $I^2$ of 48%, so we conducted a random-effects model for abdominal pain. The result showed that there was no discernible effect between the two groups on the abdominal pain. ($MD = -0.43$, 95% CI -0.92 to 0.06, $P = 0.08$, Figure 5)

The effectiveness of herbal enema on abdominal distention

There was a high statistical heterogeneity for abdominal distention with $I^2$ of 79%, so we only did descriptive analysis. Two studies showed that herbal enema was likely to lessen the abdominal distention of IBS-D patients.

The effectiveness of herbal enema on defecation frequency

There was a high statistical heterogeneity for defecation frequency with $I^2$ of 80%. The descriptive analysis showed that herbal enema was likely to reduce the defecation frequency of IBS-D patients.

The effectiveness of herbal enema on mucous stool scale

There was a heterogeneity for abdominal pain with $I^2$ of 15%, so we conducted a random-effects model for mucous stool scale. The results indicated that herbal enema as the sole intervention or combined with other treating methods could significantly ameliorate mucous stool scale in the IBS-D patients compared to calcium channel blocker ($MD = -0.25$, 95% CI -0.40 to -0.10, $P = 0.001$, Figure 6)

Recurrence rate

Three studies$^{[21,23,24]}$ reported the recurrence rate of herbal enema for IBS-D patients, with 133 patients and 109 patients in treatment groups and control groups, respectively. There was no heterogeneity ($\chi^2 = 1.69$, $P = 0.43$, $I^2 = 0%$), so we used the fixed effect model to make the meta-analysis. The results indicated that the recurrence rate in IBS-D patients with the treatment of herbal enema was lower than the control group ($RR = 0.30$, 95% CI 0.18 to 0.52, $P < 0.0001$, Figure 7).

The safety of herbal enema in IBS patients

Only two studies$^{[20,23]}$ reported the adverse reactions and there was a high statistical heterogeneity with $I^2$ of 80%, so we only did descriptive analysis. One study$^{[20]}$ reported 10 patients in the experimental group felt slight nausea or abdominal discomfort. The other$^{[23]}$ reported 2 patients in the control group felt slight dizzy or nausea. The drug delivery route by rectum might be the cause of a large population in herbal enema group that felt uncomfortable.

Discussion

The result from this meta-analysis indicates that herbal enema as the sole intervention or combined with other treating methods could significantly improve the global clinical effectiveness of treatment in IBS and decrease the recurrence rate compared to the calcium channel blocker administration. By assessing the clinical symptoms, we found this intervention may significantly relieve the mucous stool and be similar to the control group on the abdominal pain. And herbal enema
as the sole intervention or combined with other treating methods was likely to improve the abdominal distention and defecation frequency in IBS-D patients. However, due to the specificity of drug-delivery route, the RCTs could not achieve the blinding of participants and personnel, which may influence the quality of studies. In addition, there existed the possibility of improper handling resulting in patients’ discomfort.

IBS is a chronic and recurring functional bowel disorder, but there is still no agreement over the treatment owing to its complex pathogenesis\(^\text{[20]}\). There are a lot of animal studies and RCTs to prove that calcium channel blocker (pinaverium bromide or otilonium) has an obvious effect on the IBS\(^\text{[13, 27, 28]}\). But the side-effects of drugs and the recurrence of IBS should be noticed\(^\text{[20]}\). Traditional Chinese medicine serves as a common alternative therapeutic approach in China and benefits IBS patients globally\(^\text{[36]}\). There are increasing number of systematic reviews and animal studies on the effect, safety and functional mechanisms of traditional Chinese medicine (including prescriptions, acupuncture and moxibustion) in treating IBS. A lot of evidence showed that Chinese medicine is superior in increasing the curative effect and decreasing the side-effects\(^\text{[8,30–34]}\). However, adverse reactions and toxicity incidents through long-term oral administration with Chinese herbs were reported in IBS trials\(^\text{[11,30]}\). On the other hand, herbal enema is a tropical administration of herbal fluid into rectum. Compared with the orally administered route, the rectal administration might be more efficient\(^\text{[37]}\). Actually, the rectal administration of suppository has been studied and used in the Children’s antipyretic drug, acute hemorrhoids and ulcerative colitis\(^\text{[38–41]}\). Some studies showed rapid absorption and high absolute bioavailability by rectal administration\(^\text{[11,42]}\), and direct effect of Chinese herbs can be exerted locally through intestinal absorption. Therefore, herbal enema may decrease the adverse reactions and toxicity and increase the therapeutic effects.

In conclusion, the current evidence suggested that herbal enema as the sole intervention or combined with other treating methods obtained beneficial effect for IBS patients. Thus, herbal enema could be recommended as one assistant therapeutic means. However, this method still requires the pharmacists' complicated and inefficient handling, which may limit large-scale use in the IBS patients. Therefore, technique improvement should be considered to better popularize herbal enema. In addition, only two relevant RCTs recruited more than 100 patients and the herbal enema was compared with other intervention. The sample size and the multiple interventions may weaken the reliability of our conclusion. Moreover, treatments of Chinese medicine base on syndrome differentiation and herbal decoction is usually prescribed by the syndrome differentiation, so the herbal decoction is hard to be in accord.

All in all, it’s difficult to avoid the studies of low quality. Therefore, further standardized preparation, multicentre, large-scale, double-blind RCTs are required.

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**Conflict of interest**

The authors declare that there are no conflicts of interest.

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