Therapeutic Effects of Lactobacillus in Treating Irritable Bowel Syndrome: A Meta-analysis

Bian Tiequn¹, Chao Guanqun² and Zhang Shuo³

Abstract

Objective As the lack of reliable treatment for irritable bowel syndrome (IBS) prompts interest in the development of new therapies, we aimed to systematically evaluate the effect of Lactobacillus in treating this disease.

Methods We searched MEDLINE, PubMed, Scopus, Web of Science and the Cochrane Central Register of Controlled Trials for the period from 1966 to August 2013 for double-blind, placebo-controlled trials investigating the efficacy of Lactobacillus treatment in the management of IBS. The studies were screened for inclusion based on randomization, controls and reported measurable outcomes. We used the Jadad score to assess the quality of the articles. The STATA 11.0 and Revman 5.0 software packages were used for the meta-analysis. The STATA 11.0 software program was also used to assess indicators of publication bias according to Begg’s and Egger’s tests.

Results Six randomized, placebo-controlled clinical trials met the criteria and were included in the meta-analysis. The Jadad score of the articles was >3, and three articles were of high quality. We analyzed the heterogeneity of the studies and found no heterogeneity in the meta-analysis. In the forest plot, the diamond was on the right side of the vertical line and did not intersect with the line. The pooled relative risk for clinical improvement with Lactobacillus treatment was 7.69 (95% confidence interval: 2.33-25.43, p=0.0008). For adults, the pooled relative risk for clinical improvement with Lactobacillus treatment was 17.62 (95% confidence interval: 5.12-60.65, p<0.00001). For children, the pooled relative risk for clinical improvement with Lactobacillus treatment was 3.71 (95% confidence interval: 1.05-13.11, p=0.04). Using the STATA 10.0 and Revman 5.0 software programs, we confirmed that Lactobacillus exhibited significant efficacy in treating IBS.

Conclusion Compared with the placebo, Lactobacillus treatment was found to be associated with a significantly higher rate of treatment responders in the overall population with IBS, without any side effects. As to limitations of the analysis, additional research is needed.

Key words: irritable bowel syndrome, Lactobacillus, meta-analysis

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teric nervous system, inflammatory processes, diet and (recog-
nized more recently) microbiota. In patients with IBS, con-
stitution can be acute or chronic, with chronic constipa-
tion defined as that with a duration greater than three
months. The Rome III criteria for chronic constipation in-
clude the presence of two or more of six symptoms for at
least 12 weeks within the preceding six months (1. straining
at defecation on at least 1/4 occasions; 2. lumpy/hard stools
on at least 1/4 occasions; 3. the sensation of incomplete
evacuation on at least 1/4 occasions; 4. the need for manual
maneuvers to facilitate defecation on at least 25% of oc-
casions; 5. the sensation of anorectal obstruction/blockage on
at least 25% of occasions; 6. fewer than three bowel move-
ments a week).

Despite the findings of numerous studies targeting treat-
ment for IBS (3, 4), there is currently no universally ac-
cepted satisfactory treatment protocol for this condition. Re-
cently, the administration of probiotics, defined as live mi-
croorganisms that, when administered in adequate amounts,
confer a health benefit on the host (5), has been proposed as
a treatment for functional gastrointestinal disorders. Probiot-
ics have been shown to have beneficial effects on various
aspects of human health, as well as several gastrointestinal
disorders, including adult and pediatric diarrhea, antibiotic-
associated diarrhea and pouchitis (6).

Four meta-analyses (7-10) have previously evaluated the
effects of probiotics for the treatment of IBS, primarily in
adult populations, with each reaching slightly different con-
clusions. Currently, Lactobacillus and Bifidobacteria are
among the most commonly studied probiotics in patients
with IBS (11). Regarding the pediatric population, a Co-
chrane systematic review (12) concluded that there is no evi-
dence that Lactobacillus supplementation is effective in
managing children with recurrent abdominal pain. We there-
fore performed a meta-analysis of randomized controlled tri-
als to assess whether there are any benefits to Lactobacillus
treatment in improving symptoms and/or the health-related
quality of life in patients with IBS, among both adults and
children.

Materials and Methods

Search strategy

We searched MEDLINE, PubMed, Scopus, Web of Sci-
ence and the Cochrane Central Register of Controlled Trials
for studies investigating the efficacy of Lactobacillus supple-
mentation for treating IBS. Data were collected from 1966
to 2013 (up to August). The search terms were as follows:
“Lactobacillus” or “lactic acid bacteria” and “irritable
bowel,”“functional bowel diseases” or “irritable colon.” The
search was restricted to the English-language literature. We
searched the references of the reviewed articles for addi-
tional articles missed in the computerized database search.
All primary and review articles, as well as their references,
were reviewed independently in duplicate.

Study selection

All controlled trials investigating the efficacy of Lactoba-
cillus therapy in patients with IBS were considered. The
studies were screened for inclusion through a review of the
published articles based on the following criteria: randomi-
zation, controls and reported measurable outcomes. Each ar-
ticle was reviewed in duplicate for inclusion, with substi-
tual inter-rater agreement. A trial was disqualified if it was
not controlled or its outcomes did not consider efficacy. The
reviewers independently extracted data for patient character-
istics, therapeutic regimens, dosages, trial duration and out-
come measures.

Methodology quality assessment

We used the Jadad score to assess the quality of each arti-
cle. The Jadad score, which evaluates studies based on their
description of randomization, blinding and dropouts (with-
drawals), was used to determine the methodological quality
of the trials (13). The quality scale ranged from 0 to 5
points, with a low quality report indicated by a score of ≤2
and a high quality report indicated by a score of ≥4.

Data synthesis and statistical analysis

All analyses were performed using the STATA Software
(version 11.0, Stata Corporation, College Station, USA) and
Revman (version 5.0, The Cochrane Collaboration, Oxford,
UK). Data from selected studies were extracted into 2×2 ta-
bles. All included studies were weighted and pooled. The
relative risk (odds ratio; OR) and 95% confidence interval
(CI) were calculated, and an effect size (weighted mean dif-
fERENCE) meta-analysis was performed using the STATA 11.0
and Revman 5.0 programs. The event rate in the experimen-
tal (intervention) group against that in the control group was
calculated using a l’Abbe plot as an aid to explore the het-
rogeneity of the effect estimates. In cases of homogeneity,
a fixed-effects model was used for the meta-analysis; other-
wise, the random-effects model was applied.

Publication bias

The STATA 11.0 program was used to identify indicators
of publication bias according to Begg’s and Egger’s tests. A
p value of ≥0.05 indicated the absence of publication bias.
In addition to Kendall’s t-test (14), funnel plots were used
to identify indicators of publication bias (15).

Results

Article selection

The literature search identified 67 citations involving Lac-
tobacillus and IBS, six of which met our inclusion crite-
ria (11, 16-20). Of the 61 excluded articles, 18 were review
articles, two were observational studies comparing Lactoba-
cillus supplementation with other medicines, three were ani-
mal experiments, four were not in English, three were arti-
67 articles were identified
- review articles n=18
- observational studies that compared with other medicines n=2
- experiments n=3
- Not only about lactobacillus n=31
- Can not access n=3
- Not in English n=4

6 articles were included.

Figure 1. Flow diagram of the study selection process

<table>
<thead>
<tr>
<th>Reference</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Withdraws and dropouts</th>
<th>Total Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>16</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>17</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>18</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>19</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>20</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1. Jadad Quality Scores of the Randomized Controlled Trials Included in the Meta-analysis

<table>
<thead>
<tr>
<th>Reference</th>
<th>Mean age</th>
<th>IBS subtype</th>
<th>Side effect</th>
<th>Daily dosage</th>
<th>duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>41.9</td>
<td>ND</td>
<td>0</td>
<td>2×10⁹ CFU BID</td>
<td>4 weeks</td>
</tr>
<tr>
<td>16</td>
<td>12</td>
<td>ND</td>
<td>0</td>
<td>10⁶ CFU BID</td>
<td>6 weeks</td>
</tr>
<tr>
<td>17</td>
<td>11.6</td>
<td>ND</td>
<td>0</td>
<td>3×10⁹ CFU BID</td>
<td>4 weeks</td>
</tr>
<tr>
<td>18</td>
<td>6.4</td>
<td>ND</td>
<td>0</td>
<td>3×10⁹ CFU BID</td>
<td>8 weeks</td>
</tr>
<tr>
<td>19</td>
<td>44.6</td>
<td>D-IBS</td>
<td>0</td>
<td>1×10⁹ CFU BID</td>
<td>4 weeks</td>
</tr>
<tr>
<td>20</td>
<td>36.53</td>
<td>ND</td>
<td>0</td>
<td>10⁶ CFU BID</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of the Papers Included in the Meta-analysis

Jadad score assessment
The quality of the seven selected studies was assessed according to the Jadad score (Table 1). Three studies had a score of 3, and three studies had a score of 4. So therefore, six articles were of high quality.

The patient characteristics, IBS subtype, dose, side effects and duration of treatment/follow-up in each study are reported in Table 2. All subtypes of IBS (diarrhea-predominant, constipation-predominant and alternating) were incorporated in the included studies. The meta-analysis included 440 IBS patients (273 adults and 167 children) randomized to receive either Lactobacillus or a placebo. The definition of a clinical response in each study is reported in Table 3.

The Rome III criteria for IBS are presented in Table 4.

Heterogeneity test
We performed the heterogeneity analysis using the χ² test. χ²=26.58, p<0.0001 (Fig. 2), χ²=4.52, p=0.10 (Fig. 3), χ²=6.21, p=0.04 (Fig. 4) and found heterogeneity in the meta-analysis. Therefore, a random-effects model was used for the meta-analysis. The cause of heterogeneity may be the limited number of studies and small sample sizes.
Table 3. Response to Treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>Definition of response</th>
<th>lactobacillus</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>Change of score of abdominal pain or discomfort</td>
<td>16/20</td>
<td>7/20</td>
</tr>
<tr>
<td>16</td>
<td>Change in the abdominal pain severity score</td>
<td>11/25</td>
<td>10/25</td>
</tr>
<tr>
<td>17</td>
<td>Treatment success defined as no pain at the end of intervention</td>
<td>16/18</td>
<td>7/19</td>
</tr>
<tr>
<td>18</td>
<td>Change in abdominal pain according to the VAS score</td>
<td>33/42</td>
<td>17/38</td>
</tr>
<tr>
<td>19</td>
<td>Change in symptom score and intestinal permeability</td>
<td>6/14</td>
<td>1/15</td>
</tr>
<tr>
<td>20</td>
<td>Frequency and intensity of abdominal pain, bloating and feeling of incomplete rectal emptying</td>
<td>82/105</td>
<td>8/99</td>
</tr>
</tbody>
</table>

Table 4. Rome III Criteria for IBS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>lactobacillus</th>
<th>placebo</th>
<th>Odds Ratio</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Weight</td>
<td>M-H, Random, 95% CI</td>
</tr>
<tr>
<td>Bausserman M [16],2005</td>
<td>11</td>
<td>25</td>
<td>25</td>
<td>18.2%</td>
</tr>
<tr>
<td>Ducrotté P et al[20],2012</td>
<td>82</td>
<td>105</td>
<td>99</td>
<td>19.5%</td>
</tr>
<tr>
<td>Francavilla R [19],2010</td>
<td>33</td>
<td>42</td>
<td>38</td>
<td>18.9%</td>
</tr>
<tr>
<td>Gawronska A [17],2007</td>
<td>16</td>
<td>18</td>
<td>19</td>
<td>14.8%</td>
</tr>
<tr>
<td>Sinn DH et al[11],2008</td>
<td>16</td>
<td>20</td>
<td>20</td>
<td>16.5%</td>
</tr>
<tr>
<td>Zeng J et al[19],2008</td>
<td>6</td>
<td>14</td>
<td>1</td>
<td>12.1%</td>
</tr>
</tbody>
</table>

Total (95% CI): **224 216 100.0% 7.69 [2.33, 25.43]**

Merging and meta-analysis

The meta-analysis showed that the heterogeneity among the six studies was statistically significant (p<0.0001); therefore, we performed the random-effects model for the meta-analysis. In the forest plot, the diamond was on the right side of the vertical line and did not intersect with the line. As shown in Fig. 2, the OR was **7.69 (95%CI: 2.33-25.43, z=3.35, p=0.0008)** (Fig. 2), which indicated that Lactobacillus supplementation had an effect on irritable bowel syndrome. As shown in Fig. 3, when we used the random-effects model for the meta-analysis (p=0.10), the OR was **17.62 (95%CI: 5.12-60.65, z=4.55, p<0.00001)**, which indicated that Lactobacillus treatment had an effect in the adult irritable bowel syndrome patients. In Fig. 4, we applied the random-effects model for the meta-analysis (p=0.04) and found an OR of **3.71 (95%CI: 1.05-13.11, z=2.04, p=0.04)**, which indicated that Lactobacillus therapy had an effect in the pediatric irritable bowel syndrome patients. However, because the number of included articles was limited, further research and analysis is required in the future.

Publication bias assessment

The reasons for publication bias include the fact that positive results were published easily, whereas negative results were not. Alternatively, negative results may have caused the researchers to abandon their studies, meaning that the negative results were not published, thus affecting the meta-analysis. In our analysis, we performed Begg’s test (Fig. 5A) and Egger’s test (Fig. 5B), both of which showed no publication bias in the meta-analysis (Begg’s test, p=1.000; Egger’s test, p=0.932).

Figure 2. Effects of Lactobacillus in the IBS patients
abdominal pain and/or discomfort with alterations in bowel habits in addition to a range of other features, including bloating, distension, flatulence, borborygmi and disturbances in the defecatory function (21). The therapeutic efficacy of Lactobacillus supplementation is likely impacted by the heterogeneous pathogenesis of the disease, which includes altered intestinal motility, visceral hypersensitivity, abnormal brain-gut interactions, food intolerance, altered intestinal permeability and post-infectious and/or inflammatory changes (22). Due to its obscure pathophysiology, treating IBS remains difficult, prompting interest in the identification of new and safe treatment options.

According to published guidelines, the primary treatment options for abdominal pain include antispasmodics or anti-depressants at low doses, while anti-diarrheal and/or laxative agents are very rare. Therefore, probiotics are good candidates for controlling the symptoms associated with IBS, especially when treatment safety is paramount in non-lethal disorders, such as IBS (26). While the exact mechanisms by which probiotics exert their effects in patients with IBS are not fully understood, several potential mechanisms have been suggested. As Lactobacillus is currently a popular probiotic, we accumulated data and conducted an analysis of the treatment efficacy of Lactobacillus supplementation.

In our research, we found six articles that met the inclusion criteria, including three articles about children and three articles about adults. According to the results of the meta-analysis, Lactobacillus treatment has an effect in both children and adults with IBS, without any side effects. In addition, the meta-analysis showed that the level of heterogeneity observed in this study may have been due to the patient’s age or dose of medication. The random-effects model was more accurate for the analysis. Furthermore, this meta-analysis showed that Lactobacillus therapy is beneficial in IBS patients, although the mechanism of action underlying this benefit remains a matter of debate. While IBS is likely...
multifactorial in etiology, recent findings in both experimental animal and clinical studies suggest that disturbances in gut flora, as observed in the setting of small-intestinal bacterial overgrowth, occur in patients with irritable bowel syndrome and that such abnormalities contribute to the development of IBS-type symptoms. However, this review is associated with some limitations. Our results are considered preliminary, and our findings must be confirmed in additional
Lactobacillus is a good candidate for assessment in a large multicenter trial of IBS patients, including both adults and children. With respect to the limitations of this meta-analysis, there is a strong need for further research to confirm the effects of probiotic treatment. As the exact mechanism of action of Lactobacillus supplementation is not known, further experimental studies are needed.

The authors state that they have no Conflict of Interest (COI).

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