Efficacy of Somatostatin Analogues Combined With Conventional Treatment Versus Conventional Treatment For Adhesive Intestinal Obstruction: A Meta-Analysis In China

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Abstract

Aim: To assess the efficacy of somatostatin analogues combined with conventional treatment as compared to conventional treatment for adhesive intestinal obstruction.

Methods: The Cochrane Library, Embase, Pubmed, Web of science, VIP, and Wanfang databases were systematically searched to select the relevant randomized controlled trials (RCT) and quasi-RCT. Study quality was assessed; relevant data were extracted. Inter-study heterogeneity was assessed using the Cochran Q test, \( I^2 \) test, and the Galbraith figure. The source of heterogeneity was determined using subgroup and sensitivity analyses. Publication bias was tested using funnel plots; funnel plot asymmetry was tested using Egger’s and Begg’s tests.

Results: Sixteen RCT including 1460 patients were included in this meta-analysis. The somatostatin group had obvious advantages in: (1) duration of abdominal pain and abdominal distension; (2) time of abdominal pain relief; (3) gastrointestinal decompression drainage amount; (4) hospitalization time. Following subgroup analysis based on somatostatin administration routes, i.e., subcutaneous injection and intravenous infusion, the somatostatin group had advantages for: (5) rate of conversion to surgery; (6) rate of effectiveness. The two groups had identical time of abdominal distension relief.

Conclusions: Somatostatin analogues combined with conventional treatment is superior to conventional treatment alone for intestinal obstruction.

Keywords: Adhesive intestinal obstruction; somatostatin; conventional treatment; efficacy; meta-analysis

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I. Introduction

Intestinal obstruction is a common surgical acute abdomen [1]; it refers to the inability of the intestinal contents to pass smoothly through the intestinal tract. Adhesive intestinal obstruction is the most common type. Postoperative adhesions are associated with abdominal injury, pelvic surgery, infection, and abdominal inflammatory disease [2,3]. Adhesion may lead to various diseases, including acquired female infertility, small intestinal obstruction, and organ damage during repeat surgery [4–9]. The risk of postoperative adhesions is highest in ovarian surgery and colorectal surgery, where the risk of readmission within 10 years is up to 7.5% and 8.8%, respectively, due to complications associated with direct adhesion [10–12]. When adhesive intestinal obstruction occurs, a large amount of digestive juices are retained in the intestinal tract, where it can lead to a series of pathological and pathophysiological changes, affecting the patient’s quality of life. The main clinical manifestations of intestinal obstruction include abdominal pain, vomiting, abdominal distension, and stopping the exhaust and defecation [13–16]. The physiological activity of somatostatin analogues is similar to that of somatostatin, including visceral vasoconstriction, which promotes the absorption of water and electrolytes in the gastrointestinal tract, suppressing intestinal and pancreatic secretions and changes in gastrointestinal motility [17]. In recent years, there has been much clinical research on the combination of somatostatin with conventional treatment versus conventional treatment alone for adhesive intestinal obstruction [18–33]. Currently, there is a lack of systematic and rigorous meta-analyses of somatostatin analogues treatment for adhesive intestinal obstruction. In this study, we used Cochrane system evaluation, and performed a comprehensive search for randomized controlled trials (RCT) of somatostatin analogues combined with...
conventional treatment versus conventional treatment for adhesive intestinal obstruction.

II. Materials And Methods

2.1. Search strategy

We searched the Cochrane Library, Embase, Pubmed, Web of science, CNKI, VIP, and Wanfang databases up to August 2017 to find the relevant RCT and quasi-RCT. The search terms included “intestinal obstruction” OR “bowel obstruction” OR “ileus” and “somatostatin” OR “stilamin” OR “octreotide” OR “lanreotide”. We performed a manual search to supplement the relevant articles. We did not restrict the publication language.

2.2. Study selection

The inclusion criteria were: Diagnosed with adhesive intestinal obstruction in the clinic; compared somatostatin analogues treatment and conventional treatment; had objective and relevant indicators that could be monitored; no study setting, age, gender, race, language, or publication status restrictions. The exclusion criteria were: Duplicate publications; other types of intestinal obstruction; treatment group used methods other than somatostatin or somatostatin analogues, e.g., hormones, ileus tube, traditional Chinese medicine; control group was treated with somatostatin or somatostatin analogues; non-RCT.

2.3. Data extraction

Two investigators independently screened, extracted, and cross-checked the data. Differences between the two researchers were resolved by a third reviewer. The information extracted from the included studies was: patient demographics (age, sex, country), interventions, outcome measure, details concerning study design (sample size, study quality).

2.4. Quality assessment

We assessed the quality of the included studies using the Cochrane risk of bias tool. The assessment of bias risk involved the following six aspects: Adequacy of random sequence generation; participant and personnel blinding; allocation concealment; incomplete outcome data and blind outcome assessment; selective outcome reporting.

2.5. Data synthesis and analysis

The data were analyzed using RevMan 5.3 and Stata 14.0. We used the Cochran Q test and I² test to assess inter-study heterogeneity. If there was obvious heterogeneity (P < 0.1, I² > 50%), we applied the random effects model; otherwise, the fixed effects model was used. According to the Cochrane Handbook for Systematic Reviews of Interventions version 5.0, I² < 40% indicated low heterogeneity, I² > 30% and I² < 60% indicate moderate heterogeneity, I² > 50% and I² < 90% indicate substantial heterogeneity, I² > 75% indicates severe heterogeneity, and if I² > 50%, we conducted subgroup analysis or meta-regression analysis; we performed sensitivity analysis when necessary. If there were >9 relevant studies, we tested publication bias by constructing a funnel plot, and tested the asymmetry of the funnel plot using Begg’s test and Egger’s test; an asymmetrical funnel plot and P < 0.05 indicated publication bias.

III. Results

3.1. Study selection

According to the search strategy, we retrieved an initial 2087 reports, and no additional records were identified through other sources. After removing duplicate studies, 1516 records remained; 1354 records were excluded because they were irrelevant (n = 904); case–control studies (n = 205); cohort studies (n =183); case reports (n = 25), or were reviews, comments, letters, or editorials (n = 35). We assessed 162 full-text articles for eligibility, and excluded 146 articles because they were non-randomized (n = 60), had irrelevant interventions and outcomes (n = 22), or involved other types of intestinal obstruction (n = 64). An eventual sixteen RCTs [18–33] were included in the meta-analysis. Figure 1 shows flow diagram of study identification and selection.

3.2. Study characteristics

In the sixteen included RCTs, the total number of samples was 1460; the treatment group contained 731 cases, and the control group contained 729 cases. Table 1 shows the specific study characteristics. All studies had been conducted in China and had been published in 2012–2016; the sample size of each study was between 42 and 183. All patients were diagnosed with adhesive intestinal obstruction. The control group was treated with conventional treatment, including diet, effective gastrointestinal decompression, intravenous fluid replacement, correction of electrolyte disorder, parenteral nutrition support, antibiotics, and enema. The treatment group was treated with somatostatin based on conventional treatment.

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3.3. Quality assessment
Of the sixteen studies [18-33], all reported that the treatment was randomized. Four studies [21,22,25,30] used the random number table method, one drew lots [33], and the remaining studies did not describe the methods of randomization and allocation concealment. Study quality was evaluated using the Cochrane risk assessment tool (Figure 2).

![PRISMA flow diagram](Image)

Figure 1: PRISMA flow diagram.
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample (n)</th>
<th>Gender</th>
<th>Age (yr)</th>
<th>Intervention</th>
<th>Outcome measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Qiu et al<a href="2012">18</a></td>
<td>35/35</td>
<td></td>
<td></td>
<td>Conventional treatment and octreotide 0.1mg subcutaneously, once every 8h, treatment for 72 h.</td>
<td>Abdominal pain score, time of abdominal pain relief, gastrointestinal decompression drainage amount, establish supine abdominal plain film and clinical remission were observed.</td>
</tr>
<tr>
<td>Mo et al<a href="2012">19</a></td>
<td>70/70</td>
<td></td>
<td></td>
<td>Conventional treatment and Octreotide 25 μg /h continuous intravenous injection, After the symptoms improved, somatostatin 0.1mg was injected subcutaneously once every 8h.</td>
<td>Gastrointestinal decompression drainage amount,duration of abdominal pain and abdominal distension , hospitalization time, adverse reactions and clinical effect.</td>
</tr>
<tr>
<td>Xu et al<a href="2012">20</a></td>
<td>40/40</td>
<td>27/13</td>
<td>46±18</td>
<td>Conventional treatment and somatostatin 6mg + 50 ml NS(normal saline) , continuous intravenous infusion at a rate of 250 μg /h.</td>
<td>Duration of abdominal pain and abdominal distension , gastrointestinal decompression drainage amount during 48h , number of cases of conversion to surgery and hospitalization time.</td>
</tr>
<tr>
<td>Study</td>
<td>n</td>
<td>n</td>
<td>Study Time</td>
<td>Mean ± Standard Deviation</td>
<td>Treatment Details</td>
</tr>
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<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>Hu et al[21]</td>
<td>30</td>
<td>30</td>
<td>13/17</td>
<td>41.15 ± 18.23</td>
<td>Conventional treatment and somatostatin 25µg / h micro pump intravenous injection</td>
</tr>
<tr>
<td>Jing et al[22]</td>
<td>40</td>
<td>45</td>
<td>25/20</td>
<td>53.2 ± 6.4</td>
<td>Conventional treatment and somatostatin 3mg + 250 ml NS continuous intravenous infusion(somatostatin 0.25mg slow shock injected for the first time 5 min, then 0.25 mg/h by continuous infusion)</td>
</tr>
<tr>
<td>Lei et al[23]</td>
<td>45</td>
<td>45</td>
<td>2/24</td>
<td>51.4 ± 6.3</td>
<td>Conventional treatment and somatostatin Subcutaneous injection of 0.1mg</td>
</tr>
<tr>
<td>Zhu et al[24]</td>
<td>22</td>
<td>20</td>
<td></td>
<td></td>
<td>Conventional treatment and somatostatin 6mg + 48 ml NS, continuous intravenous infusion for 24 hours.</td>
</tr>
<tr>
<td>Study</td>
<td>Total</td>
<td>Conventional Treatment</td>
<td>Somatostatin Treatment</td>
<td>Efficacy Parameters</td>
<td></td>
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<td>------------------------</td>
<td>----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Wang et al[25] (2013)</td>
<td>34</td>
<td>34</td>
<td>19/15</td>
<td>45.1 ± 5.2 Conventional treatment and Somatostatin 0.1mg subcutaneous injection until the anus to restore defecation exhaust or turn to the surgical treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20/14</td>
<td>45.6 ± 5.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gastrointestinal decompression drainage amount, hospitalization time, rate of conversion to surgery and recurrence rate.</td>
<td></td>
</tr>
<tr>
<td>Tan et al[26] (2013)</td>
<td>93</td>
<td>90</td>
<td>19/11</td>
<td>50.21 ± 2.1 Conventional treatment and somatostatin 0.6 mg + 48 ml NS, continuous pump for 24 h, used for a period of 4 days</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21/9</td>
<td>52.9 ± 0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Relief time of abdominal pain, abdominal distension and vomiting, recovery time of normal bowel sounds, time to start eating, time of the level of liquid and gas disappear and rate of conversion to surgery.</td>
<td></td>
</tr>
<tr>
<td>Liu et al[27] (2013)</td>
<td>30</td>
<td>30</td>
<td>19/11</td>
<td>50.21 ± 2.1 Conventional treatment and somatostatin 6mg + 48 ml NS, continuous intravenous infusion for 24 hours, the dosage of somatostatin was determined according to the condition of patients, Medication time was 2.3 - 6.5 d, with an average of 3.7 d.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21/9</td>
<td>52.9 ± 0.9</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fasting time, hospitalization time, number of cases of conversion to surgery and clinical effect.</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>No.</td>
<td>No.</td>
<td>No.</td>
<td>No.</td>
<td>Value</td>
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<tr>
<td>Xian et al[28] (2014)</td>
<td>49</td>
<td>49</td>
<td>25/24</td>
<td>26/23</td>
<td>45.1 ± 11.6</td>
</tr>
<tr>
<td>Zhu et al[29] (2015)</td>
<td>39</td>
<td>39</td>
<td>20/19</td>
<td>19/20</td>
<td>70.64 ± 5.21</td>
</tr>
<tr>
<td>Xu et al[30] (2015)</td>
<td>45</td>
<td>45</td>
<td>23/22</td>
<td>25/20</td>
<td>46.7 ± 5.4</td>
</tr>
</tbody>
</table>

Conventional treatment drainage amount, rate of conversion to surgery, duration of abdominal pain and abdominal distension, hospitalization time and clinical effect.

Zhu et al[29] (2015)

Hospitalization time, gastrointestinal decompression drainage amount, duration of abdominal pain and abdominal distension, and clinical effect.

The changes of serum endotoxin, diamine oxidase (DAO) and procalcitonin (PCT) levels of patients in two groups before and 5 days after medical treatment were observed and compared, and the clinical curative effect and untoward effect were evaluated as well.
### Efficacy Of Somatostatin Analogues Combined With Conventional Treatment Versus...

<table>
<thead>
<tr>
<th>Study</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Duration of abdominal pain and abdominal distension, hospitalization time, fasting time, and rate of conversion to surgery.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kang et al[31] (2015)</td>
<td>34</td>
<td>34</td>
<td>15/19 43/18 43.12 ± 11.30 42.75 ± 11.57 Conventional treatment and somatostatin 750 μg + 48 ml NS, continuous pump for 48 h, if the treatment is invalid or the condition is aggravated, then turn to the surgical treatment.</td>
</tr>
<tr>
<td>Zhang et al[32] (2015)</td>
<td>82</td>
<td>82</td>
<td>45/37 43/39 62.0 ± 1.0 62.1 ± 1.0 Conventional treatment and somatostatin 3mg + 250 ml NS continuous intravenous infusion(somatostatin 0.25mg slow shock injected for the first time 5 min, then 0.25 mg/h by continuous infusion, the interval of the dressing change was controlled within 3 min.)</td>
</tr>
<tr>
<td>Li et al[33] (2016)</td>
<td>43</td>
<td>43</td>
<td>Abdominal pain score, time of abdominal pain relief, hospitalization time and clinical effect.</td>
</tr>
</tbody>
</table>
Figure 2. Assessment of study quality.

Table 1. Study characteristics.
Figure 3. Forest plot: (a) Duration of abdominal pain and abdominal distension. (b) Time of abdominal pain relief. (c) Time of abdominal distension relief. (d) Gastrointestinal decompression drainage amount.

Figure 4. Forest plot: (a) Hospitalization time. (b) Rate of conversion to surgery.
Efficacy Of Somatostatin Analogues Combined With Conventional Treatment Versus…

Figure 5. Forest plot: Rate of effectiveness.

Figure 6. (a) Heterogeneity testing for hospitalization time. Notes Scattered points represent each study.

Horizontal axis represents 1/SE of each study. Vertical axis represents the Z-value. The area between the top and bottom lines represents the 95% CI. A scatter point falling outside the lines indicates substantial heterogeneity.

(b) Sensitivity analysis of hospitalization time. Notes The middle vertical line (-3.21) refers to the total combined effect. The left and right vertical lines represent the 95% CI. The horizontal lines of each study correspond to the combined effect of the remaining studies after one study was removed. We used the following two strategies to determine the impact of a study on the total combined effect: (1) After removing a study, we
recalculated the combined effect and whether it fell outside the 95% CI of the total combined effect; (2) After removing a study, we recalculated the combined effect and whether it was significantly different from the total combined effect.

Funnel plot: (c) Hospitalization time. (d) Rate of effectiveness.

3.4. Data synthesis and analysis

3.4.1. Duration of abdominal pain and abdominal distension

Five studies [19,20,24,28,29] reported the duration of abdominal pain and abdominal distension. No statistical heterogeneity was found between the five studies \((P = 1.00, I^2 = 0\%\)\), so the fixed effects model was chosen. The results showed a statistically significant difference between the studies \((MD = -1.24, 95\% CI: [-1.54, -0.95])\) and that the treatment group had significantly shorter abdominal pain and abdominal distension relief time than the control group (Figure 3(a)).

3.4.2. Time of abdominal pain relief

Three studies [18,23,33] reported on abdominal pain. There was no heterogeneity between the three studies \((P = 0.47, I^2 = 0\%\)\), so the fixed effects model was chosen. The results showed a statistically significant difference between the studies \((MD = -28.58, 95\% CI: [-30.66, -23.51])\) and that the treatment group had significantly shorter time of abdominal pain relief than the control group (Figure 3(b)).

3.4.3. Time of abdominal distension relief

Two studies [31,32] reported on abdominal distension. There was severe heterogeneity between the two studies \((P < 0.00001, I^2 = 97\%\)\), so the random effects model was chosen. The results showed no statistically significant difference between the studies \((MD = -0.91, 95\% CI: [-1.83, 0.02])\) and no significant difference between the time of abdominal distension relief in the treatment and control groups (Figure 3(c)).

3.4.4. Gastrointestinal decompression drainage amount

Five studies [20,24,25,28,29] reported on the gastrointestinal decompression drainage amount after treatment. There was moderate heterogeneity between the studies \((P = 0.20, I^2 = 33\%\)\), so the fixed effects model was chosen. The results showed a statistically significant difference between the studies \((MD = -193.12, 95\% CI: [-212.74, -173.51])\) and that the treatment group had significantly less gastrointestinal decompression drainage than the control group (Figure 3(d)).

3.4.6. Hospitalization time

Eleven studies [19,20,22,24,25,27–29,31–33] reported on hospitalization time after treatment. There was obvious heterogeneity between four studies \((P = 0.0006, I^2 = 67\%\)\). At the same time, we use the Galbraith figure to test the heterogeneity (Figure 6(a)); in the figure, three points in the regression line indicate heterogeneity. We performed subgroup analysis based on the routes of somatostatin administration: subcutaneous injection [25,33] and intravenous infusion [19,20,22,24,27–29,31,32]. Heterogeneity did not decrease following subgroup analysis (subcutaneous injection subgroup: \((P = 0.02, I^2 = 80\%\)\); intravenous infusion subgroup: \((P = 0.001, I^2 = 69\%\)\)). We did not find an obvious source of heterogeneity, so the random effects model was chosen. The results showed a statistically significant difference between the treatment group and control group \((MD = -3.21, 95\% CI: [-3.68, -2.73])\) and that the treatment group had a significantly shorter hospital stay time than the control group (Figure 4(a)). We also conducted sensitivity analysis (Figure 6(b)). After removing one study [28], the change in the combined effect was obvious, i.e., from -3.21 to -2.99, and was significantly different from the total combined effect. There was moderate heterogeneity between 10 studies \((P = 0.07, I^2 = 43\%\)\); heterogeneity was decreased significantly. We did not find a significant source of sensitivity. We assessed publication bias using a funnel plot (Figure 6(c)), and used Begg’s test \((P = 1.000)\) and Egger’s test \((P = 0.931)\) to test the asymmetry of the funnel plot; as \(P > 0.05\), it suggested no significant publication bias.

3.4.7. Rate of conversion to surgery

Seven studies [20,22,24-27,31] reported on the rate of conversion to surgery after treatment. There was no heterogeneity between the studies \((P = 0.83, I^2 = 0\%\)\), so the fixed effects model was chosen. The results showed a statistically significant difference between the studies \((RR = 0.35, 95\% CI: [0.23, 0.53])\) and a significantly lower conversion rate in the treatment group than the control group (Figure 4(b)).

3.5. Rate of effectiveness

Ten studies [18,19,21,24,27–30,32,33] reported on the rate of effectiveness after treatment. There was no heterogeneity between the studies \((P = 0.97, I^2 = 0\%\)\). We found no heterogeneity between the subcutaneous injection subgroup [18,33] \((P = 0.89, I^2 = 0\%\)\) and intravenous infusion subgroup [19,21,24,27–30,32] \((P = 0.94, I^2 = 0\%\)\), so the fixed effects model was chosen. The results showed statistical significance between the
subgroups (RR = 1.19, 95%CI: [1.13, 1.25]) and that the rate of effectiveness was higher in the treatment group (Figure 5). We assessed publication bias using a funnel plot (Figure 6(d)), and used Begg’s test ($P = 0.858$) and Egger’s test ($P = 0.995$) to test the funnel plot asymmetry; as $P > 0.05$ for both tests, it suggested no significant publication bias.

IV. Discussion

4.1. Interpretation and conclusions

In this study, we included sixteen RCTs [18–33] according to our inclusion and exclusion criteria. We evaluated the quality of each study according to the Cochrane risk of bias tool, and extracted the study characteristics. There was good consistency for aspects such as the source of participants and the intervention measures.

We used the Cochran Q test, $I^2$ test, and the Galbraith figure to assess inter-study heterogeneity. No heterogeneity was found for duration of abdominal pain and abdominal distension, time of abdominal pain relief, hospitalization time, rate of conversion to surgery, and rate of effectiveness. There was moderate heterogeneity for the amount of gastrointestinal decompression drainage. There was substantial heterogeneity for hospitalization time, and subgroup analysis and sensitivity analysis did not reveal an obvious source of heterogeneity. There was severe heterogeneity for time of abdominal distension relief. It is likely there are too few studies in this area to cause heterogeneity.

The meta-analysis revealed that the somatostatin analogues treatment group had obvious advantages for: duration of abdominal pain and abdominal distension; time of abdominal pain relief; gastrointestinal decompression drainage amount; hospitalization time; rate of conversion to surgery, and rate of effectiveness. There was no significant difference between the treatment and control groups for time of abdominal distension relief; too few studies included this outcome measure, so the results may not be meaningful. We divided the included studies into subcutaneous injection and intravenous infusion subgroups for subgroup analysis (Figure 4(a) and Figure 5). The subgroup analysis results were consistent with the total results, and showed no significant difference between the two subgroups. Somatostatin is a factor that inhibits growth hormone release from the hypothalamus, which is widely distributed in the nervous system and gastrointestinal tract [34]. Somatostatin can suppress the secretion of gastrointestinal, pancreas and bile, increase the absorption of intestinal canal, reduce the retention of fluid in the intestine, reduce the expansion, inflammation and necrosis of the intestinal canal, and promote intestinal recanalization [35]. It is beneficial to the recovery of the blood circulation of the intestinal wall, and the accelerated inflammatory response subsides [36]. Demetriades et al. [37] found that somatostatin significantly reduced abdominal distention and electrolyte loss in rats with small bowel obstruction. This is consistent with our meta-analysis results.

We performed sensitivity analysis for hospitalization time (Figure 6(b)), and one study had relatively high sensitivity. When we removed it, heterogeneity was reduced significantly. Despite careful reading of the literature, we did not find a source of heterogeneity. When more than 10 studies are included in a meta-analysis, it is necessary to determine publication bias. We found no significant publication bias (Figure 6(c) and Figure 6(d)), as proved by both Egger’s test and Begg’s test.

4.2. Limitations

First, this meta-analysis did not search all databases, so relevant studies may have been omitted. Second, after completing the article retrieval according to the search strategy, we found that the RCT that met the inclusion criteria were all from China, which may have generated regional bias. Third, the RCT that could be included were not of high quality. Fourth, the included studies had small sample sizes.

4.3. The significance of this meta-analysis
Adhesive intestinal obstruction is a common complication after abdominal surgery, and it is also one of the most common surgical acute abdomen. The present meta-analysis compared the clinical efficacy of somatostatin treatment and conventional treatment for adhesive intestinal obstruction. There are few meta-analyses in this field at present. We hope that this meta-analysis provides feasible options to physicians facing a patient with adhesive intestinal obstruction, and somatostatin should be used more widely in this field.

4.4. Directions of future research
The present meta-analysis found that the clinical effect of somatostatin analogues was obviously better than that of conventional treatment, but further study of high-quality and large-sample RCTs are still needed. We hope that the relevant RCTs are not confined to China, and are performed in more countries or regions.


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References


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