Effectiveness of Traditional Chinese Medicine External Therapy for Diabetic Constipation: A Meta-Analysis

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Abstract: Background: Diabetic constipation is a common complication of diabetes mellitus(DM), which not only leads to pains of patients such as abdominal pain and abdominal distention, but increases the economic burden of patients and society. Whether external therapy of traditional Chinese medicine(TCM) an effective way to treat diabetic constipation has not yet come to a conclusion. Therefore, this study aimed to evaluate the efficacy of TCM external therapy for treating diabetic constipation. Methods: We searched 7 databases from inception to 21 December, 2021. The databases included PubMed, Embase, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang database, China Science and Technology Journal Database (VIP) and Chinese BioMedical Literature Database(CBM). All analyses were conducted by RevMan5.4 and Stata12.0. The Cochrane risk of bias assessment tool was used for quality assessment and risk of bias assessment. Results: A total of 40 RCTs were included in the meta-analysis, involving 3074 diabetic constipation patients. The results showed that TCM external therapy increased in total effective rate and weekly defecation times compared with control group. TCM external therapy also showed more reduction in defecation time, fecal traits score and FBS level than control group. Conclution: TCM external therapy effectively relieves the costive symptom of DM patients. This meta-analysis demonstrated that TCM external therapy was more effective in treating diabetic constipation patients than common therapy or routine defecation medicine. However, the quality of most included studies were low. More multicenter, randomized, double-blind, and placebo controlled clinical trials will be needed in the future.

Keywords: Traditional Chinese Medicine, External therapy, Diabetic constipation, Meta-analysis

1. Introduction

Constipation is one of the most gastrointestinal symptoms among diabetic patients [1]. Among gastrointestinal symptoms, constipation was reported by the highest percentage of diabetic patients [2]. It was estimated that about 60% of patients with diabetes may experience constipation [3][4]. The symptoms of constipation can impair patients’ quality of life and may impose a substantial economic burden on patients and society [5]. Abdominal pain and abdominal distention resulting from constipation can lower the QOL score and make a negative impact on labor productivity [6].

Possible mechanisms of gastrointestinal symptoms in diabetes include autonomic neuropathy, hyperglycemia and intestinal neuropathy, but they are still controversial [5][7]. Autonomic nerves in the digestive system can be damaged by DM, which can contribute to delayed gastrointestinal function including colonic transit and cause constipation in diabetic patients [2][8]. The underlying pathogenesis of Diabetic autonomic neuropathy (DAN) is multifactorial such as gastrointestinal motility dysfunction and alterations in gastrointestinal hormone secretion [9]. Long-term hyperglycemia significantly affects the microenvironment of the intestinal nervous system. When hyperglycemia persists, glucose metabolism within neurons changes and glycosylation end products accumulate, leading to cell damage and death [10].

Some western drugs treating constipation such as osmotic laxatives, stimulant laxatives, secretagogues, and serotonin 5-HT receptor agonists can generate side effects including headache, diarrhea, nausea, and abdominal pain [11][12]. Although western drugs have a good short-term effect on
diabetic patients, it is easy to relapse after drugs withdrawal. If treatment is a long-term maintenance, drug dependence will easily occur. TCM has been used to treat diseases for more than 2000 years in China. TCM are well received by the general population for its efficacy and safety, regarded as an important complementary therapy. External therapies of TCM refer to acupuncture, moxibustion, acupoint application, auricular point sticking, massage and a series of external therapies with simple operation and less adverse reaction. External therapy of TCM is based on holistic concept and syndrome differentiation of TCM, using different methods to apply drugs to the skin, orifices and acupoints etc, in order to play a role on clearing the meridians, reconciling blood, detoxicating and removing blood stasis. External therapy of TCM can balance the viscera of Yin and Yang to readjust and improve, so as to enhance the recovery of body function and achieve the goal of treatment in DM.

Despite an increasing number of RCTs have been reported the effectiveness of TCM external therapy in treating diabetic constipation, it is to be proved whether TCM external therapy is an effective way to treat diabetic constipation. There has been no studies on TCM external therapy used to treat diabetic constipation in English electronic databases. The primary objective of this meta-analysis is to assess the effectiveness of TCM external therapy in treating diabetic constipation.

2. Methods

2.1. Search strategies


2.2. Inclusion and exclusion criteria

The inclusion criteria of studies were as follows: (1) Only randomized controlled trials (RCTs) were included; (2) Patients were definitely diagnosed with diabetes mellitus combined with functional constipation; (3) Any TCM external therapy, including electroacupuncture, acupuncture, needling, moxibustion, catgut embedding, acupoint injection, acupoint application, auricular point pressing, umbilical therapy, tuina, massage and enema were included in the intervention group; (4) Treatment in the control group included common therapy such as hypoglycemic drugs, insulin, diets, exercise, psychology, health education and nursing, or in combination with routine defecation medicine.

The exclusion criteria of studies were as follows: (1) Studies were not published in English or Chinese; (2) Conference, review, case report, animal experiment, research proposal, irrelevant literature and republished literature; (3) The control group received external treatment of TCM; (4) The outcome data was incomplete or incorrect.

2.3. Literature screening and data collection

EndNote X9 was used to review and screen literatures, and literatures that did not meet the inclusion criteria were removed. Two authors conducted literature screening respectively, and discussed with the third researcher if they had different opinions. Using Excel for data collection, which included: (1) Basic information (first author, year of publication, sample size, baseline); (2) Treatment information (interventions, courses of treatment); (3) Outcome measures (total effective rate, defecation time, fecal traits score, weekly defecation times, FBS).

2.4. Quality assessment

We used the Cochrane risk of bias assessment tool to assess the risk of bias of included studies. The
assessment tool covered seven items, including random sequence generation, allocation sequence concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. The results were divided into three levels: low risk, high risk, and uncertain risk.

2.5. Statistical analysis

Stata 12.0 software and Review Manager 5.4 software were used to analyze the data. Dichotomous variables were represented by odds ratios (RR) and 95% confidence intervals (CI). Continuous variables were represented by weighted mean difference (WMD) and 95% confidence interval (CI). I² test was used to assess heterogeneity of selected studies. When I² ≤ 50%, there was no statistically significant difference in heterogeneity among studies, and we could use fixed effects model for analysis. When I² > 50%, the heterogeneity was high, random effects model could be used. Considering high heterogeneity, we performed subgroup analysis on different methods of external treatments of TCM, different scoring standards or different courses separately. In addition, sensitivity analysis helped us find the stability of outcomes. Using funnel plot and Egger’s test to assess publication bias by Stata 12.0 software.

3. Results

3.1. Study selection

A total of 820 studies were identified by 7 databases. Using Endnote X9 software we deleted 282 duplicate studies. By preliminary screening, conference, review, case report, animal experiment, research proposal and irrelevant literature up to 434 studies were excluded. For the remaining 104 articles, we read the full text and finally included 40 articles in the meta-analysis [23-62]. The selection flow chart is shown in Figure 1.

![Figure 1: Study selection flow chart](image)

3.2. Study characteristics

40 RCTs were included in the meta-analysis, which characters were listed in Table 1, with a total of 3074 patients (1541 in TCM external therapy group, 1533 in control group). All the included RCTs conducted in China and based on common therapy. 13 experimental groups used routine defecation medicines combined with TCM external therapies. 1 study used Maren Runchang pill plus acupoint
application. 1 study used Jiawei Zengye Decoction plus moxibustion. 1 study used bifidobacterium tetravaccine tablets plus acupoint application. 1 study used Jiawei Muchang drink plus acupoint application. 3 studies used Liuwei Dihuang Pill plus acupoint application. 1 study used medicinal dishes plus moxibustion. 1 study used Mosapride Citrate plus electroacupuncture. 1 study used Jiawei Zengye Decoction plus acupoint application. 1 study used Mosapride Citrate plus acupuncture. 1 study used Hospital self-made TCM, Yiqi Ziyin Runzao formula, plus acupoint application. 1 study used Hospital self-made TCM, Runchang pill, plus auricular point pressing and abdominal massage. 27 experimental groups used TCM external therapies only. 1 study used electroacupuncture. 5 studies used auricular point pressing. 3 studies used acupoint application plus massage. 9 studies used acupoint application. 1 study used tuina. 2 studies used auricular point pressing plus massage. 1 study used Baduanjin plus moxibustion. 3 studies used auricular point pressing plus acupoint application. 1 study used low frequency pulse acupoint stimulation. 1 study used acupuncture. The detailed characters were presented in Table 1.

### Table 1: Characteristics of included RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Study location</th>
<th>IM</th>
<th>Sample size</th>
<th>TP</th>
<th>Outcomes</th>
<th>Adverse event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bai P, 2017 [51]</td>
<td>China</td>
<td>CT+MRP+A-A</td>
<td>Co 42 41</td>
<td>4d 4w 1,2</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Liu X et al, 2018 [30]</td>
<td>China</td>
<td>CT+APP+Ma</td>
<td>Co 42 42</td>
<td>NaM NM 1</td>
<td>C:3 (Abdominal pain and diarrhea 2, nausea and vomiting)</td>
<td></td>
</tr>
<tr>
<td>Liu Y, 2018 [39]</td>
<td>China</td>
<td>CT+LDP+AA</td>
<td>Co 30 30</td>
<td>3d 3w 1,2</td>
<td>T:2 (skin red and itchy)</td>
<td></td>
</tr>
<tr>
<td>Ruan et al, 2013 [56]</td>
<td>China</td>
<td>CT+AA+Ma</td>
<td>Co 40 40</td>
<td>4d 4w 1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Hu et al, 2016 [42]</td>
<td>China</td>
<td>CT+APP</td>
<td>Co 30 30</td>
<td>NM 1</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Liu X et al, 2018 [30]</td>
<td>China</td>
<td>CT+APP+Ma</td>
<td>Co 42 42</td>
<td>NaM NM 1</td>
<td>C:3 (Abdominal pain and diarrhea 2, nausea and vomiting)</td>
<td></td>
</tr>
<tr>
<td>Wu F et al, 2016 [49]</td>
<td>China</td>
<td>CT+MC+El</td>
<td>Co 24 24</td>
<td>4w 1</td>
<td>T:5 (skin itchy 2, nausea 1, vomiting 2)</td>
<td></td>
</tr>
<tr>
<td>Ye, 2018 [50]</td>
<td>China</td>
<td>CT+MC+El</td>
<td>Co 24 24</td>
<td>4w 1</td>
<td>C:3 (Abdominal pain, diarrhea and slight vomiting)</td>
<td></td>
</tr>
<tr>
<td>Yang, 2019 [51]</td>
<td>China</td>
<td>CT+AA+Ma</td>
<td>Co 34 34</td>
<td>4d 4w 1,2</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

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**Note:** The detailed characters were presented in Table 1.
Annotation: T, treatment group; C, control group; BD, baseline data; Co, comparable; NM, not mentioned; IM, intervention methods; TP, Treatment period; w, weeks; d, days; CT, common therapy; El, electroacupuncture; APP, auricular point pressing; AA, acupoint application; Ma, massage; Tu, tuina; Ba, Baduanjin; Mo, moxibustion; AS, low frequency pulse acupoint stimulation; Ac, acupuncture; SD, Syndrome differentiation and treatment; MC, Mosapride Citrate; LAC, Liuwei Anxiao capsule; DM, defecation medicines; PYC, Paidu Yangyan capsule; MSC, Maren Soft capsule; Pr, prepulsid; Do, Domperidone; MRP, Maren Runchang pill; JZD, Jiawei Zengye Decoction; BTT, bifidobacterium tetravaccine tablets; JMD, Jiawei Muchang drink; IHT, Itopride Hydrochloride Tablets; LDP, Liuwei Dihuang Pill; MD, medicinal dishes; JZD, Jiawei Zengye Decoction; HT, Hospital self-made TCM; YZR, Yiqi Ziyin Runzao formula; RP, Runchang pill; Outcomes: 1. total effective rate; 2. defecation time; 3. fecal traits score; 4. weekly defecation times; 5. Fasting blood sugar (FBS)

3.3. Assessment of quality and the risk of bias

All included studies were evaluated for quality and the risk of bias by the Cochrane risk of bias assessment tool. All included studies used randomization, of which 17 studies used random sequence generation following random number table method and envelope method while the remaining 23 studies mentioned randomization only. Only 2 studies used allocation concealment while the remaining did not reported. None of studies used blindness. No selective reporting bias was observed in all studies because all outcomes predesigned in the methods had been reported. Other bias was unclear among all the studies. The risk of bias assessment was listed in Figure 2.

![Figure 2: Risk of bias graph](image)

3.4. Results of Meta-analysis

3.4.1. The total effective rate

In the all included studies, 37 studies reported the total effective rate of TCM external therapy for diabetic constipation. Because of low heterogeneity between the studies, we pooled analysis using the fixed effects model ($P=0.04, I^2=30.8\%$). Meta-analysis results showed that the TCM external therapy group was more effective than that of the control group, and the difference was statistically significant ($RR = 1.32, 95\% CI = 1.27 to 1.37, P < 0.001$). The details were shown in Figure 3(A).

3.4.2. Defecation time

Defecation time was shown in 13 studies and the results presented significant heterogeneity ($P < 0.001, I^2 = 95.0\%$). The results of meta-analysis showed that the defecation time of the TCM external therapy group was shorter than that of the control group, and the difference was statistically significant ($WMD = -3.75 95\% CI = -4.68 to -2.83, P < 0.001$). The details were shown in Figure 3(B). Strong heterogeneity existed among the 13 studies. Sensitivity analysis showed that the outcome was stable (Figure 4(A)). By subgroup analysis, we found that heterogeneity had no connection with publication year, sample size, intervention measures, scoring criteria for defecation time, course of treatment and study quality. No obvious source of heterogeneity was found. The sources of heterogeneity need to be further explored.
3.4.3. Fecal traits score

Nine studies mentioned fecal traits score. We evaluated the heterogeneity by random effects model ($P < 0.001, I^2 = 80.3\%$). The results of meta-analysis showed that the fecal traits score of the TCM external therapy group was lower than that of the control group, and the difference was statistically significant ($WMD = -0.35, 95\% CI = -0.38 to -0.33, P < 0.001$).

According to different fecal traits scoring criteria, the 9 studies were divided into 3 subgroups. The score of fecal traits in subgroup 1 were 0, 1, 2 and 3. Subgroup 2 divided fecal traits score into three degrees (degree 1 = 0, degree 2 = 2, degree 3 = 4). Subgroup 3 did not mention the scoring criteria of fecal traits. The lower the score, the milder the symptoms of constipation. Fixed effects model and WMD were used to analyze the 3 subgroups. Outcome showed that there were no heterogeneity in subgroup 1 ($P = 0.436, I^2 = 0.0\%$) and subgroup 3 ($P = 0.208, I^2 = 0.0\%$), low heterogeneity in subgroup 2 ($P = 0.428, I^2 = 0.0\%$). Different fecal traits scoring criteria is one of the sources of heterogeneity. The difference was statistically significant in subgroup 1 ($WMD = -0.34, 95\% CI = -0.37 to -0.32, P < 0.001$), 2 ($WMD = -0.72, 95\% CI = -1.10 to -0.34, P < 0.001$) and 3 ($WMD = -1.09, 95\% CI = -1.35 to -0.83, P < 0.001$). TCM external therapy can improve the fecal traits. The details were shown in Figure 3(C).

3.4.4. Weekly defecation times

A total of 9 studies reported weekly defecation times. The heterogeneity test was obviously high ($P < 0.001, I^2 = 85.8\%$), so the random effect model was adopted. The results of meta-analysis showed that the weekly defecation times of the TCM external therapy group was more than that of the control group, and the difference was statistically significant ($WMD = 1.98, 95\% CI = 1.69 to 2.27, P < 0.001$). The details were shown in Figure 3(D).

Strong heterogeneity existed among the 8 studies. The outcome was stable by sensitivity analysis (Figure 4(B)). By subgroup analysis, the reason for heterogeneity increase could not be screened out. High heterogeneity might be related to multiple factors.

3.4.5. FBS

A total of 9 studies reported FBS. We used the fixed effect model to analyze because the heterogeneity was less than 50% ($P = 0.087, I^2 = 43.8\%$). The results of meta-analysis showed that the FBS of the TCM external therapy group was lower than that of the control group, and the difference was statistically significant ($WMD = -0.78, 95\% CI = -0.96 to -0.59, P < 0.001$). External treatment of TCM can not only improve the symptoms of constipation in diabetic patients, but also improve their FBS level. The details were shown in Figure 3(E).

3.4.6. Adverse events

A total of 14 studies discribed adverse events, 4 of which reported they had no adverse events happening. All the adverse events were not serious. The main adverse events included red skin, itchy skin, abdominal pain, abdominal distention, diarrhea, nausea and vomiting. Using the fixed effect model to analyze the heterogeneity ($P = 0.279, I^2 = 17.8\%$). The results of the meta-analysis showed that there were no statistical significance between TCM external therapy group and control group ($RR = 0.61, 95\% CI = 0.37 to 1.02, P = 0.062$). TCM external therapy did not increase the incidence of adverse events. The details were shown in Figure 3(F).

3.5. Publication bias

The funnel plots of the total effective rate and defecation time were shown in Figure 5(A) and Figure 5(B). Egger's test was used to detect publication biases of the total effective rate and defecation time. No publication bias was detected defecation time ($P = 0.253$)(Figure 5(C)). Publication bias was detected in the total effective rate ($P < 0.001$)(Figure 5(D)). Publication bias of the total effective rate was analyzed by shear compensation method, finally finding the outcome was stable.
Annotation: A, Comparison of the total effective rate; B, Comparison of the defecation time; C, Comparison of the fecal traits score; D, Comparison of weekly defecation times; E, Comparison of FBS; F, Comparison of adverse events

Figure 3: Forest plot

Annotation: A, Sensitivity analysis of defecation time; B, Sensitivity analysis of weekly defecation times

Figure 4: Sensitivity analysis
4. Discussion

Epidemiological studies reported that the prevalence of constipation in diabetic patients was 11% to 60%. Compared with the general population, the prevalence of constipation in diabetic adults is higher. Despite being one of the most commonly gastrointestinal symptoms in patients with DM, there are very limited evidence-based treatments for DM constipation [63][64]. Western medicine such as osmotic and stimulant laxatives can alleviate the symptoms to a certain extent. However, side effects including colonic damage, exacerbated constipation and melanosis coli have been reported. After medicine withdrawal, it is easy to relapse and produce drug dependence [13][65].

TCM has a history of more than 2000 years in China, usually being regarded as a supplementary or "alternative" form of medicine [66]. Many clinical studies have shown that TCM has a significant effect on constipation, with high cure rate, low recurrence rate and few adverse reactions [67]. TCM external therapies such as moxibustion, acupuncture, tuina, acupoint application, auricular acupressure were proved to be effective for constipation and had few adverse reactions [68][69][70][71][72].

Moxibustion plays a role of drugs, acupoints and meridians, warming meridians, dispersing cold, promoting Qi and activating blood circulation. Tianshu point has the function of strengthening the spleen, warming the stomach and regulating the intestines. Shenque point is the main pivot of the meridians, adjacent to the large intestine, which can warm the kidney, help Yang, strengthen the spleen and stomach. Moxibustion on Tianshu and Shenque can warm yang, strengthen spleen, regulate Qi and eliminate stagnation, so as to restore the conduction function of large intestine [73]. Modern medical research has confirmed that acupuncture generates excitement by manually stimulating acupoints on the skin with a needle. The excitement reaches the nucleus pulposus center through the afferent nerve. After integration through the cerebral cortex center, it can gradually improve the movement disorder of gastrointestinal smooth muscle and increase gastrointestinal peristalsis [74]. TCM tuina can increase the times of gastrointestinal peristalsis and shorten the emptying time by directly stimulating the abdominal or back meridians and acupoints [75]. Acupoint application is a method for drugs to directly penetrate into the body through skin acupoints, making up for the shortcomings of internal treatment and giving play to acupoint stimulation and drug effect. The application of Shenque point can regulate the intestines and stomach, strengthen the spleen and kidney, warm yang and replenish Qi, remove blood stasis and disperse knots, having the effect on regulating patients’ Yin and Yang, promoting gastrointestinal peristalsis and improving constipation [76]. The twelve meridians of the human body are connected with the ear. Auricular acupoint sticking and pressing can dredge the meridians and run Qi and blood. By stimulating the subacupoint nerve, it can strengthen the autonomic nerve reflex and excite the parasympathetic nerve.
Then the intestinal peristalsis and defecation will be enhanced [77].

We included 40 studies in our Meta-analysis, taking the total effective rate, defecation time, fecal traits score, weekly defecation times and FBS as the result. The outcome was as follows: (1) External treatments of TCM can relieve the symptoms such as improving the total effective rate, reducing fecal traits score and FBS level, shortening defecation time and increasing weekly defecation times. The difference was statistically significant (P < 0.05). (2) TCM external therapy did not increase the incidence of adverse events (P > 0.05). Some reported adverse events were mild. (3) Different fecal traits scoring criteria was the source of heterogeneity in fecal traits score. (4) The sources of heterogeneity of defecation time and weekly defecation times have not been found.

The Meta-analysis still had the following shortcomings: (1) The quality of the included studies was low and was not conducted by blind method; (2) Some high heterogeneity among studies reduced the reliability of the outcomes; (3) The included RCTs were all Chinese studies, sample source single; (4) Publication bias existed when analyzing the total effective rate.

5. Conclusions

Until now, TCM external therapy definitely effective for treating diabetic constipation has not be concluded. This Meta-analysis concluded that TCM external therapy was effective for diabetic constipation patients. However, the persuasion of effectiveness was not strong because of the low quality of studies. More multicenter, double-blind, randomized and placebo controlled trials need to be carried out in the future and more high-quality studies need to be included.

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