A meta-analysis of randomized controlled trials of a traditional Chinese medicine prescription, modified RunChang-Tang, in treating functional constipation

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Abstract

Background: Modified Runchang-Tang (MRCT), a Chinese herbal medicine, is widely used to treat functional constipation (FC), which is a common digestive system disease. However, its efficacy has not been evaluated systematically and objectively. Thus, a meta-analysis was conducted to assess the efficacy and safety of MRCT for treating functional constipation.

Methods: We searched for relevant publications from Embase, Medline, The Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Scientific Journals Database, and Wanfang Data for relevant literature. The timeframe of retrieval was set from the founding date of each database to July 15, 2020.

Result: A total of 26 randomized controlled trials with 2103 individuals were included in this meta-analysis. All trials were conducted in mainland China and were written in Chinese. The results showed that MRCT monotherapy provided better symptom relief in FC patients compared to prokinetic agent monotherapy (odds ratio, [OR] = 4.06), osmotic laxatives (OR = 4.39) and stimulant laxatives (OR = 2.99). Additionally, there were no obvious adverse effects in MRCT group compared with control group.

Conclusion: MRCT treatment is an efficient and safe treatment for FC. However, considering the limitations of this study, further well-designed randomized controlled trials are required to validate this conclusion.

Abbreviations: FC = functional constipation, MRCT = modified Runchang-Tang, OR = odds ratio, RCTs = randomized controlled trials.

Keywords: functional constipation, herbal formula, laxatives, modified Runchang-Tang, traditional Chinese medicine

1. Introduction

Functional constipation (FC) is a benign disease diagnosed through reduced frequency of bowel movements, dry stools and/or difficulty in bowel movements.\textsuperscript{[1]} The prevalence of constipation is about 16% globally,\textsuperscript{[2]} 6% in China,\textsuperscript{[3]} and 33.5% in the population aged over 60.\textsuperscript{[4]} Although constipation is not a life-threatening condition, it may directly or indirectly increase the probability of developing other mental or physical illnesses.\textsuperscript{[5,6]} Its impact on the life quality may be as great as other chronic diseases. Due to the severity and high prevalence, constipation put a considerable burden on health care resources.\textsuperscript{[7,8]}

Modified Runchang-Tang (MRCT), a well-known traditional Chinese medicine prescription, is developed from the herbal adjustment of Runchang-Tang according to syndrome differentiation (Principles of Chinese medicine treatment). It predominantly contains the following traditional Chinese herbs (Fig. 1, Table 1): Danggui (dried roots of \textit{Angelica sinensis} Diels, Fig. 1A), Taoren (kernel of \textit{Prunus persica} Batsch or \textit{P. davidiana} Franch mature seed, Fig. 1C), Zhihe (dried immature fruit of \textit{Citrus aurantium} L. and its cultivars, Fig. 1E). In the original literature, Runchang-Tang is mainly used to treat constipation characterized by “intestinal dryness and fluid depletion” (from traditional Chinese medicine theory). For people with the stagnation of qi, add Chenpi (dried mature fruit of ...
peel of *Citrus reticulata* Blanco and Houpo (dried bark of *Magnolia officinalis* Rehd. et Wils or *M. officinalis* Rehd. et Wils. var. *biloba* Rehd. et Wils.), with deficiency of qi, add Renshen (dried roots of *Panax ginseng* C. A. Mey.), with deficiency of yang, add Fuzi (dried roots of *Aconitum carmichaeli* Debx) and Rougui (dried bark of *Cinnamomum cassia* Presl). As long as permitted by local laws, the above herbs can be easily obtained outside of China. The procedure of making MRCT is as follows: Mix all the herbs, add an appropriate amount of water, boil and simmer for a certain period, and filter out the herb residue. The resulting herb solution should be taken orally 2 or 3 times a day. Because of the merits of safety, effectiveness, low cost and low toxic-side effects, MRCT has been commonly used to treat FC for centuries.

Increasing number of clinical trials have reported that MRCT successfully alleviates clinical symptoms of FC. However, the efficacy and safety of MRCT has not been systematically and objectively evaluated. Therefore, we conducted a meta-analysis to provide reliable assessment for clinical treatment of FC.

2. Methods

2.1. Ethics statement

As all analyses were based on previously published studies, no ethical approval or patient consent was required.

2.2. Literature search

Publications dated prior to July 15, 2020 and indexed in Medline, Embase, The Cochrane Library, Chinese Biomedical Literature Database, China National Knowledge Infrastructure, Chinese Scientific Journals Database or Wanfang Data were searched using keywords “Runchang” or “Run chang”. Regardless of the language and publication area, the studies returned from the search were included if they met the conditions defined in 2.2 and 2.3.

2.3. Inclusion criteria

The included studies should meet the following PICOS approach.

(1) Patients were diagnosed using recognized criteria of FC.
(2) Intervention group received oral administration of MRCT component for a complete treatment process.
(3) Control group received monotherapy of other recognized drugs for a complete treatment process.
(4) Outcome was measured by treatment efficacy, such as total effective rate or symptom scores.
(5) Studies included in the meta-analysis were randomized controlled trials (RCTs).

2.4. Exclusion criteria

A study will be excluded if it meets any of the following PICOS criteria:

(1) patients with unclear diagnosis criteria for FC, individuals <18 years old, pregnant or puerpera,
(2) intervention group including intervention methods other than MRCT receiving MRCT with composition not derived from the decoction of “Shen’s Zunsheng Book”, or with non-oral administration of MRCT,
(3) control group involving monotherapy of unrecognized drugs or combination therapy,
(4) outcome measured using non-dichotomy statistical results or having no statistical results, and

| No | Name                                      | Dose (gram) | King, Ministers, Adjutants, and Messengers |
|----|-------------------------------------------|-------------|--------------------------------------------|
| a  | Danggui (the dried roots of *Angelica sinensis* Diels). | 10g         | King                                      |
| b  | Shengdi (dried fresh roots of *Rehmannia glutinosa* Libosch). | 30g         |                                           |
| c  | Maren (the kernel of *Cannabis sativa* L mature seed). | 15g         | Ministers                                  |
| d  | Taoren (the kernel of *Prunus persica* Batsch or *P. davidiana* Franch mature seed). | 10g         |                                           |
| e  | Zhike (dried immature fruit of *Citrus aurantium* L. and its cultivars). | 10g         | Adjutants                                  |

MRCT = Modified Run-Chang-Tang.
(5) study type being report and review, animal experiments, non-clinical findings, duplicate publications, unverified RCT studies, or with no or inappropriate control group.

2.5. Study selection
Articles were extracted according to the following steps. Firstly, we retrieved the publications from the database and browsed titles, abstracts and keywords to determine whether they were appropriate. Relevant publications were summarized by authors’ names, publication year, diagnostic criteria, type of control group, treatment of duration, age and the number of individuals, intervention drugs, symptom improvement and adverse events. The summary was independently checked and reconfirmed to ensure the accuracy of extracted data. Finally, the extracted data were used for meta-analysis.

2.6. Outcome categorization
The following results were considered as successful relief of constipation symptoms: the term “patient with significantly improved symptoms” was defined as bowel movements 2 to 3 times a week, with soft stools but poor bowel movements. The term “asymptomatic patient” was defined as bowel movements more than 3 times a week and no other symptoms.

2.7. Quality critical appraisal
The quality of literature was carefully evaluated to ensure the accuracy of the final analysis outcome. Quality evaluations were independently conducted via Cochrane Bias Risk Tool, which includes the following 6 aspects: selection bias, performance bias, detection bias, attritions bias, attritions bias, reporting bias, and other biases.

2.8. Statistical analysis
Review Manager 5.3 (Cochrane Collaboration) software was used for statistical analysis. P and I² were used to assess the statistical heterogeneity between studies. When P > .1 and I² < 50%, a fixed-effects model was used. Otherwise, a random-effects model was applied. For the dichotomous data, the odds ratio (OR) and corresponding 95% confidence interval (CI) were calculated. P < .05 is considered statistically significant.

3. Results
3.1. Literature search
A total of 1669 studies were retrieved according to the above strategies and methods. The unrelated studies were excluded based on titles, abstracts, and keywords. Then, the remaining 150 articles were previewed in full-text. Finally, 26 RCTs[9–34] that included 2,103 individuals were analyzed. All studies in the final sample were conducted in mainland China and written in Chinese (Fig. 2).

3.2. Methodological quality of studies included
Using a Cochrane Bias Risk Tool, we conducted a risk of bias analysis for these included studies (Fig. 3). All studies mentioned the approach of random assignment of participants. However, only 8 studies[9,10,13,14,16,22,26,27] mentioned specific randomization methods: six[9,14,16,22,26,27] used a random number table, 1[10] used lottery, and 1[13] performed randomization by dice-throwing. None of the studies mentioned allocation concealment, blinding of outcome assessment, or blinding of participants and personnel. All studies have completed outcome data, low reporting and other biases. Hence, all included studies were of medium quality.

3.3. Study characteristics
The study characteristics were summarized in Table 2. The age of the participants ranged from 16 to 84 years. The studies were published between 2004 and 2018. The intervention duration ranged from 10 days to 8 weeks. Eighteen studies employed the Roman criteria for diagnosis of FC. In 4 studies[10,11,17,25] the authors applied Diagnostic efficacy of standard TCM syndrome (DESS). The remaining 4 trials[15,18,24,29] used the guidelines for diagnosis and treatment of chronic constipation in China (GDTC). Nine studies[9,10,12,13,16,19,26,27,34] reported adverse events. Eleven studies[9,10,14,17,21,22,25,29,30,33,34] compared MRCT treatment with prokinetic agents (N = 1010), ten studies[11–13,19,20,23,24,26,27,31] compared MRCT treatment with osmotic laxatives (N = 762), and 5 studies[15,16,18,28,32] compared MRCT treatment with stimulant laxatives (N = 331) (Fig. 4).
3.4. Results of functional constipation meta-analysis

All of the 11 RCTs\(^9,10,14,17,21,22,25,29,30,33,34\) comparing MRCT treatment with prokinetic agents reported that MRCT showed better remission ability in FC (OR = 4.06, 95% CI: [2.80, 5.88]; \(P < .00001\)) (Fig. 5). The heterogeneity test (\(I^2 = 0\%\)) also indicated no heterogeneity between the studies. Ten clinical trials\(^11–13,19,20,23,24,26,27,31\) compared MRCT treatment with osmotic laxatives. Meta-analysis showed that MRCT was more effective for symptomatic relief in patients with FC than osmotic laxatives [OR = 4.39, 95% CI: (2.59,7.44); \(P < .00001\)] (Fig. 5). The heterogeneity test showed no heterogeneity (\(P = .95, I^2 = 0\%\)) across the studies. Five trails\(^15,16,18,28,32\) tested the efficacy of MRCT treatment against stimulant laxatives in FC. Meta-analysis revealed that MRCT was significantly better in relieving constipation symptoms [OR = 2.99, 95% CI: (1.61, 5.54); \(P = .0005\)] (Fig. 5). Heterogeneity test showed homogeneity across the 5 trails (\(P = .61, I^2 = 0\%\)).

3.5. Adverse events

Adverse events were measured in 9 studies. Six\(^9,10,12,19,26,27\) reported no adverse event in either the experimental group or the control group. In the other 3 RCTs,\(^13,16,34\) all of the adverse events (abdominal pain and diarrhea) occurred in the control group. The probability of adverse events was 26.2% in prokinetic agents,\(^34\) 10.7% in osmotic laxatives\(^13\) and 21.2% in stimulant laxatives.\(^16\) Therefore, the available data showed that MRCT had a lower rate of adverse events compared with prokinetic agents, osmotic and stimulant laxatives.

4. Discussion

MRCT is a traditional Chinese medicine prescription and it is a unified whole. The combinational use of herbal medicines is at the heart of traditional Chinese herb medicine. It is the use of synergistic compound prescriptions that a main therapeutic tool, rather than a single herb. In actual application, the traditional Chinese medicine doctors use a prescription to treat diseases instead of using a single herb. In the existing literature, we have not found a comparison study of single herb effect and MRCT. Thus, the effect of MRCT and single herb are not comparable.

Runchang-Tang is formed according to the traditional principles of combining medicinal substances (King, Ministers, Adjutants, and Messengers). King (Danggui, Shengdi) is the substance that provides the main therapeutic effect in the prescription. Ministers (Maren, Taoren) enhance or assist the therapeutic actions of King. Adjutants (Zhike) provide 1 or more of the following functions: treating accompanying symptoms, moderating the harshness or toxicity of the primary substances, assisting King and Ministers in accomplishing their main objectives, or providing assistance from another therapeutic direction. Messengers either guide the other herbs in the formula to a specific channel or organ or exert a harmonizing influence\(^35\) (Table 1). It is generally believed that adding or subtracting in types or doses of herbs will not change the main status of King and Ministers herbs, nor will it change the main therapeutic effect of Runchang-Tang on FC. Therefore, the comparison of these RCTs in this study is reasonable.

The current medications for FC treatment are predominantly prokinetic agents, osmotic and stimulant laxatives. However, their efficacies are limited. Up to 47% of individuals were dissatisfied with these treatments,\(^36,37\) and prolonged treatment...
| Study              | Diagnostic criteria | Control group | Treatment duration | Age (years) | Number of patients | Intervention drugs | Percentage of symptom improvement |
|-------------------|---------------------|---------------|------------------|-------------|--------------------|-------------------|-----------------------------------|
| Cai et al (2016)  | RIIC/CDTC           | Prokinetic agents | 1 mo             | 49.11 ± 6.48 | 48.76 ± 6.24 | Mosapride (5 mg, TID) | 94.12% (32/34)                 |
| Chen et al (2014) | DESS                | Prokinetic agents | 10 d             | 72.3 ± 2.45  | 74.2 ± 5.13  | Mosapride (5 mg, TID) | 92% (46/50)                      |
| Deng et al (2015) | DESS                | Osmotic laxatives | 15 d             | 54-70       | 54-70         | Lactulose Oral Solution (10 g, SO, bid) | 96.00% (48/50)                  |
| Fang et al (2017) | RIIC/ CGND          | Osmotic laxatives | 28 d             | 45.30 ± 6.71 | 43.56 ± 6.81 | Mosapride (5 mg, TID) | 97% (30/31)                      |
| Han (2015)        | RIIC/ CGND          | Osmotic laxatives | 3 wk             | 57.6 ± 11.6  | 60.8 ± 10.2  | Mosapride (5 mg, TID) | 91.5% (27/30)                   |
| Hou et al (2014)  | RIIC/ DESS          | Prokinetic agents | 4 wk             | 43.28 ± 8.51 | 42.36 ± 8.13 | Mosapride (5 mg, TID) | 90% (27/30)                      |
| Jiang (2016)      | GDTC                | Stimulant laxatives | 28 d             | 45.30 ± 6.71 | 43.56 ± 6.81 | Mosapride (5 mg, TID) | 97% (30/31)                      |
| Li (2009)         | RIIC/ CGND          | Stimulant laxatives | 4 wk             | 56.26 ± 8.81 | 57.45 ± 8.41 | Mosapride (5 mg, TID) | 91.5% (27/30)                   |
| Li et al (2013)   | DESS                | Prokinetic agents | 2 wk             | 50-72       | 50-72         | Mosapride (5 mg, TID) | 92.00% (23/25)                  |
| Lu et al (2011)   | GDTC                | Stimulant laxatives | 3 wk             | 57.6 ± 11.6  | 60.8 ± 10.2  | Mosapride (5 mg, TID) | 86.7% (26/30)                   |
| Shi et al (2008)  | RIIC                | Osmotic laxatives | 4 wk             | 32-60       | 36-60         | Mosapride (5 mg, TID) | 96.7% (29/30)                   |
| Song et al (2007) | RIIC                | Prokinetic agents | 4 wk             | 26-62       | 24-60         | Mosapride (3 mg, TID) | 97.2% (35/36)                   |
| Sun (2007)        | RIIC/DTSS           | Prokinetic agents | 1 mo             | 16-68       | 16-68         | Mosapride (10 mg, TID) | 88% (88/100)                    |
| Tang et al (2009) | RIIC/ CGND          | Osmotic laxatives | 4 wk             | 42.75 ± 13.98| 44.59 ± 15.80| Mosapride (5 mg, TID) | 96.08% (49/51)                  |
| Wan et al (2016)  | GDTC                | Osmotic laxatives | 3 wk             | 62.00 ± 3.50 | 64.00 ± 4.10 | Mosapride (10 mg, TID) | 97.78% (44/45)                  |
| Wang (2004)       | DESS                | Prokinetic agents | 3 wk             | 20-52       | 18-50         | Mosapride (10 mg, TID) | 91.7% (33/36)                   |
| Wei (2016)        | RIIC/ CGND          | Osmotic laxatives | 1 mo             | 69.67 ± 5.63| 70.00 ± 5.62 | Mosapride (10 mg, TID) | 93.3% (28/30)                   |
| Wu (2013)         | RIIC/ CGND          | Osmotic laxatives | 4 wk             | 59.97 ± 8.84| 60.90 ± 9.58 | Mosapride (10 mg, TID) | 93.3% (28/30)                   |
| Xin et al (2014)  | RIIC/DESS           | Stimulant laxatives | 4 wk             | 68 ± 7.5 | 70.7 ± 8.7 | Mosapride (10 mg, TID) | 94.2% (33/35)                   |
| Xu (2010)         | DESS                | Prokinetic agents | 30 d             | >60         | >60          | Mosapride (10 mg, TID) | 93.75% (75/80)                  |
| Yang (2010)       | RIIC                | Prokinetic agents | 4 wk             | 46.62 ± 8.33| 45.95 ± 9.12 | Mosapride (5 mg, TID) | 89.4% (42/47)                    |
| Yang et al (2017) | RIIC/ CDTC          | Osmotic laxatives | 4 wk             | 25-76       | 25-76         | Mosapride (10 mg, TID) | 93.3% (28/30)                   |
| Zhang (2015)      | RIIC                | Stimulant laxatives | 4 wk             | 43.06 ± 9.67| 42.38 ± 10.41| Mosapride (200 mg, TID) | 92.70% (38/41)                  |
| Zhang (2018)      | RIIC/CDTC           | Prokinetic agents | 4 wk             | 45.76 ± 5.07| 46.01 ± 5.12 | Mosapride (5 mg, TID) | 94.74% (36/38)                  |
| Zhao (2011)       | RIIC                | Prokinetic agents | 3 wk             | 62-81       | 60-84         | Mosapride (10 mg, TID) | 88% (37/42)                      |

**Legend:**
- BID, twice a day; CDTC = consensus opinion on diagnosis and treatment of chronic constipation for TCM; CGND = clinical guideline of new drugs for TCM; DESS = diagnostic efficacy of standard TCM syndrome; DTSS = diagnostic and treatment routine for TCM syndrome in Shanghai; GDTC = guidelines for diagnosis and treatment of chronic constipation in China; MRCT = modified Run-Chang-Tang; NR = no record; OD, once a day; RIC = Rome II Criteria; RIIC = Rome III Criteria; SO = solution; TID, three times a day.
duration could increase the incidence of adverse reactions. This meta-analysis found that MRCT monotherapy showed better efficacy of symptom relief in FC and lower incidence of adverse events compared with prokinetic agents, osmotic and stimulant laxatives.

Previous research\cite{38} found that herbal medicine was better than placebo (OR = 3.83, I^2 = 62%) and similar to conventional pharmacological drugs (OR = 1.19, I^2 = 22%) in treating FC, thus indicating that herbal medicine is a potentially well-tolerated and effective treatment for FC. However, their outcomes were based on a few subgroups, insufficiently included studies, and larger heterogeneity than the present study. Moreover, it could
not define which formula had the highest probability in improving FC symptoms. Furthermore, another research found the effects of MBYT (Modified Buzhong-Yiqi-Tang) monotherapy on FC were superior to stimulant laxatives (OR = 1.21), osmotic laxatives (OR = 1.32) and prokinetic agents (RR = 1.18).[39] However, our meta-analysis found that FC patients with MRCT treatment displayed 4.06-fold higher probability of symptom relief than prokinetic agents, 2.99-fold higher than stimulant laxatives and 4.39-fold higher than osmotic laxatives. Moreover, no heterogeneity between studies (I² = 0%) was detected. Taken together, these findings suggest that MRCT monotherapy may be a more effective treatment than MBYT for the relief of clinical symptoms of FC.

Although adverse events were rarely mentioned in the studies included in this study, the available data showed that MRCT had less adverse events compared with prokinetic agents, stimulant and osmotic laxatives. This is consistent with the results of a previous study.[39] Hence, MRCT can be considered a relatively safe treatment.

Although the mechanisms of MRCT on FC treatment are unclear, results from mouse model of slow transit constipation indicated that MRCT treatment may act through restoration of the stem cell factor/c-kit pathway, increasing the count of interstitial cells of Cajal, and enhancing its function by increasing intracellular Ca²⁺ concentration.[40] In addition, a study from Korea indicated that herbal intervention could decrease phylum Firmicutes and genus Blautia in fecal microbiota, suggesting its potential to be used as a prebiotic.[41]

There are some limitations in the present study. Specifically, all of the included RCTs were of medium quality. Many of them did not describe the randomization methods, allocation concealment, blinding of participants, personnel and outcome assessment. Most of the studies did not record adverse events during the study. Moreover, A common problem[42] of traditional Chinese medicine prescriptions study at home and abroad also exists in this study, that is, the instability of the prescriptions, which will more or less affect the efficacy evaluation of MRCT. Finally, all of the studies were conducted in mainland China and written in Chinese, therefore publication bias is highly possible, the meta-analysis outcomes can only be confirmed to some extent. More clinical trials of higher methodological quality, larger sample size, and possibly multi-centered, should be incorporated to further confirm this conclusion.

5. Conclusion

This meta-analysis demonstrates that MRCT is an efficient and safe herbal medicine for FC treatment. However, considering the limitation of this study, further well-designed RCTs are required to confirm this conclusion.

Author contributions

Data curation: Xiankun Zhao, Feng Qin, Hanlin Gong.
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