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WORD COUNT	3769	TIME SUBMITTED	17-SEP-2021 10:48AM
		PAPER ID	76731257

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 68632

Manuscript Type: META-ANALYSIS

The efficacy of Chinese herbal medicine for functional constipation

A systematic review and meta-analysis

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Abstract

BACKGROUND

Functional constipation (FC) is a common and chronic gastrointestinal disease, and its treatment remains challenging.

AIM

To evaluate the efficacy and safety of CHM on efficacy rate, global symptoms, bowel movements, and the Bristol Stool Scale score in patients with FC by summarizing current available randomized controlled trials (RCTs).

METHODS

Randomized controlled trials with CHM to treat FC were identified by a systematic search of six databases from inception to October 20, 2020. Two independent reviewers assessed the quality of the included articles and extracted data. Meta-analyses were performed to odds ratios (OR), mean differences (MD), and 95%CI using random-effects models. Subgroup analyses and sensitivity analyses were used to explore and interpret the sources of heterogeneity. The funnel plot, Begg's test, and Egger's test were used to detect publication bias.

RESULTS

Ninety-seven studies involving 8,693 patients were included in this work. CHM was significantly associated with a higher efficacy rate (OR 3.62, 95%CI 3.19-4.11, $p < 0.00001$) and less severe global symptoms (OR 4.03, 95%CI 3.49-4.65, $p < 0.00001$) compared with control treatment, with the low heterogeneity between studies[LWC2] ($I2 = 0\%$, $P = 0.76$). And CHM also associated with more frequent bowel movements (MD 0.83, 95%CI 0.67-0.98, $p < 0.00001$), a lower score on the Bristol Stool Scale (OR 1.63, 95%CI 1.15-2.32, $p < 0.006$), and a non-significant recurrence rate (OR 0.47, 95%CI 0.22-0.99, $P = 0.05$). No serious adverse effects of CHM were reported.

CONCLUSION

In this meta-analysis, we found that CHM may have potential benefits in increasing the number of bowel movements, improving stool characteristics, and alleviating global symptoms in FC patients. However, a firm conclusion could not be reached because of the poor quality of the included trials. Further trials with higher quality are required.

Key Words: Functional constipation; Chinese herbal medicine; efficacy; Systematic review; Meta-analysis

Lyu Z, Fan Y, Bai Y, Liu T, Zhong LL, Liang H. The efficacy of Chinese herbal medicine for functional constipation. *World J Clin Cases* 2021; In press

Core Tip: In this meta-analysis, we found that CHM may have potential benefits in increasing the number of bowel movements, improving stool characteristics, and alleviating global symptoms in FC patients. However, a firm conclusion could not be reached because of the poor quality of the included trials. Further trials with higher quality are required.

INTRODUCTION

Functional constipation (FC) is a common and chronic gastrointestinal disease. It has a prevalence of 14% population in Asia [1], and 15.6% of the population in Hong Kong [2], representing a huge care burden. It is estimated that about 3.2 million FC patients in the United States visited medical centers in 2012, and the direct cost per patient for chronic constipation ranged from $1,912 to $7,522 per year [3]. In addition, functional constipation greatly affects the quality of life of patients, creating an important mental and physical burden [4].

The treatment of functional constipation remains challenging. Osmotic laxatives, irritant laxatives, and stool softeners are commonly used to treat FC [5]. However, up to 47% of patients were not completely satisfied with such treatment, mainly due to concerns

about treatment efficacy, safety, adverse reactions, and cost [6]. Therefore, patients with FC usually take a self-management approach and try to seek complementary and alternative therapy, Chinese herbal medicine is their usual choice. Through a randomized controlled trial (RCT), McRorie J.W. *et al* founded that Psyllium, a herb, was superior to docusate sodium, a laxative, for the treatment of chronic constipation [7]. Two systematic reviews reported that Chinese herbal medicine (CHM) was effective in treating constipation [8-9]. But they were not clear whether herbs improve bowel movement, increase the frequency of voluntary defecation, or alleviate symptoms of constipation. Some people even have concerns about the safety of Chinese herbs. Therefore, the purpose of the review was to evaluate the efficacy and safety of CHM on efficacy rate, global symptoms, bowel movements, and the Bristol Stool Scale score in patients with FC by summarizing current available RCTs.

MATERIALS AND METHODS

This systematic review was conducted following the guideline of Preferred reporting items for systematic review and Meta-analysis (PRISMA) statement [10].

Eligibility Criteria

Studies meeting the following criteria will be included: (1) Participants: patients met established diagnostic criteria of FC, including Rome I, II, III, IV criteria, without restrictions for age, sex, ethnicity, or setting type; (2) Type of studies: only randomized controlled trials were eligible; (3) Type of intervention: studies compared any CHM with Western medicine (WM) or placebo. For studies using other agents as the third arm, only the two arms using CHM would be included for analysis; (4) Type of outcome measurements: the efficacy rate (ER); the frequency of bowel movement (BM); the assessments of the global symptom (GS); the score of the Bristol Stool Scale (BSS); the recurrence rate (RR) within follow-up, and reported adverse effects (AEs).

Exclusion Criteria

Trials were excluded: (1) did not meet the criteria above; (2) involved animal studies or *in vitro* studies; (3) case series or reviews and conference abstracts; (4) valid original

data were unable to obtain even when contacting the author; (5) similar studies were reported without additional data to analyze and extract.

Search Strategy and Study Selection

MEDLINE, Embase, SinoMed, China National Knowledge Infrastructure (CNKI), Wanfang Database, and China Science and Technology Journal Database (VIP) were searched. An electronic search of the databases was performed from 1994, the year of the establishment of Rome criteria, up to June 2020, using the following search terms: (functional constipation) AND (Chinese herbal medicine OR Chinese traditional medicine OR Oriental medicine OR complementary medicine). We also hand-searched conference abstracts. Reference lists of all retrieved articles and reviews were screened as well. We limited the literature search to RCTs on human subjects. No language restrictions were used. Search strategies used for the Medline database were as supplement 1. Two reviewers (LZP and BY) independently read the title and abstract to initially select the studies that meet the eligibility criteria. Further reading the full text to determine the included studies. If the reviewers had different opinions, the third researcher (ZLD) finally made a decision.

Data Extraction

Two reviewers (LZP and BY) independently extracted data on participant characteristics from the selected studies in a standardized data extraction form. We extracted the following information from each included article: first author, year of publication, publication language, number of participants, participant characteristics, duration of intervention and follow-up period, number of dropouts, controlled intervention, and outcome data. Authors of trials were contacted for missing data and additional information. Any disparities between the two reviewers were discussed and resolved by consensus.

Definition of Outcomes

The efficacy rate (ER) was considered a primary outcome. The frequency of bowel movement (BM), the assessments of the global symptom (GS), the score of the Bristol Stool Scale (BSS), the recurrence rate (RR) within follow-up, and reported adverse

effects (AEs) were considered to be the second outcome.
(1) ER: To access the efficacy of CHM on the number of participants with any self-assessed relief of constipation symptoms.
(2) BM: to determine the efficacy of CHM on the frequency of bowel movement (BM) per week, *e.g.* 4 times/ week.
(3) GS: to assess the efficacy of CHM on the number of participants with any self-assessed relief of global symptoms (including symptoms other than constipation).
(4) BSS: to assess the efficacy of CHM on the number of participants with normal stool evaluated by Bristol Stool Scale ("soft sausage shape, soft lumps, muddy and watery stools" as normal stools).
(5) RR: recurrence means aggravation of constipation symptoms or reduction of BM to an untreated condition or less within the period of followed-up.
(6) AEs: including adverse events and clinical laboratory evaluations.

Risk of Bias Assessment

Two review authors (LZP and BY) assessed potential risks of bias for all included studies using Cochrane's tool for assessing the risk of bias. The tool assesses bias in six different domains: sequence generation; allocation concealment; blinding of participants, personnel, and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. Each domain receives a score of high, low, or unclear depending on each review author's judgment. A third review author (ZLD) acted as an adjudicator in the event of disagreement. Where doubt existed as to a potential risk of bias, we contacted the study authors for clarification. Results were tabulated into a "risk of bias graph" and a "risk of bias summary table".

Data Synthesis

In this meta-analysis, odds ratio (OR) and 95% confidence interval (CI) was considered as the effect size for dichotomous outcomes; mean differences (MD) with 95%CI were calculated as the effect size for continuous outcomes. Forest plots were produced to visually assess the effect size and corresponding 95%CI using random-effects models. Heterogeneity between studies was assessed *via* the forest plot, while I2 values

described the total variation between studies. When I2 values >50%, it indicates high heterogeneity [11]. Subgroup analyses were used to explore and interpret the sources of heterogeneity; to evaluate whether the effects were modified by treatment characteristics and study quality, we specified it based on CHM ingredients, western medicine treatment, and high-quality study. We used sensitivity analyses to explore the sources of high heterogeneity. Funnel plots, Begg's test, and Egger's test would be adopted to detect publication bias only when at least 10 studies were reporting the primary outcomes [12]. Statistical analysis was performed with RevMan software (version 5.4; The NordicCochrane Centre, The Cochrane Collaboration), and STATA software, version 13.0 (StataCorp, College Station, TX).

RESULTS

The meta-analysis outcomes of each outcome and subgroup are reported in Table 2.

Studies Selection

There were 1,764 studies *via* electronic databases and 12 trials by supplementary retrieval of reference lists of relevant literature. After the deletion of duplicate records, 1,232 trials were screened, and 1,078 trials were excluded by reviewing titles and abstracts. The remaining 154 trials were reviewed by full text. Ultimately, 97 trials involving 8,693 FC patients were included in this work. The selection process of research was detailed by the PRISMA flow diagram as shown in Figure 1.

Description of Trials Identified

Ninety-seven studies [13-109] were included basing on the eligibility criteria in this work. As shown in Table 1, five studies [13,26,35,40,108] were published in English, the others in Chinese. 5 studies [17,50,68,72,77] included patients using the Rome II criteria, 15 studies [16,25,36,38,42,44,49,58,62,63,67,82,83,90,95] using the Rome IV criteria, whereas the other 70 studies using Rome III criteria. The intervention of the treatment group was reported as CHM, and the ingredients were shown in Supplement 2. Besides, 6 types of intervention of the control group included PEG, mosapride, lactulose, phenolphthalein, probiotics, and placebo. Duration in the retrieved studies ranged from 1 to 8 wk. Efficacy rate was

reported in 97 studies and the global symptom was available in 69 studies. Bowel movement was reported in 15 studies. The recurrence rate within the follow-up period was reported in 5studies. Bristol Stool Scale was available in 7 studies while adverse effects of CHM were reported in 26 studies. Characteristics of the included trials are listed in Table 1, and quality evaluations of the included trials are shown in Table 1 and Figure 2.

Risk of Bias

Among the 97 studies included, 3 trials [13,26,108] were found to be of high methodological quality. 13 trials [18,27,43,46,50,57,60,79,87,98,99,103,107] were deemed to have a high risk of bias. All trials mentioned "random" in terms of allocation, but 12 trials [18,43,46,50,57,60,79,87,98,99,103,107] didn't describe the specific method of randomization. 5 trials [13,26,53,61,108] described allocation concealment and used blinding of participants, personnel, or outcome assessors. Drop-outs and withdrawals were reported in 5 trials [13,19,24,26,108] which just left out the cases without qualified result data. We considered 8 trials [18,50,57,60,79,98,103,107] to be of selective reporting bias as these trials failed to report all the prespecified outcomes mentioned in their method section. Other potential sources of bias considered in all included studies were unclear. Therefore study methodologies were incompletely described in majorities. The result of the assessment was showed in Figure2, and the detail was showed in supplement 3.

Results

The meta-analysis outcomes of each outcome and subgroup are reported in Table 2.

Efficacy Rate

Ninety-seven studies measured efficacy rate (ER). 89.9% (4,007/ 4,455) patients in the Chinese herbal medicine treatment group and 72.7% (3,079/ 4,238) patients with western medicine were responded. Results from 97 studies showed the treatment for FC was significantly in favor of CHM (OR 3.62, 95%CI 3.19-4.11, p < 0.00001) (Table 2 and Figure 3). There was no significant heterogeneity between studies (I2 = 0%, P = 0.76). In the subgroup analysis, CHM had a significant effect compared with PEG (OR 2.42, 95%CI 1.91-3.08, p < 0.00001), mosapride (OR 3.49, 95%CI 2.67-4.56, p < 0.00001),

lactulose (OR 3.71, 95%CI 2.86-4.82, p < 0.00001), phenolphthalein (OR 4.59, 95%CI 2.71-7.76, p < 0.00001), probiotics (OR 4.95, 95%CI 3.21-7.65, p < 0.00001), and specifically compared with placebo (OR 7.09, 95%CI 4.83-10.43, p < 0.00001). There was no significant heterogeneity between studies in each subgroup (Table 2 and Figure 3).

Global Symptom

Seventy-eight studies measured global symptoms (GS), and the results showed the treatment for FC was significantly in favor of CHM (OR 4.03, 95%CI 3.49-4.65, p < 0.00001) (Table 2 and supplement 4). There was no significant heterogeneity between studies (I2 = 0%, P = 0.68). In the subgroup analysis, CHM had a significant effect compared with PEG (OR 2.69, 95%CI 2.06-3.51, p < 0.00001), mosapride (OR 3.98, 95%CI 2.93-5.41, p < 0.00001), lactulose (OR 3.89, 95%CI 2.97-5.09, p < 0.00001), probiotics (OR 6.21, 95%CI 3.60-10.70, p < 0.00001), and specifically compared with placebo (OR 8.40, 95%CI 5.64-12.52, p < 0.00001). There was no significant heterogeneity between studies in each subgroup (Table 2 and supplement 4). However, there was only one study that compared the global symptom between CHM and phenolphthalein (OR 5.85, 95%CI 1.22-28.05).

Bowel Movement

Fifteen studies measured bowel movement (BM). Results from 15 studies showed the treatment for FC was significantly in favor of CHM (MD 0.83, 95%CI 0.67-0.98, p < 0.00001) (Table 2 and Figure 4). There was significant heterogeneity between studies (I2 = 80%, p < 0.00001). In the subgroup analysis, CHM had a significant effect compared with PEG (MD 0.83, 95%CI 0.67-0.98, p < 0.0006), mosapride (MD 0.65, 95%CI 0.28-1.02, p < 0.00001), and specifically compared with placebo (MD 0.99, 95%CI 0.87-1.11, p < 0.00001). There was no significant heterogeneity between studies in the placebo subgroup (Table 2 and Figure 4). However, there was only one study that compared CHM with lactulose (MD 0.98, 95%CI 0.81-1.15, p < 0.00001), and probiotics (MD 0.61, 95%CI 0.39-0.83, p < 0.00001). No study in the phenolphthalein subgroup.

Bristol Stool Scale

A total of 7studies compared CHM with western medicine and reported the Bristol Stool Scale. The results showed the treatment for FC was significantly in favor of CHM (OR 1.63, 95%CI 1.15-2.32, p < 0.006) (Table 2 and supplement 5). There was no significant heterogeneity between studies (I2 = 0%, *P* = 0.94). In the subgroup analysis, CHM had no significant effect compared with PEG (OR 1.48, 95%CI 0.96-2.28, *P* = 0.15) and mosapride (OR 1.88, 95%CI 0.79-4.44, *P* = 0.15). There was no significant heterogeneity between studies in the two subgroups (Table 2 and supplement 5). However, there was only one study that compared CHM with probiotics (OR 2.07, 95%CI 0.90-4.74, *P* = 0.09).

Recurrence Rate

Five studies compared CHM with western medicine and reported the recurrence rate (RR). The results showed CHM was not superior to western medicine in controlling the recurrence rate of FC (OR 0.47, 95%CI 0.22-0.99, *P* = 0.05) (Table 2 and Figure 5). There was no significant heterogeneity between studies (I2 = 9%, *P* = 0.35). In the subgroup analysis, CHM had no significant effect compared with placebo (OR 0.5, 95%CI 0.08-3.19, *P* = 0.46). There was no significant heterogeneity between studies in this subgroup (Table 2 and Figure 5). However, there was only one study that compared CHM with PEG (OR 0.66, 95%CI 0.20-2.13, *P* = 0.49), and lactulose (OR 0.31, 95%CI 0.10-0.91, *P* = 0.03) (Table 2 and Figure 5).

Adverse Events

Ten trials [13,17,19,26,33,38,46,79,81,90] reported digestive symptoms when using CHM, including abdominal pain or bloating, nausea, stomach discomfort, diarrhea and passing of gas. There were also other adverse effects were recorded in CHM groups, such as headache [17,81], transient hypertension [35] and insomnia [81]. While 21 studies [13,15,19,25-26,29,33,35,38-39,46,54-55,68,70,79,81,85,86,94,107] had digestive symptoms in Western medicine group, and mainly happened when used mosapride and lactulose.

Subgroup Analysis

Three studies were evaluated as high quality with a low risk of bias in their

methodology. Their compared CHM with western medicine and reported efficacy rate (ER). Results showed the treatment for FC was significantly in favor of CHM (OR 2.89, 95%CI 1.29-6.46, p < 0.01) (Table 2 and Figure 6). There was no significant heterogeneity between studies (I2 = 0%, *P* = 0.94).

Two CHM ingredients commonly used in the treatment of functional constipation, Cannabis Fructus and Cistanche, were analyzed in a subgroup by measuring efficacy rate (ER). In the Cannabis Fructus subgroup, the results showed Cannabis Fructus had no significant effect compared with western medicine (OR 1.88, 95%CI 0.97-3.65, *P* = 0.06). There was significant heterogeneity between studies (I2 = 61%, *P* = 0.08) (Supplement 1 and Figure 7). In the Cistanche subgroup, the results showed Cistanche had a significant effect compared with western medicine (OR 3.49, 95%CI 2.76-4.41, p < 0.0001). There was significant heterogeneity between studies (I2 = 0%, *P* = 0.71) (Supplement 1 and Figure 8).

Publication Bias and Sensitivity Analyses

Visual inspection of funnel plots (Figure 6), Begg's test (*P* = 0.31), and Egger's test (*P* = 0.26) revealed no evidence of publication bias for the examined primary outcomes. We did sensitivity analyses by excluding seven trials [17,19,64,76,87,96,103] using the decoction; the results showed that the results did not change.

DISCUSSION

+ADw-html+AD4APA-p+AD4-A total of 97 RCTs involving 8,693 patients with FC were recruited in the review. Pooled data showed a tendency for improvement of clinical efficacy in the CHM group, comparing with most Western medicine, such as PEG, mosapride, lactulose, phenolphthalein, probiotics, and placebo. The results showed that CHM was significantly superior to western medicines in improving efficacy rate, the frequency of bowel movement, global symptom assessment, and Bristol Stool Scale score of FC. However, there was significant heterogeneity between the 7 studies that reported the frequency of bowel movement (I2 +AD0- 80+ACU-, p +ACY-lt+ADs- 0.00001). Besides, five studies compared CHM with western medicine

and reported the recurrence rate showed the treatment for functional constipation was no sign in favor of CHM.+ACY-nbsp+ADsAPA-br /+AD4-Our study found that CHM treatment of FC significantly improved physical symptoms, including constipation-related symptoms (abdominal distension, reduced bowel frequency, difficulty defecating) and systemic symptoms (dry mouth, insomnia, and dyspepsia), compared to Western medicine or placebo. Similar findings have been found in related studies +AFs-110,111+AF0-: they found that herbal medicine can produce synergistic therapeutic effects, such as spasmolysis, tonifying, wind-repelling, anti-inflammatory, and local analgesia. We believe that TCM can effectively address the challenge of simultaneously addressing multiple symptoms other than constipation faced by Western medicine in the treatment of FC.+ADw-br /+AD4-The normal frequency of defecation is 3 to 21 times per week +AFs-112,113+AF0-. A recent meta-analysis showed that osmotic and irritant laxatives increased stool frequency by 2.5 times per week in patients with FC +AFs-114+AF0-. Our study found that CHM had a significant effect compared with PEG (MD 0.83, 95+ACU-CI 0.67-0.98, p +ACY-lt+ADs- 0.0006). However, six studies were included in this meta-analysis, and significant heterogeneity between studies (I2 +AD0- 87+ACU-, p +ACY-lt+ADs- 0.00001). The strong conclusion that CHM improves defecation frequency needs to be validated by more high-quality studies. At the same time, we found that many current RCTs recorded stool frequency, but translated into effective results at the time of reporting. This leads to a lack of detailed data on stool frequency. Our study, therefore, suggests that similar future studies should report detailed stool frequency and compare them to baseline, such as Zhong et al. Despite beneficial findings from meta-analyses, the results of these trials should be interpreted with caution due to the generally low methodological quality of the included studies. Although only RCTs were included, with insufficient information on how the random allocation was generated and/ or concealed in most studies, it was uncertain about selection bias. Secondly, considering clinical efficacy was a subjective index, it could introduce performance bias and detection bias without blinding participants, healthcare providers, and assessors. Thirdly, missing data due to attrition

or exclusions was found in some studies, but only a few handled it appropriately. Finally, protocols were not available to confirm free of selective reporting. For all these reasons, further validation of the findings is necessary. Besides, longer follow-up (12 wk) is necessary taking the placebo effect into account For the safety of CHM, adverse effects were reported, such as abdominal pain or bloating, nausea, stomach discomfort, diarrhea, and passing of gas. But there were only (12/ 97) of studies mentioned the safety of interventions or the AEs investigated as one of the main outcome indicators. In addition, many traditional Chinese medicines have been widely used by Chinese traditional medicine practitioners for nearly two millennia. This supports their security. Therefore, more attention should be paid to record and report the harmful effects of these interventions.

We searched main English and Chinese databases under well-designed searching strategies and made the comparison between CHM and different WM therapies more clear. There are several limitations to this systematic review. Firstly, missing articles that might be relevant. Although we searched through databases and did not limit the language of the article, we may still miss relevant articles in regional journals. Because the articles published in these regional magazines are not included in the database we searched. Secondly, most of the studies we included were published only in Chinese, which limited readers' review of the original research. This situation may be improved with the worldwide promotion of CHM. Thirdly, the studies we included were all conducted in the Asian region, so the extrapolation of these results is limited by geography.

CONCLUSION

In conclusion, in this meta-analysis, we found that CHM may have potential benefits in increasing the number of bowel movements, improving stool characteristics, and alleviating global symptoms in FC patients. However, a firm conclusion could not be reached because of the poor quality of the included trials. Well-designed and high-quality reported RCTs are needed to confirm more definitive conclusions in the future.

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