ZX Bian 卞兆祥
CW Cheng 鄭頌華
LZ Zhu 朱力行

Chinese herbal medicine for functional constipation: a randomised controlled trial

Key Messages

1. This was an 18-week prospective, randomised, double-blind, placebo-controlled clinical study on a Chinese herbal medicine—MaZiRenWan (MZRW)—for the treatment of functional constipation.
2. 120 subjects with functional constipation (Rome III criteria) were randomised (60 per arm) into the MZRW and placebo groups. Respective responder rates for the two groups were 43.3% and 8.3% during treatment, and 30.0% and 15.0% in the follow-up period ($p<0.05$). The MZRW group was superior to the placebo group in terms of increased complete spontaneous bowel movement as well as reduction in severity of constipation, straining at evacuation, and use of rescue therapy. No serious adverse effects were reported.
3. The dose of MZRW (7.5 g bid) was determined in a separate clinical trial. This study entailed a dose determination study and then a placebo-controlled clinical trial and can be a good reference for future studies.

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Hong Kong Baptist University: School of Chinese Medicine
ZX Bian, CW Cheng
Department of Mathematics, Faculty of Science
LZ Zhu

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Principal applicant and corresponding author:
Prof Bian Zhao-xiang
Clinical Division, 1/F, Jockey Club School of Chinese Medicine Building, 7 Baptist University Road, Kowloon Tong, Hong Kong SAR, China
Tel: (852) 3411 2905
Fax: (852) 3411 2929
Email: bzxiang@hkbu.edu.hk

Introduction

Constipation is a common gastrointestinal complaint, and Chinese herbal medicine has become a popular alternative treatment for it.[1,2] MaZiRenWan (MZRW) is composed of *Fructus Cannabis, Radix et Rhizoma Rhei, Radix Paeoniae Alba, Semen Armeniacae Amarum, Fructus Aurantii Immaturus*, and *Cortex Magnoliae Officinalis*. It was first recorded in a Chinese medicine classic—*Discussion of Cold-induced Disorders*—for the treatment of constipation. Current available evidence cannot confirm whether MZRW is effective for functional constipation.[3] This study aimed to determine the efficacy and safety of MZRW for the treatment of functional constipation in Excessive Syndrome (a disease/disorder presentation in Chinese medicine theory).

Methods

This study was conducted from September 2007 to August 2009. An 18-week, prospective, randomised, double-blind, placebo-controlled clinical trial was performed. It entailed 2 weeks of run-in, followed by 8 weeks of treatment, and 8 weeks of follow-up. Patients aged 18 to 65 years with functional constipation in Excessive Syndrome were recruited. Diagnosis of functional constipation was based on Rome III criteria,[4] whereas the diagnosis of Excessive Syndrome was based on the Chinese medicine theory. Participants were required to maintain a diary, in which details of bowel movements, improvement in related symptoms, and/or any adverse effects were recorded. This study was in accordance with the Declaration of Helsinki and approved by the Committee on the Use of Human & Animal Subjects in Teaching and Research of the Hong Kong Baptist University. All patients gave their informed consent and were free to withdraw at any time.

Both MZRW and placebo granules were prepared by PuraPharm International (HK) Limited. The entire manufacturing process was in compliance with the standards of Good Manufacturing Practice. Granules were packed in sealed opaque aluminium sachets and put in a zip lock bag (28 sachets per bag). Only the treatment code and lot number were printed outside the package to ensure successful blinding.

Participants recorded in a diary their stool frequency, stool form, feeling of complete evacuation (yes/no), and the intake of MZRW/placebo granules, rescue drug, or any other medication. They were interviewed at the end of weeks 2, 6, 10, and 18. A 7-point ordinal scale (0=not at all, 6=very severe) was used to measure individual's constipation and related symptoms. Global symptom improvement (improved, same, worse) was defined as a subjective feeling of adequate relief of their symptoms after medication. The primary end point was complete spontaneous bowel movement (CSBM). Participants with a mean increase of CSBM ≥1/week were defined as responders. The safety profiles of MZRW were assessed based on adverse events and clinical laboratory evaluations. The success of blinding was evaluated for both the investigator and patients in the last visit.

In a previous dose determination study, the responder rate of MZRW (7.5 g bid) was 53.1%, and a difference in resolution rate of at least 30% between MZRW and placebo was considered clinically significant.[5] Therefore, 60 patients per

group were needed to achieve 80% power at a significance level of 0.025 and 15% drop-out rate. Analysis was based on an intention to treat. Missing values were imputed by the last observation carried forward method. Continuous variables were calculated with Student's *t*-test, whereas the Chi-square test was used for categorical data. All statistical tests were two-sided, and a P value of <0.05 was considered statistically significant.

Results

Of 456 patients screened, 120 were randomised into MZRW (n=60) or placebo (n=60) group (Fig). The baseline variables of the two groups were comparable. Of the 120 patients, 17 (9 from MZRW group and 8 from placebo group) withdrew from the study. The mean number of CSBM per week increased from 0.33 (95% confidence interval [CI], 0.16-0.49) to 1.62 (95% CI, 1.11-2.13) in MZRW group and from 0.52 (95% CI, 0.34-0.69) to 0.72 (95% CI, 0.44-1.00) in placebo group during treatment (P=0.003, Table 1). The responder rates were 43.3% in MZRW group and 8.3% in placebo group (P<0.001, Table 2).

An increase from baseline in the overall number of bowel movements and CSBMs per week was noted in both groups during treatment (weeks 3-10). A sustained increment in the frequency of CSBMs during the follow-up period (weeks 11-18) was noted (Table 1). The responder rates in the follow-up period for the MZRW and placebo groups were 30.0% and 15.0%, respectively (P=0.049, Table 2). Patients receiving MZRW took less rescue drug during and after treatment, compared to baseline values (P<0.05, Table 1).

Compared with the baseline period (weeks 0-2), improvement in the global symptom at week 6 (during treatment), week 10 (end of treatment), and week 18 (end of follow-up) were 81.7%, 80.0%, and 50.0% for the MZRW group, and 46.7%, 53.3%, and 51.7% for the placebo group, respectively. In contrast, five participants in the MZRW group and 11 in the placebo group reported worse symptoms. The scores of individual symptom assessments (including severity of constipation, sensation of straining, incomplete evacuation, sensation of bloating, sensation of abdominal pain/cramping, nausea and passing of gas) were generally lower than at baseline.

Of the 109 participants who attended the last follow-up, 44% correctly guessed the groups they were allocated to, compared with 63.3% by the study investigator. For the 16 subjects who received placebo and made correct guesses, the factors on appearance, colour, texture, taste, and efficacy of the placebo (that did not look like true Chinese herbal medicine) were also determined.

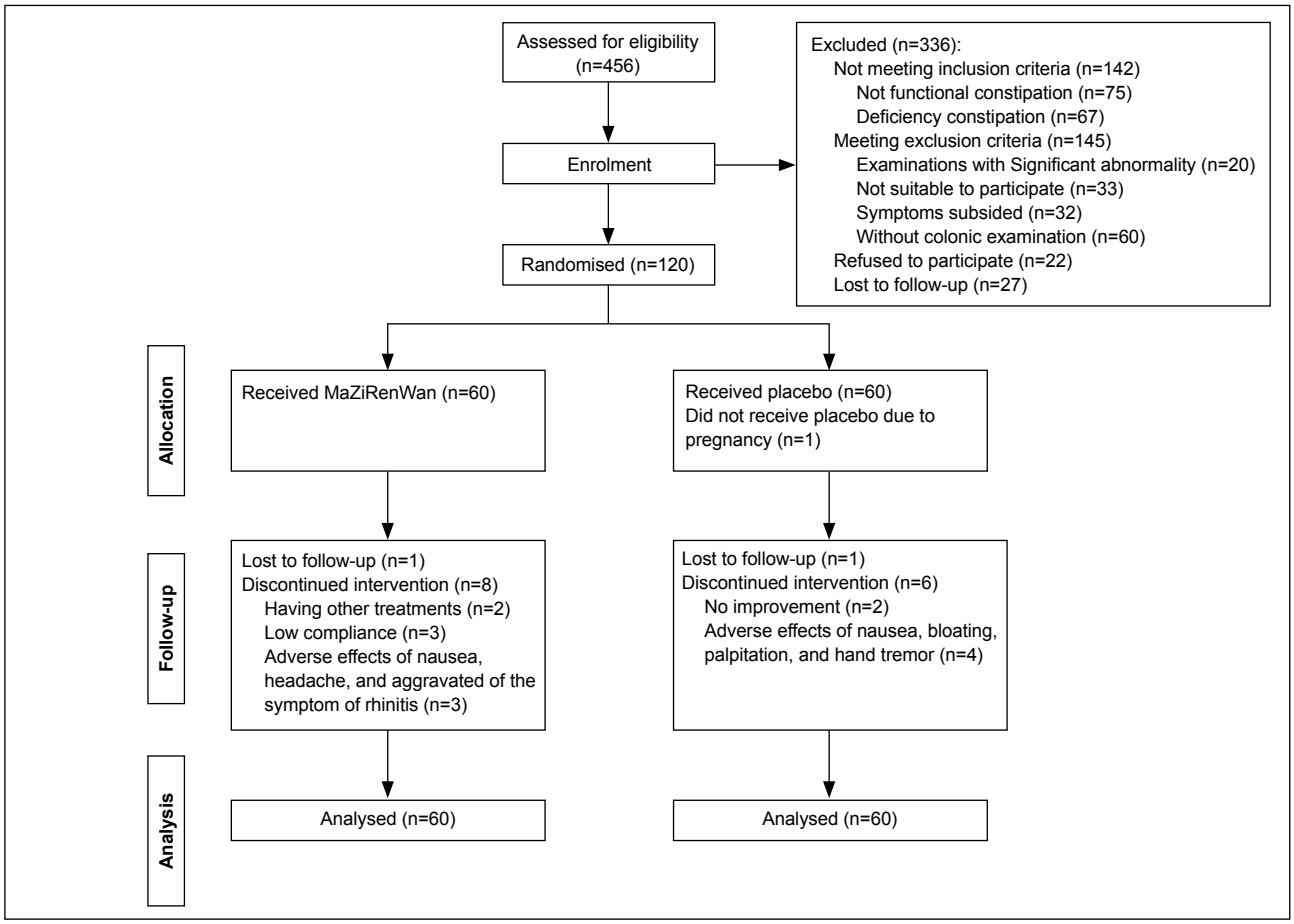

Fig. Flow chart of participants during different stages

Table 1. Comparison of the treatment effects between and within groups

Outcome measure	MaZiRenWan (7.5 g bid) [n=60]	Placebo (7.5 g bid) [n=60]	P value		
			Between groups	Within MaZiRenWan	Within placebo
Mean (95% CI) no. of days taking rescue therapy/week					
Baseline (weeks 1-2)	0.93 (0.59-1.27)	0.84 (0.54-1.14)	0.686	Ref	Ref
Treatment (weeks 3-10)	0.39 (0.18-0.60)	1.10 (0.73-1.47)	0.001	<0.001	0.033
Follow-up (weeks 11-18)	0.68 (0.41-0.95)	1.10 (0.68-1.53)	0.097	0.094	0.088
Mean (95% CI) no. of bowel movement/week					
Baseline (weeks 1-2)	2.79 (2.47-3.12)	3.31 (2.89-3.72)	0.052	Ref	Ref
Treatment (weeks 3-10)	4.72 (4.11-5.33)	3.73 (3.33-4.13)	0.008	<0.001	0.021
Follow-up (weeks 11-18)	3.65 (3.08-4.23)	3.61 (3.20-4.03)	0.902	0.002	0.111
Mean (95% CI) no. of complete spontaneous bowel movement/week					
Baseline (weeks 1-2)	0.33 (0.16-0.49)	0.52 (0.34-0.69)	0.121	Ref	Ref
Treatment (weeks 3-10)	1.62 (1.11-2.13)	0.72 (0.44-1.00)	0.003	<0.001	0.035
Follow-up (weeks 11-18)	1.06 (0.62-1.49)	0.75 (0.44-1.05)	0.246	0.001	0.040

Table 2. Comparison of responder rates during treatment and follow-up periods

Period	Responder rate (% of patients experienced an increase of ≥1 complete spontaneous bowel movement/week compared with baseline)		P value
	MaZiRenWan	Placebo	
Treatment (weeks 3-10)	43.3	8.3	<0.001
Follow-up (weeks 11-18)	30.0%	15.0%	0.049

Most patients tolerated the medication well and no serious adverse effect was noted. There was no impairment of liver or renal function. In all, 11 and 7 patients in the MZRW and placebo groups, respectively, experienced at least one adverse effect (eg abdominal bloating/pain and nausea).

Discussion

During treatment, compared to those taking placebo, patients taking MZRW experienced increased CSBMs as well as reduction in the severity of constipation, straining at evacuation, and use of rescue therapy. Moreover, there were sustainable significant benefits for the MZRW group in terms of responder rates during the follow-up period (P=0.049), although same trend could not be confirmed for global and individual symptom assessments.

By evaluating the feedback from patients and the investigator, correct guesses for MZRW and placebo groups were 59.3% and 29.1% in the patients and 77.8% and 49.1% in the investigator, respectively. Correctly identifying the placebo regimen was less than natural probability (chance). Thus, the blinding process in this study was successful.

Adverse effects affecting the lower gastrointestinal tract (abdominal pain/cramping, bloating, diarrhoea, and passing gas) were more common in the MZRW than placebo group (13.3% vs 3.3%). Such side effects are common among laxatives and may be related to the active compound chrysophanol in *Radix et Rhizoma Rhei*, one of the herbal components of MZRW.

This study addressed the theme of "treatment derived from syndrome differentiation" according to the traditional Chinese medicine theory. In addition, it included a dose determination study and a placebo-controlled clinical trial. Proper dosage is an important prerequisite to determine the efficacy and safety of an intervention; selection based on clinical experience alone may not be optimal. Therefore, it is necessary to explore the optimal dose using a robust method, and then determine the efficacy and safety of an intervention in a separate placebo-controlled trial.

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