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Original Article

Whether Syndrome Differentiation Affects Treatment Result: Study Protocol of MaZiRenWan (麻子仁丸) for Functional Constipation in A Randomized Controlled Trial*

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ABSTRACT **Background**: Syndrome is one of the most important concepts in Chinese medicine (CM) theory. However, it was not well accounted in most of randomized controlled trials (RCTs). **Objective**: To determine whether CM syndrome differentiation affects the treatment results, functional constipation (FC) was selected as a target disease, and MaZiRenWan (麻子仁丸, MZRW), a classic CM formula commonly used for constipation with excessive heat syndrome, was selected for study. **Methods**: It is an 18-week prospective double-blinded, double-dummy RCT, including 2-week run-in, 8-week treatment and 8-week post treatment follow-up. A total of 120 FC patients diagnosed as excessive heat syndrome will be recruited from the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine and the Baokang Affiliated Hospital of Tianjin University of Traditional Chinese Medicine. Patients will be randomly allocated into fixed MZRW (f_MZRW) granule group, modified MZRW (m_MZRW) granule group or bisacodyl group. For m_MZRW group, no more than two herbal granules can be added according to the syndrome differentiation for individual participants. The primary end point is the mean of complete spontaneous bowel movements (CSBMs) per week during the treatment period. Secondary end points include mean of CSBMs per week during follow-up, stool form, global symptom improvement, constipation and constipation-related symptoms assessment, CM syndrome change, and reported adverse events. **Discussion**: This trial is designed to evaluate the effectiveness of these three interventions for FC patients with the CM syndrome of excessive heat, and to determine the change of CM syndrome and the progress of disease during the treatment course. The results are important to explore whether syndrome differentiation is important for the therapeutic effect of a formula on a disease. [Trial registration: Chinese Clinical Trial Registry (Reg No. ChiCTR-TRC-13003742); protocol version: MZRW/NSFC-81173363 (2015.05.04)]

KEYWORDS functional constipation, Chinese herbal medicine, syndrome differentiation, MaZiRenWan, randomized controlled trial

Well designed and properly implemented randomized controlled trials (RCTs) are believed as the most reliable evidence on the efficacy and safety of healthcare interventions.[1] From the first RCT on Chinese medicine (CM) published in 1982,[2] the number of related publications increases greatly.[3] However, the debate on whether the explanatory setting of RCT is appropriate for assessing the benefits and harms of CM intervention has never been stopped.[4-6]

According to CM theory, syndrome (also called pattern) is a dynamic concept, which is the summary of the cause, nature, and location of the pathological change at a certain stage of disease.[7] It is the

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groundwork for making individualized diagnosis, prescription and prognosis. Therefore, patients with same kind of syndrome can be treated with same method even though they are with different diseases. Conversely, patients with same disease will be treated with different method if they are in different syndromes. For example, constipation can be characterized into the syndromes of excess heat, pathological accumulation of qi, insufficient fluid lubrication or lack of propulsion power from the deficiency of qi or yang.[8] The former two belong to excessive constipation, for which constipation is relieved by removing the heat and redirecting the flow of qi stagnation. The latter three belong to deficient syndrome, for which constipation is relieved by replenishing the deficiency and moistening the dryness. Undoubtedly, the prescriptions of these primary syndromes are different. In addition, some changeable secondary syndromes also exist with them. Therefore, how to introduce the idea of syndrome differentiation into clinical study design is a big conundrum. Our research team has conducted a RCT for functional constipation (FC), and found that MaZiRenWan (麻子仁丸, MZRW) is safe and effective for alleviating FC by comparing with placebo for patients in excessive syndrome.[9] Although syndrome was well considered when screening for the eligible, the treatment protocol and the interventions were no longer modified during the whole study. How do the syndromes and the nature of disease change among the individuals and within the groups? Are they synchronous? How do these changes affect the outcome assessment? These questions have not been well investigated.

In this study, 120 FC patients with excessive heat syndrome will be randomly allocated, with 1:1:1 ratio, into fixed MZRW (f_MZRW) group, modified MZRW (m_MZRW) group or bisacodyl group. First, the effectiveness of these three interventions for FC patients with syndrome of excessive heat will be evaluated. Subsequently, the change of CM syndrome and the severity of disease during the treatment will be determined. We would also try to evaluate the correlation between treatment effectiveness for disease and that for CM syndrome. The results are important to evaluate the change of syndrome in the treatment and importance of CM syndrome differentiation in treatment.

METHODS

Study Design

It is an 18-week prospective double-blinded, double-dummy RCT, including 2-week run-in (Week–2–Week0), 8-week treatment (Week0–Week8) and 8-week post-treatment follow-up (Week8–Week16). Ethical approval has been granted by the Ethics Committees of Tianjin University of Traditional Chinese Medicine (Approval No. TJUTCM-EC20130003), while the study protocol has been registered at Chinese Clinical Trial Registry (Reg No. ChiCTR-TRC-13003742). The presentation of current protocol is adherence to Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) in order to enhance the transparency and completeness.

Diagnostic Criteria

Diagnosis of FC is on the basis of Rome Ⅲ criteria: (1) two or more of following occurrences for at least 25% of defecations: straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual maneuvers to facilitate, or fewer than 3 defecations per week; (2) rare presence of loose stools without the use of laxatives; and (3) insufficient criteria for irritable bowel syndrome.[10] Excessive heat syndrome of constipation are diagnosed with any 4 from 6 chief symptom manifestations: (1) dry and hard stools, (2) abdominal bloating, (3) abdominal pain, (4) dry mouth or halitosis, (5) red tongue with yellow coating, and (6) rapid or slippery pulse.[11-13]

Inclusion and Exclusion Criteria

Patients will give their written, informed consent and only be recruited who report all of the followings: (1) ⩽3 complete spontaneous bowel movements (CSBMs) per week (CSBM defined as feeling that defecation leads to complete passage of stool but without the use of a laxative or enema within 24 h); (2) normal colonic examination (barium enema or colonoscopy) within 12 months; and (3) normal liver and renal function within 3 months. On the contrary, patients will be excluded with any of the followings: (1) secondary constipation (e.g. drug-induced constipation, constipation after abdominal surgery); (2) severe organic diseases; (3) history of CM allergy; (4) women in pregnant or lactating; or (5) psychiatric patients. Patients who fail to complete the bowel diary record or constipation cannot be confirmed within the run-in period will also be excluded.

Participants

All in- or out-patients with FC (aged 18–65

years) from the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine (China) or the Baokang Affiliated Hospital of Tianjin University of Traditional Chinese Medicine (China) will be referred for this study. Besides, open recruitment will be made by organizing press conference, putting posters in clinics and publishing advisements in newspapers.

Study Process

During the 2-week run-in period, all patients need to complete a bowl diary to record their daily stool and symptom in order to confirm their diagnosis and eligibility. Then the eligibles will randomly assigned to f_MZRW group, m_MZRW group or bisacodyl group at Week0 for 8-week treatment (Figure 1). Participants are required to maintain the diary in which they record the details of bowel movement and/or any adverse event (AE) detected, and extra 5 visits will be arranged for outcome assessment. Syndrome differentiation and treatment modification will be made for all participants during the visits at Week0, 2, 4 and 6, and the treatment modification for the adjustment of formulation will be based on the dosage and increasing the additional two herbs based on syndrome differentiation. Three phone calls will be made for following the cases at Week10, 12 and 14. Routine blood test, urine test, stool test and biochemical test [aspartate transaminase (AST), alanine transaminase (ALT), blood urea nitrogen (BUN), creatinine (Cr)] will be carried out before and after treatments. The schedule of enrolment, interventions and assessments is shown in Appendix 1.

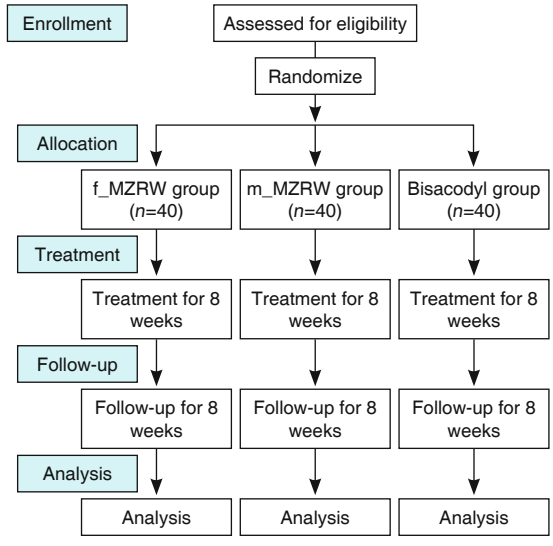

Figure 1. Flow Diagram of Selection and Evaluation of Functional Constipation Patients

Assignment and Masking

Stratified block randomization on research centers will be carried out in 1:1:1 ratio. Two sets of randomization sequence table will be generated by an independent statistical research staff by using SAS 9.1 Software. The research medication is packed according to the randomization sequence, while one set of randomization sequence table are stored in clinical in-charge unit for decoding, if applicable. Randomization table (without blind decoding information) kept in sealed opaque envelopes will be used for patient enrolment. Research assistant (RA) is responsible to contact with patients while clinical investigator (CI) is responsible to differentiate the CM syndromes of patients and make the modification of MZRW interventions. RA, CI and patients are blinded in the whole study. Therefore, treatment assignments will not be revealed until the termination of the whole study. The flowchart depicting the selection and evaluation of participants is shown in Figure 1.

Interventions

The composition and daily dosage of each herbal granule in MZRW are reference to our previous dose determination study and placebo-controlled study[9] as followings: *Cannabis Fructus* 21.6 g, *Rhei Radix et Rhizoma* 10.8 g, *Armeniacae Semen Amarum* 10.8 g, *Paeoniae Radix Albo* 5.4 g, *Magnoliae Officinalis Cortex* 6.6 g and *Aurantii Fructus Immaturus* 5.4 g. Through the combined action of these herbs, MZRW can drain heat, moisten the intestine, promote the movement of qi, and unblock the bowel.[9] For m_MZRW group, no more than 2 out of 10 herbal granules can be added according to the syndrome differentiation for individual participants. These 10 herbs for secondary CM syndrome are selected after thorough discussion among our research team with gastroenterological experts. They are *Pseudostellariae Radix* 15 g and *Atractylodis Macrocephalae Rhizoma* 15 g for deficiency of qi, *Ophiopogon Japonicas* 15 g and *Rehmanniae Radix* 10 g for fluid depletion, *Gardeniae Fructus* 10 g and *Scutellariae Radix* 10 g for excessive of fire, *Sophorae Flos* 15 g and *Sanguisorbae Radix* 15 g for hemorrhoid bleeding, *Arecae Pericarprim* 10 g and *Citri Sarcodactylis Fructus* 10 g for severe abdominal bloating. The compositions and actions of MZRW and each additional herb are summarized in Appendixes 2 and 3, respectively.[14,15] The placebos of MZRW and individual herbs for modification are made from 2% of granules and 98% of dextrin to

Chin J Integr Med 2019 Mar;25(3):175-181

achieve color, smell, taste and texture comparable to those of herbal granules. MZRW, additional herbs for modification and their placebos are prepared by the Beijing Kangrentang Pharmaceutical Co. Ltd. (China) in strict compliance with the standards of Chinese Pharmacopoeia and Good Manufacturing Practice. They are packed in sealed opaque aluminum sachets and placed in a ziplock bag (28 sachets each). Only the name of research project, names of medications and lot numbers are printed on the packets. None of RA, CI and participants can identify the true medications and matching placebo to ensure successful of blinding. Participants will be instructed to dissolve the granules in 150 mL of hot water, and take this solution orally, twice daily for 8 weeks.

The active control is bisacodyl, which is an effective and safe stimulant laxative commonly prescribed in routine practice.[16] It can stimulate colonic secretion and induce powerful and propulsive motor activity. The bisacodyl, 5 mg sugar-coated tablets, is manufactured by the German Company Boehringer Ingelheim and repacked in bottle (28 tablets each) by the Guangzhou Huahai Pharmaceutical Co. Ltd. (China). The matching placebo tablets are also prepared by the Guangzhou Huahai Pharmaceutical Co. Ltd. to achieve color, shape, size and packing comparable to those of bisacodyl. Participants will be instructed to take 2 tablets orally, once daily before bed time for 8 weeks.

After 2-week run-in, patients who meet all the inclusion criteria will be randomly assigned to one of the following three groups. Participants in f_MZRW group will receive MZRW granule, herbal placebo granule and bisacodyl placebo, while m_MZRW group will receive MZRW granule, herbal granule and bisacodyl placebo, and bisacodyl group will receive MZRW placebo granule, herbal placebo granule and bisacodyl. Rescue enemas, to ensure a bowel movement, will be allowed only to participants who do not have a bowel movement for 3 or more consecutive days during the study.

Main Outcome Measures

Participants need to record their bowel movement, including frequency, feeling in complete evacuation, form with Bristol stool scale (ranging from "separate hard lumps" to "watery"),[17] consumption of research medication or use of rescue enema throughout the study in the bowel diary. Investigators will interview participants at Week0 (baseline), Week2/4/6/8 (treatment), and Week16 (follow-up) for symptoms, compliance, differentiation of syndromes, and occurrence of AEs. Data on global symptom improvement, constipation-related symptoms assessment, CM syndrome change will also be collected.

Global symptom improvement is the subjective feeling of patients on adequate relief of symptoms. Participants will be asked "During past 7 days, do you have adequate relief of constipation when comparing with your baseline (Week0)? (0=markedly worse to 6=markedly better). Individual assessment of constipation and related symptoms, including sensation of straining, incomplete evacuation, abdominal bloating and abdominal pain, will be recorded using a 7-point ordinal scale recommended by Rome Ⅲ (0=not at all to 6=very severe). The overall constipation assessment is the sum of all individual constipation-related symptoms of each visit, which will be compared with their baseline. CM symptom change assessment is on the basis of the 6 chief symptom manifestations of excessive heat constipation. The ratings of each item are: (1) stool type on Bristol Stool Scale (type 1=6 points, type 2=4 points; type 3=2 points; other=0 point); (2) abdominal bloating (no=0 point to very severe=6 points); (3) abdominal pain (no=0 points to very severe=6 points); (4) abnormal taste (dry mouth=3 points; halitosis=3 points; other=0 point); (5) diagnosis of tongue (red tongue=3 points; yellow coating=3 points; other=0 point); and (6) diagnosis of pulse (slippery pulse=3 points, rapid pulse=3 points, other=0 point). Maximum point for each item is 6 points, while the total is 36 points.

The primary end point is the mean of CSBMs per week during the treatment period. It is a clinically meaningful end point by combining an objective measure (stool frequency) with a subjective measure (feelings of completeness of defecation).[9] By comparing the mean of CSBMs between the groups, the effectiveness of treatments targeting on CM syndrome (f_MZRW group), conventional disease (bisacodyl group) and dynamicity of CM syndrome (m_MZRW group) can be determined. Secondary end points include mean of CSBMs per week during follow-up, mean of bowel movements frequency per week during treatment and follow-up, stool form, global symptom improvement, constipation and constipation-related symptoms assessment and use of rescue enema. Furthermore, CM syndrome and its change

during treatment and follow-up will also be evaluated. The results are important evidences to account the role of CM syndrome in modern clinical researches.

For the safety issue, any occurrence of AE during the study will be recorded. Further statistical analysis and implementation of safety evaluation will also be made. For every AE, we will record in detailed and judge the time of occurrence, symptoms, lasting time, severity, management measures and time of disappearance. The principle investigator (PI) will make the decision whether termination of study is necessary. Further medical treatment or referral to the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine or the Baokang Affiliated Hospital of Tianjin University of Traditional Chinese Medicine will be arranged. For severe cases, the investigators will also report to the Clinical Research Centre of the Tianjin University of Traditional Chinese Medicine within 24 h.

Sample Size Determination and Statistical Analysis

This is a novel design for evaluating the significance of syndrome differentiation in outcome assessment, 120 patients (40 patients for each arm) will be recruited as a pilot study. Statistical analysis will be performed using the SPSS software on the intention-to-treat population, while missing values will be imputed by the last-observation-carried-forward methods. Mean of CSBMs per week, the constipation-related symptoms, global symptom assessment and stool type will be analyzed using *t*-test or chi-square test. Incidence of AEs within the groups will also be evaluated using the chi-square test.

Personnel Training and Data Management

Data Monitoring Committee is established and led by the PI. Co-investigators (Co-I) are responsible to monitor the quality, accuracy and completeness of all data collected periodically. Changes to important protocol modifications will be reported to the Ethics Committees of the Tianjin University of Traditional Chinese Medicine. On-spot training will also be provided to all research personnel.

Online data collecting system will be set up by using Statistical Package for Social Sciences Programme, and all data entry must be completed within 2 days of each patient visit. RA will be responsible for the management of the data and the system to ensure the authenticity and accuracy of research data. All computer files are anonymous and identified with a unique subject code, while the completed questionnaires and diaries will be kept in a locked cabinet inside research centres. Only PI, Co-I and RA have rights to check the documents. All research data will be kept for 2 years after the results are published and not less than 3 years after completion of whole study. The data will then be destroyed.

Handling of Withdraw and Dropout

This is an 18-week clinical trial, each subject needs to take 8 weeks research medication, 7 regular visits, 2 blood tests, fills in a few set questionnaires, completes patient diary for the entire study period. For maximizing subjects' compliances, first, we have a thorough consent process for all participants by explaining the details of the study schedule, potential AEs of treatment, the responsibilities the subjects needed to take and together with the support and reassurance during the whole study. Second, we have a careful scrutiny (2-week run-in period) to exclude ineligible and low compliance subjects before randomization. Third, direct telephone hotlines equipping with this clinical trial are ways for the study team to actively communicate with patients and reply enquiries. Moreover, extra-visits will be arranged if patients develop AEs before the next scheduled visit. If any patient has thoughts of withdrawing or dropping out, research team will ask the reason to find solution in order to keep the patient in the study.

Termination Criteria

Trial will be terminated in specific subject if he/she has: (1) presence of severe AE; (2) hypersensitivity towards research medication; (3) participation in another research project; (4) presence of life-threatening disease. The whole research plan will be terminated for following circumstances: (1) presence of serious AE related to the research medication with supportive evidence; (2) completion of all follow-up assessments.

DISCUSSION

Syndrome is a complicated concept. Patients can suffer from 2 or more kinds of disease at a time, while more than 1 kind of syndromes can be showed in a disease.[18] Therefore, there is a long disputation about the applicability of RCT for evaluating the effectiveness of CM interventions with

the intricacies of syndromes. The opposition parties believe that individuals even with same disease are not homogenous.[5,6,18-23] Hence, RCTs with fixed CM interventions are difficult to reflect the efficacy of CM. Even for those individualized pragmatic RCTs, as the treatments have so many variations, the studies are not easy to be replicated by other researchers and the evidence produced may not be applied on clinical practice directly. Therefore, RCT is not applicable for evaluating the efficacy of CM. On the contrary, the favor parties believe that syndrome differentiation can account for the commonality from group of individuals.[21] As the RCT can manifest the causality effect for conventional intervention, it can also assess the efficacy of CM intervention in the same important value. Both positive and negative points of views seem to have their merits.

We agree that each disease itself include a variety of CM syndromes, while these syndromes are constantly changing on nature or extent. Theoretically, the efficacy of an intervention can be assessed against its effect on both disease and/or syndrome. However, most of current studies only evaluate the effects of intervention in term of disease. It may be because the efficacy of intervention on disease is easier to be understood and interpreted, while that on syndrome is just put forward in recent years. Furthermore, the consensus about how syndrome being diagnosed and measured has not yet been obtained.[24] All these factors yield many clinical trials with diversified results and impede the development of evidence-based medicine on CM.

In this study, we try to account for the effect of MZRW on FC (disease in conventional medicine) with major symptoms of excessive heat (syndrome on CM). The f_MZRW group with fix MZRW granules targets on disease and the initial syndrome of participants. The m_MZRW group with MZRW granules and available for further modification according to the change of syndrome targets on both disease and syndrome throughout the study. It is more comparable to normal clinical practice on CM. The bisacodyl group with registered bisacodyl tablet targets only on disease. By observing the therapeutic effects of f_MZRW and bisacodyl groups, the results can elucidate the impact on therapeutic effect for interventions considering the conventional disease but not the syndrome. By comparing f_MZRW group with m_MZRW group, the influence on the effectiveness for having modification according to syndrome or not can be determined under the RCT design.

The methodological limitation of this study may include small sample size. As it is a pilot study to investigate the role of syndrome in a RCT by comparing with fixed CM intervention, modified CM intervention and conventional intervention, 120 patients (40 patients per arm) are recruited without sample size calculation. The results obtained may not have enough power to detect statistical significance. For better control the internal validity and success of blinding, every modification of m_MZRW group is restricted to the addition of 2 herbs with preset dosage. Therefore, the quality of each single herb and its tailor-made placebo can be well controlled. Besides, placebo group is not included in this project to titrate the effect or tolerance of interventions. It is because the efficacy and safety of MZRW have been justified by comparing with placebo control in our previous study.[9] Therefore, we focus on studying the role of CM syndrome by introducing the groups of f_MZRW, m_MZRW and bisacodyl in the current study. However, all these interventions have their matching placebos to allow blinding and randomization.

The experience from this study is important to explore a feasible method for the combination of syndrome differentiation and RCT, and develop a scientific assessment measure for CM interventions.

Trial Status

The recruitment of participants has been finished in mid-2016.

Conflict of Interest

The authors declare that they have no competing interests. The funding agency has no role in the design and execution of this project. It will not be involved to the analysis and interpretation of data, or make decision to submit the results.

Author Contributions

All authors participate in the design of the study. Zhang L, Zhong LD and Cheng CW draft the manuscript. Bian ZX and Shang HC supervise and coordinate the clinical trial. Shi LJ and Chen J participate in outcomes assessment. Zhang L, Zhao C and Zheng R are responsible for recruiting the participants. Dai L and Kun W are responsible for data entry. Li G and Zhai JB participate in randomization and statistical analysis. Lu AP gives

critical review. All authors read and approve the final manuscript.

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