Review 述评

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·Improving the quality of randomized controlled trials in Chinese herbal medicine, part : control group design

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ABSTRACT   Objective: To discuss the types of control groups in randomized controlled trials (RCTs) of Chinese herbal medicine (CHM), and to provide suggestions for improving the design of control group in future clinical studies in this therapeutic area . Methods: A search of the Cochrane Library was conducted in July 2005 to identify RCTs of CHM, and 66 RCTs with CHM for type 2 diabetes mellitus were obtained as the basis for further analysis . Results: Of 66 RCTs with CHM for type 2 diabetes mellitus, 61 (92 .4%) trials had both a treatment group and a control group . Twenty-seven (40 .9%) RCTs compared CHM plus conventional drug

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vs conventional drug, 24 (36 .4%) compared CHM vs conventional drug, 5 (7 .6%) compared CHM vs placebo, 3 (4 .5%) compared CHM plus conventional drug vs conventional drug plus placebo, 3 (4 .5%) compared CHM plus conventional drug vs other CHM, 1 (1 .5%) compared CHM vs no treatment, 1 (1 .5%) compared CHM plus placebo vs conventional drug plus placebo, 1 (1 5%) compared CHM vs CHM plus conventional drug vs conventional drug vs placebo, and 1 (1 5%) compared CHM vs conventional drug vs CHM plus conventional drug . **Conclusion:** A variety of control groups were used in RCTs of CHM for type 2 diabetes mellitus, including placebo, active, and no treatment control groups . Justification for selecting particular types of control groups were not provided in the trials reviewed in this study . Different control groups may be appropriate according to the study objectives, and several factors should be considered prior to selecting control groups in future RCTs of CHM . **Recommendations:** (1) Investigators of CHM who design clinical trials should understand the rationale for selecting different types of control groups; (2) Control groups for RCTs should be selected according to study objectives; (3) Active control groups should select interventions for comparisons that have the strongest evidence of efficacy and prescribe them as recommended; (4) Placebo control groups should select a placebo that mimics the physical characteristics of test intervention as closely as possible and is completely inert; (5) No treatment control groups should only be used when withholding treatment is ethical and objectives outcomes will not be subject to bias due to absent blinding; (6) Crossover control groups may be appropriate in chronic and stable conditions .

KEY WORDS   randomized controlled trial; Chinese herbal medicine; methodology; quality assessment; control group

1   INTRODUCTION

In this second part of our four-part series on assessing the methodological quality of randomized controlled trials (RCTs) in Chinese herbal medicine (CHM), we discuss the issue of control groups .

The concept of using a comparison group in CHM practice appeared about 900 years ago in the Chinese medicine literature, as reported in the Atlas of Materia Medica (Bencao Tujing), originally published in 1061[1] . A trial with two participants testing the efficacy of ginseng found that the participant who did not consume ginseng appeared short of breath sooner than his counterpart who did take ginseng . However, most of the studies in CHM have traditionally evaluated efficacy based on observational studies comparing symptoms in the same patients before and after treatment, not comparing changes in symptoms with other treatment or control groups . The use of RCTs in medicine is relatively recent . The first RCT began in 1946 and was conducted to test the efficacy of immunization against whooping cough[2] . Since the results of that study were not reported until 1951, the first published RCT was in fact organized by D'Arcy Hart and Daniels to examine the efficacy of streptomycin for treating pulmonary tuberculosis[3] . In CHM, the first RCT was reported in 1983 to examine the effects of Buxux Harlandii on coronary heart disease[4] . Numerous RCTs of CHM have been conducted and published in the past two decades .

The principal aim of RCTs is to evaluate the efficacy and/ or safety of a particular intervention . For this purpose, investigators should select a control group as a basis for comparing the intervention to determine whether it is superior, equal, or inferior to alternatives, depending on the objectives of their study . Thus, the proper use and design of a control group is pivotal for evaluating the efficacy of an intervention in a RCT . The main reason for which a control group is required is to control alternative factors that may explain the observations made regarding the intervention examined in the treatment group . In RCTs for examining conventional pharmaceutical products, for example, the control group is often given inert pills, tablets, capsules, etc ., that are similar in size and color to the active intervention . Alternatively, the control group in RCTs may receive nothing at all, or even an alternative active intervention . Designing a control group for a particular RCT can be quite challenging, especially in CHM .

An important requirement for RCTs is that the treatment and control groups should be similar with

regard to baseline characteristics[5] . This is ensured by proper randomization technique (i .e . sequence generation, allocation concealment, etc .), and blinding of participants, investigators, and observers . Ideally, the only difference between the treatment and control groups in RCTs would be the presence or absence of the active intervention being examined . Without these design attributes, RCTs cannot adequately determine the efficacy of a intervention tested .

Given the importance of control groups in RCTs, this topic was examined in CHM . Hence, the primary aim of our research was to review the types of control groups used in RCTs of CHM, and provide recommendations for improving the types of control groups in RCTs of CHM in the future .

2 MATERIALS AND METHODS

2 .1 Trials

The search strategy used in this study was reported previously[6] . Briefly, the Cochrane Library Database of Systematic Reviews in July 2005 was searched, yielding 11 systematic reviews about CHM, which collectively reported on 167 RCTs . The most common indication for these RCTs was type 2 diabetes mellitus . This subgroup was select-

ed for further assessment and full-text reports were obtained through electronic and hand searching[7] .

2 .2 Data extraction and analysis

Two observers (Zhao-Xiang BIAN, Jiang-Xia MIAO) reviewed the type and composition of control groups in RCTs in each report independently . All disagreements were resolved through discussion and further verification of the original articles . In all cases, consensus between the two observers was achieved before analyses were done . The data from two reviewers were entered into an Excel file for analysis .

3 RESULTS

Of the 66 RCTs of CHM for type 2 diabetes mellitus reviewed, 61 (92 .4%) had two study groups; 4 (6 .0%) had three study groups, and 1 (1 .5%) had four study groups . Nine types of control groups were used in these 66 RCTs . The most common design (n = 27) compared CHM plus conventional drug vs conventional drug . Over 90 .9% (n = 60) of RCTs included a study group that received a conventional drug, while only 9 .9% (n = 6) of RCTs compared CHM solely to placebo or no treatment (Table 1) .

Table 1   Types of control groups in RCTs of CHM for type 2 diabetes mellitus

Study design	Quantity of RCTs (%)
CHM + conventional drug vs conventional drug	27 (40 .9%)
CHM vs conventional drug	24 (36 .4%)
CHM vs placebo	5 (7 .6%)
CHM + conventional drug vs placebo + conventional drug	3 (4 .5%)
CHM vs conventional drug vs other CHM	3 (4 .5%)
CHM vs no treatment	1 (1 .5%)
CHM + placebo vs conventional drug + placebo	1 (1 .5%)
CHM vs CHM + conventional drug vs conventional drug vs placebo	1 (1 .5%)
CHM vs conventional drug vs CHM + conventional drug	1 (1 .5%)
Total	66 (100%)

Of the 10 RCTs that used a placebo, 3 (30%) used leaves from non-medicinal plants, 4 (40%) used starch, and 1 (10%) used distilled water plus vitamin B₂ . None provided an explanation for choosing these agents as the placebo, and no statements were made about whether these ingredients were in fact inert . Studies comparing CHM to conventional drugs as a control group used drugs such as metformin, gliclazide, glibenclamide, glybenzoylamide, insulin, glipizide, and tolbutamide, in various dosages and treatment regimens . In studies self-identified as having a no-treatment control group, patients did in fact receive an intervention in the

form of counseling for dietary and lifestyle modifications .

4 DISCUSSION

Our review of control groups used in RCTs of CHM for type 2 diabetes mellitus reported that there were three main categories of control groups: (1) placebo intervention; (2) active intervention; and (3) no treatment . Several studies reported more than one type of control group, though the explanation for such a choice was not often made clear . Since each type of control group is appropriate in some circumstances, but none is usable or ad-

equate in every situation, providing a scientific rationale is very helpful to help readers determine whether a RCT selected an appropriate control group . A brief summary of common types of control groups is provided as below .

4 .1   Placebo control group

In placebo-controlled RCTs, participants are randomly assigned to a test intervention or placebo group in order to control for four points: (1) the natural history of the disease; (2) the placebo effect; (3) the observer effect; and (4) other potential influences . Changes in clinical outcomes measured in the treatment group may be due to the natural progression of the disease rather than the intervention . If this were the case, similar outcomes would be observed in the control group, nullifying changes that may otherwise have been attributed to the intervention with a placebo absent .

The placebo effect has also been the topic of great discussion in clinical research for decades[5,8,9] . This effect is based on the notion that participants given an intervention, whether active or inactive, tend to report changes in outcome measures simply from having received something and believing that it was helpful . This effect is believed to play an important role in many complementary and alternative medicine (CAM) therapies where patients receive multiple interventions, each of which may exert a placebo effect . The observer effect—also known as the Hawthorne effect—postulates that simply enrolling in a clinical study could influence the outcomes measured as participants alter their behavior because they are being observed . This may encourage those in clinical trials, for example, to modify their behavior to please the examiner at their next study visit . Results could then falsely be attributed to the test intervention with a placebo absent .

Although RCTs are designed to examine the effects of specific interventions, investigators may unwittingly introduce co-interventions that may influence the outcomes themselves . An example of this could be that participants in both the treatment and control group in a clinical trial on back pain could receive benefit from simply lying in a prone position for an extended period of time prior being seen by the investigator to receive the intended intervention or placebo . A properly designed placebo control group would help isolate the effects of the intervention being examined and minimize confounding and bias due to the above effects .

Three critical issues for placebo-controlled studies are: (1) placebo design; (2) potential activity of placebo; and (3) ethical issues . It is essential that a placebo should be identical in appearance, odor, texture, and taste to the test intervention . In practice, it is difficult for investigators to design such a placebo, especially in CHM where products have a distinct color, smell, taste, etc ., linked to the nature of their ingredients . Even when a seemingly appropriate placebo is developed in RCTs, measures must be developed to conceal allocation and minimize communication among participants in different groups that could reveal differences between the placebo and test intervention and help identify the true intervention .

Placebo design is an art as well as a science, and the results of this review indicate that more experience is necessary to develop appropriate placebos for RCTs of CHM . It is essential that these placebos be inert, which may not have been the case in the 7 RCTs where leaves from other plants and 1 RCT where vitamin B_2 was used as the placebo, both of which may have been active . Any activity due to the placebo will affect the relative efficacy of the intervention, whether positively or negatively . In addition, investigators who select an active placebo with beneficial effects will need to enroll more participants into their study to increase the statistical power to detect a smaller difference than expected between the intervention and control groups .

Numerous ethical issues must be considered prior to designing a RCT using a placebo . This type of control group must be acceptable to both participants and investigators . The Helsinki Declaration recommends against the use of placebos in clinical studies if an effective treatment is known and available[10] , and this position is supported by numerous other groups[8,9] . However, if there are no effective therapies available for the condition of interest, or available therapies have unacceptable levels of toxicity or adverse events, there are fewer ethical concerns with a placebo control group[11] . Additional considerations are given to using a placebo for stable, chronic conditions with mild symptoms, where no adverse events are expected from delayed treatment .

Given the slow, progressive onset and nature of type 2 diabetes mellitus, for example, it is generally deemed acceptable to use a placebo in RCTs during the initial stages of the disease . For more advanced cases of diabetes where uncontrolled blood sugar carries the risk of serious adverse events, or for participants with serious co-morbidities, it is not appropriate to use a placebo in RCTs since such

a design cannot meet the" principle of uncertainty "[12] . According to Freedman, this principle states" the ethics of clinical research requires equipoise, a state of genuine uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in the trial"[5] . In such cases, investigators wishing to evaluate the efficacy of interventions may choose to administer them in addition to the standard of care to determine whether any additional benefits are observed . One of the weaknesses noted in RCTs of CHM was that no details were provided as to the clinical staging of study participants (i .e .early or late, mild or severe, etc .) , making it impossible to examine these important ethical issues in evaluating use of a specific control group .

4 .2　Active control group

In other instances, investigators may prefer to compare a test intervention to an established intervention rather than to a placebo . This can be done when withholding treatment to a control group is unethical, or for equivalency trials to determine whether the efficacy of the test intervention is comparable to a more widely used intervention . Therefore, when investigators decide to choose an active control design, it is necessary for them to determine whether: (1) the evidence to support the efficacy of the active intervention is sufficiently robust[13] ; (2) the condition to be studied is an appropriate indication for the active intervention; (3) the proposed dose and treatment regimen is appropriate for the active intervention; and (4) the patients are likely to adhere to intervention instructions[14] . Without these considerations, an active intervention control group is not suitable and may bias trial results .

Based on our review, the main shortcomings of RCTs with active control groups were: (1) there was no strong evidence that the active controls were effective; (2) active controls were not used with an appropriate dose and treatment regimen; and (3) there was no monitoring of participant compliance to the treatment regimen . For example, Diamicron —a very common drug for patients with type 2 diabetes mellitus—was used as an active control in many RCTs of CHM[7] . However, studies prescribed different doses and treatment regimens with no explanation and no monitoring of participant compliance . Another RCT that used an active intervention control chose a licensed CHM intervention that is not a standard treatment for type 2 diabetes mellitus and without strong evidence to support its efficacy .

Another observation on the RCTs of CHM for type 2 diabetes mellitus with active control was that most were designed as open label studies, whereby participants were aware of the intervention they were receiving . This has been reported to affect the results of clinical trials[14] . To avoid this bias, double blinding the participants and investigators is highly recommended . The difficulty with such a design in CHM is designing appropriate placebos to interventions with known physical characteristics (e .g . odor, appearance) . In these situations, a double dummy design may be useful . This method calls for participants in both the control and intervention groups to receive a placebo in addition to a placebo or active intervention . For example, participants receiving an active decoction for which a placebo is unavailable would also receive a placebo tablet . Conversely, participants in the control group would receive that same placebo tablet in addition to an inert tea or capsule, which would then not need to be physically identical to the decoction . Participants in both groups would then be blinded as to which of the two interventions they received was active or placebo . Any differences observed between the active and control groups would then be attributed to the intervention of interest rather the placebo tablet given to both groups .

With regard to the compliance of patients in trials, a challenge exists not only in the active control group, but also in the placebo group . The 1994 report of the Task Force for compliance showed that participants frequently deviated from the prescribed treatment regimen in clinical trials, thereby decreasing their efficacy[15] . Efforts to improve or to facilitate adherence of people with type 2 diabetes to treatment recommendations did not show significant effects[16] . Thus, if patients do not adhere to the treatment regimen in a RCT, this may bias its results compared to the control group .

4 .3　No treatment control

In RCTs with a no treatment control group, participants are randomly assigned to a test intervention or no intervention . The main difference between this study design and a placebo-controlled trial is that neither the participants nor the investigators are blinded to allocation . Such a design is reasonable only when: (1) it is very difficult to double-blind to an intervention, and/ or (2) there is enough confidence that study endpoints are objective and will therefore not be influenced by the lack of blinding . These RCTs must be mindful of the

same ethical considerations as those that apply to a placebo control group .

4 .4 Multiple controls

Studies with multiple control groups, combining active control, placebo control, and or no treatment control, are increasingly common in RCTs . The considerations for selecting this type of control are the same as those outlined for each type of control group discussed above . However, investigators must consider the consequences of this study design . These include the need to enroll more participants in each group in order to maintain appropriate statistical power, as well as the need for additional study personnel training to implement a more complex protocol . This design entails the need to screen and recruit additional participants, provide additional resources for investigator training and interventions, allow for a longer trial time, more data collection and analysis, etc . Investigators should carefully weigh pros and cons in this scenario .

4 .5 Crossover control

None of the RCTs of CHM we reviewed used a crossover control, in which participants are randomly allocated to placebo or test intervention, then discontinue that intervention to minimize carryover effects (termed a washout period), and then receive placebo if they first received test intervention or test intervention if they first received placebo . Participants thus serve as their own controls, which minimizes sample sizes and resources . This design is best used in stable, chronic conditions, and may have been appropriate for some of the RCTs of CHM for type 2 diabetes .

5 LIMITATIONS

The main limitation of this study is that results are applicable only to those RCTs of CHM for type 2 diabetes mellitus identified for quality assessment . Though these studies are believed to be form a representative sample of RCTs of CHM, results may not be applicable to all RCTs of CHM .

6 CONCLUSION

Several types of control groups were used in RCTs of CHM, including placebo, active, no treatment, and supplementary intervention . Reasons for selecting particular control groups were not stated . Additional considerations must be given to the consequences of selecting specific control groups in future RCTs of CHM to ensure compliance with scientific validity, respect ethical concerns, and minimize bias .

7 RECOMMENDATIONS

To improve the quality of control group design in RCTs of CHM, we recommend as below .

(1) Investigators of CHM who design clinical trials should understand the rationale for selecting different types of control groups, as discussed briefly in this review .

(2) Investigators should select the type of control group for RCTs according to study objectives . For example, equivalence studies should select an appropriate and commonly used alternative to the intervention being tested .

(3) Studies designed with an active control group should select interventions for comparisons that have the strongest evidence of efficacy and prescribe them as recommended . This helps to ensure that the comparison is justified and valid .

(4) Studies designed with a placebo control groups should select a placebo that mimics the physical characteristics of test intervention as closely as possible and is completely inert . This helps minimize confounding and bias that may result from participants and clinicians being aware of group allocation, as well as any effects attributable to the placebo .

(5) Studies designed with a no treatment control group should only be used when withholding treatment is ethical and objectives outcomes will not be subject to bias due to absent blinding .

(6) Studies designed with a crossover control groups may be appropriate in chronic and stable conditions that are unlikely to undergo rapid clinical changes between the intervention, washout, and placebo periods .

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