

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Chronic Coronary Syndrom Patients: Study Protocol for a Randomized Controlled Trial
AUTHORS	Ma, Jing; Zhang, Jian; Li, Hua; Zhao, Lian; Guo, Ai; Chen, Zai; Yuan, Wen; Gao, Tian; Li, Ya; Li, Cui; Wang, Hong; Song, Bo; Lu, Yu; Cui, Mei; Wei, Qiu; Lyu, Shao; Yin, Heng;

VERSION 1 – REVIEW

REVIEWER	Mao Chen West China Hospital, Sichuan University
REVIEW RETURNED	15-Jan-2020

GENERAL COMMENTS	<p>This is an interesting topic in the field of CHD treatment. The study protocol is well designed and carefully considered. the investigators performed lots of preparatory work. i think it will inform a vital body of work. However, several suggestions i wanted to provided were as follows:</p> <ol style="list-style-type: none">1, the study included only patients with stable angina pectoris and excluded AMI, so the protocol title should be more specific for stable CHD.2, the study planned to include patients with NYHA III, i am afraid how many patients can complete the TCCRP.3, Meanwhile, it will be better to highlights the strength of the TCCRP and simply explain why the TCCRP is suitable for CHD.4, The study protocol does not provide rationale of the sample size estimation. Why does it plan to recruit 150 CHD patients?
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REVIEWER	Arthur de Sá Ferreira Centro Universitário Augusto Motta/UNISUAM, Brazil
REVIEW RETURNED	25-Jan-2020

GENERAL COMMENTS	<p>Introduction</p> <ol style="list-style-type: none">1. The sentence "The coordinated movement of Tai Chi postures, namely "Stirring up Dantian", "Yi-Qi Cooperation", "Spiral Silk Reeling" and "Qi Flowing to Four Tips (hair, tongue, teeth and bone)" can promote the channeling of Qi and blood to nourish the body, resist diseases and promotes immunity" needs revision. TCM professionals might be able to interpret it in the traditional context, but for those not trained in Chinese medicine theory using terms such as "blood" and "diseases" could be misleading. Please rephrase to explain that these terms are applicable in the context of TCM theory. <p>Exclusion criteria</p>
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	<p>2. This exclusion criterion is unclear: "Patients with nervous system deterioration, motor system disease, or rheumatic disease caused by combined exercise". What is meant by "rheumatic disease caused by combined exercise"?</p> <p>Randomization, allocation concealment and blinding</p> <p>3. The sample size calculation is not reported. What is the expected effect size for each of the two primary endpoints?</p> <p>TCCRP pre-phase: a 2-week exercise before the start of exercise</p> <p>4. Mastery will be determined by professional coaches. How mastery will be assessed and quantified?</p> <p>Secondary outcome measures</p> <p>5. The balance test mainly includes standing on one foot with eyes closed, standing on one foot with eyes open, standing in situ with closed eyes and so on. What variables will be evaluated for this Romberg-like test? Time until falling or losing balance? A Yes/No answer for a 10s standing period in each condition?</p> <p>Statistical analysis</p> <p>6. The first two sentences need revision. They seem connected to the same information but they are separated.</p> <p>7. The CONSORT statement advocates against the statistical comparison of groups at baseline provided that if differences are detected they are due to the randomization. Even in an exploratory analysis, there is no mention of whether the differences would be considered as confounders in subsequent analysis.</p> <p>8. Please confirm the imputation method that will be used for intention-to-treat analysis.</p> <p>Discussion</p> <p>9. The sentence "that balances the Yin and Yang in the body, promotes blood circulation and Qi for maximizing both physical and mental well-being" also needs revision according to my comment #1. TCM professionals might be able to interpret it in the traditional context, but for those not trained in Chinese medicine theory using terms such as "blood" and "diseases" could be misleading. Please rephrase to explain that these terms are applicable in the context of TCM theory.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer #1: Prof. Mao Chen

1. Response to comment: the study included only patients with stable angina pectoris and excluded AMI, so the protocol title should be more specific for stable CHD.

Response: Thanks a lot for your kind advice. We are very sorry for not defining the inclusion criteria clearly. Actually we included both stable angina pectoris and old myocardial infarction patients. Furthermore we excluded the AMI patients within 2 weeks. Therefore regarding the reviewer's advice and the latest ESC guideline published in 2019, we used the concept of "chronic coronary syndrome", and revised the protocol title as "Safety and Effectiveness of a TaiChi-based Cardiac Rehabilitation Program for Patients with Chronic Coronary Syndrome: Study Protocol for a Randomized Controlled Trial".

References:

1. Juhani Knuuti, William Wijns, Antti Saraste, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes: The Task Force for the diagnosis and management of

chronic coronary syndromes of the European Society of Cardiology (ESC). *Eur Heart J*, 2020;41(3):407-477.

We have marked in red according to the Reviewer's suggestion.

2. Response to comment: the study planned to include patients with NYHA III, i am afraid how many patients can complete the TCCRP.

Response: Thanks a lot for your kind suggestion. We have revised the inclusion criteria and removed NYHA III.

We have marked in red according to the Reviewer's suggestion.

3. Response to comment: Meanwhile, it will be better to highlights the strength of the TCCRP and simply explain why the TCCRP is suitable for CHD.

Response: Thank you for your good advice. We had described and added the detailed reason in the discussion part as the reviewer suggested as followed:

This trial is the first one to compare the safety, feasibility and benefits of TCCRP and CER in CCS patients. There are several strengths of our trial: Firstly, the proposed research study is unique and the first study about a Bafa Wubu of Tai Chi which is a new Tai Chi school. Secondly, TCCRP in this study was specifically designed for patients with CCS. Finally, this is the first time for Tai Chi study to develop a comparative training system to match the conventional exercise. Our study will supply scientific evidence for the promotion of Bafa Wubu of Tai Chi at home and abroad.

TCCRP has some features which make it more suitable for CCS patients. Firstly, the intensity of TCCRP is low, and it is much safer for patients with CCS. Secondly, TCCRP is much easier to be learned and possesses a simple structure of movements, a reasonable number of postures, and fewer practice environment limitations. Thirdly, TCCRP is not limited by location and easy to be carried out. Finally, TCCRP doesn't need money or any equipment. To sum up, compared with conventional exercise rehabilitation (CER), TCCRP is more suitable for CCS.

We have added the detailed reason in the discussion part as the reviewer suggested.

Special thanks to Prof. Chen for his good comments.

4. Response to comment: The study protocol does not provide rationale of the sample size estimation. Why does it plan to recruit 150 CHD patients?

Response: We are very sorry for our negligence of sample size calculation.

Sample size calculation will be based on the co-primary outcomes of the RCT. The SF-36 Health Survey (SF-36) and Chinese Perceived Stress Scale (CPSS) are being set as the co-primary outcome and used for sample size calculation. Sample size was calculated on the basis of the changes in the SF-36 and CPSS between comparison groups with a significance level of 5% and a two-tailed critical region to ensure the same effect size with 80% power by G*power V.3.1.9.4 software. The means and their SDs (mean \pm SD) of the SF-36 and CPSS in the control and intervention group were (64.30 \pm 13.11, 71.79 \pm 16.03)² and (42.31 \pm 8.17, 35.15 \pm 6.82)³, respectively, at postintervention according to the published literature. Because the sample size calculation of CPSS was less than SF-36, the sample size calculation of SF-36 was selected. This would require 122 participants, inflated to about 150 to account for the loss to follow-up of approximately 20% of participants, with 75 participants being assigned to each group.

2. Salvetti XM, Oliveira JA, Servantes DM, et al. How much do the benefits cost? Effects of a home-based training programme on cardiovascular fitness, quality of life, programme cost and adherence for patients with coronary disease. *Clin Rehabil*, 2008. 22(10-11):987-96.

3. Zhe Xu. Study on the perioperative nursing practice of TCM auricular compression combined with mindfulness meditation training in patients with colorectal cancer. *J Liaoning Univ Tradit Chin Med*, 2020.22(02):218-220

We have added the sample size calculation in the Methods/Design part as the reviewer suggested.

We'd like to express our special thanks to Prof. Chen for his careful revision and valuable advice.

Reviewer #2: Prof. Arthur de Sá Ferreira

1. Response to comment:

Introduction

1. The sentence "The coordinated movement of Tai Chi postures, namely "Stirring up Dantian", "Yi-Qi Cooperation", "Spiral Silk Reeling" and "Qi Flowing to Four Tips (hair, tongue, teeth and bone)" can promote the channeling of Qi and blood to nourish the body, resist diseases and promotes immunity" needs revision. TCM professionals might be able to interpret it in the traditional context, but for those not trained in Chinese medicine theory using terms such as "blood" and "diseases" could be misleading. Please rephrase to explain that these terms are applicable in the context of TCM theory. Response: Thanks a lot for your kind advice. It is really true as the reviewer suggested. People who don't have been trained in Chinese medicine theory, would get confused about the different terms. Therefore, we rephrase to explain the sentence. "Xing", "Qi" and "Yi" are scientific terms specially in Tai Chi field, whose meaning are similar to "body", "breath" and "mind". Tai Chi exercise contains three core elements, namely "body", "breath" and "mind", as pronounced in Chinese as "Xing", "Qi", "Yi" respectively. The spirits of Tai Chi are summarized to "building the body", "conveying the breath" and "using the mind".

We have revised the sentence in introduction part as marked in red.

2. Response to comment:

Exclusion criteria

2. This exclusion criterion is unclear: "Patients with nervous system deterioration, motor system disease, or rheumatic disease caused by combined exercise". What is meant by "rheumatic disease caused by combined exercise"?

Response: We are very sorry for the misunderstanding caused by our translation mistake. The sentence should be "Patients with abnormal motor function caused by nervous system deterioration, motor system disease or rheumatic disease".

We have revised the sentence in exclusion criteria part as marked in red.

3. Response to comment:

Randomization, allocation concealment and blinding

3. The sample size calculation is not reported. What is the expected effect size for each of the two primary endpoints?

Response: We are very sorry for our negligence of sample size calculation. As we answered just now. Sample size calculation will be based on the co-primary outcomes of the RCT. The SF-36 Health Survey (SF-36) and Chinese Perceived Stress Scale (CPSS) are being set as the co-primary outcome and used for sample size calculation. Sample size was calculated on the basis of the changes in the SF-36 and CPSS between comparison groups with a significance level of 5% and a two-tailed critical region to ensure the same effect size with 80% power by G*power V.3.1.9.4 software. The means and their SDs (mean \pm SD) of the SF-36 and CPSS in the control and intervention group were (64.30 \pm 13.11, 71.79 \pm 16.03)² and (42.31 \pm 8.17, 35.15 \pm 6.82)³, respectively, at postintervention according to the published literature. Because the sample size calculation of CPSS was less than SF-36, the sample size calculation of SF-36 was selected. This would require 122 participants, inflated to about 150 to account for the loss to follow-up of approximately 20% of participants, with 75 participants being assigned to each group.

2. Salvetti XM, Oliveira JA, Servantes DM, et al. How much do the benefits cost? Effects of a home-based training programme on cardiovascular fitness, quality of life, programme cost and adherence for patients with coronary disease. Clin Rehabil, 2008. 22(10-11):987-96.

3. Zhe Xu. Study on the perioperative nursing practice of TCM auricular compression combined with mindfulness meditation training in patients with colorectal cancer. J Liaoning Univ Tradit Chin

The expected effect size for each of the two primary endpoints is 80% power. We have added the sample size calculation in the Methods/Design part as the reviewer suggested.

4. Response to comment:

TCCRP pre-phase: a 2-week exercise before the start of exercise

4. Mastery will be determined by professional coaches. How mastery will be assessed and quantified?

Response: Thank you for your productive question. It is important for us to describe clearly the detailed teaching and trial process. The mastery of Tai Chi was assessed and quantified due to the following 6 factors: the body shape should keep straight and upright; the gravity center shift is right; the action moves in an order; moving speed has a sense of rhythm; action and movement contains wring and screwing; every set consumes similar time. We have constructed a testing committee including 10 Tai Chi experts who had discussed together and summerized a scoring criteria concerning the above 6 dimensions. Six professional coaches with more than 10 years of Tai Chi teaching experiences were trained about the scoring system and then coached the subjects. At the end of learning stage, 3 of coaches were chosen randomly to work as the examiner. The professional coaches scored on a percentile basis according to the above 6 dimensions. Only the participants who gained an average score higher than 80 would be certificated to be qualified and move on the to the trial step. In order to increase the quality of teaching and objectivity of judgment, professional coaches have grown from three to six who have 10 years of teaching experience.

We have also added these parts in the method part.

5. Response to comment:

Secondary outcome measures

5. The balance test mainly includes standing on one foot with eyes closed, standing on one foot with eyes open, standing in situ with closed eyes and so on. What variables will be evaluated for this Romberg-like test? Time until falling or losing balance? A Yes/No answer for a 10s standing period in each condition?

Response: Thank you for your concern. We are interested in whether TCCRP and CER have differential effect on the time difference keeping balance between before and after treatment. We used the time duration until losing balance as the evaluating variable. In our study, we respectively investigated the time duration of standing on one foot with eyes closed, standing on one foot with eyes open, strengthening Romberg's test.⁴ The participants were tested three times to record their time until they lost their balance. Finally, the best of the three was selected. Time difference were calculated as the time duration after treatment minus that before treatment.

4. Yonghao You, Ailing Wen. Human balance assessment method. Chin J Rehabil Med 2014;29(11):1099-1104.

We have also added these parts in secondary outcome measures part as marked in red.

6. Response to comment:

Statistical analysis

6. The first two sentences need revision. They seem connected to the same information but they are separated.

Response: Thanks a lot for your kind advice. Continuous variables will be described as mean \pm standard deviation (SD) for normal distributions or median for non-normal distributions, categorical variables will be described as frequency.

We have revised the sentence in statistical analysis part as marked in red.

7. Response to comment:

7. The CONSORT statement advocates against the statistical comparison of groups at baseline provided that if differences are detected they are due to the randomization. Even in an exploratory

analysis, there is no mention of whether the differences would be considered as confounders in subsequent analysis.

Response: We are very sorry that the statistical analysis was not clearly described.

Baseline data mainly describe the clinical characteristic and features of the subjects. We also tested the equalization of the two groups of variables. Continuous variables will be described as a two-sample Student's t-test for normal distributions or Wilcoxon test for non-normal distributions.

Categorical variables will be described as the chi-square test.

The group difference between intervention and control group at each time point (4 and 12 weeks after intervention or 12-week follow-up period) will be analyzed using Student's t-test or Mann-Whitney U-test. A two-way analysis of variance with repeated measures will be used to determine the effects of time and group on our dependent variables. A Bonferroni-adjusted post hoc analysis will be conducted when time-group interaction was detected.

We have revised this part in statistical analysis part as marked in red.

Response to comment:

8. Please confirm the imputation method that will be used for intention-to-treat analysis.

Response: Thanks a lot. The analysis of primary or secondary outcomes will be based on an intention to treat (ITT) principle, and participants who either drop out from the study or fail to adhere to the protocol will have their last known data carried forward. The missing data will be imputed using a multiple imputation method.

We have revised this part in statistical analysis part as marked in red.

9. Response to comment:

Discussion

9. The sentence "that balances the Yin and Yang in the body, promotes blood circulation and Qi for maximizing both physical and mental well-being" also needs revision according to my comment #1. TCM professionals might be able to interpret it in the traditional context, but for those not trained in Chinese medicine theory using terms such as "blood" and "diseases" could be misleading. Please rephrase to explain that these terms are applicable in the context of TCM theory.

Response: Thanks a lot for your kind advice. We have rephrased to explain the sentence. Tai Chi typically involves a mind-body integration practice that combines the coordination of slow movements with mental focus, deep breathing, and relaxation for promoting both physical and mental well-being. We are so happy to have such excellent advice from Prof. Arthur de Sá Ferreira. Thanks a lot for his precious time and helpful revision.

Another revision:

1. We made some rearrangement in the strengths and limitations of the study part to make it more concise.
2. We made some rearrangement in the introduction part to make it more fluent.
3. We cancelled some sentence in the discussion to emphasize the strength of our study.
4. We increased professional coaches from three to six who have 10 years of teaching experience to increase the quality of teaching and objectivity of judgment.
5. We shorten the "Patient and Public Involvement" to make it more refining.
6. We added the key word "chronic coronary syndrom" in the article.

VERSION 2 – REVIEW

REVIEWER	Arthur de Sá Ferreira Centro Universitário Augusto Motta/UNISUAM, Brazil
REVIEW RETURNED	20-Feb-2020

GENERAL COMMENTS	Thank you for your revision. The manuscript is improved from the original version. I have no further comments.
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VERSION 2 – AUTHOR RESPONSE

Reviewer #2: Prof. Arthur de Sá Ferreira

Response to comment: Please state any competing interests or state 'None declared': None declare.

Response: Thanks a lot for your kind suggestion. We have added the "None declared" in the "Competing interests" part as the reviewer suggested.

We'd like to express our special thanks to Prof. Arthur de Sá Ferreira for his careful revision and valuable advice.

During the submission and revision of our manuscript, we have experienced the warmest help and most precious advice from the editors and reviewers. Thank you so much for the great effort of all of you.

We sincerely hope you happy and healthy in the special time.