Author’s response to reviews

Title: The efficacy and safety of Shenzhu Guanxin Recipe Granules for treatment of patients with coronary artery disease: protocol for a double-blind, randomized controlled trial

Authors:

xiao jin (449189625@qq.com)
Huanlin Wu (wuhuanlinboshi@aliyun.com)
Bingxin Wu (catherine90522@163.com)
Yukai Li (936128751@qq.com)
Xia Wang (594362038@qq.com)
Guoqing Liu (LiuGQ01@hotmail.com)
Xiaojing Dang (catherine90@126.com)
Danping Xu (xudanping@hotmail.com)

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Responses to Reviewers

RE: TRLS-D-19-00162, entitled “The efficacy and safety of Shenzhu Guanxin Recipe Granules for treatment of patients with coronary artery disease: protocol for a double-blind, randomized controlled trial“

Dear Editor,

We would first like to thank you and the reviewers for your kind letter and professional advice concerning our article (Manuscript No. TRLS-D-19-00162). This advice was valuable and helpful in improving our article. All authors have seriously discussed the review and opinions on the article and based on these reviews, we have modified our manuscript to meet the requirements of your journal. In this revised version of the manuscript, changes to our manuscript are presented in red text. Point-by-point responses to the reviewers are listed below.
Reviewer reports:

There some concerns need to be addressed:

1) Would you please provide some details about the pilot study you have used to calculate sample size. It is mandatory to cite your pilot study as a reference in "sample size calculation" part. In addition, you need to provide some clarification that why you have considered 10% decrease in calcification score as a clinically significant effect of intervention.

Response:

Thank you for pointing this out. The revision has been modified to include a detailed discussion on sample size calculation. In response, we made the following changes in the determination of the sample size, which are presented on page 5, lines 14-24.

Firstly, the reason that we consider 10% decrease as the clinically significant effect size is because a coverage probability of 90% for the confidence interval in the case of bioequivalence studies has become the accepted standard when evaluating whether the average values of the pharmacokinetic parameters of two formulations are sufficiently close1. Thus, the 95% CI of the difference in the group means within the interval of -10 to +10% was defined as clinical equivalence in the current study.

Secondly, to calculate the sample size we employed the “pwr.t.test” function in R package “pwr” 2 (R package version 1.2-2. https://CRAN.R-project.org/package=pwr). As an example, say we want to be able to detect a difference of at least 6.2 in the mean CCS (about 10% decreases in CCS) with a common standard deviation of the two groups to be 10. Therefore our effect size is 6.2/10 = 0.62 according to Cohen (1988) 3. For a desired power of 80%, Type I error tolerance of 0.05, and a hypothesized effect size of 0.62, we should sample at least 84 participants per group, i.e., a total of 168 participants. If assuming there will be a dropout rate of 15% within 6 months, then 194 participants can eventually be recruited.

2) There is a similar protocol in the literature "Chin J Integr Med. 2019 Feb;25(2):96-102". What is the difference between current protocol and published protocol, since both of them are from the same institution?

Response

Thank you for your question.

Our study is completely different from the protocol in the literature "Chin J Integr Med. 2019 Feb;25(2):96-102", even though they are from the same institution. In fact, they were two different studies and completely different.

First, the protocol published in the literature "Chin J Integr Med was designed to determine the effects of Shenzhu Guanxin Recipe Granules (SGR) on exercise duration, electrocardiographic (ECG) evidence of myocardial ischemia, and incidence of major adverse cardiac events (MACE) in stable anginal patients. The inclusion Criteria mainly included: (1) stable coronary artery disease (CAD) confirmed by coronary angiography, a positive stress echocardiography showing regional wall motion abnormalities at least 3 months before inclusion according to American College of Cardiology/American Heart Association guidelines; (2) repeatable ischemic ST-segment depression of at least 1 mm and limited exercise capacity on treadmill testing (3–9 min on a modified Bruce protocol);(3) Chinese medicine syndrome of phlegm and blood stasis due to qi deficiency;

The endpoints of the protocol published in the literature "Chin J Integr Med" mainly included:

1. Change from baseline in total treadmill exercise duration, time to angina onset and time to 1 mm ST segment depression after 12 weeks of treatment.

2. Change from baseline in maximum ST-segment depression and maximal workload during exercise treadmill. 4. testing performed over a 12-week study period.5. Echocardiographic cardiac function and NT-proBNP.6. Incidence of MACE.7. Seattle Angina Questionnaire scores. 8. NYHA functional classification .9. Coronary microcirculation assessment (in selected centers only)

However, our study was designed to evaluate the clinical effectiveness and safety of SGR therapy for patients with CAD by clinical manifestations and examinations, in which coronary computed tomography angiography (CCTA) showed 50-70% of stenosis, with soft or mixed plaque. The inclusion Criteria of our study mainly included: (1) patients had been diagnosed with CAD by clinical manifestations and examinations, and CCTA showed 50-70% of coronary atherosclerotic stenosis, with soft plaque or mixed plaque; (2) the patients did not undergo PCI surgery and coronary artery bypass grafting (CABG); (3) Phlegm and blood stasis syndrome (PBSS) due to syndrome of qi deficiency.
The endpoints of our study mainly included: Coronary artery calcification score, Change of area of non-calcified plaque, and the proportion of non-calcified plaques to total plaques, Concentration of gene ABCA1 and TNF-α, IL-1, IL-6, Level of serum lipids, Level of high sensitivity C-Reactive protein (CRP), Seattle Angina Questionnaire (SAQ) score, Change of Traditional Chinese Medicine (TCM) syndrome, Evaluation of occurrence and composite of major adverse cardiac events (MACE).

Above all, our study was completely different from the protocol published in the literature “Chin J Integr Med. 2019 Feb;25(2):96-102”.”