Tropical Journal of Pharmaceutical Research May 2022; 21 (5): 1125-1134
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v21i5.30

Original Research Article

Traditional Chinese medicine combined with conventional treatment for the patients after percutaneous coronary intervention: a systematic review and meta-analysis

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Sent for review: 04 March 2022 *Revised accepted: 07 April 2022*

Abstract

Purpose: *To evaluate the efficacy, quality of care and safety of Traditional Chinese Medicine (TCM) after Percutaneous Coronary Intervention (PCI). using systematic review and meta-analysis of randomized controlled trials.*
Methods: *Relevant studies published between January 1st 2010 and August 20th, 2021, on traditional Chinese medicine (TCM) and conventional treatment (CT) after PCI were sourced from different databases including CNKI, CBM, Web of Science, PubMed, Embase and Cochrane library. The TCM was composed of preparations of chinese eaglewood, peppermint, radix notoginseng, scabrous elephant foot herb, Tongxinluo, Danhong, Naoxintong capsule, Huxin Formula and liquorice root while the CT included aspirin (100 mg/day), clopidogrel (75 mg/day), and statins. PRISMA guidelines were used. Primary outcome was to evaluate the efficacy, quality of care and safety of TCM versus conventional treatment post percutaneous coronary intervention (PCI).*
Results: *110 randomized controlled trials (RCTs) were retrieved and analyzed. The results from meta-analysis showed an enhanced left ventricular ejection fraction (LVEF) % among patients that received TCM compared to those on CT [mean difference ± sd (MD)=5.17, 95% CI (3.29-7.06), Z = 5.38, (P < 0.001)]. Further, hypersensitive C-reactive protein (HS-CRP) level in TCM group was found to be relatively lower than that of the CT group (CG) [MD=-1.44, 95% CI (-2.87-0.00), Z=1.96, (P=0.05)]. In terms of safety, TCM group relative risk score in fixed-effect model was lower than that of the CG [RR=0.66, 95% CI (0.40, 1.10), Z=1.66,].*
Conclusion: *It can be inferred from the results that TCM has more advantages in terms of clinical efficacy, quality of care and safety compared to conventional therapy. However, the lack of substantial research in deploying TCM for the treatment of CHD demands further exploration and strong evidence prior to clinical application of TCM.*

Keywords: *Traditional Chinese medicine, systematic review, meta-analysis, randomize controlled trials, Chronic Heart Disease, PCI*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

In the past decade, the number of aging populations has drastically increased in China. Aging-related ailments are prevalently observed among the Chinese population. As per the literature [3], the incidence risk of CHD in China was between 39.1% and 41.2% in 2015, and are expected to increase in China up to 7.8 million CHD events (a 69% increase) and 3.4 million deaths (a 64% increase) during the upcoming decade i.e., 2020–2029, than the previous decade i.e., 2000-2009 [1, 2, 3]. A clinical trial, conducted in UK determined an approximate of 8.8 million patients living with CHD in the year 2014 [2].

The pathogeny of CHD is coronary artery stenosis, hemodynamic change, induced myocardial ischemia and myocardial infarction [4-8]. Percutaneous Coronary Intervention (PCI) strategy is used in the treatment of CHD in which the arteries are expanded so that blood flow and the functioning of heart get improved [9-15]. PCI is effective in terms of reduced morality, improved function hindrance and life quality of patients suffering from CHD. Although the outcomes and survival of patients, with CHD, increase with PCI dramatically, irrelevant accidents caused by PCI such as severe coronary stenosis, NSAID-induced gastrointestinal bleeding and multiple coronary chronic-induced pro-inflammatory and pro-oxidative stress are challenging health issues to overcome. Further, adherence to treatment, impairment of heart and the restoration of mental functions are few common events to follow [1, 3, 16-21].

Traditional Chinese Medicine (TCM) is practiced in more than 100 countries around the world with widespread health domains [22-24]. Earlier study found that TCM promotes blood circulation, and so helps in normalization of blood physiology [25-28]. Numerous research investigations have been conducted so far to analyze the impact of TCM-based treatment upon CHD [29-35]. Though a few studies cite the application of TCM as adjuvant therapy after PCI, no meta-analysis of the studies pertaining to TCM treatment for PCI has not been done so far. In this background, the aim of the current work is to establish an evidence-based medicine for PCI treatment in combination with TCM.

METHODS

Study registration and ethics

The study was registered with International System Evaluation Expectations Register (PROSPERO) (Registration No: CRD4200202 15948), conducted and reported in strict accordance with the Systematic Evaluation and Meta-Analysis Program Preferred Reporting Project (PRISMA-P) Guide [36]. This guideline provides a comprehensive report of the methods and results in the studies considered for review.

Literature search strategies

The authors conducted an extensive search on Chinese and English databases (including China Knowledge Network Knowledge Discovery Network Platform (CNKI), China Biomedical Literature Database (CBM), Wanfang Database (Wanfang), Chongqing VIP Database (VIP), PubMed, Embase and Cochrane Library database) containing studies pertaining to the topic. The search entries included title and abstract with searches restricted for the studies published between January 1st 2010 and August 20th, 2021. The works were retrieved in the form of subject terms in conjunction with a few free words. Table 1 shows an example of search strategy followed in PubMed database while Figure 1. shows the literature screening process.

Table 1: PubMed search strategy

#1 " Percutaneous Coronary Intervention" [Mesh]
#2 Coronary Intervention, Percutaneous [Title/Abstract]
#3 Coronary Interventions, Percutaneous [Title/Abstract]
#4 Intervention, Percutaneous Coronary [Title/Abstract]
#5 Interventions, Percutaneous Coronary [Title/Abstract]
#6 Percutaneous Coronary Interventions [Title/Abstract]
#7Percutaneous Coronary Revascularization [Title/Abstract]
#8Coronary Revascularization, Percutaneous [Title/Abstract]
#9Coronary Revascularizations, Percutaneous [Title/Abstract]
#10 #1or#2or#3or#4or#5 or#6 or#7 or#8 or#9\
#11 "Traditional Chinese medicine" [Mesh]
#12 Traditional Medicine, Chinese [Title/Abstract]
#13Chinese Traditional Medicine [Title/Abstract]
#14Chinese Medicine, Traditional [Title/Abstract]
#15or#11or#12or#13or#14
#16 "Randomized controlled trial" [Mesh]
#17 and #10 and #15and #16

Study inclusion and exclusion criteria

Studies with details about PCI patients who are strictly qualified according to the recognized and authoritative diagnostic criteria (aged between 18 and 80 years) [10], were included in current analysis. However, gender and duration of the disease were not limited. RCTs that do not meet the diagnostic criteria were excluded. Case

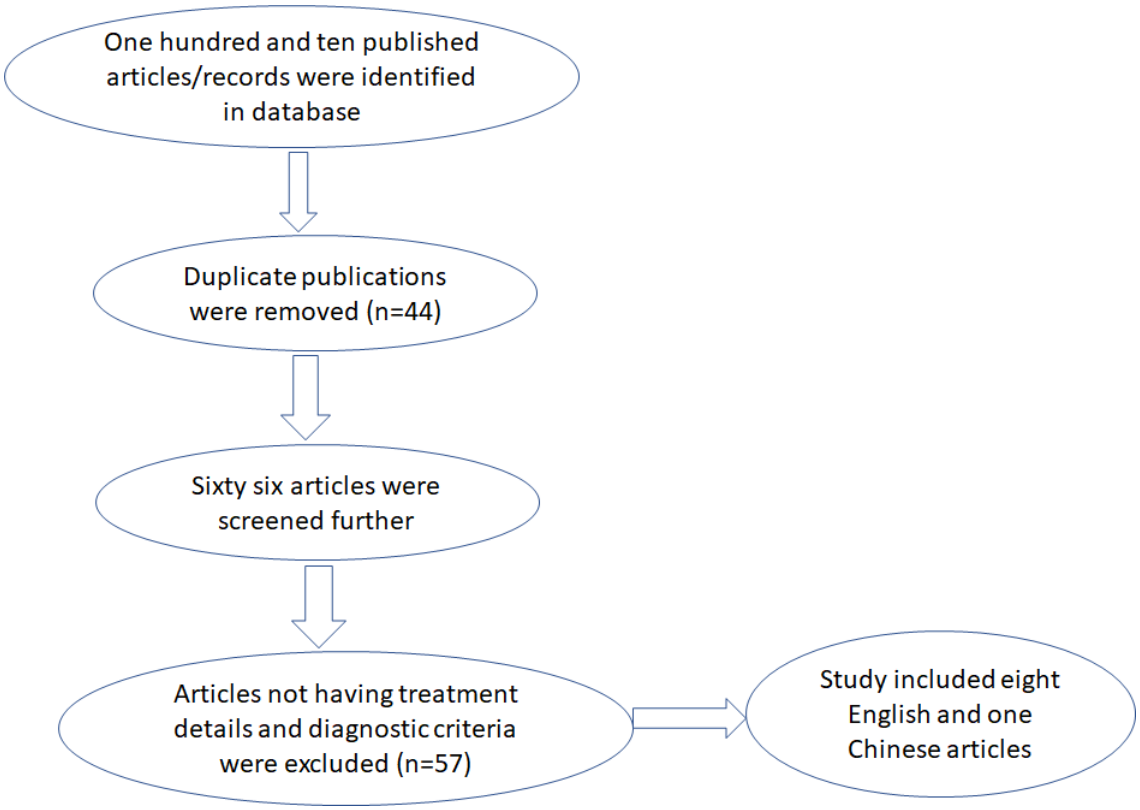

Figure 1: Flow diagram of the literature search process.

reports, laboratory reports, and other meta-analysis reports were also excluded. Study included reports only when patients received traditional Chinese medicine (TCM) contained at least one of ingredients such as chinese eaglewood, peppermint, radix notoginseng, scabrous elephantfoot herb, Tongxinluo, Danhong, Naoxintong capsule, Huxin Formula, and liquorice root. Conventional treatment included aspirin (100 mg/day), and/or clopidogrel (75 mg/day), and statins (200 mg/day). (Table 2). Patients diagnosed with tumors, or any other communicable disease were excluded.

Data extraction and quality assessment

Cochrane Collaboration Risk Assessment Tool [14] was used to evaluate the quality of the studies considered. The processes include (1) Random allocation process; (2) whether double-blind review method is adopted; (3) whether the results are evaluated; (4) whether the allocation is hidden; (5) whether selective reports of research results exist; (6) whether the results are complete in all terms; and (7) the presence of any other biases. In line with the above principles, two researchers conducted an extensive review of the studies and screened the literature using NoteExpress software to evaluate the quality of the documents. In case of disagreements over the choice of study considered, a third researcher took the final decision over selection process.

Meta-analysis was conducted using RevMan 5.3 software

Since all the studies considered for the review were RCTs, two-category variables were analyzed using Risk Ratio (RR) model. Any variability among studies was termed as heterogeneity and it was analyzed using χ^2 test. If heterogeneity that exists between the studies was significant ($P<0.05$, I^2 >50%), random effects model was adopted for further analysis; otherwise, fixed effect model was applied. The intervention includes a comparison of clinical outcomes with 95% Confidence Interval (CI).

Analysis of primary and secondary outcomes

Primary outcome was to explore the clinical efficiency, quality of care and safety of TCM compared with conventional post PCI treatment by performing *t-test* on normal distribution data or Mann-Whitney *U-test* on non-normal distribution data. The significant relation of secondary outcome adverse effect to primary outcome was

tested by a Mann-Whitney *U-test* on non-normal distribution data. Analysis of clinical efficacy safety and quality of care of treatment was done using Seattle Angina Questionnaire (SAQ) and was also based on measurement of Left ventricular ejection fraction (LVEF%). LVEF% is blood volume being pumped out of the left ventricle as an indicator of blood circulation efficacy, The SAQ a vali- dated disease-specific instrument assess the health status of patients with coronary artery disease.

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RESULTS

In this study, 110 articles were retrieved from the databases. Duplicate studies and 57 articles that did not meet the inclusion criteria were excluded. Eight studies reported in English studies and one study reported in Chinese that fulfilled the criteria for study were selected.

Characteristics of 9 RCTs

These studies covered a total number of 4002 patients among which 789 fell under TCM group and 761 under conventional treatment group. The duration of the treatment was between 1 and 12 months. In TCM group, treatment patients used herbal medicine composed of Chinese eaglewood, peppermint, radix notoginseng, scabrous elephantfoot herb and liquorice root. In control group, Conventional treatment included aspirin (100 mg/day), clopidogrel (75 mg/day), and statins. LEVF% and HS-CRP were observed in three studies each while adverse events were observed in 4 studies. Table 2 summarizes the basic information of the studies considered.

The Risk of Bias (ROB) assessment

The RoB tool provides a framework for considering the risk of bias in the findings of any type of randomized trial. It does assessment of risk of bias to be specific to a particular result for a particular outcome (and time point) in the study. In ROB assessment, four studies [38, 42, 43, 45] (2.6%) used 'Blinding of outcome assessment' whereas all the nine studies (100%) indicated of application of random method. (Figures 2 and 3).

Analysis of primary outcomes- efficacy, quality of care and safety of TCM

Low left ventricular ejection fractions (LVEF) as outcome of treatment

LVEF measured the amount of blood being pumped out of the left ventricle of the heart (the main pumping chamber) with each contraction, ultimately indicating the efficacy of blood circulation. The results from statistical analysis (Chi^2 = 4.67, df = 1 (*P* = 0.72), I^2 = 57%) suggests that the different ingredients of TCM had similar effect on treatment and they did not vary between the studies (*P*<0.001) and had better efficacy, safer with care indicating advantages of TCM over conventional treatment (Figure 4).

Subgroup analysis of Seattle Angina Questionnaire (SAQ)

The Seattle Angina Questionnaire (SAQ) is a validated disease-specific instrument for assessing the health status of patients with coronary artery disease. The included RCTs had a total of five different formula for TCM treatment and the subgroup difference test (Chi^2 = 25.49, df = 4 (*P* = 0.04), I^2 = 65%) suggested that the TCM treatment was not heterogeneous between the groups considered whereas the TCM group (*P*<0.00001) showed obvious advantages compared to conventional treatment group (Figure 5).

Hypersensitive C-reactive protein HS-CRP of TCM treatment versus conventional treatment-

The difference test (Chi^2 = 28, df = 2 (*P* = 0.05), I^2 = 93%) results suggest that TCM treatment was not heterogeneous between the groups considered whereas TCM group (*P*<0.00001) showed obvious advantages in terms of efficacy, safety, and care in comparison of conventional treatment group (Figure 6).

Analysis of secondary outcome-adverse reactions

Adverse reactions were secondary outcome which was included in study and noted during the treatment in four RCTs. There were no adverse reactions found in 3 of the 4 RCTs. Heterogeneity test results showed no heterogeneity between the results (*P*=0.17, I^2=41%). Therefore, fixed effect model is used for this analysis. As per the results i.e., RR=0.66, 95% CI (0.40, 5.62), Z=1.60, the difference between the groups is statistically significant (*P*<0.00001) and it can be inferred that TCM group had a safer outcome compared to western medicine group (Figure 7).

Table 2: Summary of studies included.

Article	Year	Sample		Intervention		Duration		Outcome
		MG	CG	MG	CG	MG	CG	
Zhang, L [37]	2018	59	60	TCM (Tongxinluo formula)	Clopidogrel (75 mg/day)	30days	30 days	Clinical Efficacy, Adverse Events
Zhang, CH [38]	2018	59	58	TCM (chinese eaglewood, peppermint, radix notoginseng)	Aspirin (100 mg/day), and Pantoprazole Sodium Enteric-Coated Capsule	4weeks	4weeks	Clinical Efficacy
Zhao, S[39]	2018	65	65	TCM (Danhong+ Naoxintong capsule)	Aspirin (100 mg/day), and clopidogrel (75 mg/day)	12 weeks	12 weeks	Clinical Efficacy
Xu, DP[40]	2015	112	72	TCM (chinese eaglewood, scabrous elephantfoot herb, Tongxinluo)	Aspirin (100 mg/day), clopidogrel (75 mg/day), and (200 mg/day).	12months	12months	Clinical Efficacy
Chu FY [41]	2010	30	30	TCM (Danhong, Naoxintong capsule, Huxin Formula and liquorice root)	Aspirin (100 mg/day), clopidogrel (75 mg/day), and (200 mg/day).	4weeks	4weeks	Clinical Efficacy
Ge, CJ [42]	2014	116	120	TCM (scabrous elephantfoot herb, Naoxintong capsule, and liquorice root)	Aspirin (100 mg/day), clopidogrel (75 mg/day), and (200 mg/day).	12months	12months	Clinical Efficacy
Wu, HL [43]	2014	316	324	TCM (Huxin Formula)	Atorvastatin (100 mg/day), statins (200 mg/day)	360 days	360 days	Clinical Efficacy
WW WU[44]	2017	32	32	TCM (Tongxinluo, Danhong, Naoxintong capsule, and Huxin Formula)	Atorvastatin (100 mg/day), statins (200 mg/day)	4weeks	4weeks	Clinical Efficacy Adverse Events
LIU Hong-ying [45]	2016	50	50	TCM (Peppermint, radix notoginseng, Tongxinluo, Danhong, and Huxin Formula)	Aspirin (100 mg/day), clopidogrel (75 mg/day), and statins (200 mg/day).	6 months	6 months	Clinical Efficacy

MG=TCM treatment group, CG=conventional treatment Group

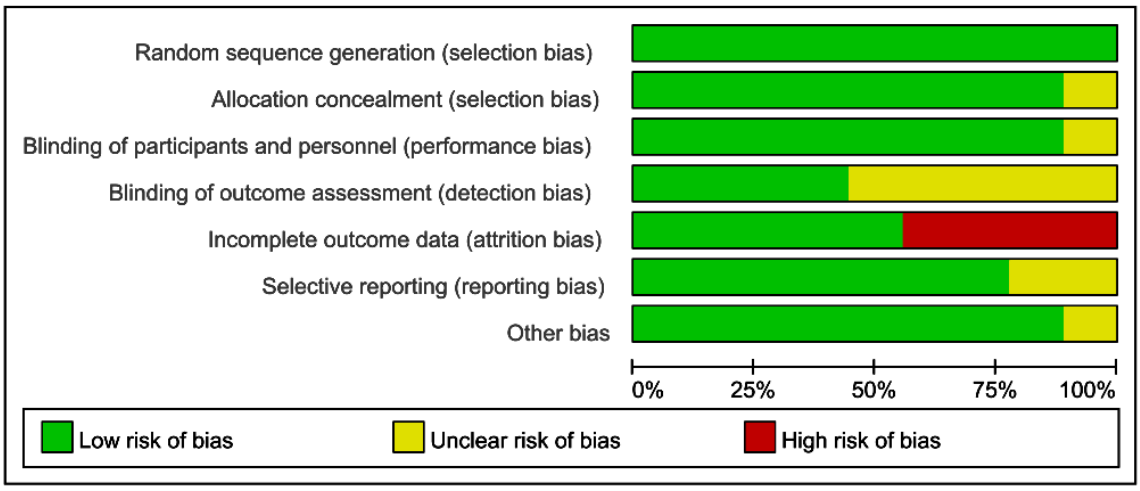

Figure 2: Bias risks

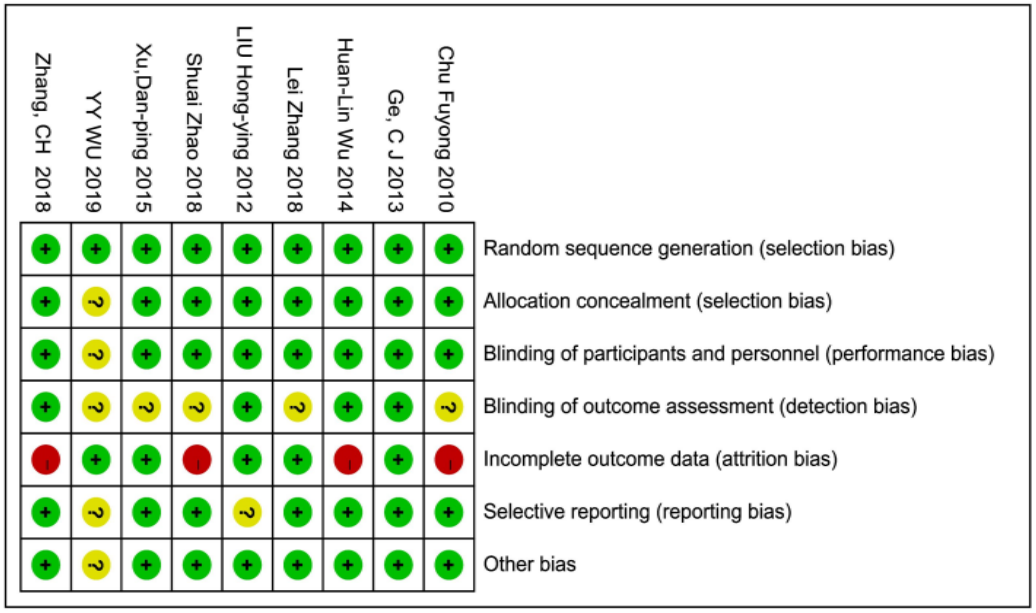

Figure 2. Bias risk (top) with a summary (bottom)
+, - and? show low, high, and unclear risks of bias

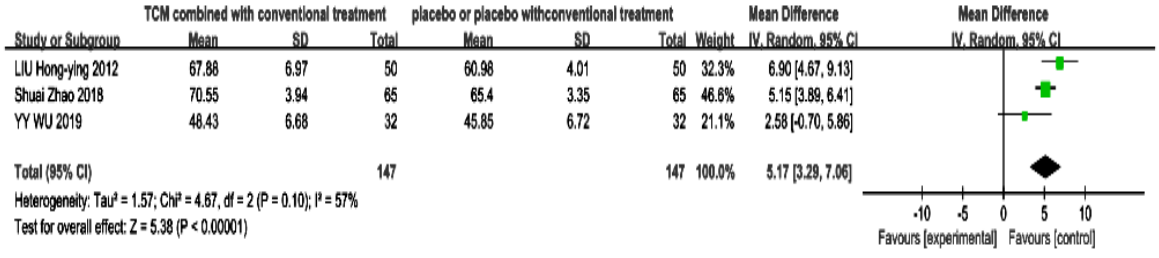

Figure 4. Forest plot of subgroup analysis of LEVF% for TCM and conventional treatment groups summarizing information on studies, amount of study heterogeneity, and estimated common effect

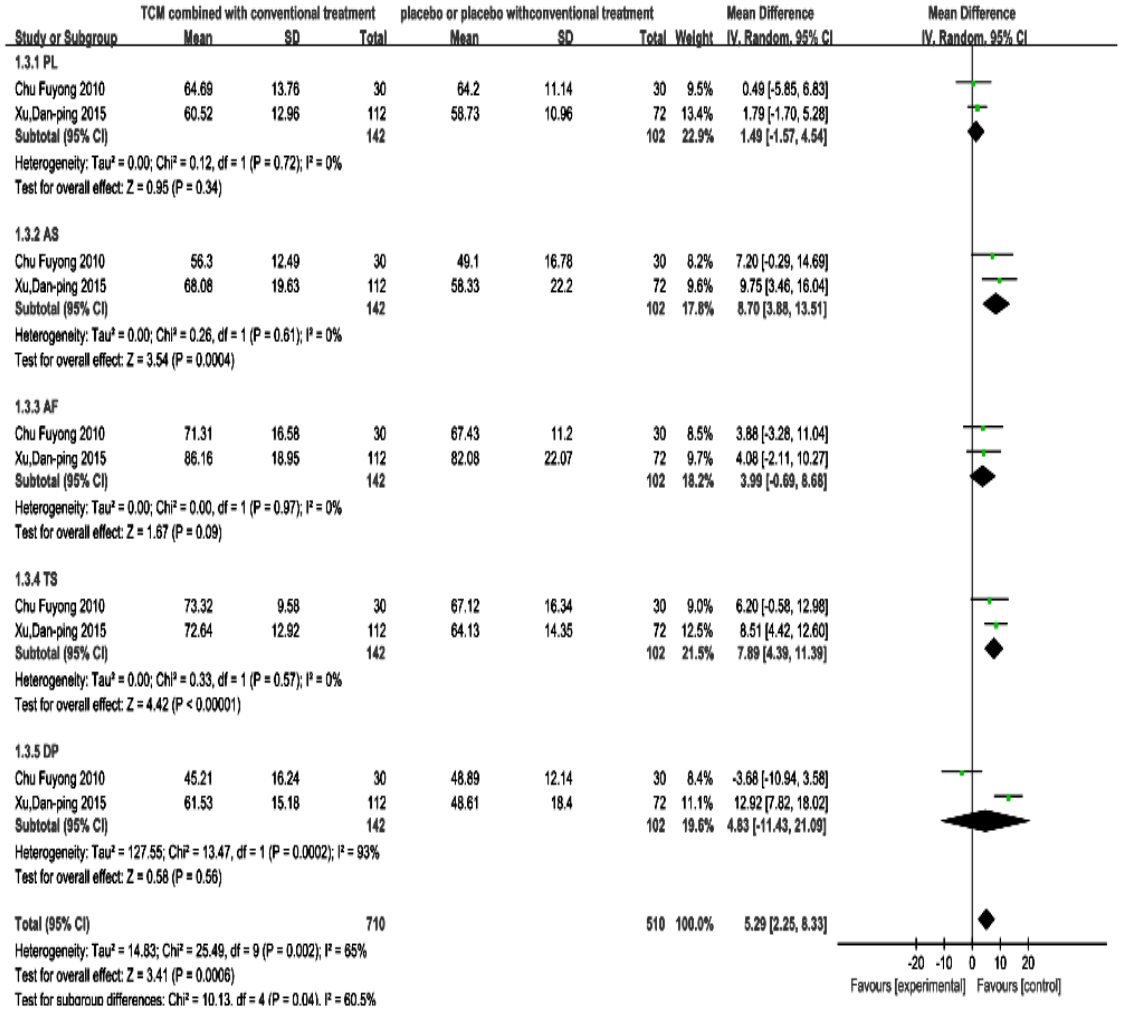

Figure 5: Forest plot for treatment regimens for both treatment groups summarizing information on individual studies, amount of study heterogeneity, and estimated common effect

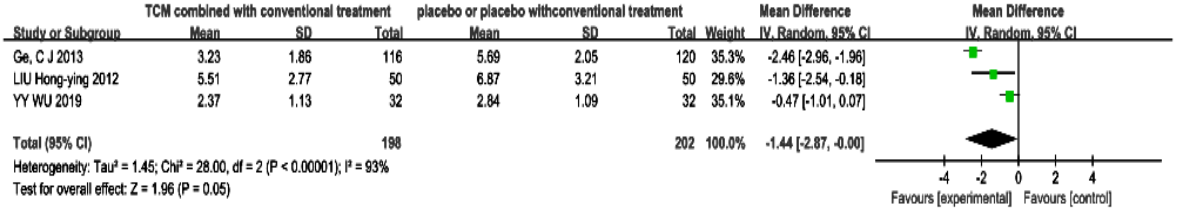

Figure 5: Forest plot for subgroup analysis of HS-CRP for TCM and conventional treatment groups summarizing information on individual studies, amount of study heterogeneity, and estimated common effect

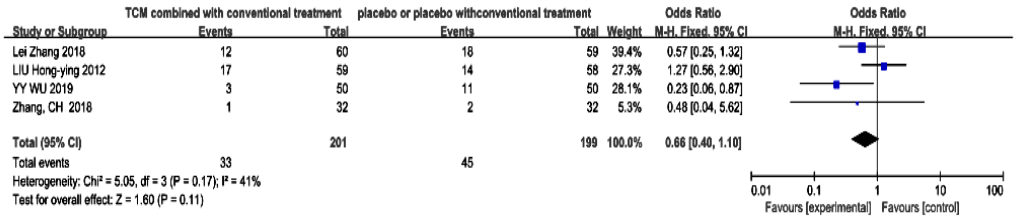

Figure 7: Forest plot analysis of adverse reaction for the TCM group and the conventional treatment group summarizing information on individual studies, amount of study heterogeneity, and estimated common effect

DISCUSSION

According to the selected randomized, double-blind, placebo-controlled trials, patients treated with TCM showed a significant improvement during treatment compared with the conventional treatment. The number of reported adverse events associated with TCM was comparable with the conventional treatment. Therefore, it suggests that TCM is a safe and effective therapy for treating patients after PCI.

TCM) is practiced around the world in various health domains disease [22-24]. Numerous research has been investigated the impact of TCM-based treatment [29-35], though a few studies cite the application of TCM as adjuvant therapy in percutaneous Coronary Intervention (PCI), a meta-analysis of the studies pertaining to TCM treatment for PCI has not been done so far. Study here establishes an evidence-based medicine for PCI treatment in combination with TCM. Meta-analysis in study uses two-category variables in Risk Ratio (RR) model using RevMan 5.3 software to study and consolidate results from published RCTs. The primary outcome clinical efficiency, quality of care, safety, and secondary outcome adverse effect of TCM were compared with conventional post PCI treatment. In current study, the authors searched for TCM studies in Chinese and English databases and based on accessibility of the publications in the most used language. The current review considered 9 RCTs with a total of 4002 patients. Meta-analysis method was followed to compare the clinical efficacy of TCM combined with conventional treatment against the placebo with conventional treatment when treating patients after PCI.

In this meta-analysis study, subgroup analysis common sense was applied to obtain the best clinically effective treatment regimen. When comparing the clinical efficacy of TCM-combined conventional treatment against placebo-combined conventional treatment, the results infer that TCM has an advantage over control conventional treatment (P<0.00001). To arrive at an optimal clinical treatment plan, the authors seek to analyze from TCM. Patients treated with TCM, after PCI, as an alternative to conventional therapy showed significant improvement compared to the patients who followed western medicine. The authors also compared LEVF% of control group and TCM group in only three RCTs. It was found that the TCM treatment had over advantage over conventional treatment group (P<0.00001) in terms of efficacy and safety of treatment. At the same time, HS-CRP of the control group was compared against the TCM group in three RCTs. In comparison with placebo, TCM group showed a reduction in HS-CRP (P=0.05). Further, in four RCT studies, adverse reactions were observed in two groups. From this, it can be concluded that TCM is safer than the control group (P=0.17). Based on the studies considered, it can be concluded that TCM is highly effective than conventional treatment in enhancing LEVF%. TCM, in combination with conventional treatment, has the potential to reduce the level of pro inflammatory HS-CRP. Besides, the comprehensive comparisons result in the conclusion that TCM's incidence of adverse reactions was very low compared to conventional treatment.

CONCLUSION

The current study established that TCM has significant clinical efficacy than the placebo treatment. So, it can be considered as an alternative to conventional therapy. Further, TCM has a few advantages in terms of enhancing LEVF% and reducing HS-CRP production than the conventional treatment. However, to some extent, the lack of substantial research with in-depth analysis for a long period of time results in ambiguity. So, with lack of quantity and quality results, the clinical application of the result requires refinement and justification before application. The relevance of this outcome to Chinese subjects needs further research since the current review may have some bias.

Limitations of the study

Despite this finding, the current study has certain limitations. First, the quality of RCT studies included in meta-analysis, is relatively low owing to a few numbers of patients and poor research methods. Further, only two groups used Statistical Blindness whereas none of the groups used allocation concealment and blinding of participants and personnel. This limitation tends to increase the possibility of selective and detection biases. Second, the uneven distribution of the treatment points which increases the possibility of implementing bias and enhances the difficulty of promotion. Third, the lack of follow-up data makes it impossible to evaluate the long-term efficacy of TCM for CHD. Finally, the studies with a smaller number of patients may have an impact on the accuracy of analysis..

DECLARATIONS

Abbreviations

CHD= coronary heart disease, PCI= percutaneous coronary intervention, RCTs=randomized controlled trials,

TCM=Traditional Chinese Medicine, ROB=the risk of bias, MG= Traditional Chinese Medicine Group, CG=Conventional treatment Group, RR=risk ratio, LEVF= left ventricular ejection fraction, saq= Seattle Angina Questionnaire, HS-CRP= hypersensitive C-reactive protein.

Availability of data and materials

All data are included in this published article and its Additional files.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them. The authors contributed equally to this research.

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