INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Traditional Chinese medicine injections with Activating Blood Circulation, equivalent effect of anticoagulation or antiplatelet, for acute myocardial infarction: A Protocol for the Systematic Review and Meta-Analysis of Randomized Clinical Trials

Li, X[1]; Lou, Y[2]; Jiang, YJ[3]; Shang, JJ[4]; Liu, HX[5]; Lai, XL[6].

Review question / Objective: **Our study outlines a systematic review and meta-analysis protocol for randomized clinical trials, aiming at evaluating the efficacy(Hospital mortality and post-onset mortality, rehospitalization rate, the incidence of malignant arrhythmia, left ventricular ejection fraction, adverse safety incident) and safety(classified by involving systems: nerve, mental system, blood routine laboratory abnormalities, skin reaction, urinary system, respiratory system, gastrointestinal tract reaction) of TCM injections (Danhong injection, Sodium Tanshinone IIA Sulfonate injection, Danshen Chuanxiongqin injection and Puerarin injection), for promoting blood circulation and removing blood stasis in the treatment of AMI under existing evidence.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 July 2021 and was last updated on 25 July 2021 (registration number INPLASY202170082).

INTRODUCTION

Review question / Objective: **Our study outlines a systematic review and meta-analysis protocol for randomized clinical trials, aiming at evaluating the efficacy (Hospital mortality and post-onset mortality, rehospitalization rate, the incidence of malignant arrhythmia, left ventricular ejection fraction, adverse safety incident) and safety(classified by involving systems: nerve, mental system, blood routine laboratory abnormalities, skin reaction, urinary system, respiratory**

system, gastrointestinal tract reaction) of TCM injections(Danhong injection, Sodium Tanshinone IIA Sulfonate injection, Danshen Chuanxiongqin injection and Puerarin injection), for promoting blood circulation and removing blood stasis in the treatment of AMI under existing evidence.

Condition being studied: The 2019 Global Burden of Disease report shows that acute myocardial infarction (AMI) is one of the major diseases with high global morbidity and mortality, causing a huge global economic and medical burden, and this situation is also the same reflected in China. According to the "Report on Cardiovascular Health and Diseases Burden in China: an Updated Summary of 2020", the overall mortality rate of AMI in China from 2002 to 2018 has shown an upward trend, and the mortality rate of AMI has shown a rapid upward trend from 2005. Although percutaneous coronary intervention (PCI) has been rapidly developed in China, it show that in 2018, China received more than 915,000 PCI treatments, and the number of cases has surpassed the United States and ranked first in the world. But China PEACE Studies have shown that however in that context, the hospital mortality rate of AMI in China has not decreased significantly. On the basis of popularizing secondary prevention of coronary heart disease actively and promoting early reperfusion treatment of AMI, whether traditional Chinese medicine can be used to help reduce the mortality of AMI patients has always been a hotspot for Chinese medical workers.Our idea is consistent with Nobel Prize winner——Professor Tu Youyou's research thought of extracting artemisinin from Artemisia annua and effectively applying to malaria treatment. Traditional Chinese medicine has a history of treating AMI for more than 2,000 years. Translating the "experience" of traditional Chinese medicine treatment of AMI into "evidence" is the crux to effectively help patients with AMI for clinical benefit. In the 1970s, Professor Chen Keji discovered a type of Chinese medicine with anticoagulant and antiplatelet effects on the basis of reading a large number of ancient Chinese medicine books, which calls "activating blood and removing blood stasis" drugs, can play a role in myocardial protection.In the 1980s, Professor Chen Keji led the team to conduct the evaluation of the first traditional Chinese medicine for promoting blood circulation and removing blood stasis called Guanxin No. 2 (consisting of chuanxiong rhizoma, carthami flos, salvia miltiorrhiza bunge, paeoniae radix rubra, and dalbergia odorifera T. Chen), which interfered with coronary heart disease and angina pectoris. A multi-center, randomized, double-blind, placebo-controlled clinical study showed that Guanxin No. 2 has myocardial protective effects such as reducing coronary heart disease angina pectoris, improving myocardial ischemia and abnormal hemorheology. As the research went on, it has gradually been discovered that "blood-activating and removing blood stasis" drugs with equivalent anticoagulant and antiplatelet effects can help reduce the mortality of AMI patients, cardiovascular events in stable coronary heart disease, the risk of stenosis,and coronary stent recurrence. At present, "activating blood circulation and removing blood stasis" medicine has become the most commonly used Chinese herbal medicine for coronary heart disease in Chinese mainland.

METHODS

Search strategy: The search database and search time range are as follows: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, China Biological Literature Database, CNKI, Weipu Database and Wanfang Data Knowledge Service Platform. All database search times are selected for database establishment From the date to the present, the search strategy is shown in Appendix 1. In addition to the documents retrieved from the electronic database, this study will also search for documents whose topics in the reference list attached to the documents may be related to this study, and will manually check the paper books and magazines in the fields related to the research content to ensure that they are included as much as possible The

literature is comprehensive, and relevant clinical trials will be searched in "ClinicalTrials.gov" to determine whether there are unpublished literature that meets the inclusion criteria. Search Query #1 Myocardial Infarction[MeSH] #2 Myocardial infarction OR acute myocardial infarction OR AMI OR infarction, myocardial OR cardiovascular stroke OR infarctions, myocardial OR myocardial infarctions OR cardiovascular strokes OR heart attack OR strokes, cardiovascular OR myocardial infarct OR infarct, myocardial OR stroke, cardiovascular[Title/Abstract] #3 #1 OR #2; #4 Injection[Mesh]; #5 Injection OR injectables OR injectable OR injections[Title/Abstract]; #6 #4 OR #5; #7 Puerarin OR Danhong OR Dan red OR Sulfotanshinone sodium OR Sodium Tanshinone IIA Sulfonate OR Tanshinone IIa OR Salviae miltiorrhizae and ligustrazine hydrochloride injection OR Danshen Chuanxiongqin[Title/Abstract]; #8 Randomized controlled trial[publication type]; #9 #3 AND #6 AND #7 AND #8.

Participant or population: Patients who meet the diagnostic criteria for AMI.

Intervention: Observation group was combined with puerarin injection, Danhong injection, tanshinone IIA sodium sulfonate injection and Danshen ligustrazine injection on the basis of western medicine treatment, one of TCMI.

Comparator: The intervention measures in the control group were Western medicine treatment alone or placebo.

Study designs to be included: Randomized controlled trial (RCT).

Eligibility criteria: Types of studies: Randomized controlled trial (RCT). Research objects:Patients who meet the diagnostic criteria for AMI. Types of intervention: Observation group was combined with puerarin injection, Danhong injection, tanshinone IIA sodium sulfonate injection and Danshen ligustrazine injection on the basis of western medicine treatment, one of TCMI; The intervention measures in the control group were Western medicine treatment alone or placebo. Western medicine treatment principles include: general treatment (including vital signs monitoring, symptom relief, etc.), reperfusion therapy (including PCI, thrombolysis and coronary artery bypass surgery), drug therapy (including: antiplatelet, anticoagulant, lipid-lowering, etc.), not including Chinese herbal medicine, Chinese medicine, acupuncture and other traditional medical treatment.

Information sources: The search database and search time range are as follows: PubMed, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, China Biological Literature Database, CNKI, Weipu Database and Wanfang Data Knowledge Service Platform. All database search times are selected for database establishment From the date to the present.In addition to the documents retrieved from the electronic database, this study will also search for documents whose topics in the reference list attached to the documents may be related to this study, and will manually check the paper books and magazines in the fields related to the research content to ensure that they are included as much as possible The literature is comprehensive, and relevant clinical trials will be searched in "ClinicalTrials.gov" to determine whether there are unpublished literature that meets the inclusion criteria.

Main outcome(s): Hospital mortality and post-onset mortality.

Additional outcome(s): Rehospitalization rate (myocardial infarction, stroke, unstable angina or heart failure hospitalization), the incidence of malignant arrhythmia, left ventricular ejection fraction (LVEF), poor safety events (classified by involving systems: nerve, mental system, blood routine laboratory abnormalities, skin reaction, urinary system, respiratory system, gastrointestinal tract reaction).

Data management: After the literature search is completed, the EndNote 20.1 software will be imported for management, and the two participants will process the

literature data independently, find duplicate literature, only keep the latest published and the most complete literature, and eliminate those not meeting the research inclusion criteria or meeting the exclusion criteria literature, and record the reasons for document removal. The extracted data includes the title of the literature, all authors, year of publication, journals published, number of cases, limit characteristics of the research object, treatment measures, blind methods, random methods, outcome indicators and adverse reactions.We'll collect the above information In a table. If there is a disagreement, the third participant will make judgments and adjustments.

Quality assessment / Risk of bias analysis: Two reviewers evaluated and recorded the quality of the included literature according to the quality evaluation standards recommended by the Cochrane System Review Manual, including 6 items: selection bias (random allocation sequence generation and allocation concealment), implementation bias (for subjects, Researcher blinding), measurement bias (blinding the outcome assessor), follow-up bias (result data completeness), reporting bias (no selective reporting), and other biases.

Strategy of data synthesis: RevMan 5.3.0 software was used for statistical analysis of the extracted clinical research information. If the index to be analyzed is count data, select the relative risk (RR) analysis statistics; if the index to be analyzed is measurement data, select the mean difference (MD) when the unit of measurement is the same, and select the standardized mean when the unit of measurement is different Difference (SMD) analysis statistics, both of which are expressed with 95% confidence interval (CI). Use RevMan software to draw a forest map. When the 95% CI horizontal line does not intersect the invalid vertical line and the horizontal line falls to the right of the invalid line, it can be considered that the incidence of the experimental group is greater than that of the control group; its 95% CI When the horizontal line does not intersect with the invalid vertical line, and the horizontal line falls to the left of the invalid line, the incidence of the test group can be considered to be less than the incidence of the control group.

Subgroup analysis: This study will conduct the following subgroup analysis of patients with acute myocardial infarction:AMI type (STEMI, NSTEMI); Whether to accept reperfusion therapy; Intervention measures (different TCMI).

Sensitivity analysis: In order to confirm the robustness of our research results, we will conduct sensitivity analysis based on the different bias levels of the included studies. In order to evaluate the internal validity of the study or the adequacy of the treatment, we will subsequently use the metafor package and leav1out functions to delete the "high risk of bias" studies, the "unclear risk of bias" studies, and the"low risk of bias" studies.

Language: English and Chinese.

Country(ies) involved: China.

Keywords: Promoting blood circulation to remove blood stasis, Traditional Chinese medicine injections, Acute Myocardial Infarction, Systematic Review, Meta-analysis, Protocol.

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