INPLASY PROTOCOL

A meta-analysis of the effectiveness and safety of Shengmai injection in preventing and treating adriamycin-related cardiotoxicity

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None.

Liu, LC[1]; Liu, C[2]; Duan, L[3]; Bai, J[4]; Mao, QY[5]; Wang, J[6].

Review question / Objective: **To evaluate the effectiveness and safety of Shengmai injection combined with conventional therapy versus conventional therapy in doxorubicin-related cardiotoxicity, and to evaluate the improvement of cardiotoxicity rate, echocardiography, electrocardiogram, and myocardial enzymes. If possible, evaluate the incidence of side effects, allergies, and toxic reactions to analyze safety.**
Condition being studied: **Adriamycin (ADM), also known as Doxorubicin (DOX), is one of the most commonly used anthracycline broad-spectrum antitumor drugs, and is the core drug of a variety of malignant tumor chemotherapy regimens. A wide range of clinical studies have shown that ADM presents serious toxicity, and its toxic effect on the heart is particularly obvious. In severe cases, it can cause heart failure, etc.The cardiotoxicity of ADM has been widely valued by medical workers since its discovery. How to prevent and treat doxorubicin cardiotoxicity is currently the focus of clinical research. Studies have shown that the affinity of ADM to myocardial tissue is significantly higher than that of other tissues, leading to the accumulation of ADM in myocardial cells, making myocardial tissue more susceptible to ADM damage and presenting a dose-dependent irreversible damage characteristic. This greatly limits the dosage of ADM used in clinical treatment, and increases the morbidity and mortality of cardiovascular disease in cancer treatment survivors. Once obvious cardiomyopathy caused by chemotherapy drugs appears, the prognosis is extremely poor.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 09 September 2020 and was last updated on 09 September 2020 (registration number INPLASY202090040).

INTRODUCTION

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METHODS

Search strategy: The following electronic databases will be systematically and comprehensively searched: Cochrane Library, EMBASE, PubMed, Science Network, China National Knowledge Infrastructure, China Biomedical Literature Database, Wanfang Database and Chinese Journal Database, for randomized controlled trials that used Shengmai injection for treating the adriamycin-related cardiotoxicity through September 2020. The search strategies were using the following key words and search terms: Shengmai injection, adriamycin, doxorubicin, cardiotoxicity, cardiomyopathy, randomized controlled trial.

Participant or population: Inclusion criteria: (1) The standard of cardiotoxicity was evaluated according to the acute and subacute toxicity standard of anti-cancer drugs established by WHO. (2)Adopt a first-line standard joint solution based on ADM. (3)A randomized controlled trial of Shengmai injection in the prevention and treatment of adriamycin-related cardiotoxicity. Exclusion criteria: (1) People with acute myocardial infarction, severe arrhythmia, heart failure, severe neurosis, and menopausal syndrome in the past six months. (2) Patients with severe primary diseases such as liver, kidney and hematopoietic system and mental illness.

Intervention: Shengmai injection is a modern injection form of traditional Chinese medicine, mainly composed of ginseng, Ophiopogon japonicus and Schisandra chinensis. Its mechanism of preventing the cardiotoxicity of anti-cancer drugs may be to enhance the contractility of myocardial cells, excite myocardium, and increase cardiac output. In recent years, many clinical reports have proved that Shengmai injection can improve the pumping function of the heart, improve the LVEF of patients, reduce the cardiac afterload, and reduce the occurrence of arrhythmia.

Comparator: The control interventions include : Malignant lymphoma patients should use CHOP regimen [CTX+ADM+VCR+Pred], breast cancer patients should use CAF regimen [CTX+ADM+5-FU], ovarian cancer patients should use CAP regimen [CTX+ADM+DDP], multiple bone marrow tumor patients should be treated with VAD chemotherapy [VCR+ADM+DEX].

Study designs to be included: (1) randomized controlled trial. (2) language is Chinese or English. exclusion criteria: (1) non-therapeutic research, animal experiments, case reports, review literature. (2) literature without control

group, duplicate publications, incorrect data and no data available.

Eligibility criteria: The Population, Intervention, Comparison and Outcomes (PICO) principles will be applied to the research design. The inclusion criteria are as follows:(1) Article was written in Chinese or English;(2) A randomized controlled trial; (3) Conformed to expert consensus regarding the standard diagnosis and treatment of adriamycin-related cardiotoxicity; The exclusion criteria are as follows:(1) Use of a non-RCT design;(2) Use of a quasi-RCT study design;(3) Important data were unavailable;(4) Repeated publication;(5) Animal model experiments; (6) Reviews or case reports; (7) Interventions that included other TCM therapies such as acupuncture or massage. The contents of the data extraction included the author and publication year of the literature, baseline characteristics(Age, gender), the intervention method(Shengmai injection), the Comparator method(conventional therapy), the number of result cases, the outcomes(cardiotoxicity rate, echocardiography, electrocardiogram, and myocardial enzymes).Two reviewers (Mao and Liu) independently conducted data extraction, In case of disagreement, the third reviewer (Duan) participated in the discussion and resolved.

Information sources: We will search China National Knowledge Infrastructure, China Biomedical Literature Database, Wanfang Database and Chinese Journal Database, for randomized controlled trials that used Shengmai injection for treating the adriamycin-related cardiotoxicity through September 2020.Grey literature will be retrieved through Open Grey. Full texts will be obtained through library interlibrary loan or purchase. The manual review of references in published articles will be conducted to identify other relevant studies. The missing data or additional details will be handled by contacting the study investigators by E-mail .If there are any questions or confusion about the original researchin the process, we will be contacted again to get specific answers.

Main outcome(s): Cardiotoxicity rate.

Additional outcome(s): Echocardiography, electrocardiogram, and myocardial enzymes.

Data management: Noteexpress is used for data management.Data extraction using a pre-defined excel spreadsheet.STATA and RevMan 5.3 will be used for statistical analysis of the selected literature.

Quality assessment / Risk of bias analysis: The researchers performed quality assessments and information extraction on the included literature based on the Cochrane 5.3 bias risk assessment form, which included selection bias (random sequence generation, allocation concealment), implementation bias, measurement bias, follow-up bias, reporting bias, and other biases.

Strategy of data synthesis: The relative data (OR) is used as the combined statistics. For the whole analysis, if $P \geq 0.1$ and $I^2 < 50\%$, the literatures can be considered to be homogenous, the fixed effect model can be used for meta-analysis. If $P < 0.1$, $I^2 \geq 50\%$, it can be considered that the included literature is heterogeneous, using a random effects model; If descriptive analysis of heterogeneity cannot be judged, and no meta-analysis is performed.

Subgroup analysis: Subgroup analysis of the year of publication and different cancer types to see if there are differences in the outcome indicators.

Sensibility analysis: Sensitivity analysis will be used to test the stability and reliability of meta-analysis. It can be done by eliminating each study individually or using random-effects model (D-L method) to test the results after using the fixed effect model.

Language: English; Chinese-Simplified.

Country(ies) involved: China.

Keywords: Systematic review; meta-analysis; Shengmai injection;Traditional Chinese Medicine; adriamycin-related cardiotoxicity; doxorubicin-related cardiotoxicity; randomized controlled trial; effectiveness; safety.

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