INPLASY PROTOCOL

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Conflicts of interest:
None declared.

Pharmaceutical preparations of periplaneta Americana for Skin Ulcer: a protocol for a meta-analysis of randomised controlled trials

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Review question / Objective: **This meta-analysis was designed to assess the effect of topical KFX on the rate of healing of chronic skin ulcer in any care setting and to explore its optimal frequency of use.**
Eligibility criteria: **(1) This study is a randomized controlled trial; (2) Participants had localized skin ulcers without topical medication prior to treatment, excluding women who might be pregnant or breastfeeding or skin ulcers caused by tumors; (3) The study evaluated an intervention group and a control group, including topical KFX or KFX in combination with other drug treatment or physical treatment in the intervention group and non-KFX in the control group; (4) Specific steps for topical KFX :The medical gauze was soaked with KFX and applied externally to the affected area, and the outer layer was wrapped with sterile gauze; (5) The baseline status before treatment was clear, and the baseline difference was not statistically significant.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 23 May 2022 and was last updated on 23 May 2022 (registration number INPLASY202250131).

INTRODUCTION

Review question / Objective: **This meta-analysis was designed to assess the effect of topical KFX on the rate of healing of chronic skin ulcer in any care setting and to explore its optimal frequency of use.**

Condition being studied: **Skin ulcers refers to the ulcers that occur on the skin and underlying tissue, mainly including Buruli ulcer, leg ulcer, pressure ulcer, and pyoderma gangrenosum. Of note, the most common chronic wounds, including venous leg ulcers, diabetic foot ulcers, pressure**

ulcers and arterial ulcers, due to the high cost of wound care, long healing time, high incidence, recurrence rate and hospitalization rate, affect millions of individuals annually, posing both significant health risks and financial burdens. To date, the standard of initial care for the chronic ulcers, based on clinical presentation and classification, includes compression therapy, debridement, revascularization, antithrombotic drugs, regular relief from prolonged pressures by constantly, and so on[3, 5]. However, when these ulcers are unable to heal by conventional approaches, it may be beneficial to implement more advanced adjuvant therapeutic option such as bioengineered skin, platelet-derived growth factors, platelet-rich plasma, and hyperbaric oxygen, etc. However, there are still high cost, complicated operation and other factors to prevent wound healing. Despite growing awareness of this serious and widespread public health problem, the chronic ulcer field continues to be plagued by a lack of well-designed randomized clinical trials (RCTs) . The tremendous difficulties of initiating appropriate research in the field of chronic ulcers, such as wound debridement and decompression, are often subjective and difficult to standardize, and play an incontestable role in trial failure. Thus, it is urgent to find high-quality evidence can facilitate to improve the treatment standardization in this field.

METHODS

Search strategy: Two reviewers will independently search the literature published up to May 2022 in major English and Chinese databases with no language restriction, including PubMed, EMBASE, Web of Science (WOS), Cochrane Central Register of Controlled Trials (CENTRAL), China Network Knowledge Infrastructure (CNKI), Chinese Biomedicine (CBM), Chinese Scientific Journals Database (VIP), and WanFang Database. For any relevant ongoing or unpublished trials, we will search the US National Institutes of Health Ongoing Trials Register (http://www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch) and the metaRegister of Controlled Trials (http://www.controlledtrials.com). Conference abstracts will be searched for potentially relevant trials from inception to May 2022 in OpenSIGLE (opensigle.inist.fr).

Participant or population: Participants had localized skin ulcers without topical medication prior to treatment, excluding women who might be pregnant or breastfeeding or skin ulcers caused bytumors.

Intervention: Specific steps for topical KFX :The medical gauze was soaked with KFX and applied externally to the affected area, and the outer layer was wrapped with sterile gauze.

Comparator: Non-KFX in the control group.

Study designs to be included: Randomized controlled trial.

Eligibility criteria: (1) This study is a randomized controlled trial; (2) Participants had localized skin ulcers without topical medication prior to treatment, excluding women who might be pregnant or breastfeeding or skin ulcers caused by tumors; (3) The study evaluated an intervention group and a control group, including topical KFX or KFX in combination with other drug treatment or physical treatment in the intervention group and non-KFX in the control group; (4) Specific steps for topical KFX :The medical gauze was soaked with KFX and applied externally to the affected area, and the outer layer was wrapped with sterile gauze; (5) The baseline status before treatment was clear, and the baseline difference was not statistically significant.

Information sources: PubMed, EMBASE, Web of Science (WOS), Cochrane Central Register of Controlled Trials (CENTRAL), China Network Knowledge Infrastructure (CNKI), Chinese Biomedicine (CBM), Chinese Scientific Journals Database (VIP), and WanFang Database. For any relevant ongoing or unpublished trials, we will search the US National Institutes of Health Ongoing Trials Register (http://

www.clinicaltrials.gov), the WHO International Clinical Trials Registry Platform (http://www.who.int/trialsearch) and the metaRegister of Controlled Trials (http://www.controlledtrials.com). Conference abstracts will be searched for potentially relevant trials from inception to May 2022 in OpenSIGLE (opensigle.inist.fr).

Main outcome(s): The effective rate: complete healing rate plus remarkably effective rate.

Additional outcome(s): The improvement of pain; healing time; recurrence rate; incidence of adverse reactions.

Quality assessment / Risk of bias analysis: The two review authors independently assessed the risk of bias in included studies using standardized key assessment tools developed using the Cochrane Collaboration Tool. The tool covers the following seven aspects of evaluation: random sequence generation, allocation hiding, blinding of participants and personnel, blinding of outcome evaluation, incomplete outcome data, selective reporting, and other sources of bias. The evaluation results will be agreed upon by all review authors. The charts generated by Review Manager 5.4 software will be used to assess the risk of bias.

Strategy of data synthesis: We will analyze and synthesize the meta-review research problems into quantitative and qualitative data respectively. The synthesis will perform meta-analysis by generating forest maps. The prism shows the aggregating effect of a particular type of study (depending on the covariates of the meta-regression). The fixed effect model will be fitted for calculating pooled estimates, 95%CIs and combined p values if the heterogeneity test indicates there is no substantial heterogeneity between studies (I2 <50%). If substantial heterogeneity is indicated by I2 ≥50%, the random-effects model will be performed.

Subgroup analysis: Subgroup analysis will be performed according to primary and secondary objectives to detect possible heterogeneity of outcomes. We will investigate the effects in two subgroup analyses: 1. Different types and locations of ulcers; 2. Frequency of KFX. In addition, if we detected any significant and significant covariates leading to changes in the intervention effect through meta-analysis, additional subgroup analyses will be performed based on these covariables.

Sensitivity analysis: Sensitivity analysis will be performed to explore the robustness of the primary outcome. To assess the internal validity or treatment adequacy of the studies, we will then use metafor package[15] and leave 1 out function to delete studies with high bias risk, studies with unclear bias risk, and studies with low bias risk.

Language: Restricting the inclusion criteria to English and Chinese papers.

Country(ies) involved: China.

Keywords: Skin Ulcer; Kangfuxin; periplaneta Americana.

Contributions of each author:

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