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Original Article
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External Treatment of Pyritum for Musculoskeletal Trauma: a protocol for systematic review

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Objectives: Musculoskeletal trauma is a common type of injury that can result from damage to the muscular or skeletal system and has been recognized as a leading cause of death and disability worldwide. This study aims to analyze the efficacy of Pyritum external treatment for musculoskeletal trauma.
Methods: Randomized controlled trials evaluating the external treatment effect of Pyritum on various types of musculoskeletal traumatic injuries will be considered and identified in the searches of eight databases from their inception to Feb 2023. There will be no restrictions with respect to the publication status, language, or country. The experimental intervention group will be treated with external application of Pyritum alone or in combination with other therapies, and the comparator intervention group will include all types of control interventions. The primary outcome will be measured as treatment efficacy rate, and secondary outcomes will include pain reduction, pain disappearance time, swelling, joint function, and recovery period. Assessment of the methodological quality of this study will be concluded using the risk of bias assessment recommended by the Cochrane Collaboration. If there are sufficient numbers of studies per group in terms of specific rating scales to compare the treatment effects of Pyrium alone and combined external treatment groups, we will consider subgroup analysis.
Results: This systematic review will be conducted in compliance with the PRISMA-P statement.
Conclusion: We will conduct an extensive search on the proposed topic within the available literature and provide systematic evidence for the efficacy and safety of external application of Pyritum for all types of musculoskeletal trauma. The evidence generated will help design interventions for the external use of Pyritum for this patient group.

Keywords: pyrite, pyritum, musculoskeletal trauma, external treatment, protocol, systematic review

INTRODUCTION

Musculoskeletal trauma is a common type of human injury resulting from damage to the muscular or skeletal system, including the bones, muscles, tendons, ligaments, nerves, and blood vessels. Musculoskeletal trauma is the main cause of death and disability worldwide, and [1-5] includes minor injuries, such as contusions, sprains, and strains, to severe injuries, like bone fractures. The degree of injury dictates the level of pain and limitations in the range of motion [4]. Pain associated with musculoskeletal disorders is commonly regarded as a global medical and socioeconomic burden [5, 6].

Because people in modern society are constantly exposed to traumatic injuries caused by sports, and traffic or industrial accidents, the demand for traditional medicines, including Korean medicine (KM) and traditional Chinese medicine (TCM) for traumatic injury, is increasing. Hence, the need for systematic KM treatment for patients with trauma is also growing [4]. In KM and TCM, the concept and main pathology of trauma can be approached by identifying blood stasis [4, 7]. Blood sta-

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sis involves the structural and functional stagnation of blood circulation. Blood stasis is mainly used in traditional medicine to explain the cause of persistent pain during traumatic injury [7]. Herbal medicine prescriptions for blood stasis treatment are recognized.

External treatment of herbal medicines in TCM and KM is a unique method that has been traditionally used for thousands of years [8, 9]. The external treatment method is where the drug is absorbed directly into the affected area or acupuncture point. Because herbal medicines are applied directly to the affected area, they are more effective than orally administered drugs, and can be used in patients who have difficulty taking decoctions. Herbal medicines have been used to treat numerous diseases in TCM and KM using various harmonizing agents [9, 10]. Among the various applications, topical application of herbal medicine is one of the traditional treatment methods used for wounds, muscle pain, spasms, and bruises [11, 12].

Pyritum (pyrite) is a mineral-based drug in Asian traditional medicine with a long history, with the functions of promoting bone formation, healing fractures, removing blood clots, and relieving pain. Because it is a mineral drug, its safety and effectiveness in KM and TCM clinical practices are crucial; therefore, it is generally prescribed in a calcined or processed form [13-16].

The Donguibogam, an encyclopedia that collects Chinese and Korean classical medical books, is one of the representative classics of KM medicine listed as the "Memory of the World." It states that pyritum is neutral in nature, spicy in taste, and nontoxic. Moreover, pyritum heals palpitations, treats fractures, disperses blood, relieves pain, drains pus, eliminates blood stasis, and connects muscles and bones. Pyritum is a bone-attaching medicine, and its qi-regulating and blood-activating effects are strong. It is mainly prescribed for oral administration; however, some books state that an appropriate amount can be powdered and applied externally [13, 17].

In KM clinical practice, although pyritum has often been used alone or as a part of combination therapy, only a few clinical studies have been published [18]. There are even fewer reports of the external use of pyritum than of it being used orally. Recently, many effective herbal medicines and complex prescriptions have been developed as Chinese patent medicines, which are widely used and are significantly effective in TCM clinical practice [19]. Clinical studies using several Chinese patent medicines, including pyritum, as external medicines for musculoskeletal trauma have been described in the literature [20, 21]. However, a systematic literature analysis on the efficacy and safety of the external application of pyritum in musculoskeletal trauma diseases is lacking. We hope to provide an important reference for clinical treatment decisions by presenting reliable research evidence through a systematic review of the efficacy and safety of pyritum external treatment for musculoskeletal trauma.

MATERIALS AND METHODS

Our study protocol is registered in the International Prospective Register of Systematic Reviews (PROSPERO) under accession number CRD42023388673. Our systematic review protocol complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol [22].

Ethical approval was not required for this systematic review, as we did not recruit patients or use individual patient data. The results of this systematic review will provide an effective and reliable basis for external pyritum treatment for musculoskeletal trauma.

1. Study design

A systematic review was used to identify randomized controlled trials (RCTs) evaluating the external treatment effects of pyritum for all types of musculoskeletal traumatic injuries.

2. Study selection (eligibility criteria)

Based on the pre-developed Population, Intervention, Comparison, Outcomes and Study (PICOS) eligibility criteria outlined in Table 1, the eligibility of the studies selected through the literature search were determined.

1) Inclusion criteria

(1) Population

This study included all participants with musculoskeletal trauma, regardless of the type of traumatic injury. No restrictions were placed in terms of sex, age, race, or nationality.

(2) Intervention/Exposure

The experimental intervention group was treated with an external application of pyritum alone or in combination with other therapies. All studies in which external application of pyritum was used as a single treatment or as an adjunct to other treatments for patients with musculoskeletal trauma were in-

Table 1. Inclusion and exclusion criteria

PICOS	Inclusion criteria	Exclusion criteria
Population	All participants with musculoskeletal trauma, regardless of the type of traumatic injury	Animal or cellular studies
Intervention/exposure	External application of Pyritum alone or in combination with other therapies	-
Comparison	All types of control interventions	-
Outcome	Primary outcome: therapeutic efficacy rates Secondary outcomes: pain reduction, pain disappearance time, swelling, joint function, and recovery period.	-
Study design	Randomized controlled trial studies	Non-randomized controlled trials, retrospective clinical studies, literature studies and case studies
Language	No restriction	-
Race or nationality	No restriction	-

cluded, so long as the RCTs involving other treatments provide the same treatment to both the control and intervention groups.

Both external treatment with pyritum alone and concurrent treatment with other therapies were considered acceptable, if the external treatment containing pyritum was only applied to the intervention group and any other treatment was provided equally to both the intervention and control groups.

(3) Comparison

For the comparator intervention group, all types of control interventions were included.

(4) Outcomes

Therapeutic efficacy rates were measured as the primary outcomes. The secondary outcomes were pain reduction, assessed using a visual analog scale, pain disappearance time, swelling, joint function, and recovery period.

(5) Study design

This review comprised randomized controlled trials (RCTs) evaluating the external treatment effects of pyritum for all types of musculoskeletal traumatic injuries without language restrictions.

2) Exclusion criteria

Non-RCTs, retrospective clinical studies, animal or cellular studies, literature studies and case studies were excluded.

3. Search strategy

Eight databases, including EMBASS, PubMed, Cochrane Central Register of Controlled Trials, China National Knowledge Infrastructure, Oriental Medicine Advanced Searching Integrated System, Research Information Service System, National Digital Science Library, and Korean Studies Information Service System, were searched from their inception to March 2023. For any type of musculoskeletal traumatic injury, RCTs involving the external application of drugs containing pyritum (pyrite/zirantong) were considered eligible. There were no restrictions with respect to the publication status, language, or country.

4. Study selection

Two reviewers (JHH and SHC) reviewed all retrieved articles to assess their eligibility for inclusion in our analysis. If any information was unclear, the authors of the article were contacted to obtain additional information. All articles identified in the database were subjected to duplicate identification and qualification evaluation using EndNote X9 software (Clarivate Analytics, New York, USA). After deduplication, two reviewers (JHH and SHC) independently checked the retrieved articles and applied the eligibility criteria based on the titles and abstracts. The PRISMA flow chart for the detailed study selection process is displayed in Fig. 1.

5. Data extraction/Data collection

Data were extracted by reviewers JHH and SHC using a predefined data extraction format. A list of details follows that were included for each study encompassed in the final phase.

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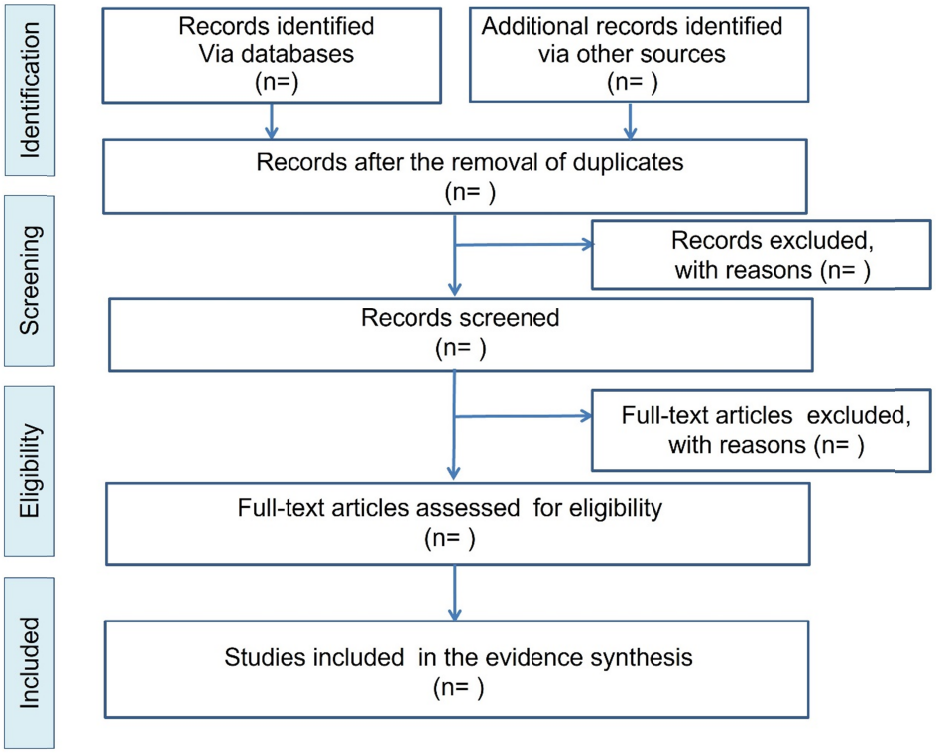

Figure 1. Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram for the identification, inclusion and exclusion of studies.

Any discrepancies or uncertainties arising from the review process were resolved through discussion and consensus among all researchers.

a. First author, title, year of publication, journal name
b. Country
c. Study design (intervention, randomization, blinding, interventional, controlled treatment)
d. Sample size (number of patients)
e. Participant characteristics (ages, sex)
f. Duration of treatment
g. Main outcomes
h. Adverse events
i. Summary of results and key messages

6. Assessment of risk of bias (quality) in included studies

The risk of bias (ROB) was measured using the Cochrane Handbook ROB assessment tool to consider random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessments, incomplete outcome data, selective reporting, and other sources of bias, and two reviewers (JHH and SHC) were involved in the process. If we could obtain the relevant information to perform the assessment from the articles, we contacted the corresponding author for assistance. We only included available data in our primary analysis. The quality assessment was performed independently by two people. If there was a disagreement between the two, the literature was checked again. If the disagreement persisted, it was resolved through a discussion among all the researchers.

7. Data synthesis and analysis strategy for evaluating treatment effects

Our main outcome of interest was the effect of pyritum external treatment, and we analyzed the differences between the pyritum external intervention group and the control group according to the data characteristics. Differences between the intervention and control groups were assessed. Mean differences (MDs) with 95% confidence intervals (CIs) were used to present the continuous data of the treatment effects, and other forms of data were converted to MDs. For outcome variables on different scales, standard MDs with 95% CIs were used, and the dichotomous data of the treatment effects were presented as relative risks (RRs) with 95% CIs. Other binary data were converted to RR values.

All statistical analyses were conducted using the software program Review Manager version 5.4 (The Nordic Cochrane

Centre, The Cochrane Collaboration, Copenhagen, Denmark) for Windows. Because we found enough studies to allow for a meta-analysis, we pooled the data across studies and performed a meta-analysis using a fixed or random effects model. We described them with forest plots to provide an overall summary of pyritum external treatment effect estimates using odd ratios and standardized MDs with CIs for individual studies and overall. GRADEpro from Cochrane Systematic Reviews was used to summarize the findings.

Subgroup or subset analyses have not yet been planned. If there are enough studies per group in terms of specific rating scales to compare the treatment effects of pyrium alone and combined external treatment groups, we will consider subgroup analysis.

RESULTS

This systematic review was reported in compliance with the PRISMA-P statement.

DISCUSSION

Due to continual exposure to traumatic injuries caused by sports, and traffic or industrial accidents, there is a high demand for treatment for various musculoskeletal injuries worldwide. Pyritum, with strong qi-regulating and blood-activating effects, has been prescribed since ancient times for musculoskeletal disorders, especially fractures. External application of herbal medicines is one of the most frequently used treatment methods for patients with musculoskeletal disorders in traditional medicine. However, because pyritum is mainly prescribed for oral administration, there is limited reliable evidence for its effectiveness as an external medicine. Therefore, to provide a reliable basis for the clinical application of pyritum as an external medicine in patients with various musculoskeletal injuries, this study systematically evaluated the current evidence on its effectiveness and safety in external applications. This will provide more treatment options for patients with musculoskeletal trauma and encourage practitioners and researchers to conduct further studies in the future.

However, this systematic review was not without limitations. As a limitation, due to the characteristics of pyritum, a mineral traditional Asian medicine, there may be a possibility of regional bias in studies, and the number of studies may not be sufficient because external treatment is not the main route of administration of pyritum.

CONCLUSION

This study analyzed the efficacy and safety of pyritum external treatment for musculoskeletal trauma. The evidence generated will help clinicians design interventions for the external use of pyritum for this patient group.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding the publication of this paper.

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