

INPLASY PROTOCOL

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None declared.

INTRODUCTION

Review question / Objective: Orthopedic surgeons have long struggled with the delayed union of fractures. Chinese herbal decoction Bushen Tiansui (BSTSD) has shown remarkable clinical effectiveness and safety in the treatment of fractures that

A Systematic Review and Meta-analysis of Bushen Tiansui Decoction's Impact on Delayed Fracture Healing

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Review question / Objective: Orthopedic surgeons have long struggled with the delayed union of fractures. Chinese herbal decoction Bushen Tiansui (BSTSD) has shown remarkable clinical effectiveness and safety in the treatment of fractures that have not yet fully healed. Therefore, in order to confirm the therapeutic benefits of this decoction on delayed fracture healing, we integrated and examined a number of clinical trials that use BSTSD as a treatment regimen.

Eligibility criteria: The outcome indicators of the included literature were extracted, including bone GLA protein (BGP), alkaline phosphatase (ALP), scale score, effective rate, complication rate, etc.; 5) Two researchers checked the data extracted by each other. The researchers discussed and resolved the opinions through discussion.

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have not yet fully healed. Therefore, in order to confirm the therapeutic benefits of this decoction on delayed fracture healing, we integrated and examined a number of clinical trials that use BSTSD as a treatment regimen.

Rationale: Chinese Biomedical Literature Database, Wanfang database, Chinese Scientific Journals Database, Web of Science, PubMed, Embase, and Cochrane library databases were all used throughout the search. The deadline date for inclusion was September 13, 2022, and randomised controlled studies that incorporated the BSTSD therapy for delayed fracture healing were chosen. The outcome measure from which data were taken was the incidence of negative consequences. Using the Cochrane Collaboration's risk assessment technique, each category's contained literature's calibre was evaluated separately. The Cochrane Collaboration's RevMan software was used for the meta-analysis of the data, while Stata was utilised for the sensitivity analysis.

Condition being studied: One of the most common injuries to the musculoskeletal system, a bone fracture, can occur because of numerous reasons and can be of various types (Jiao et al., 2020). Fractures were usually caused by traffic accidents, industrial accidents, and sports injuries (Xiao-Dong et al., 2020). Recently, the number of accidents that lead to fractures has gradually increased (Liu et al., 2022). Repair after rupture is a complex process. The usually healed bone tissue can return to a stable structure and hardness as before the fracture, restoring the standard skeletal space shape (Ding et al., 2022). Despite most fractures healing without delay, 5%–10% of patients experience non-union or delayed fracture healing (hereafter collectively referred to as DFH) (Jyotsna et al., 2017). The latest data on open fractures of long bones show that up to 17% of patients develop non-union, while about 8% show delayed union (Jiang et al., 2019). The process leading to the delayed union of bone tissue is usually the initial intramembranous ossification after a fracture that terminates in response before the bone tissue is fully connected (Li et al., 2021). At the same time, non-union may be caused by the cessation of intramembranous ossification of the fracture tissue and the lack of after the cessation of intraosseous ossification—a valid connection (Kim et al., 2018). The scar

tissue in the fracture gap, insufficient stability of the fracture end, and a large amount of cartilage than callus tissue during the callus formation are the most notable factors that lead to delayed union or non-union of fractures (Marongiu et al., 2020).

METHODS

Search strategy: Chinese Biomedical Literature Database, Wanfang database, Chinese Scientific Journals Database, Web of Science, PubMed, Embase, and Cochrane library databases were all used throughout the search. The deadline date for inclusion was September 13, 2022, and randomised controlled studies that incorporated the BSTSD therapy for delayed fracture healing were chosen. The outcome measure from which data were taken was the incidence of negative consequences. Using the Cochrane Collaboration's risk assessment technique, each category's contained literature's calibre was evaluated separately. The Cochrane Collaboration's RevMan software was used for the meta-analysis of the data, while Stata was utilised for the sensitivity analysis.

Participant or population: The inclusion criteria are as follows: 1) The test subjects were patients with a definite diagnosis of delayed fracture union, and the diagnostic criteria for delayed fracture union are listed in the article; 2) The experimental group (BSTSD group) used BSTSD as an interventional treatment measure or adjuvant treatment measures, while the control group (conventional treatment group) was treated with conventional surgery (autologous bone grafting, reaming surgery, etc.) or other drug treatments (GS, NSAIDs, etc.); 3) Outcome indicators: The text clearly specifies clinical efficacy indicators or safety evaluation indicators; 4) Research design: The study was a randomized controlled trial; 5) Reporting language: We imposed no restriction on the language used in the literature.

Intervention: The literature screening steps are as follows: 1) Two researchers used the

Citavi software to screen the literature independently; 2) Duplicate studies were removed; 3) The title, bibliography, abstract, and other parts were read and preliminarily screened according to the established inclusion and exclusion criteria; 4) When the researchers read the full text of the literature that fulfilled the inclusion criteria and could not determine whether to exclude it or not, they included it only after reading the full text twice; 5) Two researchers checked each other's included literature, and in case of a disagreement, asked the third researcher to arrive at a consensus.

Comparator: The experimental group (BSTSD group) used BSTST as an interventional treatment measure or adjuvant treatment measures, while the control group (conventional treatment group) was treated with conventional surgery (autologous bone grafting, reaming surgery, etc.) or other drug treatments (GS, NSAIDs, etc.).

Study designs to be included: The experimental group (BSTSD group) used BSTST as an interventional treatment measure or adjuvant treatment measures, while the control group (conventional treatment group) was treated with conventional surgery (autologous bone grafting, reaming surgery, etc.) or other drug treatments (GS, NSAIDs, etc.).

Eligibility criteria: The outcome indicators of the included literature were extracted, including bone GLA protein (BGP), alkaline phosphatase (ALP), scale score, effective rate, complication rate, etc.; 5) Two researchers checked the data extracted by each other. The researchers discussed and resolved the opinions through discussion.

Information sources: The search was completed according to the proposed search strategy, and 33 relevant documents were obtained, including two articles in PubMed, four in Cochrane Library, three in Embase, four in the Web of Science, seven in CNKI, 11 in Wanfang, one in CSJD-VIP, one in CBM, and no article supplemented by other resources. Using the Citavi

software and manual literature screening strategy, after reading the title, bibliography, full text, and reviews, 26 papers were excluded, and seven papers were finally decided to be included. The literature screening process is depicted in Figure 1.

Main outcome(s): BSTSD has good clinical efficacy in the adjuvant treatment of DFH. It is considered safe and worthy of clinical application when used to treat DFH. Clinically, BSTSD is combined with conventional surgery to treat DFH and significantly improve the clinical efficacy of DFH, including improving bone metabolism indexes BGP and ALP, improving Harris hip score, and reducing the incidence of complications. To further improve the application of BSTSD in the treatment of DFH, multi-center high-quality clinical research and laboratory research can be conducted to determine its. In review9 pharmacological mechanism and target and improve the TCM compound to increase the therapeutic effect.

Quality assessment / Risk of bias analysis: The effective rate of BSTSD adjuvant treatment for delayed fracture healing was 239 used as the standard error (SE) in the meta-analysis as the Y-axis. The RR was used as the X-axis to draw a vulnerability map, as shown in Figure 12. The results show that all scatter points are in the vulnerability map, and the distribution patterns are concentrated, indicating low publication bias. However, the lack of included studies still cannot fully explain the problem of bias.

Strategy of data synthesis: All the obtained data were summarized and analyzed. The data analysis process was as follows: 1) Analysis by independent data statisticians; 2) Meta-analysis using the RevMan software (version 5.4.1) provided by Cochrane Collaboration; 3) Dichotomous variables using the hazard ratio or relative risk (RR) was used as the effective index, and the weighted mean difference (WMD) was selected as the effective index for continuous variables when the measurement units of the included

literature were consistent, and the standard mean difference (SMD) was selected as the effective index when the units were inconsistent; 4) The point estimates and 95% confidence intervals (95% CI) of each effect size are expressed, and $P < 0.05$ was regarded as statistically significant; 5) The heterogeneity was obtained by the Q test, the probability was obtained by chi-square test, and the quantification by I^2 . The degree of consistency of description was used to evaluate the heterogeneity. For $I^2 < 50\%$ and $P \geq 0.1$, the heterogeneity was considered minor, and a fixed-effect model was selected for analysis. For $I^2 \geq 50\%$ and $P < 0.1$, the heterogeneity was considered significant. The random-effects model was used for analysis. If the analysis results still showed significant heterogeneity, the reasons for the heterogeneity were searched. The Stata software (version 16.0) was used to conduct a sensitivity analysis of the reasons for the heterogeneity; 6) The funnel plot was used to ascertain whether there existed any publication bias.

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Subgroup analysis: Due to the close baseline indicators of the sample data and no significant characteristic differences, subgroup analysis was not conducted.

Sensitivity analysis: We imported the BGP and ALP data into the R software for sensitivity analysis considering the 246 heterogeneity. The results showed that all studies were significant, indicating that the outcome 247 indicators were stable. The sensitivity analysis results of BGP and ALP are shown in Supplementary 248 Figures S2 and S3, respectively.

Country(ies) involved: China.

Keywords: delayed fracture healing, Bushen Tiansui decoction, traditional Chinese medicine⁹ decoction, meta-analysis, Chinese medicine compound.

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