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INPLASY

The efficacy and safety of different fixation methods for acute syndesmosis injuries: protocol for a network meta-analysis of randomized and observational studies

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 06 August 2024 and was last updated on 06 August 2024.

INTRODUCTION

Review question / Objective Acute unstable syndesmosis injuries require accurate reduction and stable fixation to improve short and long term outcomes. There are several different fixation methods for acute syndesmosis injuries, with pros and cons of each. The objective of this network meta-analysis of randomized and observational studies is to explore which is the optimal fixation method for acute syndesmosis injuries.

Condition being studied The tibiofibular syndesmosis is essential for ankle stability and weight transmission. Tibiofibular syndesmosis injuries are quite frequent in clinical orthopaedics. It is estimated that 5% to 10% of all ankle sprains, and 39% to 45% of operatively treated ankle fractures involve tibiofibular syndesmosis injuries. The anatomy and biomechanics are well understood, but the timely diagnosis and reasonable treatment are sometimes very difficult, leading to underestimation and secondary joint degeneration at last.

Most isolated syndesmosis injuries, or so-called high ankle sprains, are treated conservatively. Acute syndesmosis injuries with ankle fractures are usually unstable, requiring accurate reduction and stable fixation. Being considered as the gold standard, the metallic syndesmosis screws still have some drawbacks, such as the need for secondary screw removal, screw loosening or breakage. For these reasons, more new fixation methods have been introduced to the clinical practice. For example, the suture button has become a promising fixation method for acute syndesmosis injuries. However, the optimal fixation method for acute syndesmosis injuries remains controversial.

Previous meta-analyses had made great efforts to compare the different fixation methods, but these studies all had significant limitations and did not provide reliable results. The 2023 meta-analysis by Xu et al. showed that suture-button had significantly better functional scores and lower reoperation rates and local irritation rates for patients with syndesmosis injuries. In another study by Liu et al., the authors found that dynamic fixation had significantly improved functional

scores than the metal screw and bioabsorbable screw fixation methods. However, these two meta-analyses were all traditional pairwise meta-analysis, with direct comparison of only two interventions. In contrast, network meta-analysis (NMA) is a newly developed and established method of evidence-based medicine. NMA can compare multiple (two or more) interventions directly and indirectly, even if there is no direct head-to-head comparison. NMA allows to rank the estimated effects of each from best to worst. It has been increasingly used in the healthcare system.

In 2020, Grassi et al. conducted a meta-analysis that included seven randomized controlled trials (RCTs) to compare the efficacy of dynamic fixations and screw fixation. The number of included RCTs was still small. The review did not include "real-world" evidence from studies beyond RCTs. The results had comparable limitations to an extent. In 2022, the GRADE Working group suggested that health decision-makers should comprehensively weigh the advantages and disadvantages of RCTs and observational studies, and give a full play of observational studies. In 2024, an updated Cochrane systematic review found that there was no substantial difference in significant effect estimates between RCTs and observational studies in meta-analyses.

To better understand fixation methods for acute syndesmosis injuries, we will conduct a comprehensive network meta-analysis combining RCTs and observational studies. The goal is to compare the efficacy and safety of different fixation methods in the treatment of acute syndesmosis injuries.

METHODS

Search strategy We will comprehensively search five electronic databases, including PubMed, the Cochrane Library, CNKI (China National Knowledge Infrastructure), Wanfang Data, and Embase. The literature published up to July 29, 2024, related to the fixation methods for acute tibiofibular syndesmosis injuries will be collected. The search strategy will employ a combination of subject terms and free-text keywords. The search strategy for the PubMed database is presented in supplement file 2. We will also search the clinical trial registry websites for unpublished or gray literature (http://clinicaltrials.gov/, http://www.chictr.org/cn/). The reference lists of included studies will also be further retrieved. Studies will be limited to English or Chinese.

Participant or population The review will include data from adult patients aged between 18 and 60 years with acute syndesmosis injuries, who were diagnosed by radiological evidence or intraoperative confirmation test. Patients with a prior history of ankle ligament injuries or fractures will be excluded. Biomechanical studies will not be included.

Intervention This study will include the studies comparing at least two of the following interventions: metallic syndesmosis screw, Endo-Buttons, Suture-Buttons (TightRope or ZipRope), bioabsorbable screw, elastic syndesmosis hook plate, anterior inferior tibiofibular ligament (AITFL) repair with suture anchor, AITFL repair with suture anchor combining screw, Nice knot elastic fixation, hybrid fixation (suture-button combining screw). Single or two 3.5/4.5-mm screws penetrating 3 or 4 layers of syndesmosis cortical bone are all included.

Comparator The patients who treated by any of the above interventions will be considered as the comparator.

Study designs to be included Both RCTs and observational studies will be included. We will exclude case reports, case series, or reviews. The literature with a follow-up period of less than six months will not be included.

Eligibility criteria The review will include data from adult patients aged between 18 and 60 years with acute syndesmosis injuries, who were diagnosed by radiological evidence or intraoperative confirmation test. Patients with a prior history of ankle ligament injuries or fractures will be excluded. Biomechanical studies will not be included.

Information sources We will comprehensively search five electronic databases, including PubMed, the Cochrane Library, CNKI (China National Knowledge Infrastructure), Wanfang Data, and Embase. The literature published up to July 29, 2024, related to the fixation methods for acute tibiofibular syndesmosis injuries will be collected. The search strategy will employ a combination of subject terms and free-text keywords. We will also search the clinical trial registry websites for unpublished or gray literature (http://clinicaltrials.gov/, http://www.chictr.org/cn/). The reference lists of included studies will also be further retrieved. Studies will be limited to English or Chinese.

Main outcome(s) The functional outcome, radiological indicators, postoperative complications at 3, 6, and 12 months post-surgery and final follow-up will be included. The most

commonly used scoring systems for the functional outcome are the American Orthopaedic Foot & Ankle Society (AOFAS) ankle-hindfoot scale, the Olerud-Molander Ankle (OMA) scale, the visual analog scale (VAS) and the time to full weight bearing. The AOFAS scale is divided into subjective (pain, function) and objective (alignment), with 100 being the best result. The OMA scale is a patient self-administered questionnaire, which has been recommended for scientific investigations. Radiological indicators comprise postoperative tibiofibular clear spaces (TFCS), postoperative tibiofibular overlap (TFO) and medial clear spaces (MCS) in the plain film. In addition, postoperative complications, such as surgical site infection, implant irritation, fixation failure, malreduction, and reoperation (not including planned implant removal), will be evaluated.

Data management Two reviewers (SW and TD) will independently extract data from all final included studies according to the standardized data extraction table. The following information will be extracted: publication (e.g., author, publication year, country), study design (e.g., randomization process, blinding method, follow-up duration), participants (e.g., sample size, age, sex distribution, injury mechanism, concomitant injuries or fractures,), intervention characteristics (e.g., the detailed fixation method in each group, number of screws, number of cortices engaged, time to full weight-bear), and relevant outcomes data. We will extract data from the graphs through the Engauge Digitizer software if relevant information is provided in the figures. If some data cannot be directly obtained from the papers, we will try to contact the authors to obtain those data. Any disagreement between the two reviewers will be resolved by another reviewer (SJ).In cases where analyses of RCTs were performed by both intention-to-treat and per-protocol, only the data from the ITT will be adopted.

Quality assessment / Risk of bias analysis The risk of bias of all RCTs and observational studies will be assessed by the Cochrane risk-of-bias tool (RoB 2) and the Newcastle-Ottawa Scale (NOS), respectively. Two reviewers (SW and XY) will conduct the risk of bias assessment independently, and any disagreement will be resolved by a discussion with another reviewer (GQ).

Strategy of data synthesis 1 Pairwise meta-analyses
If there are at least three studies provide related data, conventional pairwise meta-analyses between different interventions will be performed. The evidence from RCTs and observational studies will be analyzed separately. For postoperative complications, the effect size will be assessed by relative risk (RR) and corresponding 95% confidence intervals (CIs). For differences in functional scores and radiological indicators, the effect size will be assessed by weighted mean difference (MD) and corresponding 95% CIs. We will apply the DerSimonian-Laird random effects model to pool outcome data, using Review Manager software Version 5.3. The I2 statistic will be used to assess the heterogeneity of the included studies. I2 values of more than 50% suggest substantial variability between studies. The trial sequential analysis (TSA) will be applied to calculate the required information size. The type I error is defined as 0.05, and relative risk reduction (RRR) is defined as 15%.
2 Network meta-analyses
The three-level Bayesian hierarchical model will be used to explicitly analyse the data in this NMA incorporating evidence of RCTs and observational studies. First, the network meta-analyses will be performed using RCTs and observational studies data separately. Second, the results from randomized and observational studies will be combined without bias adjustments. Third, the analysis from step 2 will be repeated incorporating the bias adjustments. The NMA will be performed using Markov Chain Monte Carlo (MCMC) simulation, with a burn-in of 10,000 iterations and sampling of 50,000 iterations. The network geometry will be applied to show all the interactions among the included studies. The global and local consistency between the direct and indirect evidence will be evaluated by the design-by-treatment interaction model and node-splitting analysis individually. The relative rankings for each intervention will be assessed according to the surface under the cumulative ranking curve (SUCRA) values and rankograms. All statistical analyses will be implemented with R software Version 4.1.2.

Subgroup analysis For our pairwise analyses, we plan to undertake subgroup analyses to investigate the heterogeneity of included studies, such as the number of screws used, fracture types (Weber type B or C, pronation-external rotation or supination-external rotation), three or four cortical bones.
Sensitivity analysis For both pairwise and network meta-analyses, we will conduct sensitivity analyses to detect whether pooled results are sensitive to the removal of studies with a high risk of bias overall.

Country(ies) involved China.

Keywords syndesmosis injuries, fixation methods, network meta-analysis, randomized controlled trials, observational studies, protocol.

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