INPLASY PROTOCOL

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Review Stage at time of this submission: Preliminary searches.

Conflicts of interest:
There is no conflict of interest.

Comparison of the effectiveness of autologous grafts for anterior cruciate ligament reconstruction: protocol for an overview of systematic review and network meta-analysis

Jin, J[1]; Fang, P[2]; Hu, Z[3]; Chen, J[4]; Wang, R[5]; Wang, X[6].

Review question / Objective: To evaluate the methodological quality of published systematic reviews on the efficacy of different autografts in anterior cruciate ligament reconstruction, and conduct a network meta-analysis of randomized controlled trials that meet the requirements in them.

Condition being studied: Anterior cruciate ligament (ACL) rupture is a common motor system injury, and the most effective treatment is anterior cruciate ligament reconstruction(ACLR). Choosing the right graft is an important factor to ensure the success of the surgery. Current research shows that the clinical effect of autologous ligaments is better than that of allogeneic ligaments and artificial ligaments. However, there are differences between the autogenous ligaments, and how to choose them is still controversial. This study evaluated the published systematic reviews (SRs) on the efficacy of different autologous ligament grafts in ACLR, and based on this, conducted a network meta-analysis (NMA) of related randomized controlled trials (RCTs).

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 14 September 2020 and was last updated on 14 September 2020 (registration number INPLASY202090061).

INTRODUCTION

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METHODS

Search strategy: We comprehensively searched the databases including PubMed, Embase, Web of Science, Cochrane Library, Chinese biomedical literature database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang Database. There are no restrictions on the search. All searches were until August 31, 2020. Grey literature and references included in the literature will also be reviewed. We combined medical subject headings (MeSH) and free words with boolean logical operators to construct a search strategy, the search terms include "Anterior cruciate ligament", "Reconstruction", "Autograft", "Systematic review", "meta-analysis", etc. The search strategies were formulated separately according to the characteristics of each database.

Participant or population: Clinical diagnosis of anterior cruciate ligament rupture, the first time to receive anterior cruciate ligament reconstruction, and the patient's age, gender, nationality, race, injury time is not limited.

Intervention: All types of autologous tendon grafts, including bone-patellar tendon-bone, quadriceps tendon, hamstring tendon, peroneus longus tendon, etc.

Comparator: Different types of autologous ligament grafts.

Study designs to be included: Systematic reviews and meta-analyses that meet the inclusion and exclusion criteria and the RCTs included in them.

Eligibility criteria: Inclusion criteria (1) Participations: Clinical diagnosis of anterior cruciate ligament rupture, the first time to receive anterior cruciate ligament reconstruction, and the patient's age, gender, nationality, race, injury time is not limited (2) Intervention: All types of autologous tendon grafts, including bone-patellar tendon-bone, quadriceps tendon, hamstring tendon, peroneus longus tendon, etc (3) Comparator: Different types of autologous ligament grafts (4) Outcomes: The main outcome indicators include IKCD score, clinical failure rate (including revision surgery, graft rupture, +2 pivot shift or higher, and side-to-side arthrometer difference >5 mm), Lachman test, Lysholm score, instrument laxity test, joint range of motion, Tegner score, complications. (5) Peer-reviewed articles published in Chinese or English (6) SRs including RCTs, meta-analysis results, and consistent with established PICO. Exclusion criteria (1) Animal research (2) Letters, conference papers (3) Descriptive research (4) Full text is not available (5) Repeated publications (6) Important data are missing and cannot be obtained after contacting the authors.

Information sources: We comprehensively searched the databases including PubMed, Embase, Web of Science, Cochrane Library, Chinese biomedical literature database (CBM), Chinese National Knowledge Infrastructure (CNKI), and Wanfang Database. There are no restrictions on the search. All searches were until August 31, 2020. Grey literature and references included in the literature will also be reviewed. If important information is

missing in the article, we will get it by contacting the author.

Main outcome(s): The main outcome indicators include IKCD score, clinical failure rate (including revision surgery, graft rupture, +2 pivot shift or higher, and side-to-side arthrometer difference >5 mm), Lachman test, Lysholm score, instrument laxity test, joint range of motion, Tegner score, complications.

Quality assessment / Risk of bias analysis: AMSTAR2 is an instrument for rigorously evaluating the systematic review of randomized controlled clinical trials which contains 16 items and 7 of them are critical items.It can be evaluated as "Yes", "Partial Yes", "No" or "No meta-analysis conducted". Furthermore, based on critical items, the overall confidence in the results of SRs can be divided into four levels: high, moderate, low, and critically low. We will use the GRADE to assess the quality of evidence. The limitations of research, consistency of effect, imprecision, indirectness, and publication bias will be mainly considered.Before the assessment, the evidence quality of all results is assumed to be "high" and will eventually be evaluated as "high", "moderate", "low" or "very low".The Cochrane's risk of bias tool will be used to assess the bias risk of included RCTs. For each result, it will be assessed according to the evaluation criteria as low risk of bias, high risk of bias, and uncertain bias or lack of relevant information. The evaluation process is completed independently by two reviews, and if there is a disagreement, it will be discussed and resolved with the third.

Strategy of data synthesis: We will conduct a descriptive analysis of the included SRs and present them in a table. The differences in the methodological quality of the SRs will be presented by drawing bubble charts, which also includes information on the number of RCTs contained in the SRs and the types of interventions.The network evidence map will be drawn to compare the relationship between different interventions directly or indirectly. The odds ratio (OR) and its 95%

confidence interval (CI) will be used to synthesize the results of the dichotomy, while the mean difference (MD) and its 95% confidence interval (CI) will be used for continuous variables. $P < 0.05$ was considered to be statistically significant. Heterogeneity analysis will be conducted for the studies included, and the I2 value represents the strength of heterogeneity. If I2≤50%, it means that there is a low heterogeneity and the fixed effects model will be adopted. If I2≥50%, it means that the heterogeneity is high, and the source of the heterogeneity will be further analyzed, and the random-effects model will be adopted after the heterogeneity is excluded. Studies with high heterogeneity will be subjected to subgroup analysis or sensitivity analysis. The Egger test and funnel chart will be used to assess potential publication bias. NMA combines direct and indirect evidence within the Bayesian framework and uses WinBUGS statistical software (version 1.4.3) to implement Markov Chain Monte Carlo (MCMC) method. The SUCRA graph predicts the efficacy of each graft. SUCRA is a ratio, expressed as the percentage of the efficiency of intervention to the result.When the treatment effect is better, the value is closer to 100%, and vice versa, the value is closer to 0%. The node-splitting model assesses the inconsistency of this network meta-analysis. A significance level of less than 0.05 is interpreted as inconsistent evidence.

Subgroup analysis: According to the results of data extraction and analysis, we will analyze different subgroups such as gender, age, and different surgical methods, etc. If possible, we will do some additional subgroup analyses based on the results of heterogeneity and inconsistency.

Sensibility analysis: If the evidence is sufficient, we will conduct a sensitivity analysis to exclude those important data missing, low quality or small studies, and high risk of bias trials to ensure the stability of the results.

Language: The Language is limited to English and Chinese.

Country(ies) involved: China.

Keywords: anterior cruciate ligament reconstruction, autograft, overview, systematic review, network meta-analysis.

Contributions of each author:
Author 1 - Jiaxin Jin - Conceived this study and revised the manuscript.
Author 2 - Pengzhong Fang - Constructed a search strategy and drafted the manuscript.
Author 3 - Zhiwei Hu - Literature screening, data extraction, and drafted the manuscript.
Author 4 - Jinlei Chen - Literature screening and data extraction.
Author 5 - Ruirui Wang - Literature screening and data extraction.
Author 6 - Xin Wang - Conceived this study and provide methodological and clinical guidance.