INPLASY PROTOCOL

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The authors have no conflicts of interest to disclose.

Impact of the numbers of injections of platelet rich plasma on the clinical outcomes in patients with knee osteoarthritis: a protocol for an updated network meta-analysis

Wang, P[1]; Li, K[2]; Jiang, Z[3]; Qiu, B[4]; Nie, C[5]; Luo, H[6]; Li, Z[7].

Review question / Objective: **Two published meta-analyses have investigated the effects of the number of injections of platelet rich plasma (PRP) on clinical outcomes in knee osteoarthritis patients, however multiple injections including double and triple options were not investigated separately. So, it is unclear the appropriate number of injections of PRP in patients with KOA.**
Information sources: **Because previous topic-related meta-analysis searched all potential citations published between 1970 to July 2019, we will therefore perform an additional search to capture any potential records reported between August 2019 and October 2020. The additional search will be conducted by two independent reviewers in PubMed, Embase, and China National Knowledgement Infrastructure (CNKI). We will use the combination of text words and MeSH terms to construct a search strategy and amend to be applicable to individual database according to the unique requirements of each database. The search strings of all targeted databases were documented in Table S2. We will also manually check the reference lists of all eligible studies and meta-analyses tin order to include any potential studies.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 10 November 2020 and was last updated on 10 November 2020 (registration number INPLASY2020110043).

INTRODUCTION

Review question / Objective: **Two published meta-analyses have investigated the effects of the number of injections of platelet rich plasma (PRP) on clinical outcomes in knee osteoarthritis patients, however multiple injections including double and triple options were not investigated separately. So, it is unclear the appropriate number of injections of PRP in patients with KOA.**

Rationale: As a common disabling disease, KOA has been estimated to affect more than 250 million people worldwide. It is noted that articular cartilage regeneration is very difficult; once damaged, it is difficult to repair. Although knee replacement surgery provides an effective solution for severe knee KOA, the Osteoarthritis Society International (OARSI) recommends conservative treatment rather than surgery as the first-line management solution for KOA, which emphasizes the importance of conservative treatment in the treatment of KOA. As one of the conservative treatments, injectable medications such as hyaluronic acid (HA), steroids, nonsteroidal antiinflammatory drugs, and platelet-rich plasma (PRP) have been proved having ability of promoting the regeneration in tissue and alleviation of symptoms. Among injectable options for symptom relief and functional improvement in patients with knee OA, PRP has increased in popularity in recent years. Several systematic reviews and meta-analyses have further determined the potential of PRP in treating KOA.

Condition being studied: After demonstrating the efficacy of PRP for the treatment of KOA, researchers and practitioners changed attention to further explore the optimal numbers of PRP injection. To date, several randomized controlled trials focused on this topic have been reported, and a recent meta-analysis has also compared clinical effectiveness of single versus multiple injections of platelet-rich plasma in the treatment of knee osteoarthritis and suggested that a single injection was as effective as multiple PRP injections in pain improvement; however, multiple injections seemed more effective in joint functionality than a single injection at 6 months. Moreover, a recent network meta-analysis also investigated the comparative efficacy of single between multiple injections for the treatment of KOA, and found no significant difference of these two regimes for pain relief and improvement of joint function. Unfortunately, two previous meta-analyses all missed some eligible studies, which obviously impaired the robustness of pooled results. Moreover, these two meta-analyses only investigated the comparative efficacy of single and multiple injections, multiple injections including double and triple options were not investigated separately.

METHODS

Participant or population: Patients who were clinically and radiographically diagnosed with KOA.

Intervention: PRP injections.

Comparator: PRP injections.

Study designs to be included: Only randomized controlled trials will be considered.

Eligibility criteria: Generally speaking, patients who were clinically and radiographically diagnosed with KOA defined by any recognized diagnosis criteria, and with a minimum follow-up of 3 months were deemed to be eligible. We will only consider randomized controlled trials (RCTs) investigating the effect of the number of PRP injections regardless of category on clinical outcomes including pain (measured with visual analog scale [VAS] or visual numerical scale [VNS]) and joint function (measured with Western Ontario and McMaster Universities Arthritis Index [WOMAC], International Knee Documentation Committee [IKDC] subjective knee evaluation form, or Lequesne index [LI]) among KOA patients. Only research reported in English or Chinese language will be considered to be eligible.

Information sources: Because previous topic-related meta-analysis searched all potential citations published between 1970 to July 2019, we will therefore perform an additional search to capture any potential records reported between August 2019 and October 2020. The additional search will be conducted by two independent reviewers in PubMed, Embase, and China National Knowledgement Infrastructure (CNKI). We will use the combination of text words and MeSH terms to construct a search strategy

and amend to be applicable to individual database according to the unique requirements of each database. The search strings of all targeted databases were documented in Table S2. We will also manually check the reference lists of all eligible studies and meta-analyses tin order to include any potential studies.

Main outcome(s): We will consider pain (measured with visual analog scale [VAS] or visual numerical scale [VNS]) and joint function (measured with Western Ontario and McMaster Universities Arthritis Index [WOMAC], International Knee Documentation Committee [IKDC] subjective knee evaluation form, or Lequesne index [LI]) among KOA patients as the outcomes of interesting.

Quality assessment / Risk of bias analysis: We will grade the quality of each eligible study according to the assessment result of the risk of bias, which will be appraised with the Cochrane risk of bias assessment tool. Risk of bias will be examined according to the following six domains: randomization, allocation, blind, incomplete data, selectively reported and other bias sources. A study will be allocated to have a label of 'low', 'unclear', or 'high' risk of bias according to the match level between actual information and criteria. Any divergence at risk of bias will be resolved by a third senior investigator. Eventually, we will obtain the overall quality of an individual study (low, moderate or high quality) according to the result of labelling of the risk of bias.

Strategy of data synthesis: We will express it as standard mean difference (SMD) with 95% confidence interval (CI). We will firstly qualitatively inspect the heterogeneity across studies with the Chinese square test (Q statistic), and then quantitatively estimate the heterogeneity using I2 statistic. All studies will be thought to be homogenesis when $P > 0.10$ and $I2 < 50\%$. For studies reporting the standard error of the mean (se), we will calculate the standard deviation (sd) according to the method recommended by Cochrane handbook. When not able to obtain the SD of a record after trying to contact the study authors, we will use the range-rule-of-thumb method to estimate the missing SD. Moreover, we will use net changes in measurements, which will be estimated using the method recommended by Cochrane handbook to estimate the efficacy of all treatments. A P value < 0.05 will be defined as the threshold for statistical significance. We will perform traditional direct meta-analysis based on the random effects model depending on the Review Manager (RevMan) version 5.3. We will drew funnel plot to inspect the possibility of presence of publication bias when the accumulated number of eligible studies for individual outcome was greater than 10. After investigating direct comparisons of single versus multiple injections, single versus double injections, and single versus triple injections, we will also perform network meta-analysis to investigate the comparative efficacy of double and triple injections with OpenBUGS software version 3.2.3 following methods described by Lu and Ades. We will use the initial value which will be automatically generated from software to fit the model. To gain convergence, we will perform each Markov chain Monte Carlo chain with 50000 iterations and 20000 burn-in. The summary treatment effect estimates will be described as SMD, with 95% credible interval (CrI), for treatment comparisons.

Subgroup analysis: No subgroup analysis will be performed in the current meta-analysis.

Sensibility analysis: No sensitivity analysis will be performed in the current meta-analysis.

Language: English and Chinese.

Country(ies) involved: China.

Keywords: knee osteoarthritis, platelet-rich plasma, intra-articular injection, number of injection, meta-analysis.

Dissemination plans: We will communicate our findings through participating in

academic conferences or submitting it to be considered for publication in peer reviewed journal.

Contributions of each author:

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Author 2 - Kai Li.
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