INPLASY PROTOCOL

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The authors declare that they have no conflict of interest.

Effect of platelet-rich plasma injections on mild or moderate carpal tunnel syndrome: an updated systematic review and meta-analysis of randomized controlled trials

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Review question / Objective: **P: carpal tunnel syndrome. I: platelet-rich plasma injection. C: placebo O: visual analogue scores (VAS) and Boston Carpal Tunnel Questionnaire (BCTQ) as evaluation tools for primary outcomes. Second outcomes comprised cross sectional area (ΔCSA) and electro-physiological indexes including distal motor latency (DML), sensory peak latency (SPL), motor conduction, sensory nerve conduction velocity (SNCV), compound muscle action potential (CMAP), and sensory nerve action potential (SNAP). S: randomized controlled trials.**
Information sources: **Firstly, a total of 34 studies (Pubmed:8, Web of science: 9, Embase: 13, Cochrane library: 4) were identified. Afterwards, we reviewed abstracts and titles of included studies, selected the relevant information, removed duplication independently and 20 studies were selected. Finally, 9 RCTs were screened out after reading the full text**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 21 October 2020 and was last updated on 21 October 2020 (registration number INPLASY2020100077).

INTRODUCTION

Review question / Objective: **P: carpal tunnel syndrome. I: platelet-rich plasma injection. C: placebo O: visual analogue scores (VAS) and Boston Carpal Tunnel Questionnaire (BCTQ) as evaluation tools for primary outcomes. Second outcomes comprised cross sectional area (ΔCSA) and electrophysiological indexes including distal motor latency (DML), sensory peak latency (SPL), motor conduction, sensory nerve conduction velocity (SNCV), compound muscle action potential (CMAP),**

and sensory nerve action potential (SNAP). S: randomized controlled trials.

Condition being studied: Carpal tunnel syndrome (CTS) is one of most disturbing entrapment neuropathy in upper limbs affecting up to 5% of the adult population. For mild to moderate CTS, conservative treatments are preferred. Since 2014, platelet-rich plasma (PRP) has gradually emerged in neuropathy, with admissible success rates. PRP is an autologous blood product collected and centrifuged from patient's blood and comprises a high concentration of platelets. Additionally, several high concentration of growth factors are believed to play crucial roles in tissue regeneration and healing either. When PRP is injected to patients themselves, aforementioned ingredients promotes wound healing, angiogenesis, and improves axonal regeneration in the entrapment area. Recently, the profit regarding nerve fiber regeneration was also demonstrated in an animal study. Nevertheless, long-term clinical outcome of PRP and the placebo effect remains unknown. What's more, it is reported that the concentrations less than 4 to 6 times or higher than 8 times may be ineffective or conversely inhibits the healing process. Indeed, the argument did exist about centrifugation technique and the enrichment percentages of blood.

METHODS

Participant or population: Carpal tunnel syndrome.

Intervention: Platelet-rich plasma injection.

Comparator: Placebo.

Study designs to be included: Randomized controlled trials.

Eligibility criteria: All RCTs of extracorporeal PRP with placebo controls for the management of patients with CTS were included in this study. The primary outcomes will be assessment of pain symptom using the visual analogue scores (VAS) and Boston Carpal Tunnel Questionnaire (BCTQ), which was designed definitely for CTS. BCTQ contains of 2 distinct scales, Symptom Severity Scale (BCTQs) and Functional Status Scale (BCTQf). Secondary outcomes involved cross sectional area (CSA) and clinical results of nerve electrophysiology related to motor and sensory nerves.

Information sources: Firstly, a total of 34 studies (Pubmed: 8, Web of science: 9, Embase: 13, Cochrane library: 4) were identified. Afterwards, we reviewed abstracts and titles of included studies, selected the relevant information, removed duplication independently and 20 studies were selected. Finally, 9 RCTs were screened out after reading the full text.

Main outcome(s): The primary outcomes will be assessment of pain symptom using the visual analogue scores (VAS) and Boston Carpal Tunnel Questionnaire (BCTQ), which was designed definitely for CTS. BCTQ contains of 2 distinct scales, Symptom Severity Scale (BCTQs) and Functional Status Scale (BCTQf).

Additional outcome(s): Secondary outcomes involved cross sectional area (CSA) and clinical results of nerve electrophysiology related to motor and sensory nerves.

Quality assessment / Risk of bias analysis: A total of 9 RCTs published with 434 patients between 2016 and 2020 were finally included in this meta-analysis. Characteristics of all studies are shown in Table 1. All studies compared clinical outcomes of PRP injection versus other conservative treatments for management of mild to moderate CTS. Besides, control groups comprised corticosteroid injection in 5 trials , saline injection in 1 trial , splint in 2 trials and blank control in 1 trial. Of the 9 included studies, 7 studies were considered to have a low risk of bias, while 2 remaining studies were found a high risk of bias. Random sequence generation was found in 5 studies. Allocation concealment was found in 8 studies and blinding of participants and personnel were found in 6 studies. Blinding of outcome assessment

was found in 7 studies. As shown in Figure 2, incomplete outcome data and selective reports were not found in 9 studies.

Strategy of data synthesis: The results were managed to Endnote X7 software and duplicate studies were deleted by two well trained authors with a sufficient understanding of this study. Next, two authors reviewed abstracts and full texts of included studies, selected the relevant information independently. Any disagreements were resolved by the third author. Data were extracted by two authors from selected studies independently and reached an agreement ultimately. Information for each eligible study included: author information, publication year, method of randomization and blinding, data sources, sample sizes, demographic database, parameters of concentration and centrifugation, detailed interventions, treatment course, outcomes, follow-up duration, and adverse events. When a 100-point NRS score was used, it was converted to a 10-point VAS score. Data in mean ± SE and median forms were converted to mean ± SD according to Cochrane Handbook. We contacted with the relevant authors in trials for more original data when necessary. Meta-analysis was performed using software RevMan 5.3. Heterogeneity was tested using the Chi-square test and quantified by calculating the I2 statistics. P50% was considered statistical heterogeneity. A random-effects model was used for heterogeneous statistical data. Otherwise, a fixed-effects model was performed. Sensitive analysis or subgroup analysis was used to investigate the source of heterogeneity. Meta-analyses results were also assessed using forest plots, and P<0.05 was considered statistically significant.

Subgroup analysis: None.

Sensibility analysis: Sensitivity analysis was performed by omitting 1 study in each turn to investigate the influence of a single study on the overall outcome. The 1 month BCTQf showed substantive difference compared to the original analysis when removing study of Mohammad (P = 0.02, I2 =0%). When Hakan's study was removed, BCTQs at 3rd months follow-up was P < 0.00001, I2 = 1% without additional heterogeneity. Similarly, there was no heterogeneity in DML after removing Noah's study (P = 0.91, I2 =0%). Besides, the results did not show substantive difference compared to the original analysis in remaining indicators.

Country(ies) involved: China.

Keywords: Platelet-rich plasma, carpal tunnel syndrome, meta-analysis, randomized controlled trials.

Contributions of each author:
Author 1 - Chunke Dong - The author drafted the manuscript.
Author 2 - Yan Sun - The author provided statistical expertise.
Author 3 - Yingna Qi - The author contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 4 - Hongyu Wei - Describe contributions of each author.
Author 5 - Chungen Li -The author read, provided feedback and approved the final manuscript .