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Efficacy of platelet-rich plasma injection versus other conservative treatments of carpal tunnel syndrome: A meta-analysis

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Abstract

Objective: Injection of platelet-rich plasma (PRP) as a proposed treatment for carpal tunnel syndrome (CTS) is a recent innovation. The aim of this analysis is to evaluate the functional and objective outcomes after PRP injection versus other conservative treatments of CTS. *Methods:* We systematically searched the electronic databases for trials that met our inclusion criteria. Two reviewers screened the studies, extracted the data, evaluated the methodological quality, and performed data analysis. Subgroup analysis was stratified by the follow-up periods. *Results:* Five randomized controlled trials (RCTs) and one prospective cohort trial met the inclusion criteria. A total of 318 subjects were reported including 160 with PRP injection and 158 with other conservative treatments. The quality of the included studies was high. The meta-analysis showed that no significant differences were detected in the visual analog scale (VAS), the Boston Carpal Tunnel Syndrome Questionnaire-the syndrome (BCTQ-S) and the Boston Carpal Tunnel Syndrome Questionnaire-the functional status (BCTQ-F) at 6 months, changes of VAS, BCTQ-S and BCTQ-F, distal motor latency (DML) and sensory conduction velocity (SCV) between the PRP injection and other conservative treatments. However, the BCTQ-S and BCTQ-F score at 3 months of PRP injection were significantly lower than other conservative treatments.
Conclusion: Current evidence revealed that there were no significant differences between PRP injection and other conservative treatment in relief pain, improving clinical symptom and functional status and electrophysiological findings at the final follow up period. However, PRP injection could improve the clinical symptom and functional status at the early period (3 months) of treatment.

Keywords: Carpal tunnel syndrome, platelet-rich plasma, median nerve, meta-analysis

INTRODUCTION

Conservative treatment of carpal tunnel syndrome (CTS) is generally offered to patients suffering from mild to moderate symptoms of CTS, including wrist splinting, oral or intravenous steroids, vitamins B6 and B12, nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroid injection.[1] Despite the availability of conservative treatment, it mostly provide only short-term relief.[2] Although surgical intervention is more effective than conservative treatment, surgery could have complications, such as injury to the median or ulnar nerve, postoperative bleeding, infection and so on.[3,4] Therefore, it is important to explore and develop a novel non-surgical intervention for CTS.

Injection of platelet-rich plasma (PRP) as a proposed treatment for CTS is a recent innovation. PRP is an autologous biologic product of concentrated platelets, the main constituent of which is thought to be degradation products that include multiple growth factors, known to be effective on inflammation and wound healing. PRP injection might lead to median nerve regeneration and might improve the neural blood supply in experimental animal models.[5-8] PRP diminishes the intracarpal inflammation of the subsynovial connective tissue in pathologic specimens from the CTS patients.[9,10] Malahias, Johnson, Babis and Nikolaou[11] initially used the PRP injection to treat CTS, and achieved encouraging mid-term results (12 weeks).

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Findings of placebo-controlled trials comparing PRP injection with other methods are not consistent.[12-15] We aimed to perform a meta-analysis of randomized trials and prospective trials comparing the clinical symptom, functional status and electrophysiological findings for all CTS using PRP injection with other conservative methods.

METHODS

We conducted this meta-analysis according to the methodological guidelines outlined by the Cochrane Collaboration (Oxford, United Kingdom), and reported our findings in accordance with Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines.[16,17] All of the included studies have achieved the ethics committee approval and informed consent of participants.

Search strategy

We searched PubMed, EMBASE, and the Cochrane library from the inception date to December 03rd, 2020, using the keywords "carpal tunnel syndrome" and "platelet-rich plasma" in the Abstract/Title to identify published trials comparing PRP injection with other conservative treatment of CTS. There were no language restrictions. We also searched the references of reviews and included studies to ensure that all relevant studies were included.

Inclusion and exclusion criteria

Trials were selected based on the following inclusion criteria: (1) randomized controlled trial (RCT) or prospective cohort trial comparing PRP injection alone or combined with another method with other conservative treatments; (2) trials enrolling patients with mild to severe CTS based on examination and electrophysiological studies; (3) trials providing outcome data; (4) the follow-up period was at least eight weeks. Exclusion criteria were: (1) trials without a control group; (2) incomplete or unavailable data; (3) surgical median nerve decompression as control group.

Evaluated outcomes

Evaluated outcomes were changes of the visual analog scale (VAS) at 3 months, changes of the Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) at 3 months and electrophysiological parameters as sensory conduction velocity (SCV) and distal motor latency (DML). BCTQ was used for evaluating the severity of symptoms (BCTQ-S) and functional status (BCTQ-F) of patients, which was assessed for validity and reliability.[18]

Study selection

Duplicates were initially excluded. Two authors independently reviewed the titles and if a title suggested the inclusion criteria could be met, the abstract was reviewed to determine if the study was eligible. Then, full texts of the retrieved studies were assessed by two reviewers independently. Disagreements during full-text inclusion were resolved by discussion, and if necessary, the third author adjudicated.

Data extraction

Using a standardized extraction method data as title, published year, authors, country, study design, number of study centers, sample size, age of subjects, sex distribution, type of interventions, duration of follow-up and evaluated outcomes were extracted.

Methodological quality assessment

A 12-item scale recommended by the Cochrane Back Review Group was used to assess the methodological quality and the risk of bias of the included trials. The following aspects were assessed: randomization, allocation concealment, similar baseline, patient blinded, care provider blinded, outcome assessor blinded, selective reporting, avoided cofactors, patients' compliance, drop-out rate, similar timing, and ITT analysis.[19]

Data synthesis and analysis

Inverse variance method was used for continuous outcome data to calculate the mean differences (MD) with a 95% confidence interval (CI) assessing the effect size. Mantel-Haenszel analysis method was used for dichotomous variables to calculate the risk ratio (RR) with a 95%CI assessing the effect size.[20] The heterogeneity among the trials was assessed for significance with Q and quantified with I^2. A p value < 0.05 was considered statistically significant. An I^2 less than 25% was considered homogeneous, an I^2 between 25% and 50% as low heterogeneity, an I^2 between 50% and 75% as moderate heterogeneity, and an I^2 above 75% as high heterogeneity.[21] A fixed effect model was applied when the studies were homogeneous or the statistical heterogeneity was low. While random effect model was applied when the statistical heterogeneity was moderate or high. Subgroup analysis was conducted according

to the follow-up periods if this was possible. To evaluate for the potential of publication bias, we performed a funnel plot from the BCTQ-S.

RESULTS

Literature search, demographic data, and characteristics of the studies

The study selection is illustrated in Figure 1. Total of 65 references were found from databases. After excluding the duplicates, twenty-five references were under title and abstract scanning. Nine full-text articles were assessed for eligibility. 3 studies were excluded. One study had no sufficient data[13], two studies were retrospective studies.[22,23] Five RCTs[12,14,24-26] and one prospective cohort trial[15] met the inclusion criteria. A total of 318 subjects were reported including 160 with PRP injection and 158 with other conservative treatments. There was no statistically significant difference in the baseline in all the included trials. Five trials included patients with mild to moderate CTS.[12,14,24-26] The severity level of CTS was categorized by electrophysiological classification: mild: only abnormal wrist SCV with normal DML; moderate: abnormal SCV and abnormal DML; severe: absence of SCV and abnormal DML.[27] One trial included patients who had numbness, pain and a tingling sensation in the distribution of the median nerve distal to the wrist and minimal to mild electrophysiological findings.[15] The demographic data, interventions, outcomes and follow-up periods of the included studies are summarized in Table 1.

Study quality assessment

The methodological quality of all included trials was high. Outcom e assessor was blinded in two trials[14,15], further details can be found in Table 2.

VAS and changes of VAS

Four trials[12,14,25,26] including 186 patients reported VAS and the changes of VAS. No significant differences were seen between the two groups for the VAS (MD = -0.67; 95%CI -1.64–0.31; p = 0.18) at 3 months and the changes of VAS (MD =0.47; 95%CI -0.21–1.14; p = 0.17) at 3 months.

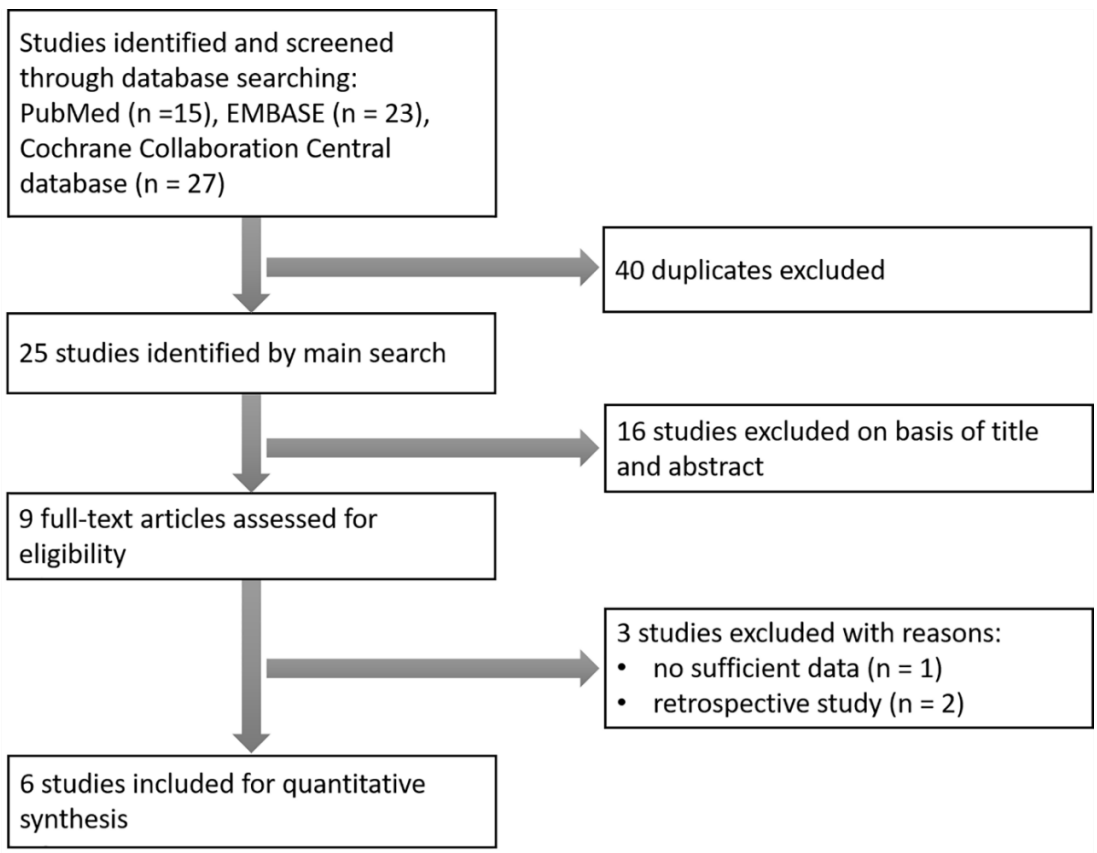

Figure 1. Study selection flow diagram

Table 1: Demographic data and characteristics of included trials

Study	Design	Country	Centers	Study group / Control group			Interventions (study group)	Interventions (control group)	Outcomes	Follow-up
				Sample size	Sex (female%)	Age (mean± standard deviation) (years)				
Hashim 2020[26]	RCT	Egypt	One	20 / 20	72% / 72%	48.8 ± 6.62 / 49.15 ± 6.06	PRP injection	40mg/1ml methylprednisolone acetate injection	VAS, BCTQ, Electrodiagnostic testing	3 months
Senna 2019[25]	RCT	Egypt	One	43 / 42	81.4% / 85.7%	38.3±6.4 / 40.7±9.4	2 ml PRP injection	1 ml of methyl prednisolone acetate 40mg/ml injection	VAS, Paresthesia, Phalen's test and Tinel's test, BCTQ, Electrodiagnostic testing, cross sectional area of the median nerve by ultrasound.	3 months
Shen 2019[24]	RCT	Chia	One	26 /26	96.2% / 84.6%	56.8±8.7 / 58.5±10.7	3 ml PRP injection	3 ml 5% dextrose injection	BCTQ, Cross-sectional area (CSA) of MN, electrophysiological parameters (SNCV, DML)	6 months
Raeissadat 2018[12]	RCT	Iran	One	21 / 20	All the enrolled patients were female	51.2±9.82 / 47.23±7.11	1 ml PRP injection plus splint; the concentration of PRP: 4-6 times that of whole blood	splint	VAS, electrophysiological parameters (SNAP-PL and CMAP-OL), BCTQ, complications and changes in the severity of CTS	10 weeks
Wu 2017[14]	RCT	China	One	30 / 30	90% / 85.3%	57.87±1.51 / 54.27±1.34	3 ml PRP injection; the concentration of PRP: 2.7 ± 0.4 times that of whole blood	splint	VAS, BCTQ, Cross-sectional area (CSA) of MN, electrophysiological parameters (DML and SCV), finger pinch,	6 months
Uzun 2017[15]	Prospective cohort trial	Turkey	One	20 / 20	80% / 80%	48.8±5.8 / 48.5±6.1	2 ml PRP injection; the concentration of PRP: 6.4 times that of whole blood	40mg/1 ml triamcinolone acetonide injection	BCTQ, electrophysiological parameters (DML and SCV), no complications	6 months

Table 2: Methodological quality assessment of included randomized controlled trials

Included studies	Randomized adequately[❖]	Allocation concealed	Similar baseline	Patient blinded	Care provider blinded	Outcome assessor blinded	Avoided selective reporting	Similar or avoided cofactors	Patients' compliance[¶]	Acceptable drop-out rate[*]	Similar timing	ITT[§] analysis	Quality
Hashim 2020[26]	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Senna 2019[25]	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Shen 2019[24]	Yes	No	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Raeissadat 2018[12]	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No	High
Wu 2017[14]	Yes	Unclear	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	High
Uzun 2017[15]	No	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	No	High

❖ Only if the method of sequence generated were explicitly described could get a "Yes"; sequence generated by "dates of admission" or "patients number" receive a "No";
¶ Intermittent treatment or therapeutic duration less than 6 months means "Yes", otherwise "No";
* Drop-out rate ≥ 30% means "No"; < 30% means "Yes";
§ ITT: intention to treat, only if all randomized patients are analyzed in the group they were allocated to could receive a "Yes";
# The frequencies of "Yes" ≥ 7 means "High"; > 4 and < 7 means "Moderate"; ≤ 4 means "Low".

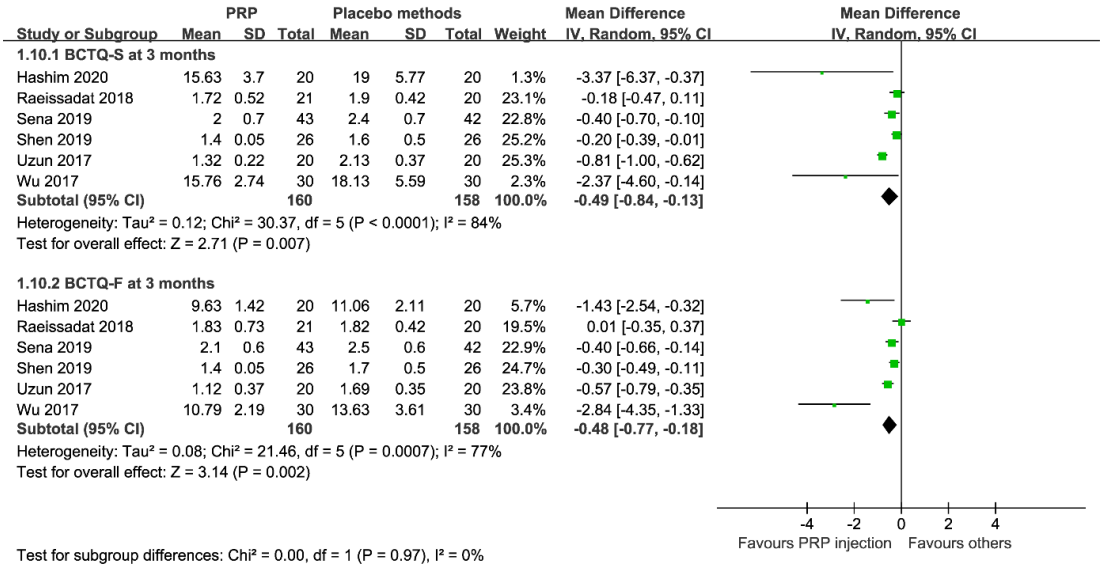

Figure 2 Forest plot of BCTQ-S and BCTQ-F at 3 months between the PRP injection and the placebo methods

BCTQ-S and changes of BCTQ-S

Subgroup analysis was conducted in the BCTQ-S according to the follow-up periods. Six trials[12,14,15,24-26] reported the BCTQ-S at 3 months, while three trials[14,15,24] reported the BCTQ-S at 6 months. Three trials[12,14,24] reported the changes of BCTQ-S at 3 months. The BCTQ-S score of PRP group was significantly lower than control group at 3 (MD = -0.49; 95%CI -0.84–-0.13; p = 0.007, Figure 2), but not at 6 months (MD = -0.16; 95%CI -0.43–-0.11; p = 0.24, Figure 2). While, no significant difference was found in the changes of BCTQ-S at 3 months (MD = 0.30; 95%CI -0.32–0.92; p = 0.34). Moderate to high heterogeneity was seen in the BCTQ-S at 3 months (I^2 = 84%; p < 0.0001), 6 months (I^2 = 51%; p = 0.13) and the changes of BCTQ-S at 3 months (I^2 = 70%; p = 0.04), respectively.

BCTQ-F and the changes of BCTQ-F

Subgroup analysis was conducted in the BCTQ-F according to the follow-up periods. Six trials[12,14,15,24-26] reported the BCTQ-F at 3 months, while three trials[14,15,24] reported the BCTQ-F at 6 months. Three trials[12,14,24] reported the changes of BCTQ-F at 3 months. The BCTQ-F score of PRP group was significantly lower than control group at 3 months (MD = -0.48; 95%CI -0.77–-0.18; p = 0.002, Figure 2). However, no significant differences were detected in BCTQ-F at 6 months (MD = -0.27; 95%CI -0.75–0.21; p = 0.26) and the changes of BCTQ-F at 3 months (MD = 0.60; 95%CI -0.31–1.52; p = 0.20). High heterogeneity was seen in these three outcomes, so the random effect model was used in each comparison.

Electrophysiological parameters (DML and SCV)

Five trials[14,15,24-26] reported electrophysiological parameters including DML and SCV. Subgroup analysis was conducted in these two comparisons according to the follow-up periods. No significant difference was found in DML at 3 and 6 months and SCV at 3 and 6 months (Table 3).

Table 3: Outcomes of electrophysiological parameters

Outcomes	Follow-up	I^2	P-heterogeneity	Effect model	MD	95% CI	P-value
DML	3 m	65%	0.02	Random	-0.03	[-0.42, 0.17]	0.40
DML	6 m	0%	0.42	Fixed	0.02	[-0.04, 009]	0.44
SCV	3 m	41%	0.17	Fixed	0.62	[-0.34, 1.57]	0.20
SCV	6 m	15%	0.31	Fixed	0.22	[-1.13, 1.57]	0.75

DML: distal motor latency; SCV: sensory conduction velocity; MD: mean differences; CI: confidence interval.

Publication bias

The shape of the funnel plot was asymmetric, suggesting possible publication bias. However, the assessment should not be considered robust because of the small number of eligible studies.

DISCUSSION

We performed a meta-analysis comparing PRP injection to other conservative methods in the treatment of CTS. Only BCTQ-S and BCTQ-F score of PRP group was significantly lower than control group at 3 months. However, there were no significant differences concerning VAS, BCTQ-S and BCTQ-F at 6 months, the changes of VAS, BCTQ-S and BCTQ-F, DML and SCV.

Two conservative treatment methods were included in our meta-analysis: wrist splint and corticosteroid injection. A large volume of evidence suggested that wrist splinting in a neutral position could alleviate the symptoms of CTS. One small randomized controlled trial showed that splinting provided adequate relief of symptoms and avoided surgery for 37% of patients.[28] Injection of corticosteroid into the carpal tunnel was commonly used for the treatment of CTS and as a diagnostic tool. A meta-analysis showed that corticosteroid injection for CTS provided greater clinical improvement in symptoms one month after injection compared to placebo.[29]

Various experimental studies[5,7,30-32] had reported positive effects of PRP on the regeneration of peripheral nerves without considerable safety risks in different settings, which made clinicians apply PRP for the treatment of CTS.[11] Although positive effects had been achieved in many experimental studies, the effects on patients with CTS were still controversial.[12,14,15] Some small sample studies[11,13] or case reports[33] showed that PRP injection could achieve encouraging effects on pain and electrophysiological parameters in CTS. However, our meta-analysis showed that no significant differences were detected on pain and electrophysiological parameters. This difference might result from the small sample groups in the studies or the heterogeneity of our meta-analysis. The currently available trials all had small study groups and a very short follow-up period. More high quality randomized controlled trials with larger sample size, longer follow-up periods are needed to improve the evidence and clarify this.

Furthermore, the ideal concentration of platelets in PRP remains controversial. The regenerative effects of PRP may be affected by the qualitative and quantitative platelet changes. Clinically effective PRP has been defined as having at least 4 times the normal platelet concentration.[34] In our meta-analysis, the concentration of the PRP used in two trials was over 4 times the normal platelet concentration[12,15], while that of one trial was less than 4 times.[14] However, the trial that used the lowest concentration of PRP showed that PRP injection was safe and effective for relieving pain and improving disability in the patients with CTS.[14]

The results of this study should be interpreted with caution because of the following limitations. Firstly, only six studies met our inclusion criteria, and this left only 318 patients for analysis. Secondly, there was moderate to high heterogeneity among the studies in most of the outcomes.[12,14,15] This might result from the different conservative treatment methods, the different dose of PRP and the different platelet concentration of PRP. Thirdly, because we were limited by the number of included studies in each outcome, we could not perform subgroup analysis or meta-regression to explore the effects of PRP dosage on CTS. Although the quality of all included studies was assessed, high randomization was not conducted in one study, allocation concealment was not conducted in two studies, and patient blinding and physician blinding were not used in all studies.

Current evidence revealed that there were no significant differences between PRP injection and other conservative treatment in relief pain, improving clinical symptom and functional status and electrophysiological findings at the final follow up period. However, PRP injection could improve the clinical symptom and functional status at the early period (3 months) of treatment.

DISCLOSURE

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Conflicts of interest: None

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