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GENERAL REVIEW • WRIST - BIOMATERIAL

Platelet-rich plasma injections for carpal tunnel syndrome: a systematic and comprehensive review

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Abstract

A series of clinical trials focused on the use of ultrasound-guided platelet-rich plasma (PRP) infusions for the treatment of patients with carpal tunnel syndrome (CTS) were published over the last few years. However, the role of PRP for CTS remains unclear. We performed a systematic review according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines. Two reviewers independently conducted the search using multiple databases: MEDLINE/PubMed, SCOPUS, Cochrane Database, and Web of Science. These databases were searched using terms "platelet" AND "rich" AND "plasma" AND "carpal" AND "tunnel". To maximize the search, backward chaining of references from retrieved papers was also undertaken. From the initial 19 studies, only five met our eligibility criteria. These articles included one randomized controlled double-blind study, one randomized controlled single-blind study, one randomized controlled non-blind study, one case–control study, and one case report. The vast majority of the included studies supported that PRP infusion improved the clinical condition of the patients and that PRP infusion was beneficial for patients with mild-to-moderate CTS. Therefore, PRP seems to be an interesting alternative for the treatment of mild-to-moderate CTS which, still, has not been thoroughly investigated. However, despite the promising results of the present studies, PRP has to be further tested before we reach to a definite conclusion regarding its therapeutic value.

Keywords Carpal tunnel syndrome · Platelet-rich plasma · Ultrasound-guided injections · Systematic review · Comprehensive review

Introduction

Numerous animal studies have examined the effect of platelet-rich plasma (PRP) on neural tissue, suggesting its potential value for therapeutic applications [1–9]. In carpal tunnel syndrome (CTS), it is proven that several growth factors that are released and activated after a PRP injection might lead to median nerve regeneration [10–13] and improve the neural blood supply by protecting the "blood–nerve barrier" [14, 15]. As a result, PRP might counteract the "microischemia" and the "miniature closed compartment syndrome" that are developed into the carpal tunnel in patients with CTS [16]. Furthermore, PRP diminishes the intracarpal inflammation of the subsynovial connective tissue that recently has been considered as the underlying mechanism causing CTS [17, 18]. Histological studies have illustrated that PRP perineural injections may influence the frequency of production of type I and III collagen fibers by reversing it to the direction of modification of the tissue to the normal [19].

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In contrast to the plentitude of preclinical studies, only limited clinical data are available regarding the application of PRP in peripheral neuropathies in humans. In the study of Anjayani et al., which involved 60 patients with Hansen's disease, perineural administration of PRP showed positive effects on sensory symptoms [20]. Sanchez et al. presented a healthy young man suffering from peroneal nerve palsy with drop foot following multiple ligament knee joint injuries, who was successfully treated with ultrasonography (US)-guided PRP injections in the peroneal nerve [21]. In another case report, Kuffler et al. treated a patient with a 3-year ulnar nerve transection and a large gap, and illustrated that a collagen tube filled with platelet-rich fibrin could stimulate the sensory and motor regeneration of the nerve [22]. Similarly, Hibner et al. described a surgical technique for the treatment of persistent neuralgia of the pudendal nerve after initial failed surgical decompression [23]. Finally, Scala et al. concluded that the use of PRP gel in patients who underwent superficial parotidectomy has a protective role against iatrogenic lesions of the facial nerve [24].

More recently, a number of clinical studies that focused on the outcomes of US-guided PRP injections in patients suffering from CTS were conducted [25–30]. However, no systematic or comprehensive or any other type of literature review has been published yet, and the role of PRP in CTS remains unclear. Therefore, to enhance the literature, we performed this systematic and comprehensive review to study whether US-guided PRP perineural injections are safe and effective for the treatment of patients suffering from mild to moderated CTS, and whether the quality of evidence of the already published studies on the use of PRP injections in CTS is adequate. Our hypothesis was that PRP injections are safe and effective for these patients.

Materials and methods

A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [31]. Two reviewers (DC and MM) independently conducted the search using the MEDLINE/PubMed, SCOPUS, Cochrane Database, and Web of Science databases. These databases were queried with the terms "platelet" AND "rich" AND "plasma" AND "carpal" AND "tunnel." To maximize the search, backward chaining of reference lists from retrieved papers was also undertaken. Assessment of only the titles and abstracts of the search results was initially performed, and then a careful review of the full-text publications was done.

Inclusion criteria included (1) prospective or retrospective clinical studies, (2) clinical and/or functional and/or US and/or nerve conduction studies (NCS) recorded follow-up, (3) international publications in English language, (4) published studies by March 21, 2018 (end of literature search), (5) US-guided PRP injections, and (6) US-guided PRP injections only for CTS. Exclusion criteria included (1) full-text papers not available, (2) animal and preclinical studies, (3) publications not in English language, (4) no recorded follow-up as above, (5) unguided PRP injections, and (6) studies other that PRP injections for CTS (Fig. 1). The quality of the evidence was classified using the US Preventive Services Task Force system for ranking level of evidence. Differences between reviewers (DC and MAM) were discussed until agreement was achieved. Independent reviewers extracted data from each study and assessed variable reporting of outcome data. Descriptive statistics were calculated for each study and parameters were analyzed. The methodological quality of each study and the different types of detected bias were assessed independently by each reviewer, and then were combined synthetically. Selective reporting bias like publication bias was not included in the assessment. The primary outcome measure was the postoperative statistically significant improvement of the clinical, functional, US and NCS scores used in comparison with the preoperative scores per study. Apart from the systematic analysis, a comprehensive review of the eligible studies was also performed.

Results

Systematic review

From the initial 19 studies, only five met our eligibility criteria [25–29]. These included one randomized controlled double-blind study [25], one randomized controlled single-blind study [26], one prospective randomized controlled non-blind study [27],one case control study [28], and one case report [29] (Table 1). Four of the five papers (80%) were comparative [25–28], and three were level I studies [25–27].

There were 192 patients included in this review (98 patients who received PRP treatment versus 94 patients who received control treatment) (Table 2). The vast majority of the patients were females ($F/M = 170{:}22$). The mean age of the patients administered PRP injections was 55.3 years, whereas the mean age of the patients receiving control treatment was 52.3 years. The follow-up end-assessment was 6 months in three studies [26, 28, 29], 3 months in one study [25], and 10 weeks in another study [27]. Three studies suggested that PRP is safe and effective for patients with CTS [25, 26, 29]. One study concluded that PRP can be rather used for the temporary symptomatic relief of mild CTS [28], whereas another study reported that PRP does not significantly influence the beneficial impact of wrist splints in patients with CTS [27].

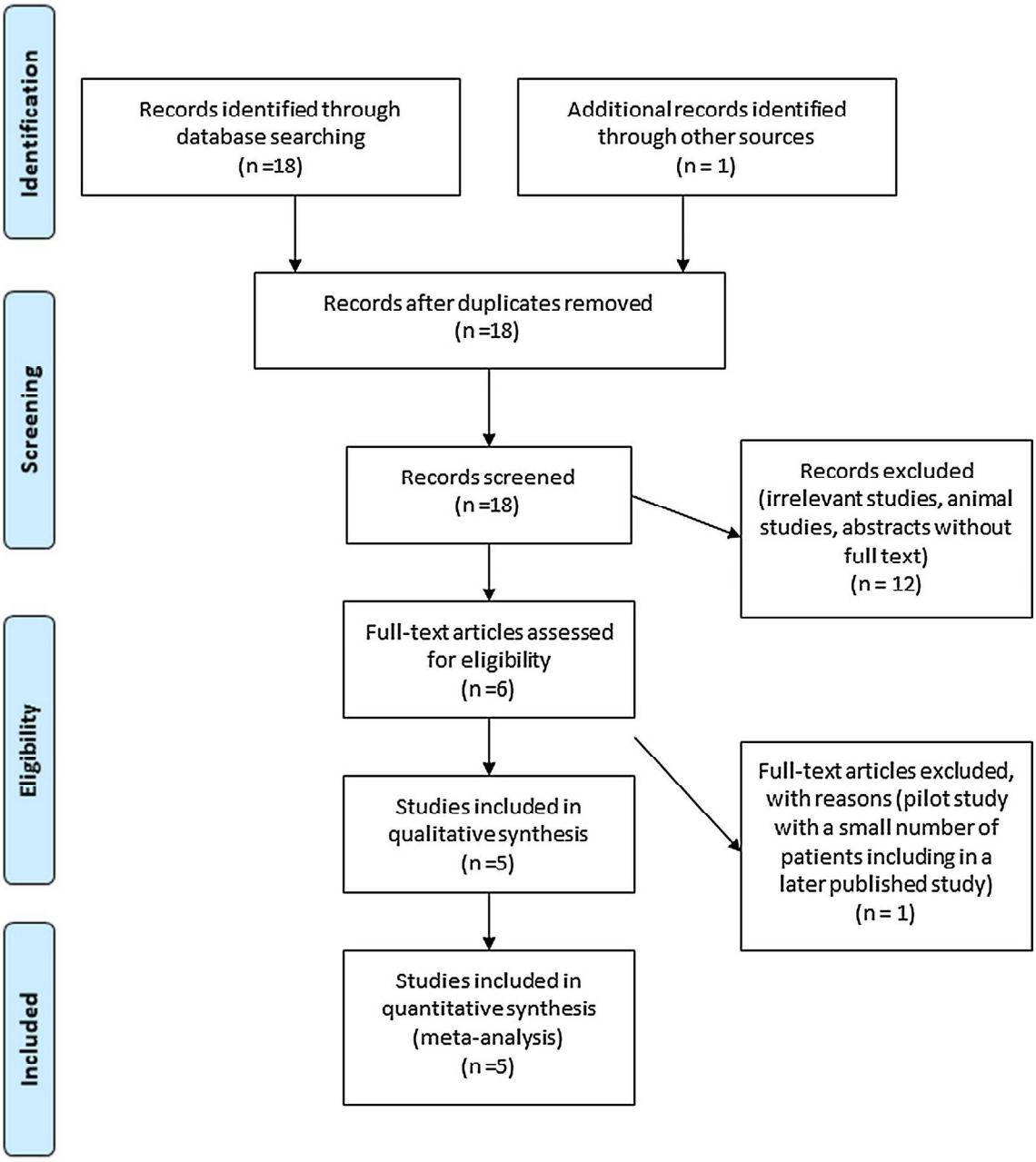

Fig. 1 PRISMA 2009 flowchart of the present systematic review

Visual analog scale (VAS)

All studies showed clinical improvement in VAS scores with PRP compared to the baseline, but the results were controversial when compared with the control groups [25–29]. Three of the five studies used the VAS score for evaluation of outcomes [25–27]. While Malahias et al. [25] and Raeissadat et al. [27] showed that no statistically significant difference existed between the groups that received PRP compared to the controls, Wu et al. [26] reported a statistically significant superior difference in the group treated with PRP. Nevertheless, according to all three papers [25–27], in both the PRP and the control groups, the VAS score significantly improved in comparison with the baseline values (Table 3). One study assessed the patients' outcomes with the Q-DASH score and reported a statistically significant improvement in the group treated with PRP [25].

NCS

All studies reported controversial NCS results. NCS with electromyography (EMG) was used in four studies

Table 1 Summary of the included studies

Study	Type of study	Complications	Follow-up	Conclusion
Kuo et al. [19]	Case report	None	6 months	PRP injection could be an option for the treatment of CTS
Wu et al. [16]	Prospective randomized single-blinded	None	6 months	PRP injection is safe and effective for the treatment of CTS
Uzun et al. [18]	Case–control	None	6 months	PRP injections could provide a temporary symptomatic improvement in mild CTS
Malahias et al. [15]	Prospective randomized double-blinded	None	12 weeks	PRP injection could be effective for patients with carpal tunnel syndrome
Raeissadat et al. [17]	Prospective randomized, non-blinded	Pruritus in four patients, pain in the fingers in one patient, and burning sensation in one patient (PRP group)	10 weeks	A single injection of PRP did not significantly influence the beneficial impact of wrist splints to patients with CTS

Table 2 Demographics and levels of evidence of the included studies

Study	Patients (*n*)	Sex (*F*/*M*)	Mean age (years)	Level of evidence
Kuo et al. [19]	1	Female	56	V
Wu et al. [16]	60 (two groups of 30 patients)	PRP: 27/3 Control: 25/5	PRP: 57.9 Control: 54.3	I
Uzun et al. [18]	40 (two groups of 20 patients)	PRP: 16/4 Control: 16/4	PRP: 48.8 Control: 48.5	III
Malahias et al. [15]	50 (two groups of 26 and 24 patients)	44/6	PRP: 60.5 Control: 57.2	I
Raeissadat et al. [17]	41 (two groups of 21 and 20 patients)	Female	PRP: 51.2 Control: 47.2	I

Table 3 Risk of bias, outcome measures, and significant differences of the included studies

Study	Outcome measures	Significant differences	Risk of bias
Kuo et al. [19]	NCS	Motor and sensory latencies	High risk of performance, selection and attrition bias
Wu et al. [16]	VAS, BCTQ, U/S CSA, NCS, and finger pinch strength	VAS, BCTQ, U/S CSA	High risk of performance bias
Uzun et al. [18]	BCTQ, Functional Status Scale, NCS	BCTQ, Functional Status Scale	High risk of selection and performance bias
Malahias et al. [15]	Q-DASH, VAS-pain, DeltaCSA	Q-DASH (a. MCID > 8; b. > 25% improvement), final DCSA: 0–0.002 cm^2	Low risk of bias
Raeissadat et al. [17]	BCTQ, VAS, NCS	None	High risk of performance bias

[26–29]. Raeissadat et al. showed that median sensory nerve action potential peak latency (SNAP PL) and median compound muscle action potential onset latency (CMAP OL) were not statistically significantly different between the PRP and the control groups, while the CMAP OL was not statistically significantly different in the PRP group in comparison with the baseline [27]. Wu et al. [26] and Uzun et al. [28] reported statistically insignificant differences between the PRP and the control groups regarding the SCV and the DML, and Uzun et al. [28] showed that the DML in the two groups did not statistically significantly differ from the baseline.

Boston carpal tunnel questionnaire (BCTQ)

The BCTQ was used in three studies [26–28]; these studies reported significant improvement of BCTQ after treatment, but the results of the PRP-treated group were controversial when compared to a control group. Wu et al. reported a statistically significant improvement in the PRP group compared to the control group in terms of symptom severity and function, and significant improvement in both groups in comparison with the baseline [26]. In contrast, Raeissadat et al. did not find a significant difference of symptom severity and function between the PRP group and the control

group, although these parameters in both groups were significantly ameliorated in comparison with the baseline [27]. Finally, although it was found by Uzun et al. that symptom severity and function were significantly better in both groups in comparison with the baseline, the PRP group showed significant improvement compared to the control group only at the 3-month follow-up [28].

US measurements

US measurements were reported in three studies [25, 26, 29], with controversial results. Although Malahias et al. [25] reported a not significant difference between the PRP group and the control group, Wu et al. [26] showed that the PRP group was significantly superior to the control group.

Finger pinch strength

One study used the finger pinch strength for the evaluation of outcomes [26]. The authors reported a significant improvement of both groups in comparison with the baseline, however, without a statistically significant difference between the PRP and the control groups at follow-up [26].

Shortened disabilities of the arm, shoulder and hand questionnaire (Q-DASH)

One study used Q-DASH to evaluate the therapeutic value of a single PRP injection in comparison with a placebo injection [25]. According to the primary success rate of that level I randomized, double-blind, controlled clinical trial (Q-DASH difference > 25% between the initial and the final individual's value), the PRP-treated patients significantly improved when compared to the placebo-treated group [25].

Complications

Four studies reported no complications after PRP injections [25, 26, 28, 29], while Raeissadat et al. reported pruritus in four patients, pain in the fingers in one patient and burning sensation in another patient [27]. Overall, it seems that US-guided PRP perineural injection into the carpal tunnel is a safe procedure.

Risk of bias

Four studies were assessed as having high risk of possible performance bias [26–29]. Two studies were suspected of selection bias [28, 29], while one study (20%) was found with possible attrition bias [29]. Finally, only one study (20%) from this review had a low risk of possible bias [25].

Comprehensive review

Wu et al. published a prospective, randomized, single-blinded, comparative, clinical study (RCT) that compared the clinical effects of PRP injections with those of night splinting in patients with CTS [26]. The PRP group showed a significant improvement (decrease) in VAS score, BCTQ score and CSA of the median nerve, compared to the control group ($p < 0.05$). The authors concluded that PRP is a safe treatment that alleviates pain and improves the functional status of patients with CTS. This result is consistent with the study of Malahias et al. regarding the positive effect of PRP [25], while the study of Wu et al. was limited by being a single-blinded study, although with a longer follow-up [26]. Based on a pilot study [30], Malahias et al. performed a prospective, randomized, double-blinded study including two groups of patients suffering from mild to moderate CTS [25]. The first group (26 patients) underwent a US-guided PRP injection into the carpal tunnel, via hydrodissection, while the second group (24 patients) received placebo (0.9% normal saline). The PRP group showed a significant improvement of the Q-DASH score before and after the PRP injection compared to the control group at the 12-week follow-up. Although VAS improvement after the PRP injection was not significantly different between the two groups at 12 weeks, the authors showed that a single US-guided PRP injection is effective for CTS.

Uzun et al. compared the effectiveness of PRP with that of corticosteroids [28]. The DML changed in both groups, as improvements of the SCV were recorded in both groups at follow-up, and NCS were not different between the two groups. Symptom severity score and functional capacity score as measured with the BCTQ were significantly better in the PRP group compared to the corticosteroid group at the 3-month follow-up. Differences were not significant at the 6-month follow-up. The authors concluded that PRP injections could be used for symptomatic (short-term) relief of patients with mild CTS; results were not encouraging regarding the long-term efficacy of PRP [28]. On the other hand, Raeissadat et al. showed that when a wrist splint is used, additional treatment with PRP injections provides no benefits [27]. Although both groups (combined PRP and wrist splint versus splint alone) in their study improved significantly in comparison with the baseline, there was no statistical difference between groups. The major drawback of this study was related to the high risk of performance bias, because neither the treating physician nor the patients were blinded to the treatment [27].

When comparing PRP with a placebo injection, PRP was found significantly superior at a 12-week follow-up, but not different to placebo at a 4-week follow-up [25]. The strengths of this study were the design (randomized, double-blind, comparative), the satisfactory power analysis, and the

inclusion of all patients at the last follow-up (no patient was lost to follow-up) [25]. The primary weak point is the relatively small number of patients (50 patients) and the absence of long-term results [25]. Kuo et al. applied perineural PRP infusions to a patient suffering from CTS and measured possible changes in NCS [29]. They found a significant improvement of distal motor and sensory latency, as well as of the sensory nerve action potential (SNAP) amplitude. They concluded that PRP injections may be an alternative to surgery in patients who do not respond to night splints, nonsteroidal anti-inflammatory drugs, and corticosteroid injections. However, although it confirms previous studies, a single case report cannot lead to safe conclusions [29].

Discussion

All studies included in the present systematic and comprehensive analysis showed that the clinical outcomes of the patients with CTS treated with PRP injections significantly improved in comparison with the baseline [25–29] (Table 4). However, the clinical, US and NCS results of the PRP injections were not always superior compared to controls, and controversies existed with respect to VAS and BCTQ scores, US CSA and NCS EMG values. It seems that further studies are required to establish whether PRP yields better outcomes than other types of conservative treatments such as night splints and corticosteroid injections for CTS. Especially in patients with severe CTS, PRP is not recommended as an alternative treatment option by any of the studies included in this review.

The quality of evidence of the included studies was moderate to high; the majority of the studies were level I, whereas performance bias were identified as the most common type of bias at high risk. The follow-up end point was short for all five studies, ranging from 10 weeks to 6 months; no assessment of the mid- and long-term effects of PRP in patients with CTS was performed. In addition, the number of patients treated with PRP injections was very small, and the protocols used for the preparation of PRP varied between studies or were not mentioned. Even the number of injections per patient (one or more) was not stable among studies. Therefore, the effect of PRP for CTS cannot be documented with accuracy.

Undoubtedly there is a trend toward new studies on the clinical efficacy of PRP injections in patients with peripheral

Table 4 Clinical and US mean scores at baseline and follow-up of the included studies

Study	Mean scores at baseline	Mean scores at follow-up
Kuo et al. [19]	N/A	N/A
Wu et al. [16]	VAS PRP: 6.5/10 VAS control: 6.3/10 BCTQ-severity PRP: 26.2 BCTQ-severity control: 24.9 BCTQ-function PRP: 19.2 BCTQ-function control: 18.1 Finger pinch strength PRP (kg): 3.3 Finger pinch strength control (kg): 3.7 U/S CSA PRP: 14.01 U/S CSA control: 10.9	VAS PRP: 2/10 VAS control: 2/10 BCTQ-severity PRP: 14.1 BCTQ-severity control: 16.2 BCTQ-function PRP: 10.4 BCTQ-function control: 12.9 Finger pinch strength PRP (kg): 4.5 Finger pinch strength control (kg): 4.7 U/S CSA PRP: 12.9 U/S CSA control: 10.9
Uzun et al. [18]	BCTQ-severity PRP: 3.0 BCTQ-severity control: 3.0 BCTQ-function PRP: 2.0 BCTQ-function control: 1.9	3-month BCTQ-severity PRP: 1.3 3-month BCTQ-severity control: 2.1 6-month BCTQ-severity PRP: 2.4 6-month BCTQ-severity control: 2.6 3-month BCTQ-function PRP: 1.1 3-month BCTQ-function control: 1.7 6-month BCTQ-function PRP: 1.7 6-month BCTQ-function control: 1.9
Malahias et al. [15]	Q-DASH PRP: 48.1 Q-DASH control: 42.1 VAS PRP: 67.9 VAS control: 54.0 DeltaCSA PRP: 0.06 Delta CSA control: 0.05	Q-DASH PRP: 19.4 Q-DASH control: 35.1 VAS PRP: 28.5 VAS control: 42.9 DeltaCSA PRP: 0.04 Delta CSA control: 0.04
Raeissadat et al. [17]	VAS PRP: 6.8/10 VAS control: 6.2/10 BCTQ-severity PRP: 2.4 BCTQ-severity control: 2.7 BCTQ-severity PRP: 2.4 BCTQ-severity control: 2.5	VAS PRP: 4.0/10 VAS control: 3.5/10 BCTQ-severity PRP: 1.7 BCTQ-severity control: 1.9 BCTQ-severity PRP: 1.8 BCTQ-severity control: 1.8

neuropathies and especially CTS [32]. Results of currently available high quality published studies will be expanded in the future in various directions, in both clinical and preclinical studies. Such investigations could include delineation of the pathophysiological mechanisms of CTS at a microscopic level, activity of PRP growth factors in neural tissue, as well as the role of the connective tissue of the transverse carpal ligament. The diversity of the present studies strongly suggests that a consensus on the clinical application of PRP as well as the best means for its production would be of great value.

Conclusion

PRP seems to be a promising alternative for the treatment of patients with mild to moderate CTS, but not in patients with severe CTS. However, despite the encouraging results of the present studies, PRP has to be further tested before we reach to a definite conclusion regarding its therapeutic value.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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