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Effectiveness of platelet rich plasma injections for non-surgical management of carpal tunnel syndrome: a systematic review and meta-analysis of randomized controlled trials

Running Title: PRP for Carpal Tunnel Syndrome: Systematic Review

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Abstract

Objective: To systematically review and evaluate the efficacy and complication profile of platelet-rich plasma (PRP) injection into the carpal tunnel for management of carpal tunnel syndrome (CTS).

Data Sources: PubMed, MEDLINE, SCOPUS, EMBASE, Google Scholar, Cochrane Central Register of Controlled Trials, and Web of Sciences (from inception to January 1st, 2019).

Study Selection: Controlled trials addressing PRP for CTS.

Data Extraction: Two reviewers independently screened the titles, abstracts, and full texts, extracting data from eligible studies. The outcomes of interest were the visual analog score (VAS) for pain and the Boston Carpal Tunnel Questionnaire (BCTQ), including the subscales of the symptom severity scale (SSS) and the functional status scale (FSS). Other reported outcome measures and complications were analyzed descriptively.

Data Synthesis: Four randomized control studies satisfied the inclusion criteria and analyzed a total of 191 cases with a final follow-up of either 3 or 6-months. Control groups included splinting in two studies, corticosteroid injection in one study, and saline injection in one study. There was a statistically and clinically significant improvement in the BCTQ {Std. Mean Difference(95%CI) = -2.06[-3.41, -0.70], p=.003} between groups. Subgroup analysis showed significant improvement in SSS {Std. Mean Difference(95%CI) = -1.95[-3.65, -0.25], p=.02} but not for FSS {Std. Mean Difference(95%CI) = -2.19[-4.77, 0.40], p=.10}. There was a similar improvement in VAS and nerve conduction studies in those receiving PRP compared to controls. Complication rate in the included studies was low with 4/97 participants receiving PRP injections experiencing transient pruritis, burning and/or tingling.

Conclusion: PRP represents a promising therapy for patients with mild to moderate CTS; however, included studies were limited as follow-up was short, included patients were heterogeneous, and the number of included studies was low. Further investigation is necessary to determine its true efficacy and effect and to better delineate the long-term results in patients with CTS.

Key Words: Platelet-rich Plasma, Carpal Tunnel Syndrome, Non-operative

Abbreviations: PRP=Platelet-Rich Plasma, CTS= Carpal Tunnel Syndrome, visual analog score = VAS, BCTQ = Boston Carpal Tunnel Questionnaire, SSS = Symptom severity scale, FSS = Functional status scale,

Carpal tunnel syndrome (CTS) is the most common mononeuropathy affecting 2.7%-5.8% of the adult population[1]. CTS has been described as a progressive condition, that without treatment, begins with mild, intermittent and potentially reversible sensory symptoms and progresses to permanent motor weakness[1–3]. Multifactorial mechanisms underlie the compression and traction of the median nerve at the carpal tunnel which ultimately set the stage for medial nerve demyelination[4]. These mechanisms include inflammation and hypertrophy of sub-synovial connective tissue that surrounds the median nerve and flexor tendons, micro-circulation injury, breakdown of blood nerve barrier, and nerve ischemia and swelling[4].

Multiple non-surgical interventions have been trialed to reduce inflammation in the early stages of the disease with the hopes of symptom resolution and nervous regeneration. Current non-operative treatments are aimed at symptomatic pain relief and functional improvement and have proven effective in a proportion of patients. Those that continue to progress symptomatically despite conservative interventions of activity modification and night splint are routinely offered local corticosteroid injections in the carpal tunnel. The local steroid injections, although effective in the short-term, have not shown long term benefits[5]. None of the conservative options appear to prevent disease progression, although a proportion of cases resolve spontaneously over time[1,6–8]. Many patients go on to receive surgical decompression of the carpal tunnel, which prevents further progression but have an unpredictable effect on peripheral nerve regeneration depending on disease severity[9,10] and may be less successful with variable improvements in symptoms for individuals with mild electrophysiologic studies[11,12].

Platelet Rich Plasma (PRP) is a derivative of autologous blood created by centrifuging autologous blood in order to extract the plasma portion which contains platelets and a high-concentration of growth factors[13–15]. Platelet rich plasma holds a key therapeutic potential for

neural tissue repair in the early stages of CTS as previous in vivo studies have demonstrated improved Schwann cell proliferation, function, and migration[16]. Due to heterogeneity in preparation methods with varying spin cycles and additive activators[15], different PRP preparations may have different clinical outcomes. Several basic science studies have identified the effect PRP as modulation of the neuroinflammatory environment and assisting in nervous tissue remodelling and healing[17,18]. Further, varying preparations have been shown to promote neuronal and axon regeneration *in vitro*[16,19–22] and *in vivo*[23,24]. In the recent years[25–28], few published studies and a qualitative review that examined the safety and efficacy of ultrasound-guided perineural PRP injection in CTS reported PRP to be a promising alternate treatment option in mild – moderate CTS. However, sufficient evidence for justification of this theory is still lacks pending quantitative analysis of high-quality clinical trials.

Therefore, the objective of this meta-analysis is to examine the clinical outcome and complication profile of PRP from high-quality clinical trials as a technique to address CTS. We hypothesize that PRP, at least in the short term, will reduce pain and improve sensation and function with a low complication rate, thus serving as a reasonable alternative for mild to moderate CTS.

Methods

The review protocol was registered on PROSPERO via study number CRD42018092141.

Search Strategy

Six databases (PubMed, MEDLINE, SCOPUS EMBASE, Google Scholar, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Sciences) were searched from database inception to January 1st, 2019 for controlled trials addressing platelet rich plasma

injection for carpal tunnel syndrome. The search terms “Platelet rich” or “Plasma” and “carpal tunnel” or “median neuropathy” were used.

Assessment of Study Eligibility

Studies were included if they were controlled studies that reported outcomes after platelet rich plasma injection (PRP) for carpal tunnel syndrome (CTS). There was no limitation for the therapy in the control group and this included splinting, normal saline and corticosteroid injection. Studies classified as: reviews, editorials or technique papers; animal models or cadaveric studies; and/or studies that did not have a control group were excluded.

Study Screening and Data Abstraction

Publication review, screening, and data extraction were done by two investigators independently using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[9]. Throughout the title and abstract screening stages, any article with discordance between reviewers was included to ensure that no relevant articles were prematurely excluded. The reviewers discussed any disagreements, and if consensus was not reached, it was discussed with a third author. The reference lists of all included studies were screened for additional relevant articles.

Unweighted kappa (κ) was calculated to assess agreement of study eligibility at the title, abstract and full-text screening stages between reviewers. Kappa values >0.61 indicate substantial agreement; $0.21 < \kappa < 0.60$, to indicate moderate agreement; and $\kappa < 0.20$, to indicate slight agreement[29].

Quality Assessment

The quality of included studies was assessed using the Cochrane Collaboration’s Risk of Bias tool in Review Manager Software. No scoring system was adopted; instead, quality

assessments were used for descriptive purposes. The risk of bias assessment was performed in the following domains: random sequence generation; allocation concealment; blinding of participants and personnel and outcome assessors; blinding of outcome assessment; incomplete outcome data; selective reporting and another category as others.

Statistical Analysis

Means were extracted for all reported outcomes for both experimental and control groups. Three-month endpoint was used for meta-analysis as it was a common outcome point among all included studies. The standardized mean differences of the Visual Analog Score (VAS) and Boston Carpal Tunnel Questionnaire (BCTQ) were used to calculate the pooled standardized mean difference and corresponding 95% confidence interval among experimental versus control groups. The standardized mean difference was used when studies reported the same outcome measure on different scales. For the Boston Carpal Tunnel Questionnaire, the data were extracted regarding Symptom Severity Scale, and Functional Status Scale subgroups and separate meta-analyses were conducted. The percentage of variability across studies attributable to heterogeneity beyond chance was assessed by the chi-square test and I^2 statistics. The random effects model was used if the heterogeneity test showed statistical significance (I^2 >50%, p<0.05). Otherwise, a fixed-effects model was adopted. The number of included studies was insufficient (less than 10) to assess potential publication bias. Review Manager version V5.3 (Nordic Cochrane Centre, Cochrane Collaboration, 2011. http://community.cochrane.org/tools/review-production-tools/revman-5) was used for performing meta-analyses.

Results

Study Characteristics and Demographics

The original search yielded 1,692 results after duplicates were removed. Following the title screen, 23 studies were included in abstract screening, of which 12 progressed to full-text review. A total of 8 studies were removed by the full-text review, leaving four papers included for qualitative analysis (Figure 1)[25–28]. Out of these four studies, three studies[25,27,28] reported Visual Analog Score for pain (VAS) (n = 151) and three studies reported the Boston Carpal Tunnel Questionnaire (BCTQ) (n=141)[25,26,28].

No additional articles were retrieved through manual reference search of included studies. Authors were in high agreement throughout all stages of screening, with an unweighted kappa of 0.9 for title screening, 1.0 for abstract screening and 1.0 for full-text screening. Of the four included studies, all were prospectively controlled trials. One study compared PRP to splinting, one study compared PRP and splinting to splinting only, one study compared PRP to saline injection, and one study compared PRP injection to corticosteroid injection. The mean sample size of the included studies was 48 patients (range 40-60), with a pooled total of 191 cases of carpal tunnel included. The mean age of included patients was 53.8 years old, 90% of included patients were female with a mean symptom duration of 25 months. Two studies had a final follow-up at approximately three months, while the remaining two studies had a final follow up at six months (Table 1). All the studies analyzed patients with a minimal-moderate disease with the exclusion of severe disease[25-28,].

Platelet Rich Plasma Preparations

Several different formulations of PRP were utilized. Of the four included studies, two studies utilized a single spin protocol, while two studies utilized a double spin protocol (table 2). The studies with the single spin protocol had a lower concentration of platelets as compared to the double spin protocol, although one of the double spin protocol studies did not report the final

platelet concentration. Two studies reported leukocyte preparation[25,28]. Injectate volume varied from 1mL-3mL with single spin injectate being generally higher volume. All studies utilized a similar injection technique with injectate being delivered around the proximal edge of the carpal tunnel using the ulnar approach. Two studies[25,27] preformed injection under ultrasound guidance. In addition, Wu et al. performed a co-intervention utilizing hydrodissection technique with injectate utilized to peel the median nerve from the flexor retinaculum.

Risk of Bias Assessment

The risk of bias summary and graph is presented in figure 2 and figure 3. The majority of studies scored a low risk of bias in terms of incomplete data collection, random sequence generation, and blinding of final outcome assessors. However, all studies had either high risk or unclear risk of bias from allocation concealment and blinding of participants and personnel. The lack of allocation concealment was commented to be a result of difficulty blinding patients or treating physicians because of blood drawing and distinct injectate appearance of PRP.

Meta-analysis Outcomes

Meta-analysis reporting was done at three months as most of the studies had data for this time frame. Raeissadat et al. reported outcomes at 10 weeks and was included in the meta-analysis. Meta-analysis from these trials showed no statistically significant difference in standardized mean difference in VAS (0.65, 95% CI: 1.79 to -0.48, p=0.26) (figure 4) though the treatment effect was favorable towards the PRP group. In terms of function, the meta-analysis demonstrated the overall standardized mean difference for BCTQ and corresponding 95% CI were 2.06 (95% 3.41 to 0.70, p=0.003). The results of the subgroup analysis showed significant mean difference for SSS 1.95 (95% CI: 3.65 to 0.25, p=0.02) but not for FSS (2.19 95% CI: 4.77 to -0.40, p=0.10) (figure 5).

Additional Outcomes

Additional outcomes were measured in three of four studies. Three studies documented nerve conduction studies (NCS)[25,26,28] and two studies documented median nerve cross sectional area as measured by ultrasound[25,27]. Of those measuring NCS, two studies used distal motor latencies[25,26] and sensory conduction velocities[25,26] while one study measured compound motor action potential[28] and Sensory Nerve Action Potential[28] amplitudes. There was no difference in any measure of NCS between PRP and control in all three studies. However, there was equal within group improvements of NCS in two studies in both controls and those receiving PRP. Both studies demonstrated greater improvements in cross sectional area of the median nerve compared to controls[25,27] with 14.01mm^2 to 10.93mm^2 demonstrated by Wu et al[25] and 15/26 improving in Malahias et al[27].

Complications of PRP Injection

The complication rate in the included studies was low, with 4/97 participants receiving PRP injections experiencing complications. Three of the four studies reported no complications, either permanent or transient in any included patients. One study reported complications that were transient in nature consisting of pruritus in 4 patients with additional pain in the fingers in one patient and a burning sensation in one patient. No severe complications were reported. In summary, local PRP injection for CTS appears to pose minimal risks.

Discussion

This systematic review and meta-analysis identified four high quality studies investigating the use of PRP injection to treat CTS in a prospective controlled fashion. These studies were randomized but limited by small patient numbers and short follow-up as well as a heterogeneous group of patients. Meta-analysis identified that PRP injection into the carpal

tunnel, at least in the short-term, significantly improves symptoms with the potential to improve function as defined by the SSS and FSS of the BCTQ. In addition, improvement in median nerve cross sectional area compared to baseline values and controls were reported in the studies that looked at this outcome[25,27]. Studies failed to demonstrate significant improvements in NCS or VAS when compared to controls. PRP demonstrates promise in improving the symptoms of CTS while potentially improving function, however, has failed to demonstrate consistent nervous regeneration in the form of improved NCS. The results of quantitative analysis are confounded due to the risk of bias from unclear allocation concealment and blinding that may have resulted in performance bias, differential assessment of treatment outcomes and overestimation of treatment effects.

One recent qualitative review[30] studied the safety and efficacy of Ultrasound–guided perineural PRP injections in mild – moderate CTS. However, the methodology was flawed as two out of five included studies did not meet the inclusion criteria (i.e. ultrasound-guided injection of PRP). The reported evidence was of mixed quality and included case series. Lastly, the review lacked a quantitative synthesis of the available data for measurement of the evidence of an effect.

CTS arises due to intermittent or sustained pressure changes in the carpal tunnel that impair microcirculation and cause edema in the median nerve. This leads to demyelination, contrived action potentials and ultimately axonal loss[4]. PRP has shown therapeutic potential in nerve regeneration and repair by multiple mechanisms, mainly targeting the prevention of cell apoptosis and neural protection[31]. In spite of plausible results from the basic science studies[19,20,23,31], the results from clinical studies on the efficacy of PRP have been conflicting and debatable. In this review article, there was no evidence to support the role of PRP for

improvement in pain or NCS recorded a reversal of demyelination changes. Limited evidence was suggestive of its temporary beneficial role in providing symptomatic relief to patients with mild- moderate CTS.

Although no significant improvement was demonstrated in pain measured through VAS, this may be a result of the stage of carpal tunnel in the enrolled patients. Mild-moderate CTS symptoms typically consist of tingling and/or paresthesia with limited intermittent pain only with provocation or repetitive activities[6–8,32]. In addition, previous studies of carpal tunnel release, demonstrate that those with the milder disease do not demonstrate as significant or reliable improvements in VAS[12,33–35]. As such, those with comparatively severe disease as included in the Wu et al. study demonstrated significant improvements in VAS while all other studies with minimal - mild disease demonstrated no significant improvement. Pain as measured through a VAS may not capture genuine improvements in patients with minimum -mild CTS as it is not a persistent symptom uniformly present among all participants at this stage of disease[6–8,32].

Wu et al[25] showed an increased tendency of benefits in pain VAS scores that reached statistical significance with the increase in follow up duration (6 months). This result was incongruent with studies that have shorter follow up duration[28]. These differences of treatment effects can likely be ascribed to the difference in follow up duration as the time needed for the clinical effect of PRP is not yet established. High quality evidence of similar delayed clinical effects with PRP administration have been reported in other musculoskeletal conditions like lateral epicondylitis[15,36,37] and suggests a potential disease modifying role of PRP in mild–moderate CTS. Accordingly, it is likely that PRP injections demonstrate delayed effects and the studies with shorter follow up may have missed capturing the treatment effect.

The SSS of the BCTQ evaluates symptoms more common to patients with mild to moderate CTS including the frequency, duration and severity of tingling, numbness and pain. The mean improvement demonstrated in those receiving PRP, 1.95-points compared to controls, demonstrates a statistically and clinically significant improvement. Although there is debate on the true minimally clinically important difference (MCID[38–41]) of the BCTQ, SSS, and FSS, recent sources postulate that the MCIDs are dependent upon baseline/pre-intervention scores as those with higher scores, representing more severe disease, must have a larger change score to represent a MCID compared to those with lower scores, representing more mild disease[41]. Given that mean baseline SSS was below 3 in the majority of studies a conservative value of 1.38 can be utilized to demonstrate a MCID[41]. The significant improvement in SSS and not pain as measured by a VAS may be representative of the patient population, as the predominant symptom in patients with mild-moderate disease being intermittent numbness and tingling with only a minor aspect being pain.

The FSS evaluates functional limitations on nine daily activities that typically reproduce symptoms or are limited by numbness and tingling. Using a conservative MCID of 0.84[41], the mean improvement of 2.19-points demonstrated a highly clinically important improvement. The significant variability in FSS improvement may be explained by the stage of CTS, as a minimum threshold of symptoms are needed before impacting function.

Nerve conduction studies for CTS have been demonstrated to be reliable in evaluating and assessing the presence and severity of disease, however, the exact measurement has been widely debated. Multiple measurements have been utilized with the combined sensory index demonstrating highest reliability[42–45] and motor nerve involvement representing severe disease[42–45]. In addition, nerve recovery has been demonstrated to be a slow process lasting up to 18-

months after injury after which there is limited regeneration. These factors may assist in explaining a portion of the lack of improvement in NCS between PRP injection and controls despite within group changes. First, there was significant variability among studies on the sensory and motor outcomes utilized however all studies used a single median nerve value without reference to uninjured ulnar and/or radial nerves. Given the time needed for nerve regeneration and the majority of studies on carpal tunnel release demonstrating NCS improvement were at 1-year follow-up, there may not been enough time elapsed between intervention and final follow-up for substantial remyelination or axon regrowth. The selection of a more appropriate combined sensory index in those with mild to moderate disease with limited motor involvement and longer follow-up to allow nerve regeneration may be more reliable in determining NCS changes[42–45].

In addition to NCS, cross-sectional area of the median nerve has been described as a reliable objective diagnostic measure for CTS[46]. The statistically significant improvement demonstrated in cross sectional area of the median nerve, from 10.93mm^2 to 14.01mm^2 demonstrated by Wu et al[25] and 15 of the 26 patients improving in Malahias et al[27], represents improvement similar to that seen with carpal tunnel release both via open or endoscopic techniques[3,9,47,48]. This improvement in cross sectional area would be defined in most diagnostic scales as a curative treatment similar to carpal tunnel release and represents a transition from a CTS diagnosis to not meeting the CTS diagnostic criteria[2,46,49,50].

Only one included study[26] evaluated PRP injection compared to corticosteroid, which demonstrated an improved short-term effect of PRP compared to corticosteroid at 3-months however symptoms in both groups were returned to baseline level at 6-months. Previous Cochrane review of corticosteroid injection for CTS[5], concluded that corticosteroid provides

significant relief for one-month after injection compared to placebo however prolonged improvement was not demonstrated, and corticosteroid provided no improvement compared to splinting and anti-inflammatory treatment at 8-weeks follow-up. As such, although prolonged improvement compared to corticosteroid was not demonstrated PRP may have improved short-term efficacy or improvement compared to splinted however further studies are needed to determine if these trends how true in larger studies with more homogeneous populations.

The PRP formulations used in the studies included in this review had a variable concentration of platelets and other blood components with discrete injectate volumes. No specific trends of treatment outcomes were reported based on the concentration of platelet, other blood products and the injectate volume. There is a current lack of general consensus or high-quality data on the optimal PRP preparation in terms of concentration of platelets and other blood components. Additionally, no data is available on the ideal volume of PRP to be injected into the carpal tunnel for best clinical effect without inducing ischemia in the closed tunnel. Qualitative and quantitative changes in the PRP preparation may have an effect on the healing capabilities, and the optimum concentration of PRP beneficial for the regenerative effect remains unknown.

Adverse events in those undergoing injection of PRP for CTS can be divided into two groups, those due to needling of the area and those a result of the introduction of PRP into the carpal tunnel. Side effects of needling the area, including intraneural injection, injection pain and bruising, maybe reducible with the use of ultrasound guidance, as described previously for corticosteroid[51], however, may be unavoidable. Minor, transient side effects from the introduction of PRP into the carpal tunnel including pruritis and burning, appears to be low at 6% compared to values quoted as high as 33% in those receiving corticosteroid[51]. Due to the

small number of patients receiving PRP in these studies, 97 participants, it is difficult to speculate on the rate of major complications including tendon rupture and infection which is as low as 0.1-0.05% in those receiving corticosteroid[51–54]. However, based on the biologic action of either substance, it is likely that these adverse events are not reported with PRP as there is a reduced likelihood for infection or tendon rupture[31]. Corticosteroid is thought to cause cellular apoptosis and alteration in collagen synthesis, which ultimately weakens and can rupture tendons and reduce immunological response[51,55]. This has been demonstrated in a multitude of joints, tendons and ligaments including the carpal tunnel[51–54], plantar fascia[56], Achilles[57], rotator cuff[55,58,59] and all large and small joint injections[60,61]. Given the biological action of PRP, which is thought to aid in the regeneration of tendons, ligaments and cartilage[13–15] and have an increased immunologic response[23,24], these major adverse events may not be present. However, larger, population studies are needed to determine the true incidence of these rare major adverse events.

This review demonstrates that there may be a potential utility of PRP in the treatment algorithm of CTS and PRP can be considered a safer alternative to steroids for symptomatic relief in the short term. However, the lack of significant long-term results in pain and function prohibits the use of PRP as a definitive treatment option in mild – moderate CTS. Future studies are necessary to further determine the long-term effect on a large group of homogeneous patients as well as determine the clinical indications and effect on differing CTS severities and effects of preparation and concentration of the platelets and growth factors in PRP.

Study Limitations

This review is primarily limited by short follow-up, low participant number and heterogeneity of patients including with variable disease severity and duration as well the risk of bias in the

quality of evidence available. Studies differed significantly on their diagnosis and severity of CTS and not all studies defined the duration of symptoms prior to intervention while those that did had a very long duration of symptoms. These aspects make it difficult to appropriately compare outcomes to other well-defined surgical and non-surgical treatments and determine the true efficacy of PRP. Given the complexity of PRP, it is difficult to compare different preparations or injection style due to small sample sizes and heterogeneous reporting, which may all have considerable influence on efficacy and duration of improvement.

Conclusions

PRP represents a promising non-surgical option for patients with CTS with improvement in symptoms compared to placebo, conservative interventions and local corticosteroid injections at 3-months post-intervention. Despite early results being promising, studies were limited by low participant number, short follow-up, and heterogeneous patient populations and control interventions. Further studies are necessary to delineate better the effectiveness of PRP for CTS, including the clinical indications, improvements, and long-term results in this population when compared to gold-standard treatments.

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529 Figure 1: A flow diagram of study inclusions

530 Figure 2: Risk of bias summary: low risk of bias in green; high risk of bias in red; unclear risk of

531 bias in yellow.

532 Figure 3: Risk of bias graph: low risk of bias in green; high risk of bias in red; unclear risk of

533 bias in yellow.

534 Figure 4: A forest plot of meta-analysis: comparisons between studies of VAS changes at short-

535 term (3 months) VAS= Visual Analog Score

536 Figure 5: Forest plot of meta-analysis: comparison between Boston Carpal Tunnel Questionnaire

537 at short-term follow-up (3 months). SSS=Symptom Severity Scale, FSS= Functional Status

538 Scale. Note: The standardized mean difference was used for all studies, as the Wu et al study

539 used a different scale for the same outcome measure.

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Study	Location	Journal	Study Design	Sample Size (n) cases/controls	Mean Symptom Duration (months) cases/controls	Mean Age (years) cases/controls	% Female cases/controls	Final Follow-up (Duration)	Follow-up (%)
Raeissadat et al 2018	Iran	BMC Musculoskeletal Disorders	Prospective, randomized, single blind	21/20	14.1/13.7	51.2/47.2	100/100	10-weeks	100
Wu et al 2017	Taiwan	Nature Scientific Reports	Prospective, randomized, single blind	30/30	34.4/30.7	57.9/54.3	90/83.3	6-months	100
Uzun et al 2017	Turkey	Journal of Plastic surgery and hand surgery	Active control, single blind	20/20	NR	48.8/48.5	80/80	6-months	100
Malahias et al 2017	Greece	Journal of Tissue Engineering	Prospective, randomized, double	26/24	NR	60.5/57.2	NR	3-months	100

		and Regenerative Medicine	blinded						

Table 1: Summary characteristics of included studies. NR= Not reported, n= number of participants,

Author	Grade of CTS	Clinical and/or Electrophysiological Criteria Determining Severity	PRP intervention	Control Intervention	Adverse events
Raeissadat et al 2018	Mild - Moderate Disease	Mild CTS was defined as sensory latency of longer than 3.6 ms with normal motor latency (≤4.2 ms) and moderate CTS was defined as sensory latency of longer than 3.6 ms plus a prolonged motor latency (4.3–6 ms) according to Stevens et al[60]	- Rooyagen Kit, 10 mL blood draw for 1mL injectate - Double spin at 1600rpm(12min) then 3500rpm(7min) - Activator: 1mL of sodium citrate and autologous thrombin - No USG guidance	Prefabricated nightly wrist splint in 5-degrees extension x 8 weeks	Pruritis – 4 , Burning in hand – 1, pain in hand – 1
Wu et al 2017	Mild – Moderate Disease	Median sensory nerve distal latency >3.6 ms at a distance 14 cm away from the active recording, difference in distal latencies between the ulnar and median sensory nerve >0.4 ms; and distal motor latency of the median nerve is >4.3 ms at a distance 8 cm away from the thenar muscle belly according to Padua et al[61]	- Regen Kit, 10 ml blood draw for a 3mL injectate - Single spin at 3400rpm (15min) - Activator: Sodium citrate and autologous thrombin -USG guidance	Prefabricated wrist splint	No complications reported
Uzun et al 2017	Minimal - Mild Disease	Mild NCS findings indicating CTS according to AANEM consensus[62] Moderate and Severe disease was excluded.	- 15 ml blood draw for 2mL injectate - Single spin, 4000rpm (10min) - Activator: Sodium citrate No USG guidance	Corticosteroid Injection (triamcinolone 40mg/1ml)	No complications reported
Malahias et al 2017	Mild – Moderate Disease	Positive Phanels and Tinel's testing with NCS confirmation of median nerve disease Those with Severe disease as demonstrated by NCS were excluded according to AANEM concensus[62]	- 20 ml blood draw for 2mL injectate - Double spin, rpm/time NR - No Reported additions USG guidance	Normal saline	No complications reported

Table 2: Descriptive summary of study interventions and adverse events. NR=Not Report NCS= Nerve Conduction Studies, CTS = Carpal Tunnel Syndrome, ms= milliseconds, ml= milliliters, min=minutes, AANEM= American Academy of Neuromuscular and Electrodiagnostic Medicine.

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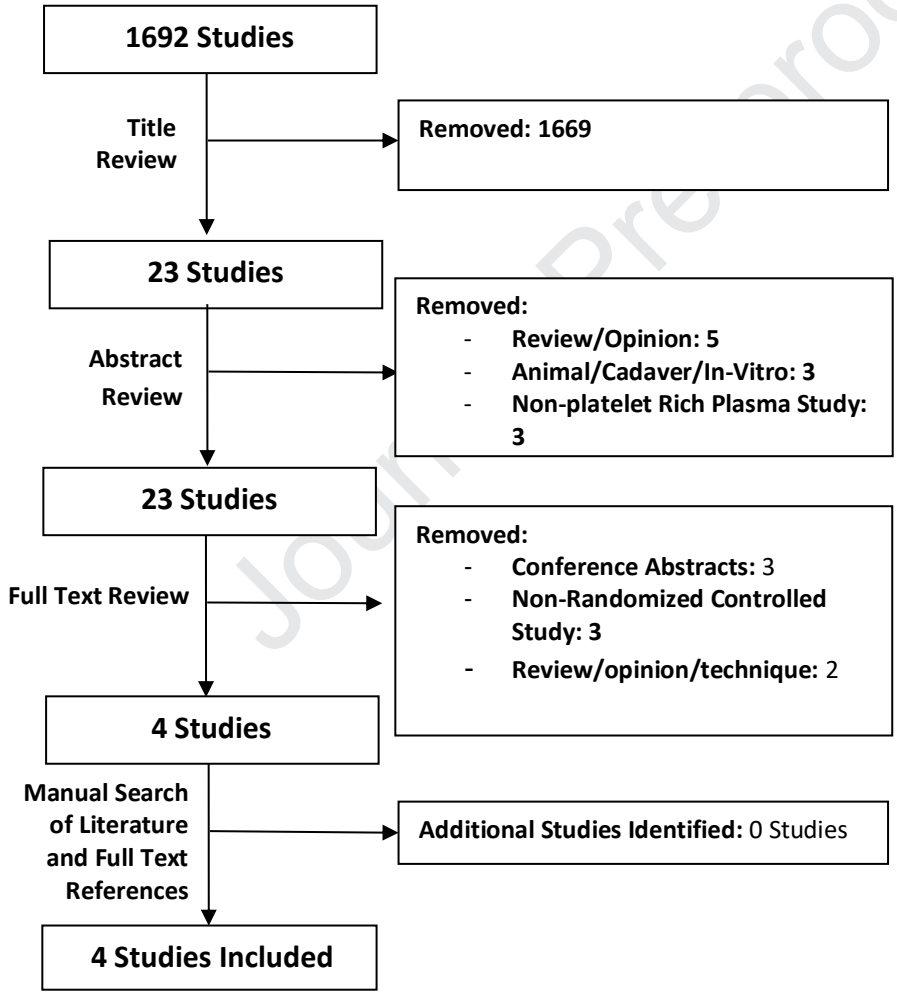
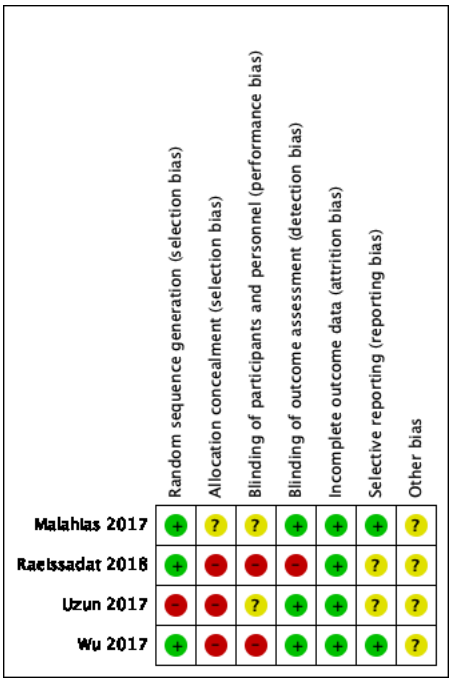
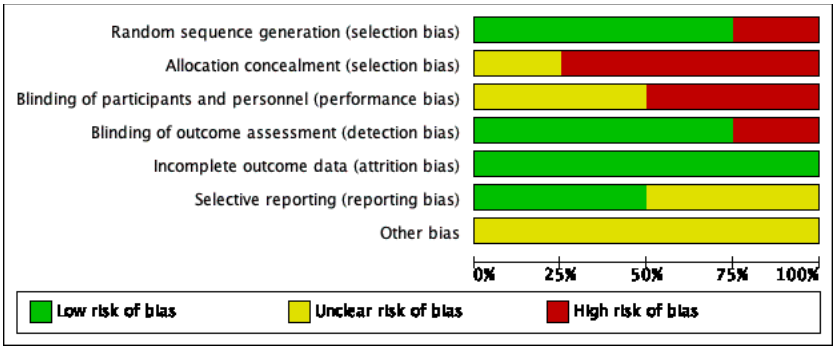
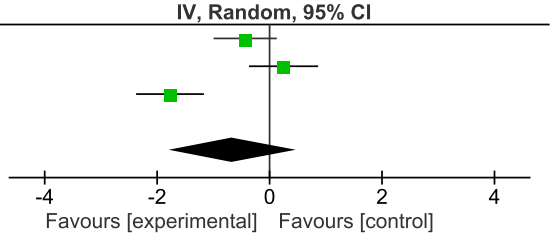


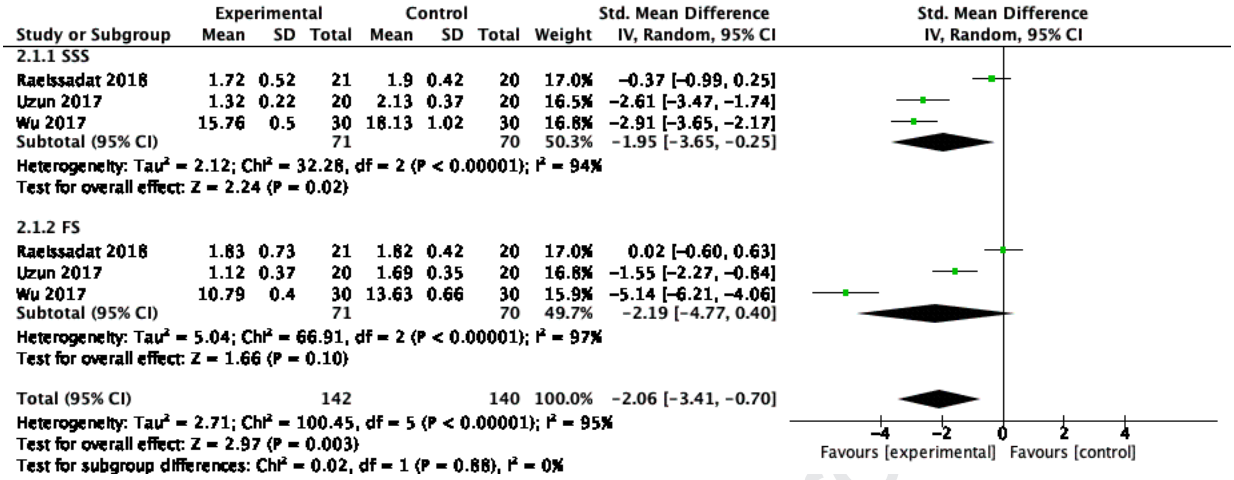




Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Malahias 2017	2.85	3.2	26	4.29	3.34	24	33.7%	-0.43 [-1.00, 0.13]
Raeissadat 2018	4.02	1.92	21	3.52	2.02	20	33.1%	0.25 [-0.37, 0.86]
Wu 2017	2.91	0.23	30	3.36	0.27	30	33.2%	-1.77 [-2.37, -1.17]
Total (95% CI)			**77**			**74**	**100.0%**	**-0.65 [-1.79, 0.48]**

Heterogeneity: Tau² = 0.92; Chi² = 22.05, df = 2 (P < 0.0001); I² = 91%
Test for overall effect: Z = 1.12 (P = 0.26)





PRP for Carpal Tunnel Syndrome

Highlights:

- PRP is theorized to reduce inflammation and promote neuronal and axon regeneration
- Four RCTs assessed the effects of PRP on pain and function in Carpal Tunnel Syndrome
- PRP results in significant improvement in the BCTQ but no change in VAS
- PRP represents a promising intervention however studies were of short follow-up
- Further investigation is necessary to determine PRPs true efficacy and effect