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Is Platelet-rich Plasma Injection Effective for Reducing Pain & Symptom Severity in Adults with Carpal Tunnel Syndrome?

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Is platelet-rich plasma injection effective for reducing pain & symptom severity in adults with carpal tunnel syndrome?

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine "Is platelet-rich plasma injection effective for reducing pain & symptom severity in adults with carpal tunnel syndrome?"

STUDY DESIGN: Systematic review of two randomized controlled trials and one non-randomized controlled trial to analyze the overall effectiveness of platelet-rich plasma (PRP) injections as a management for carpal tunnel syndrome (CTS). All three articles were published in peer-reviewed journals after the year 2016.

DATA SOURCES: These two RCTs and one non-RCT were found using Pubmed and were selected based on their year of publication, population of individuals with mild to moderate CTS, relevance to clinical question, and ability to meet POEM criteria.

OUTCOMES MEASURED: Patients in these three studies reported pain level measured by the Visual Analog Scale (VAS) and symptom severity measured by the Symptom Severity Scale (SSS)

RESULTS: Raeissadat et al. reported that PRP is not an effective treatment for CTS since there was no statistically significant evidence to support that at 10 weeks, PRP injections with a wrist splint added any benefit in VAS and SSS scoring compared to splinting alone (*BMC Musculoskelet Disord*. 2018;19(1). doi:10.1186/s12891-018-1963-4.). Wu et al. concluded that PRP is an effective treatment for CTS if used for 6 months. However, applying an endpoint of 3 months to make the study directly comparable to the others shows that a 3 month treatment period was not long enough to demonstrate statistically significant benefit of using PRP on the VAS, despite yielding statistically significant positive results on the SSS in month 3 (*Sci Rep*. 2017;7(1). doi:10.1038/s41598-017-00224-6.). In contrast, Atwa et al. showed that at the 1 and 3 month follow-ups, PRP injections were sometimes significantly better in relieving pain and symptom severity than corticosteroid injections since the PRP group overall scored lower on the VAS and SSS with p values <0.05 at both times, however the standard deviation was high enough to cause concern in the validity of these results. (*The Egypt Rheum*. 2018. doi:10.1016/j.ejr.2018.07.008.).

CONCLUSIONS: Based on the three studies analyzed, it can be concluded that PRP injection is not an effective treatment for reducing pain and symptom severity in adults with CTS.

KEY WORDS: platelet-rich plasma, carpal tunnel syndrome

INTRODUCTION

Carpal tunnel syndrome (CTS) is a type of peripheral entrapment neuropathy associated with etiologies such as repetitive overuse of the wrist. Other causes may include trauma, pregnancy, and specific disease pathophysiology like diabetes mellitus, sarcoidosis, amyloidosis, obesity, arthritis and hypothyroidism. Regardless of the specific cause, symptoms such as pain, numbness, tingling, and loss of muscle strength in the median nerve innervation arise from compression of the median nerve in the carpal tunnel under the transverse carpal ligament. Patients complain of an irritating and even painful sensation that radiates down their forearm into components of their hand, making the fingers feel weighted and unusable. Symptoms may also spread upwards towards the arm and shoulder of the affected limb. Regardless of the location of pain, patients typically see no erythema or edema.[1]

CTS makes up 90% of peripheral nerve entrapment cases,[2] and without intervention, CTS can significantly limit daily activities, hindering individuals' overall quality of life and ability to function.[3] In 2011, it was estimated that 2.7-5.8% of the general population had carpal tunnel syndrome, and the average annual incidence was 329 per 100,000 person-years.[1]

Each year in the US, CTS accounts for a total cost of $2 billion in medical costs. Mostly due to the surgical procedures required to relieve symptoms of this condition, carpal tunnel syndrome can be considered the most expensive upper extremity musculoskeletal disorder in the United States.[4] Not only does this condition cost actual dollars, but it can take away from time in the workplace, ultimately leaving most individuals with a lower income, and some, without a job. In fact, the average annual time missed from work due to carpal tunnel-related disability is 27 days. Surprisingly, this data only comes second to fractures in missed workdays.[4] Additionally, it has been noted that within 18 months of beginning a job, when an individual

worker develops CTS, there is an 18% chance they will inherently leave that job due to it.[4] CTS is undoubtedly a detrimental disorder to the United States population financially, functionally, and emotionally.

It is not known how many yearly healthcare visits occur from CTS, but it is known that CTS is more common in the working populations at an incidence of 5-21%,[4] mostly seen in occupations where repetitive wrist motions are necessary. Examples of such occupations include food processing, the logging industry, and carpentry. This is compared to a lower incidence in the general population at 1-5%.[4]

It is known that CTS is due to the physical compression of the median nerve in the transverse carpal ligament of the wrist. Typically, there is a traceable pattern of symptoms over the patient's hand and forearm that follow the median nerve innervation which helps guide the diagnosis of CTS using physical exam techniques such as Tinel sign, Phalen maneuver, or a flick sign. However, 9% of patients can have a symptomatic presentation that is unusual for the diagnosis which can prolong the diagnostic period or require additional tests.[1] If not treated properly, CTS can lead to permanent nerve damage of the affected regions.[1]

There are measures for CTS treatment that are typically used as a first-line treatment before decompression surgery. These modalities include wrist splints, NSAIDs, corticosteroid injections, and physical therapy. Unfortunately, it was reported that close to 60-70% of individuals undergoing these conventional management techniques remain symptomatic after 18 months.[4] Surgical decompression is certainly more effective than the alternative methods mentioned, but it has a large range of failure rates at 7-75%.[5] It is only truly suggested for patients with severe CTS or for patients with symptoms that are highly resistance to the previously mentioned measures of management.[5] Due to the substantial disability this condition

holds, research into effective treatment regimens is most certainly warranted. The newest research being conducted is on the use of platelet-rich-plasma (PRP) injections as an alternative to the current mainstays of treatment. PRP is a mixture dense in platelets and growth factors that has been previously used for wound healing and angiogenesis in the fields of neurosurgery, dentistry, and cosmetics, and there is strong evidence for its effectiveness in axon regeneration and repair of neurons. Using this knowledge as a basis for its therapeutic use, PRP could possibly become a treatment option for patients to relieve CTS symptoms, prolonging their need for decompression surgery or even preventing it altogether. This review uses 2 RCTs and 1 non-RCTs to analyze the overall effectiveness of PRP injections as a management for the symptoms of CTS.

OBJECTIVE

The objective of this selective EBM review is to determine "Is platelet rich plasma injection effective for reducing pain & symptom severity in adults with carpal tunnel syndrome?"

METHODS

All research and interpretation for this review including specific article selection were completed by the author. Three studies published in the English language were analyzed in this systematic review and were found using Pubmed and the keywords Platelet-rich Plasma and Carpal Tunnel Syndrome. Articles were selected based on their relevance to the clinical question, year of publication after 2016, population of individuals with mild-moderate CTS, and ability to meet POEM criteria. Exclusion criteria for this study included disease-oriented evidence, population under 20-years-old and above 60-years-old, articles written in a language other than English, and previously published Cochrane systematic reviews. Two of these studies were randomized control trials, while one was a non-randomized control trial, but they all analyzed

whether PRP is an effective treatment for mild to moderate CTS. The outcome measures used and analyzed in all three of these trials were the Visual Analogue Scale (VAS) and the Symptom Severity Scale (SSS) of the Boston Carpal Tunnel Questionnaire (BCTQ).[2, 3, 5] The intervention used in these trials was platelet rich plasma injections (PRP) into the median nerve and PRP combined with splinting, and it was compared to the interventions of corticosteroid injections into the median nerve as well as wrist splinting alone.[2, 3, 5] The statistics of this study were found using p-values, standard deviation and mean change from baseline. The patient demographics and criteria met for each article are described in Table 1.

Table 1. Demographics & Characteristics of included studies

Study	Type	# of Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Raeissadat[2] (2018)	RCT	41	Between 20-60 yo	Women at physical medicine/rehab clinics at Shahid Modarres Hospital (2016) with mild-mod CTS signs and sx and confirmed diagnosis based on H&P, + Phalen's test and electrophysiology	b/l CTS, pregnancy, hx of met d/s, corticosteroid use in last 3 months, thenar atrophy, previous CTS release, neuropathy/ radiculopathy evidence, PRP CIs (malignancy history, autoimmune or hematological disorders, NSAID consumption in last 2 days, anti-platelet/anti-coagulation use, Hb levels <12g/dL, PLT <150,000/mL)	0	PRP injection combined with night splint VS. night splint alone
Atwa[3] (2018)	Non RCT	36	Between 20-50 years old	Idiopathic mild-mod CTS being treated for 1 month w/o improvement	TCP, local infection, NSAID use, 2ndary CTS, past hx of corticosteroid injection into same wrist or severe CTS	0	PRP VS. corticosteroid injections
Wu[5] (2017)	RCT	60	Between 20-50 years old	Mild-mod unilateral CTS w/ clinical sx for 3 mo undergoing electrophysiology and ultrasound	History of wrist surgery, polyneuropathy, brachial plexopathy, thoracic outlet syndrome, hx of TCP, systemic infection, pregnancy, rheumatological disorders, previous steroid injection	0	PRP injections VS. night splint use

OUTCOMES MEASURED

The outcomes measured in this study included pain level change using the Visual Analogue Scale (VAS) and change in severity of symptoms using the Symptom Severity Scale (SSS). Data was collected through both of these measurement scales by subjects self-reporting pain and symptom severity. The VAS is a tool for patients to rate their pain on a scale of 0 (no pain) to 10 (worst pain) using pictures for reference. The SSS is a component of the BCTQ where patients rate their severity of CTS symptoms using an 11-question questionnaire with each question scaled 1 (least severe) to 5 (most severe), making a total possibility of 55 points to gauge severity of symptoms. Raeissadat et al.[2] measured these two outcomes at 10 weeks, Wu et al.[5] at 1, 3 and 6 months, and Atwa et al.[3] at 1 and 3 months to determine the efficacy of PRP injections for CTS. The endpoint of this review is set at 3 months.

RESULTS

This review uses three different studies to compare multiple forms of therapy for CTS with the intention to explain whether PRP injection is an effective treatment for CTS. All three studies include adults between the ages of 20 and 60 years old. Keeping in mind that the Raeissadat et al.[2] study concluded at 10 weeks, and the Wu et al.[5] and Atwa et al.[3] studies collected data at 3 months, the end point of this study is set at 3 months, noting this two-week discrepancy.

The study by Raeissadat et al.[2] is a randomized trial conducted at Shahid Beheshti University of Medical Sciences to show the safety and efficacy of PRP injections in the treatment of CTS. It used 41 women, placing 20 in the control group and 21 in the treatment group. All 41 subjects completed the trial. An overnight prefabricated wrist splint at 5 degree extension was used on the control group for 8 weeks.[2] The treatment group was treated with the

same splinting regimen but also with a median nerve injection of 1mL of autologous PRP. The mean change in each group of variables of VAS and SSS were recorded after 10 weeks.[2] Inclusion and exclusion criteria for this study can be found in Table 1. Although there was a mean decrease in both treatment and control groups of pain and symptom severity, the data displayed in Table 2 does not support the benefit of using PRP in addition to splinting as a treatment option for CTS.[2] Ultimately, with standard deviations calculated very close to the means and with p values considerably larger than 0.05, there is no statistically significant evidence to support the claim that PRP is effective for CTS treatment.[2]

Table 2. Pain & symptom severity reduction at 10 weeks by Raeissadat et al.

Variables	Group	Mean	SD	P value (adjusted for age)
VAS change 10 wks	Control **(n = 20)**	-2.90	2.1	0.398
	Treatment **(n = 21)**	-2.76	2.4	
SSS change 10 wks	Control **(n = 20)**	-0.70	0.3	0.629
	Treatment **(n = 21)**	-0.72	0.7	

The study conducted by Wu et al.[5] is a single-blind randomized trial that used 60 participants, 30 in the treatment and 30 in the control group to determine the six-month efficacy of PRP for CTS. All 60 participants completed the study. The research was conducted at the Tri-Service General Hospital, National Defense Medical Center in Taiwan, Republic of China. A total of 3mL of autologous ultrasound-guided PRP injection was used in subjects in the treatment group while subjects in the control group wore a wrist splint alone in the neutral position for at least 8 hours a day during the time of the study.[5] Inclusion and exclusion criteria for this study

can be found in Table 1. The mean change of the variables VAS and SSS was measured at 1 month, 3 months, and 6 months. Due to the limited time frames in the Raeissadat et al.[2] and Atwa et al.[3] studies at 10 weeks and 3 months respectively, the data in this study collected at month 6 will not be considered in this review with an endpoint of 3 months. It was seen that both groups in this study displayed a reduction in both pain and symptom severity at 1, and 3 months, however, only the SSS data at month 3 can be used as supporting evidence towards PRP injections effectiveness in CTS due to it being the only data within the 3 month endpoint with a p value <0.05 and standard reasonably low deviation.[5]

Table 3. 1, 3, and 6 month change in pain and symptom severity in corticosteroid vs PRP group as measured by VAS and SSS by Wu et al.

	PRP Group (n = 30)	Control Group (n = 30)	
	Mean Difference ± SF	Mean Difference + SF	p value
VAS-Pre	(6.50 ± 0.30)	(6.29 ± 0.31)	
VAS month 1	-2.61 ± 0.26	-2.41 ± 0.20	0.540
VAS month 3	-3.59 ± 0.34	-2.93 ± 0.20	0.104
VAS month 6	-4.53 ± 0.37	-3.30 ± 0.34	0.018
SSS-Pre	(26.17 ± 1.10)	(24.93 ± 1.22)	
SSS month 1	-8.93 ± 1.10	-6.50 ± 0.94	0.098
SSS month 3	-10.47 ± 1.17	-6.80 ± 0.93	0.017
SSS month 6	-11.76 ± 1.21	-8.73 ± 0.85	0.045

The study by Atwa et al.[3] was conducted to study PRP versus corticosteroid injections for treatment of CTS symptoms. It used 36 patients who all completed the trial, 18 patients in the control group receiving a single injection of the corticosteroid methylprednisolone 40mg/1.0mL and 18 patients in the treatment group receiving PRP injections of 2mL into the median nerve with 24 hours of rest following PRP injections.[3] Subjects were recruited from the Rheumatology

and Rehabilitation outpatient clinic, Zagazig University Hospitals. Table 1 outlines the inclusion and exclusion criteria of the study. The mean change of VAS and SSS were measured at 1 and 3 month periods.[3] The results showed with great confidence represented by the p intervals <0.05 that there was a significant total decrease in pain and symptom severity from baseline in both the treatment and control groups at 1 and 3 months although there was a slight increase in pain and symptom severity from 1 to 3 months in both groups. However, it can be said that the most significant decrease in pain and symptom severity at both 1 and 3 months from baseline was found in the group treated with PRP. On the other hand, despite the low p values, the large standard deviations on the mean values are a cause for concern. By definition of standard deviation, 99.7% of the data lies within 3 standard deviations of the mean in a normal distribution. This suggests that there may have been data points very far from the mean, which contradicts the notion that PRP was an effective treatment as a whole. Therefore, this study is not entirely supportive of the effectiveness of PRP to treat CTS.

Table 4. 1 and 3 month change in pain and symptom severity in CS vs PRP injections as measured by VAS and SSS by Atwa et al.

Parameter mean $\pm$ SD		Group I Corticosteroid (n = 18)	Group II PRP (n = 18)	p value
VAS	Baseline	7.2 $\pm$ 1.3	7.05 $\pm$ 1.4	0.8
	1 month	3.5 $\pm$ 2.35	2.1 $\pm$ 2.6	0.03
	3 months	5.2 $\pm$ 1.9	3.4 $\pm$ 2.09	0.002
	p value	0.0001	0.0001	
SSS	Baseline	36.8 $\pm$ 7	33.2 $\pm$ 6	0.1

	1 month	22.3 ± 7.4	18.6 ± 10.7	0.02
	3 months	28.6 ± 6.8	21.5 ± 10.2	0.001

DISCUSSION

Although treatments such as corticosteroid injections, wrist splinting, and NSAIDs exist, they unfortunately have little to no permanent effect for patients who severely suffer from symptoms of this syndrome. Patients are left with the option of invasive decompression surgery that commonly brings its own risks such as adjacent vessel damage, sensitive scarring and infection.[5] This selective evidence-based medicine review focused on the specific use of PRP injections as a treatment option for CTS and studied its use for pain and symptom severity in a 3 month time frame. PRP injections have been used to promote healing for alternative means such as orthopedic, dental and plastic surgery procedures since the late 1980s.[6] This review does not support much promise towards the use of PRP injections for CTS treatment. The Atwa et al. study when compared to standard treatments of splinting and corticosteroid injection use would have been very supportive if it were not for the large standard deviations.[3] The studies conducted by Raeissadat et al. and Wu et al. did not strongly and statistically show support for the effectiveness of PRP for CTS treatment either outside of the Wu et al. study's SSS results at 3 months.[2, 5]

It should be noted that none of the three studies analyzed were conducted in the United States nor were US studies on this topic found; therefore, the use of PRP injections in individuals outside of the United States may play a factor in this treatment option's efficacy in these trials. Although the use of activated PRP injections are not approved by the FDA and must be used "off-label" in the US, and there is no evidence to support its availability for use in the US, it is

being explored in other countries for the use described in this study. It should also be noted that PRP use for other therapies has been deemed safe when mixed with other substances, but it has seen its drawbacks such as for its use in musculoskeletal pain where side effects of local infection and pain at the site of the injection can be seen.[6]

Limitations to these studies are evident and may have played a role in the final outcome of the studies. Concerning the article by Raeissadat et al.,[2] in both the control and treatment group, data on the patient population was halted at 10 weeks. Conversely, the Atwa et al.[3] and Wu et al.[5] studies were conducted to 1 and 3 months and 1, 3 and 6 months respectively. Although these were indeed short follow-up times, these inconsistent time frames made it difficult to choose an endpoint for this review. With the final endpoint chosen at 3 months, there is an obvious two-week discrepancy between the Wu et al.[5] and Atwa et al.[3] studies when compared to Raeissadat et al.,[2] leaving room for a potential change in outcome if the Raeissadat et al.[2] study had been conducted two weeks longer. The longer studies also could have benefitted by questioning subjects at monthly intervals instead of at multiple month intervals. Other limitations include small sample sizes, lack of double-blinding in all three studies and lack of randomization in the Atwa et al. study.[3] In order to make an even stronger statement concerning the value of PRP injection for CTS treatment, these limitations must be addressed in future studies.

CONCLUSIONS

After analyzing these three studies for the purpose of this review, it can be concluded that PRP is not an effective treatment for CTS. The most support for this conclusion is found in the Wu et al. study which showed PRP benefit throughout the entire six-month study when compared to night splinting, but the data was provided with p values >0.05 at SSS month 1, and

VAS month 1 and 3, making the data at these time frames statistically insignificant. However, PRP injections showed benefit in regard to SSS at 3 and 6 months and VAS at 6 months with p values <0.05, but due to this review's endpoint being 3 months, it can only be stated that Wu et al. shows support for PPR injections for treatment of CTS's SSS at 3 months. The study by Raeissadat et al.[2] did not provide sufficient statistical evidence to support the claim that PRP adds any benefit to patient's CTS symptoms. Although both treatment and control groups displayed a decrease in pain and symptom severity at 10 weeks, the p values were >0.05 and standard deviations were large, making the data statistically insignificant. The final study by Atwa et al.[3] also supported the same conclusion. Although there was a significant decrease in pain and symptom severity in both the PRP and control group with p values <0.05 at both 1 and 3 months, PRP did display the greatest decrease in pain and symptom severity, showing some support for PRP effectiveness in CTS treatment. However, due to large standard deviations in the mean values recorded, there is ample room to doubt the effectiveness of the use of PRP in the treatment of CTS. Future studies would warrant larger sample sizes in order to achieve more conclusive data. Research would also benefit by selecting a study endpoint as well as a dose of PRP that is similar to previously conducted studies for the ease of comparative data.

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