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Efficacy of platelet-rich plasma injection in mild and moderate carpal tunnel syndrome: randomized control study

Souzan E. Gado* and Hanaa S. EL-Banna

Abstract

Background: Carpal tunnel syndrome (CTS) is the most common peripheral entrapment neuropathy. Typical symptoms and signs include numbness, tingling, pain, or burning sensation in the digits supplied by the median nerve and/or nocturnal paresthesia. Treatments of CTS range from conservative measures to surgical decompression of the median nerve.

Results: The PRP group showed a statistically significant reduction in the visual analog scale, Boston Carpal Tunnel Syndrome Questionnaire, for the severity and the functional capacity scores, and cross-sectional area of the median nerve compared to those of control group 3 months post-treatment ($p < 0.05$).

Conclusions: Platelet-rich plasma injection in CTS relieves pain and symptom severity and improves functional status but not significantly improve the electrophysiological parameters.

Keywords: Carpal tunnel syndrome, Platelet rich plasma

Background

Carpal tunnel syndrome (CTS) is the most common peripheral entrapment neuropathy [1]. Treatments of CTS range from conservative measures, such as non-steroidal anti-inflammatory drugs (NSAIDs), wrist splints, corticosteroids injection, local injection of insulin [2], or physical therapy to surgical decompression of the median nerve [3, 4].

Surgical intervention is considered by some authors more effective than conservative treatment for CTS [5]. However, conservative therapies are more suitable for mild to moderate cases [6]. Despite the availability of multiple conservative therapies for CTS, their efficacy is usually unfavorable or not sufficient [7]. So, it is important to develop novel therapeutic interventions for CTS.

Platelet-rich plasma (PRP) is a biologic product of concentrated platelets; it contains several growth factors well known to be effective on inflammation and wound healing. These factors include transforming growth factor (TGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), and the insulin-like growth factor-1 (IGF-1) [8, 9].

PRP was recently shown to possibly promote axon regeneration and neurological recovery. It has also been shown to have acceptable success rates in treatment of clinical peripheral neuropathies [10, 11].

Regenerative medicine techniques, which involve regenerating human cells, tissues, or organs to restore normal function, have been increasingly used in the treatment of various musculoskeletal disorders. In this regard, dextrose and platelet-rich plasma (PRP) are the two most commonly used regenerative injection regimens, and numerous in vitro and in vivo studies have shown their potential role in promoting tissue repair. Furthermore, the pathophysiology of CTS comprises increased intra-compartment pressure and microcirculatory disturbance in subsynovial connective tissue [12–14].

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A cadaveric study has demonstrated that a bolus saline injection could electively reduce the peak gliding resistance of the median nerve. Another randomized controlled trial pointed out that precise hydro-dissection of the median nerve using saline under ultrasound guidance yielded better clinical outcomes than subcutaneous saline injection. Therefore, the observed superiority of D5W over PRP (with respect to CTS symptoms) in this meta-analysis may be partly derived from a higher injection volume and the mechanical effect of nerve hydrodissection guided by ultrasound imaging [15, 16].

Methods

Inclusion criteria

Patients with confirmed clinical diagnosis (paresthesia of the hand exacerbated by repetitive use or sleep and improved by shaking the hand, numbness in the radial 3 1/2 digits and motor weakness of thenar muscles, positive Phalen's test and/or Tinel's sign) and electrophysiological diagnosis of mild and moderate CTS were included.

CTS severity was categorized by the electrophysiological classification of CTS by Padua et al. [17] as follows: mild, only abnormal sensory nerve conduction velocity (SNCV) with normal distal motor latency of the median nerve (DML); moderate, abnormal SNCV and abnormal DML; or severe, absence of SNCV and abnormal DML.

Exclusion criteria

Patients with history of previous carpal tunnel release surgery, previous steroid injection for carpal tunnel syndrome in the past 3 months, polyneuropathy, brachial plexopathy, or thoracic outlet syndrome, pregnancy, bilateral CTS, or atrophy of thenar muscles and patients with PRP contraindications including history of malignancies, autoimmune disorders, thrombocytopenia, platelet dysfunction, or systemic infection were excluded.

Study design

This study included 40 patients with unilateral mild to moderate CTS selected from the Outpatient Clinic of Physical Medicine, Rheumatology and Rehabilitation Department, University Hospitals, during 2019. The selected patients were randomly categorized into two groups (envelop randomization).

The control group and PRP group used a prefabricated wrist splint at neutral position and they were instructed to put on the splint overnight for 8 h daily.

The PRP group also received a single ultrasound-guided injection of 3 mL of PRP processed using the Rooyagen kit (made by Arya Mabna Tashkis Corporation, RN: 312,569).

Leucocytes poor PRP preparation

Ten milliliters of blood were drawn from the patient's antecubital vein using an 18-G needle, then 1 mL of acid-citrate-dextrose was added to the blood sample as an anticoagulant and passed two stages of centrifugation, first at 1600 rpm for 12 min to separate the erythrocytes and then at 3500 rpm for 7 min in order to concentrate the platelets [18, 19].

Ultrasound-guided injection

The ultrasound-guided PRP injection was performed in the Ultrasound Unit of the Rheumatology Department, University Hospitals (SAMSUNG MEDISON, UGEO H60), with linear array transducers (with frequencies ranging between 7.5 and 12 MHz) by a rheumatologist experienced in MSUS imaging. The patient's hand was comfortably rested on a pillow placed over the thighs, with the palm upwards and the wrist slightly extended; the median nerve (MN) was identified at the inlet of the proximal carpal tunnel at the pisiform bone [20]. The ultrasound-guided injection was done using the in-plane ulnar approach [21]; the needle was passed from the ulnar side of the wrist toward the MN, avoiding the ulnar artery identified by Doppler signals. Two milliliters of PRP was injected to peel the nerve off the flexor retinaculum via hydrodissection. The residual 1 mL of PRP was applied to the inferior part of the MN. The carpal tunnel was scanned to ensure that the PRP reached to the distal area of the carpal tunnel (Fig. 1). All patients were observed for 10 min after injection for pain, pruritus, or bleeding and instructed about activity restrictions by using wrist splints and icing on the injection site.

All patients of both groups were assessed before intervention and at 1 and 3 months after treatment by the following:

- Visual analog scale (VAS) [22]: the pain severity was determined on a scale from 0 (no pain) to 10 (agonizing pain).
- The Boston Carpal Tunnel Syndrome Questionnaire (BCTQ) [23] was used for evaluating the severity of symptoms and functional status of patients. The symptom severity scale consists of 11 questions, and the scores range from 1 to 5. The functional status scale consists of 8 questions, and the scores range from 1 to 5 points; higher scores mean worse severity and dysfunction.
- Cross-sectional area (CSA) of MN: CSA was measured at the proximal inlet of the carpal tunnel using the pisiform bone as a landmark (Fig. 2). The average of CSA was randomly calculated. Inter-rater reliability: all images were read independently by two observers blinded to clinical and electrophysiological findings. Two images for each patient were performed.

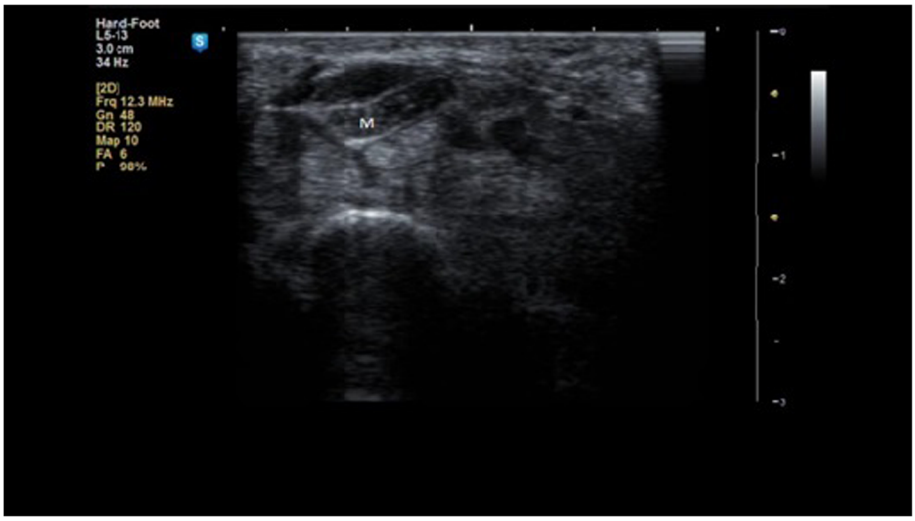

Fig. 1 The carpal tunnel was scanned to ensure that the PRP reached to the distal area of the carpal tunnel

– Electrophysiological parameters [24, 25]: antidromic SNCV and onset DML of the MN were measured in all patients by using Neuropack (USA) ® Wave electromyography device.

Statistical analysis

The collected data was analyzed using the SPSS software statistical computer package version 16. For quantitative data, the mean and standard deviation were calculated. For qualitative data, the number and percent distribution was calculated. Demographic statistics were analyzed using the independent *t* test for continuous data and chi-square test for categorical data. The univariate ANOVA followed by post hoc power analysis was performed for the data at various follow-ups in both groups. The independent *t* test was used to compare the differences between the groups. *p* values < 0.05 were considered statistically significant.

Results

All the forty patients completed the study, and twenty wrists in each study group were analyzed. The comparison between the two groups regarding clinical and

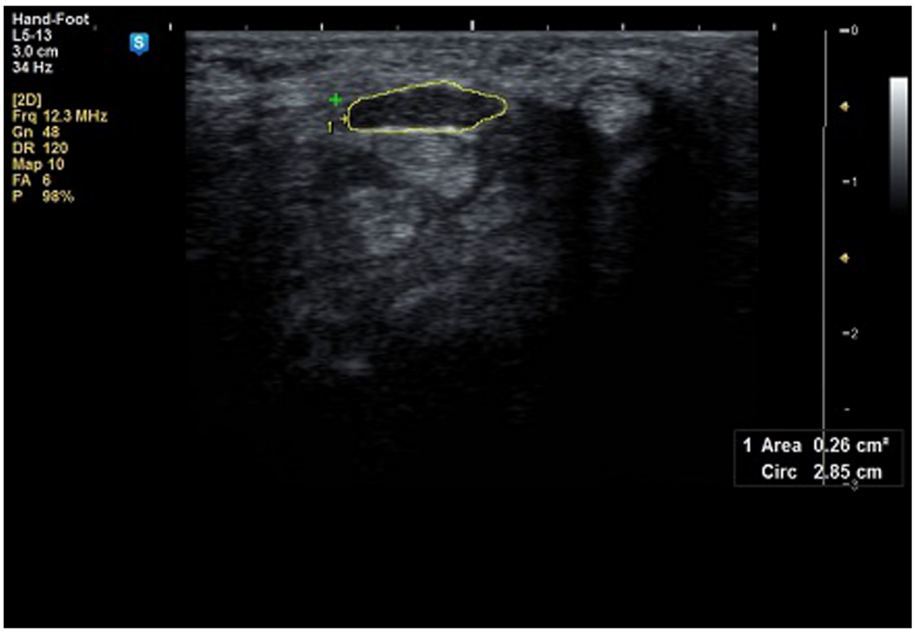

Fig. 2 CSA was measured at the proximal inlet of the carpal tunnel using the pisiform bone as a landmark

demographic variables was found to be non-significantly different at the onset of the study (Table 1).

Comparing the baseline data of VAS scores, BCTQ scores, electrophysiological study, and cross-sectional area of the median nerve, a significant improvement in all tested outcome measures (except for the sensory nerve conduction velocity) was observed in the PRP and control groups respectively at all follow-up assessments (Table 2).

Finally comparing the differences in each variable between the two groups, there was significant improvement in the PRP group at follow-up assessments in the VAS scores. Significant improvement in the PRP group BCTQ scores and CSA of the MN was only noted at the third month follow-up assessment (Fig. 3). SNCV and DML outcome measures did not significantly differ between the two groups (Table 3).

Discussion

PRP in the treatment of CTS originated from the various experimental studies that had reported positive effects of PRP on regeneration of peripheral nerves without considerable risks [26]. Other studies revealed a significant effect of PRP on functional axon recovery as PRP could stimulate Schwann cell proliferation, secretion of nerve growth factor, and neurotrophic factor in vitro [27].

Farrag et al. and Cho et al. [28, 29] demonstrated beneficial effects of PRP for facial nerve regeneration in a rat model. Sariguney et al. and Giannessi et al. [30, 31] showed that PRP enhanced the remyelination and axonal regeneration of the sciatic nerve. In contrast, Piskin et al. [32] reported that PRP does not enhance axonal regeneration of peripheral nerve repair in a rat model.

In this study, PRP injection significantly improved the pain, disease severity, and functional disabilities of CTS and cross-sectional area and the distal motor latencies of the median nerve; also, there was a significant improvement in all outcome variables in the control group. There was no significant improvement in the sensory nerve conduction velocity in both PRP and control groups (p = 0.182 and 0.149 respectively) (Table 2).

In agreement with our results, Raeissadat et al. [33] performed a randomized controlled trial to evaluate PRP safety in women with CTS (n = 20 vs. n = 21) using single blind PRP injection; they reported significant improvements in pain and symptom severity and

Table 1 Comparison between the two groups regarding clinical and demographic variables

	PRP group (***n*** = 20)	Control group (***n*** = 20)	***p*** value
Age	46.93 ± 4.41	46.75 ± 2.96	0.884
Sex			0.633
Male (*n*) (%)	2 (10)	3 (15)	
Female (*n*) (%)	18 (90)	17 (85)	
Duration (months)	15.86 ± 6.13	14.90 ± 6.70	0.641
Diabetes mellitus (*n*) (%)	2 (10)	1 (5)	0.548
Dominant hand			0.147
Right (*n*) (%)	20 (100)	18 (90)	
Left (*n*) (%)	0 (0)	2 (10)	
Side of lesion			0.519
Right (*n*) (%)	11 (55)	13 (65)	
Left (*n*) (%)	9 (45)	7 (35)	
Severity			0.288
Mild (*n*) (%)	16 (80)	13 (65)	
Moderate (*n*) (%)	4 (20)	7 (35)	
VAS	6.75 ± 0.94	6.47 ± 0.70	0.299
BCTQ-severity scale	25.53 ± 0.63	25.27 ± 0.73	0.235
BCTQ-functional scale	19.15 ± 0.73	18.83 ± 0.69	0.168
Median SNCV(m/s)	32.83 ± 3.50	33.32 ± 3.35	0.653
Median DML (ms)	4.97 ± 0.32	4.80 ± 0.36	0.112
CSA (mm^2)	13.62 ± 0.64	13.34 ± 0.71	0.196

VAS visual analog scale, *BCTQ* Boston Carpal Tunnel Syndrome Questionnaire, *SNCV* sensory nerve conduction velocity, *DML* distal motor latency, *CSA* cross-sectional area

Table 2 Outcome measures in PRP and control groups before and after treatment

	PRP group (n = 20)		Control (n = 20)	
	Mean ± SE	p value	Mean ± SE	p value
VAS-Pre	6.75 ± 0.94		6.47 ± 0.70	
1	4.38 ± 0.94	< 0.001	4.57 ± 0.69	< 0.001
2	3.52 ± 0.90	< 0.001	4.06 ± 0.65	< 0.001
BCTQs-Pre	25.53 ± 0.63		25.27 ± 0.73	
1	18.81 ± 0.93	< 0.001	18.57 ± 1.14	< 0.001
3	17.50 ± 0.90	< 0.001	17.62 ± 1.02	< 0.001
BCTQf-Pre	19.15 ± 0.73		18.83 ± 0.69	
1	13.94 ± 0.66	< 0.001	13.90 ± 0.99	< 0.001
3	12.53 ± 0.60	< 0.001	13.03 ± 1.12	< 0.001
SNCV-Pre (m/s)	32.83 ± 3.50		33.32 ± 3.35	
1	34.28 ± 3.36	0.365	34.85 ± 3.34	0.323
3	34.73 ± 3.23	0.182	35.32 ± 3.32	0.149
DML-Pre (ms)	4.97 ± 0.32		4.80 ± 0.36	
1	4.71 ± 0.32	0.028	4.54 ± 0.35	0.050
3	4.67 ± 0.31	0.012	4.52 ± 0.34	0.033
CSA-Pre (mm^2)	13.60 ± 0.67		13.34 ± 0.71	
1	12.03 ± 0.94	0.020	12.32 ± 0.84	0.047
3	11.60 ± 0.93	< 0.001	12.08 ± 0.81	< 0.001

VAS visual analog scale, *BCTQ* Boston Carpal Tunnel Syndrome Questionnaire, *SNCV* sensory nerve conduction velocity, *DML* distal motor latency, *CSA* cross-sectional area, *Pre* pretreatment

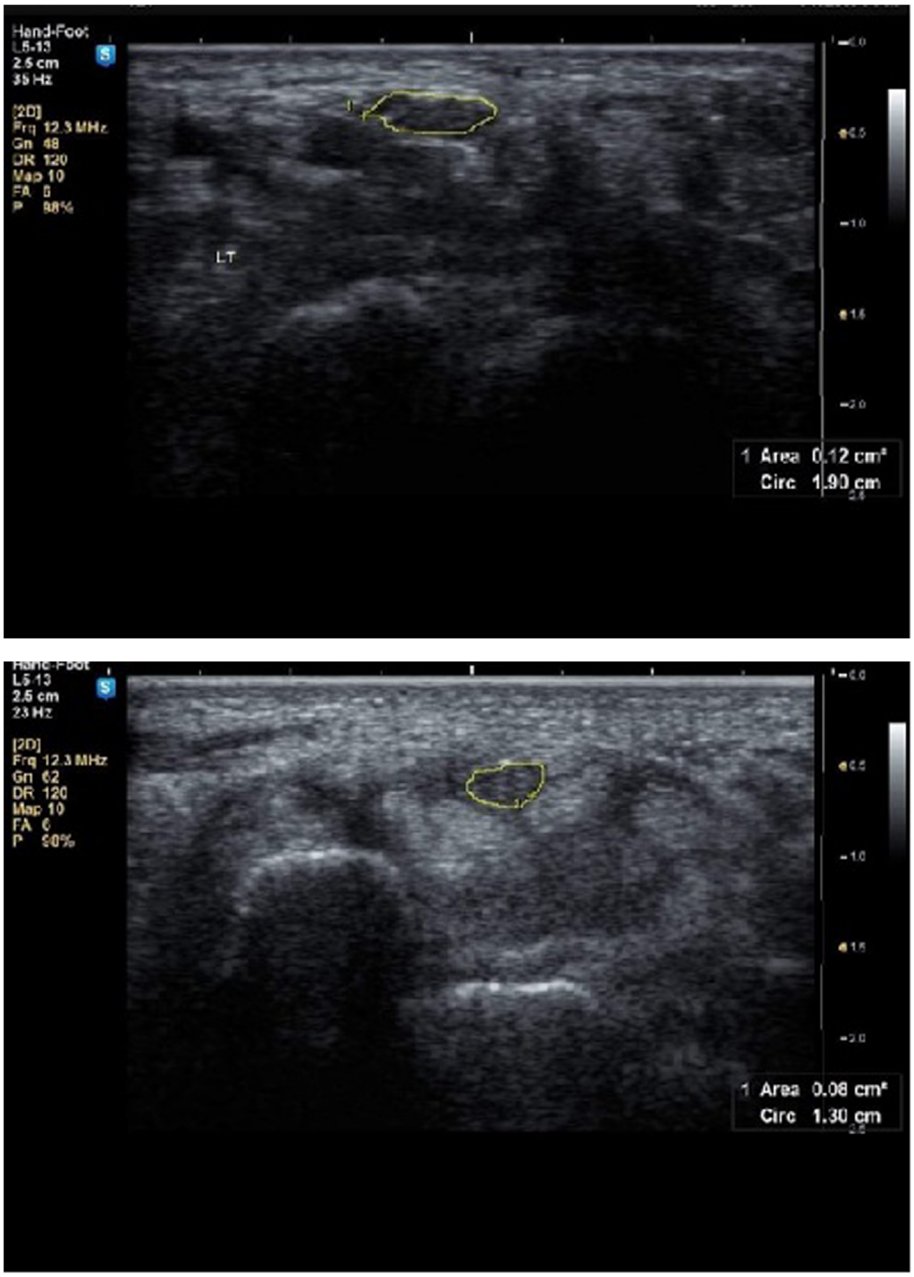

Fig. 3 Significant improvement in CSA of the MN in the PRP group was only noticed at third month follow-up assessment

functional status of patients, assessed according to the VAS and BCTQ and also electrophysiological parameters, in both PRP and splint groups, after 10 weeks of treatment except for the median CMAP onset latency in the PRP group. ($p = 0.472$).

Also, Wu et al. [34] conducted a prospective randomized, single-blind controlled trial to study the 6-month efficacy of platelet-rich plasma for mild and moderate carpal tunnel syndrome ($n = 30$ vs. $n = 30$); when comparing the VAS scores, BCTQ scores, electrophysiological study, CSA of the median nerve, and finger pinch baseline, with post-treatment data, a significant improvement in all outcome measures was observed in the PRP and control groups at all follow-up assessments ($p < 0.05$).

Uzun et al. [35] performed a non-randomized, single-blind trial to compare the effect of PRP with steroid injection in patients with minimal to mild CTS ($n = 20$ vs. $n = 20$) by using blind injection. They recorded improvements in sensory nerve conduction after 3 months in both groups, although distal motor latencies did not change in either of the groups during the follow-up period.

Table 3 Comparison of outcome measures differences between baseline and follow-up assessments in the PRP and control groups

	PRP group (***n*** = 20)	Control (***n*** = 20)	***p*** value	CI 95%	
	Mean difference ± SD	Mean difference ± SD		Upper	Lower
VAS-Pre					
VAS-1 month	− 2.37 ± 0.16	− 1.90 ± 0.17	< 0.001	0.34	− 0.73
VAS-3 month	− 0.86 ± 0.21	− 0.52 ± 0.12	< 0.001	− 0.03	− 1.05
BCTQs-Pre					
BCTQs-1 month	− 6.72 ± 0.77	− 6.70 ± 0.95	0.957	0.91	− 4.28
BCTQs-3 month	− 1.31 ± 0.48	− 0.96 ± 0.38	0.015	0.50	− 0.73
BCTQf-Pre					
BCTQf-1 month	− 5.21 ± 0.40	− 4.93 ± 0.60	0.098	0.58	− 0.50
BCTQf-3 month	− 1.42 ± 0.30	− 0.88 ± 0.36	< 0.001	0.08	− 1.08
SNCV-Pre (m/s)					
SNCV-1 month	1.46 ± 0.43	1.53 ± 0.38	0.562	1.6	− 2.71
SNCV-3 month	0.45 ± 0.34	0.47 ± 0.30	0.845	1.51	− 2.68
DML-Pre (ms)					
DML-1 month	− 0.27 ± 0.07	− 0.25 ± 0.05	0.530	0.38	− 0.05
DML-3 month	− 0.03 ± 0.04	− 0.02 ± 0.02	0.534	0.36	− 0.05
CSA-Pre (mm^2)					
CSA-1 month	− 0.66 ± 0.32	− 0.53 ± 0.28	0.195	0.60	− 0.25
CSA-3 month	− 1.40 ± 0.57	− 0.91 ± 0.45	0.004	0.26	− 0.92

VAS visual analog scale, *BCTQ* Boston Carpal Tunnel Syndrome Questionnaire, *SNCV* sensory nerve conduction velocity, *DML* distal motor latency, *CSA* cross-sectional area, *Pre* pretreatment, *SD* standard deviation

In 2015, Malahias et al. [36] first used an ultrasound-guided injection of 1–2 mL of PRP in patients with mild CTS (n = 14, no control group) with positive mid-term outcomes (3 months). Sánchez et al. [26] described a patient with recalcitrant peroneal nerve palsy who showed partial recovery and obvious improvement in the electrophysiological study 21 months after the first PRP injection (7 sessions of PRP injection in total). Anjayani et al. [10] reported a randomized, double-blind, control trial study to prove that a 1-mL PRP perineural injection could improve pain scores using a VAS, and the two-point discrimination test of peripheral neuropathy, in patients with Hansen's disease compared with a 1-mL PPP injection, 2 weeks after the injection of both types of plasma (n = 30 vs. n = 30, respectively).

In our study, while comparing the differences in outcome variables of both PRP and control groups, there was significant improvement in the PRP group at the 1st and 3rd month VAS scores, the 3rd month BCTQ-severity and functional scores, and CSA of the MN. The difference in SNCV and DML between the two groups was not statistically significant (Table 3).

Similar to our results, Wu et al. [34] found that, comparing the PRP and control groups, there was a significantly greater enhancement in the PRP group at all follow-up time points in the VAS scores, BCTQ scores, and CSA of the MN (except for the 1st and 3rd month VAS score and 1st month BCTQ-severity score), and this tendency became more pronounced as the follow-up duration increased. The difference in SNCV and DML between the two groups was not statistically significant at all follow-up assessments. It is therefore possible that PRP may exhibit a delayed effect.

Uzun et al. [35] showed that the PRP group had a significant improvement of BCTQ (both symptom and function scores) 3 months post-treatment compared with the steroid group, but the difference was not significant at the 6 month follow-up. Moreover, there was no significant change between the two groups in the electrophysiological measurements, so they considered PRP only as a temporary symptomatic relief for mild carpal tunnel syndrome

In contrast to our results, Raeissadat et al. [33] found that the changes in the evaluated outcome measures between the PRP and control groups of patients were not statistically significant even when the analyses were adjusted for age of the patients, and the PRP injection did not add considerably to the effects of wrist splint.

Several mechanisms were postulated to explain the effect of PRP on CTS relief: PRP could promote angiogenesis, neurogenesis, and regeneration via direct effects on the median nerve, PRP could reduce the flexors tenosynovitis, which would result in reduction of intracarpal pressure exerted on the median nerve, and finally, the hydrodissection could have some benefits [36–39].

Conclusion

Ultrasound-guided PRP injection is recommended for safe, effective symptomatic relief of mild and moderate carpal tunnel syndrome. More ongoing researches on PRP effects on peripheral neuropathy and CTS with longer follow-up periods are recommended to evaluate the exact mechanism of PRP, to determine its dosage regimen for best efficacy, and to investigate whether it is a long-lasting therapeutic approach or it is merely a temporary relief.

Abbreviations

CTS: Carpal tunnel syndrome; CSA: Cross-sectional area; DML: Distal motor latency; D5W: 5% dextrose in water; MN: Median nerve; PRP: Platelet rich plasma; SNCV: Sensory nerve conduction velocity; BCTQ: The Boston Carpal Tunnel Syndrome Questionnaire; VAS: Visual analog scale

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Authors' contributions

SG performed the clinical examination and electro-diagnosis. HE analyzed and interpreted the patient's data; we performed the PRP injection. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable

Ethics approval and consent to participate

The study was approved by the local Ethics Committee of Faculty of Medicine, Tanta University. Approval Code 40256/12/18. The written informed consent from all the patients was obtained, and the trial was conducted according to the Declaration of Helsinki principles.

Consent for publication

Not applicable.

Competing interests

We declare no conflicts of interest.

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