Original Article

A Randomized Controlled Trial to Compare the Effect of Ultrasound-Guided, Single-Dose Platelet-Rich Plasma and Corticosteroid Injection in Patients with Carpal Tunnel Syndrome

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Abstract

Background: Platelet-rich plasma (PRP) may aid functional recovery in compressive neuropathies. **Objective:** To compare the effect of autologous PRP with corticosteroid injection in patients with refractory carpal tunnel syndrome (CTS). **Materials and Methods:** This was a randomized controlled trial on 84 adults, who received either single-dose, ultrasound-guided PRP or corticosteroid. Boston Carpal Tunnel Questionnaire and cross-sectional area of median nerve were assessed at 0, 4, and 12 weeks. **Results:** A statistically significant 54.76% improvement ($P < 0.05$) in functional status was observed in both the groups at 12 weeks. **Conclusion:** PRP is as effective as corticosteroids in relieving pain and improving function in CTS.

Keywords: Carpal tunnel median neuropathy, interventional ultrasonography, methylprednisolone acetate, nerve regeneration, platelet-rich plasma

Introduction

Carpal tunnel syndrome (CTS) is the most common compressive mononeuropathy with annual incidence 0.5–5.1/1000 population worldwide and majority are idiopathic.[1-3] For patients with mild-to-moderate CTS, 20%–93% of the cases are successfully managed nonsurgically with splints, oral or injection of glucocorticosteroids, physical and occupational therapy techniques, yoga etc.[4] Recently, platelet-rich plasma (PRP) is being studied in neuropathies.[5] Evidence support the role of biomolecules in early inflammation and the antifibrotic effect preventing the formation of thick fibrotic perineurial scars and hastens full recovery.[6-8]

The purpose of this study was to compare the outcome between ultrasound-guided single PRP and corticosteroid injection into the carpal tunnel in patients with mild-to-moderate idiopathic CTS which is refractory to the conservative line of management. The hypothesis of the study was that there is a difference between the clinical effects of PRP and corticosteroid local injection in the management of CTS.

Materials and Methods

Study design

The study was conducted as a randomised controlled trial. The trial was registered in the Clinical Trials Registry – India

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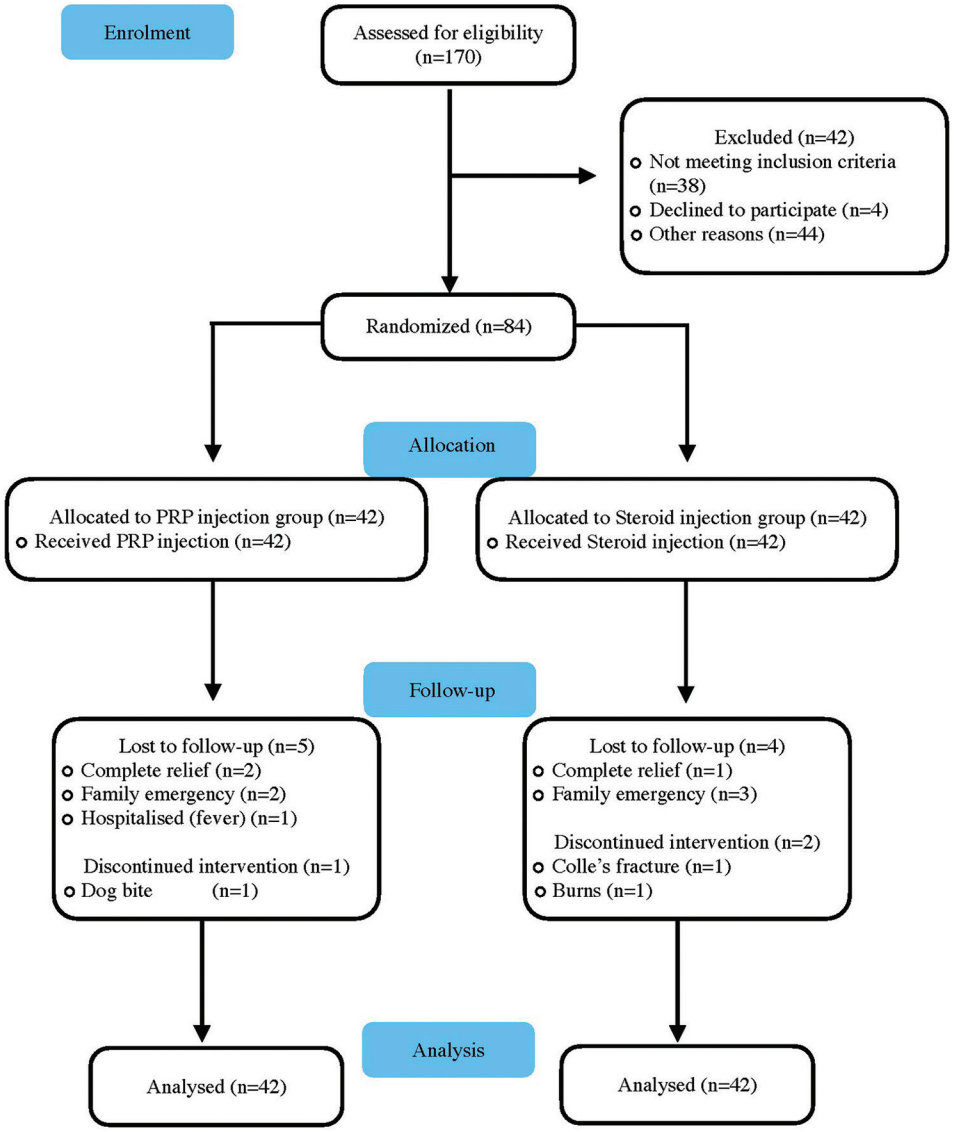

Figure 1: CONSORT 2010 flow diagram of patients throughout the course of the study

(CTRI/2017/09/009696), where the full trial protocol can be accessed. The study was commenced after approval from the institutional review board and the ethics committee, and was conducted strictly adhering to the Indian Council of Medical Research Good Clinical Practice guidelines and the revised Helsinki Declaration. The CONSORT flow diagram of the study is depicted in Figure 1.

Participants

Referring to the article by Uzun *et al*.,[9] and taking the values of Boston Carpal Tunnel Questionnaire Functional Status Scale (BCTQ FSS) at 12 weeks as reference, the minimum required sample size with 99% of power, 1% level of significance, and 20% lost to follow-up was 25 patients in each group. To reduce the margin of error, we predecided sample size as 42 in each group.

Subjects with symptoms suggestive of CTS, attending the outpatient department of Physical Medicine and Rehabilitation, All India Institute of Medical Sciences, New Delhi, India, from September 2017 to February 2019, were screened by the first author. Newly diagnosed cases were given conservative management for 4 weeks which included exercises (tendon gliding exercises; 5 times/set, 3 sets/day);[10] ergonomic modifications; nonsteroidal anti-inflammatory drug (Aceclofenac 100 mg tablets) on an as and when required basis; and using the custom-made wrist hand orthosis (wrist in neutral position, distal trim line at distal palmar crease, proximal trim line at mid forearm and worn at night time for a minimum duration of 6 h). Participants who continued to have symptoms or functional deficits even after the conservative management were enrolled into the study. In subjects with bilateral CTS, the more symptomatic side was chosen for

observation in the study. We included electro physiologically confirmed cases of CTS between 18 and 75 years of age who failed 4 weeks of conservative management. Patients with severe disease with thenar muscle atrophy, local skin infection at the site of injection, diagnosed cases of platelet dysfunction and thrombocytopenia (platelet <1.5 lakhs/μL of blood), malignancy, uncontrolled endocrine dysfunction (diabetes mellitus [fasting blood sugar >110 mg/dl, postprandial blood sugar >140 mg/dL]), hypothyroidism (thyroid-stimulating hormone >3.3 mIU/L), anemia (Hb <10 g%), diagnosed cases of rheumatoid arthritis, prior surgery or fracture in the same wrist, prior steroid injection in the same wrist within 6 months of the study, patients on anticoagulant therapy, pregnancy, cognitive difficulty to complete the questionnaire, or any other causes of peripheral neuropathy and/or cervical radiculopathy were excluded from the study. Those satisfying the inclusion/exclusion criteria were enrolled in the study after a written consent and informed of the study methodology using the patient information sheet.

Demographics, history, and clinical examination were recorded in a pro forma and the clinical severity was ascertained using the Mackinnson's classification[11] and electrophysiological grading with nerve conduction study was done using Bland's grading.[12]

Outcome measures

The primary outcome, BCTQ FSS, and the secondary outcomes, BCTQ Symptom Severity Scale (BCTQ SSS) and sonographic evaluation of median nerve cross-sectional area (CSA) at carpal tunnel inlet [Figure 2] using MyLabOne ultrasound device (model 8100, Esaote, Japan) with a linear array transducer probe, SL3116, were assessed at 0, 4 and 12 weeks by the first author under the guidance of the fifth author who has more than 10 years of experience in the field of musculoskeletal ultrasound. The follow-up frequency was tailored to assess the short and intermediate changes in the outcome measures based on a study done by Atwa *et al*.[13]

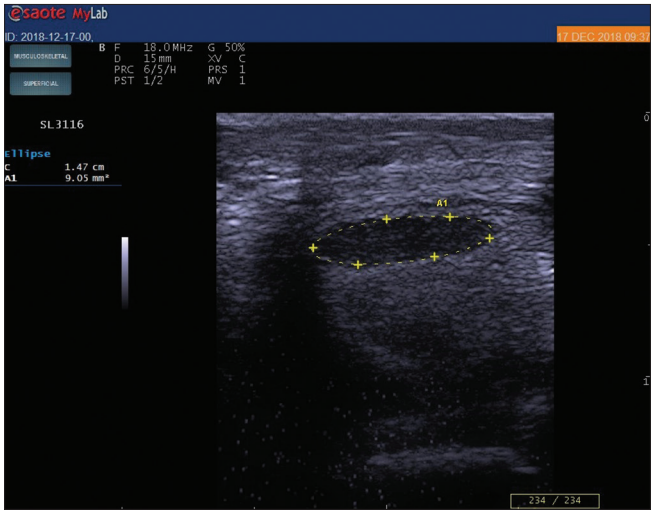

Figure 2: Method of taking CSA of median nerve using area by elliptical match. CSA: Cross-sectional area

BCTQ is a self-administered questionnaire composed of two scales, the FSS (8 questions) and the SSS (11 questions). The patient has to score his ability to perform a specific activity or the severity of the symptoms on a scale of one to five. The questionnaire has been validated in the Indian population and is translated into Hindi, Tamil and Bengali.[14] The scales were highly reproducible and internally consistent in the hands of the developer, with a reproducibility of $r = 0.91$ for the SSS and $r = 0.93$ for the FSS. Internal consistency (Cronbach's alpha) is 0.89 for the SSS and 0.91 for the FSS.[15]

Sonographic evaluation of the CSA of median nerve is a cost effective method to evaluate a patient with CTS.[16,17] Latent class analysis found that the sensitivity CSA of median nerve at carpal tunnel inlet was 91% and the specificity was 94%.[18]

Methodology

The participants were randomised in a 1:1 ratio to two groups, a PRP injection group and a steroid injection group, through a computer-based randomisation system, by the statistician. To conceal randomisation sequence, sequentially numbered opaque sealed envelope method was used. The study was conducted as an investigator blinded study. Baseline and follow-up outcome measures including the sonographic CSA of the median nerve were recorded by the first author to avoid inter-observer variations. To avoid investigator bias, group allocation and interventions were done by a separate investigator who has more than 3 years of experience in the field of ultrasound guided interventional pain management. Statistical analyses were performed blinded to the group allocation.

To prepare the autologous PRP, 12 ml of peripheral venous blood was collected from the patient's upper limb on the side opposite to the wrist observed in the study, by venepuncture and directly into four citrate vacutainer tubes (three ml each). The vacutainer tubes were then centrifuged at 1000 rpm (190 G) in Remi centrifuge (model R8C, India) for 4 min at room temperature. After centrifugation, 0.25 ml of PRP, above the red cell fraction and the "buffy coat," was aspirated under sterile precautions from each vacutainer tube and transferred to a sterile tube, and this preparation (1 ml PRP) was gently mixed and used for the intervention.

The injections were given with the patient in seated position and the hand placed palm upwards in a neutral or slightly extended wrist position. Single dose of 40 mg of methylprednisolone acetate (1 ml) or PRP (1 ml) was injected under ultrasound guidance and out of plane approach using a disposable needle (28 G, 0.5 inch) and one ml syringe into the perineural area, superficial and longitudinal to the nerve at the carpal tunnel inlet. Principles of sterile technique were followed throughout the procedure and no local anesthetic was used as the effect of acidic pH in platelet function is poorly known. Participants were observed for 30 min following the injection and were advised to rest the injected arm for 48 h. No additional medications were advised except for cold compress and acetaminophen (650 mg tablets up to a maximum of

5 times a day i.e., up to 3.25 g/day) for pain relief as and when required. Throughout the course of the study, all participants in both the groups were advised to continue the conservative management.

Follow-up

Throughout the follow-up period of 12 weeks, none in any group reported exacerbation of symptoms, thenar muscle wasting or any other complications. None of the subjects under follow-up required referral for surgical decompression during the study period. Two participants in the steroid group reported hypopigmentation at the injection site.

Statistical analysis

Data were collected, tabulated, and statistically analyzed using STATA version 14.0 software (StataCorp LP, Texas, USA). Data were tested for normality using Shapiro–Wilk test. Demographic variables, namely age, height, weight and body mass index were expressed as mean ± standard deviation (SD) and compared using independent *t*-test. The rest of the demographic data were expressed as frequency and percentage and compared using Chi-square test or Fisher's exact test, as appropriate, to check the test of proportion between the two groups. Outcome variables were expressed as mean ± SD Change in outcome between baseline and

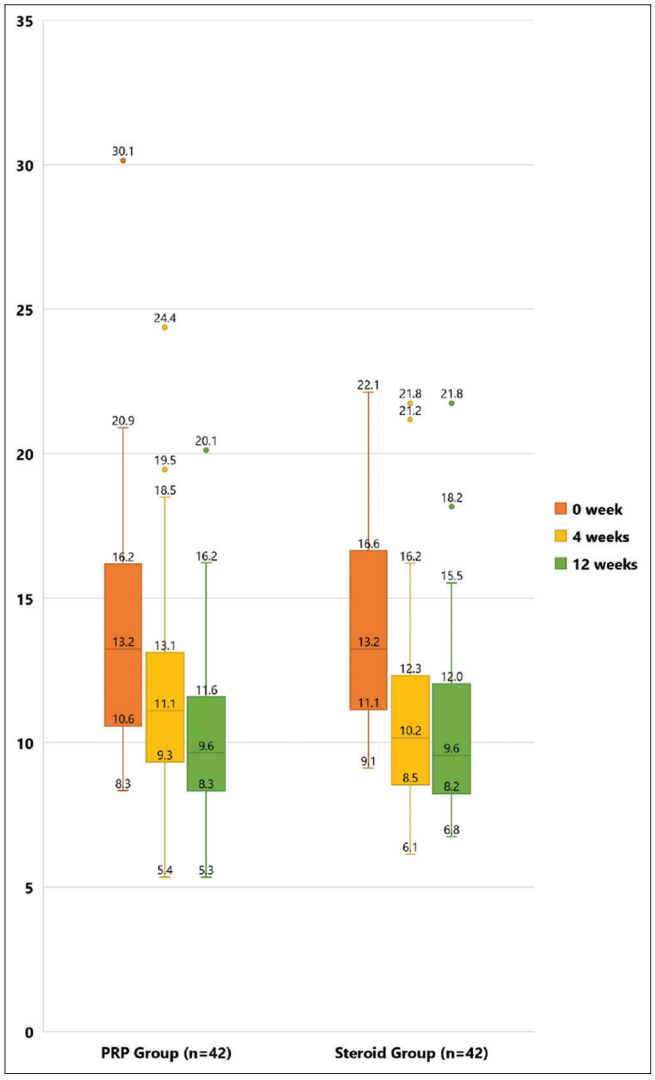

Figure 3: Box and Whisker plots of the CSA of the median nerve of patients at baseline, four and 12 weeks of study. CSA: Cross-sectional area, PRP: Platelet-rich plasma

Table 1: Baseline characteristics of the subjects in the study

Demographic variables	PRP group (*n*=42), *n* (%)	Steroid group (*n*=42), *n* (%)	*P*
Age (years)	44.7±8.8	47.0±10.3	0.2729
BMI	26.5±4.6	26.4±3.5	0.9149
Sex			
Male	9 (21.4)	6 (14.3)	0.3930
Female	33 (78.6)	36 (85.7)	
Clinical grading (Mackinnson's classification)			
Grade 1	18 (42.9)	22 (52.4)	0.3820
Grade 2	24 (57.1)	20 (47.6)	
NCS grading (Bland's grading)			
Grade 1	5 (11.9)	7 (16.7)	0.5020
Grade 2	19 (45.2)	22 (52.4)	
Grade 3	14 (33.3)	12 (28.6)	
Grade 4	4 (9.5)	1 (2.4)	
Grade 5	0	0	
Side studied			
Dominant	26 (61.9)	19 (45.2)	0.126
Nondominant	16 (38.1)	23 (54.8)	
Anatomy of median nerve			
Single	33 (78.6)	39 (92.9)	0.1310
Bifid	5 (11.9)	3 (7.1)	
Trifid	1 (2.4)	0	
Bifid with PMA	3 (7.1)	0	

P≤0.05 is statistically significant. Values expressed as mean±SD or *n* (%). Age and BMI were compared using Independent *t*-test. Other variables were compared using Chi-square test and Fisher's exact test whichever was appropriate. PRP: Platelet-rich plasma, BMI: Body mass index, NCS: Nerve conduction study, PMA: Persistent median artery, SD: Standard deviation

Table 2: Comparison of Boston Carpal Tunnel Questionnaire Functional Status Scale between groups over the follow-ups period

Groups	Baseline	4 weeks	12 weeks	*P* (0-4*)	*P* (0-12*)
PRP group (*n*=42)	4.2±0.8	2.7±0.6	1.9±0.7	<0.0001	<0.0001
Steroid group (*n*=42)	4.2±0.8	2.6±0.8	1.9±0.9	<0.0001	<0.0001
P†	0.9566	0.6270	0.9497		

*Paired *t*-test was done to compare difference from baseline to 4 and 12 weeks within each group, †Mann-Whitney *U*-test was done to compare between the two groups. Values expressed as mean±SD. PRP: Platelet-rich plasma, SD: Standard deviation

Table 3: Comparison of Boston Carpal Tunnel Questionnaire Symptom Severity Scale between groups over the follow-ups period

Groups	Baseline	4 weeks	12 weeks	*P* (0-4*)	*P* (0-12*)
PRP group (*n*=42)	4.1±0.8	2.7±0.7	1.9±0.6	<0.0001	<0.0001
Steroid group (*n*=42)	4.0±0.9	2.6±0.8	1.9±0.7	<0.0001	<0.0001
P†	0.5714	0.6352	0.7794		

*Paired *t*-test was done to compare difference from baseline to 4 and 12 weeks within each group, †Mann-Whitney *U*-test was done to compare between the two groups. Values expressed as mean±SD. PRP: Platelet-rich plasma, SD: Standard deviation

follow-ups were assessed by paired *t*-test. Mann–Whitney *U*-test was used to compare the mean between the two groups. Intention to treat analysis was performed. Results were considered significant at 5% level of significance; i.e., $P < 0.05$.

Results

One hundred and seventy patients were screened and 84 enrolled, 15 males and 69 females with age ranging from 23 to 63 years, mean of 45.8 years. On clinical examination, it was observed that Tinel's test was positive in 47.62%, Phalen's in 77.38% and Durkan's in 85.71% of the study population. Baseline characteristics [Table 1] of the study participants showed no significant difference between the groups for any variable.

Results of BCTQ are presented in Tables 2 and 3. At baseline, FSS and SSS were comparable between the two groups ($P > 0.05$). Significant improvement ($P < 0.05$) of FSS and SSS were observed at 4- and 12-week follow-up in both the groups. However, no statistically significant difference was observed between the two groups ($P > 0.05$).

Results of CSA of the median nerve are presented in Figure 3. At baseline, the data were comparable between the two groups ($P > 0.05$). Significant improvement ($P < 0.05$) was observed at 4- and 12-week follow-up in both the groups. However, no statistically significant difference was observed between the two groups ($P > 0.05$) at follow-ups.

Discussion

Our study demonstrated a statistically significant improvement with both PRP and steroid injection (pre and post) in the primary outcome, i.e., functional status (BCTQ FSS), and the secondary outcomes, i.e., symptom severity (BCTQ SSS) and CSA of the median nerve at carpal tunnel inlet, at 4 and 12 weeks. This finding is in accordance with the findings of Malahias *et al*.,[19] where encouraging results were obtained with 1–2 ml of PRP injection. But the limitations in their study include the small sample size ($n = 14$) and an absent control arm as it was a pilot study. Randomised controlled studies by Uzun *et al*.,[9] Malahias *et al*.[20] and Wu *et al*.[21] also showed similar benefits with PRP injection as in this study. But the amount of PRP injected into the carpal tunnel varied greatly between the studies. Uzun *et al*.[9] used 2 ml, Malahias *et al*.[20] used 1–2 ml and Wu *et al*.[21] used 3 ml of PRP whereas in this study, 1 ml of PRP was used. The outcome measure, BCTQ, was used by Uzun *et al*.[9] and Wu *et al*.[21] as in this study and PRP was compared with steroid and nocturnal splinting respectively in these studies. In the study by Malahias *et al*.,[20] PRP was compared with placebo (0.9% normal saline) and used quick-disabilities of the arm, shoulder and hand score and visual analogue scale as outcome measures. Improvement in the electrophysiological parameters after PRP injection in refractory CTS have also been reported.[22] However, a randomised controlled trial by Raeissadat *et al*.[23] reported no additional beneficial effect in pain, symptom relief and function (BCTQ) and electrophysiological characteristics with PRP injection when compared with wrist splinting at 10 weeks. In the current study, both the randomised groups received nocturnal wrist splints. As the superiority of steroid injection stands well established over wrist splint,[24,25] the result obtained in the current study is clinically relevant. A meta-analysis done by Catapano *et al*. demonstrated potential utility of PRP in the treatment of CTS as a promising therapy and safer alternative with fewer side effects to corticosteroids for short term symptomatic relief.[26]

In the current study, the superiority of PRP injection over corticosteroid injection was not observed in the outcome measures, namely, functional status (BCTQ FSS), symptom relief (BCTQ SSS) and CSA of the median nerve at carpal tunnel inlet. This was in contrast to the study by Uzun *et al*.[9] where 2 ml of PRP, prepared with a dedicated PRP centrifuge device, was compared with one ml triamcinolone acetonide. Hence, the difference in the results could be attributed to the dosing and the method of PRP preparation.

In the past few years, PRP therapy has grown in popularity as an adjunctive treatment option in the interventional management of musculoskeletal injuries. The presence of numerous growth factors and bioactive substances have stimulated the scientific community to search for possible benefits of using PRP in tissue and nerve regeneration. The aim of this study was to to compare the outcome between ultrasound guided PRP and corticosteroid injection into the carpal tunnel in patients with mild to moderate idiopathic CTS, the most common peripheral entrapment neuropathy.

Although the mechanism of action of PRP in peripheral neuropathy remains elusive, several different biological pathways may mediate clinical effectiveness. In CTS, the increased intracarpal pressure can cause focal demyelination initially, and with the persisting compression, blood flow to the endo-neurial capillaries gets interrupted. This leads to the development of venous congestion, ischemia and local metabolic alterations initiating a process called "chemical neuritis."[27] Growth factors in PRP like platelet derived growth

factor, fibroblast growth factor and insulin like growth factor, may be blocking this cycle and thereby control chemical neuritis.[27] Further, growth factors like vascular endothelial growth may help prevent nerve ischemia by promoting angiogenesis and finally, remyelination may be aided by growth factors like brain derived neurotrophic factor and nerve growth factor.[27] Another proposed mechanism for the development of CTS is the intraneural fibrosis and scarring, which prevent smooth gliding of the nerve bundles in its perineurial layer leading to tethering of the median nerve.[27] Growth factors in PRP like transforming growth factor-β, promote the synthesis of Type I collagen instead of Type III collagen which is found in scar tissue. This may cause structural changes, within the nerve, by shifting the "stiff scar tissue" to "benign soft scar tissue" and thus prevent the median nerve from tethering.[9]

Local corticosteroid injections, though considered to be the gold standard treatment method for idiopathic mild to moderate CTS,[24] limits the tenocyte function by reducing collagen and proteoglycan synthesis and reducing tendon progenitor cell recruitment, and thus on repeated injections can cause mechanical weakness of the tendons in the carpal tunnel.[28] In addition, local corticosteroid results in median nerve injury by its neurotoxicity.[29] The adverse events related to PRP injections, injection pain, bruising, pruritis and burning, were low[26] when compared to corticosteroids at 33%.[30] Even though the serious adverse effects of steroid injection like tendon rupture, intraneural injections and gangrene is a possibility (<0.1%) the incidence is reduced with guided injections.[30] Thereby, PRP could be an efficacious alternative for mild to moderate idiopathic CTS.

Limitations

The duration of the current study was 12 weeks but to study the long-term effects of PRP on myelination, angiogenesis and fibrosis, longer follow-ups may be needed. Anatomical variations of the median nerve like bifid and trifid median nerve could have altered the accuracy of CSA measurement. Due to the lack of standardised methods for PRP preparation, concentration and amount to be injected, further studies are recommended to determine the effect of these variables on the efficacy of PRP in CTS.

Conclusion

In conclusion, ultrasound guided single injection into the carpal tunnel of autologous PRP along with nocturnal wrist splinting, exercises and ergonomic modifications is equally effective as that of corticosteroid in refractory mild to moderate idiopathic CTS in relieving symptoms, improving function and reducing the CSA of median nerve at 12-week follow-up.

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Conflicts of interest

There are no conflicts of interest.

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