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Original Research Article

Perineural Platelet-Rich Plasma for Diabetic Neuropathic Pain, Could It Make a Difference?

Manal Hassanien, MD,* Abdelraheem Elawamy, MD,† Emad Zarief Kamel, MD,† Walaa A. Khalifa, MD,‡ Ghada Mohamed Abolfadl, MD,† Al Shimaa Ismael Roushdy, MD,§ Randa A El Zohne, MD,¶ and Yasmine S. Makarem, MD*

*Rheumatology and Rehabilitation Department, Faculty of Medicine, Assiut University, Assiut, Egypt; †Anesthesia, Intensive Care and Pain Department Department, Faculty of Medicine, Assiut University, Assiut, Egypt; ‡Internal Medicine Department, Faculty of Medicine, Assiut University, Assiut, Egypt; §Anesthesia, Intensive Care and Pain Department, Faculty of Medicine, Minia University, Minia, Egypt; ¶Clinical Pathology Department, Faculty of Medicine, Assiut University, Assiut, Egypt

Correspondence to: Prof. Emad Zarief Kamel, MD, Department of Anesthesia, Faculty of Medicine, Assiut University Hospital, Assiut 74111, Egypt. Tel: 00201007046058, 0020882413201; Fax: +2088-2335520; E-mail: emadzarief@gmail.com.

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Abstract

Objective. To evaluate the clinical effect of perineural platelet-rich plasma (PRP) injection for pain and numbness alleviation in diabetic peripheral neuropathy (DPN). **Study Design.** A randomized prospective clinical trial. **Setting.** Pain clinic and Rheumatology and Rehabilitation Departments, Assiut University Hospital. **Methods.** Sixty adult patients with type II DM accompanied by DPN of at least six months' duration were assessed by modified Toronto Clinical Neuropathy Score (mTCNS) and randomly allocated into two groups. Group I underwent ultrasound-guided perineural PRP injection and medical treatment, and Group II received medical treatment only. Patients were followed up at months 1, 3, and 6 with regard to pain and numbness visual analog scale (VAS) and mTCNS scores. **Results.** Significant improvement was recorded in pain and numbness VAS scale scores in group I vs group II ($P \leq 0.001$ during the whole study period for both parameters); at the same time, mTCNS improved in group I in comparison with group II with $P = 0.01$, 0.001, and <0.001 at months 1, 3, and 6, respectively. **Conclusions.** Perineural PRP injection is an effective therapy for alleviation of diabetic neuropathy pain and numbness and enhancement of peripheral nerve function.

Key Words: Diabetic Peripheral Neuropathy; Neuropathic Pain; Platelet-Rich Plasma

Introduction

Diabetic peripheral neuropathy (DPN) is a common complication of diabetes mellitus (DM). Among several complications that affect the diabetic patient's quality of life and life expectancy is the diabetic neuropathy in a generalized or focal form [1].

Chronic neuropathic pain is not an uncommon problem, and may occur because of improper surgical or medical management, as well as, inappropriate wound or nerve healing or regeneration [2].

The clinical symptoms of DPN range from pain and burning sensations (at rest or at night) to hypoesthesia, paresthesia, and/or numbness [3]. Diabetic neuropathy can be axonal or demyelinating and can affect large or small neurons. Schwann cells, which are the most abundant glial cells, act as nerve axon insulators and modulators of neurobiology through their role in metabolic support and injury protection [4]. In diabetic patients, church cells' function is disturbed, leading to loss of glial–axon communication and nerve homeostasis, which leads to fiber loss, neurodegeneration, and pain [5]. Nerve conduction studies can detect these changes; however, there has been no effective therapy for the treatment of DPN until now [6].

Recently, some studies have focused on chronic neuropathic pain and documented the value of local platelet-rich plasma (PRP) injection for permanent pain alleviation in such situations. The studies assumed that local PRP could enhance local healing, tissue remodeling, and nerve axonal regeneration [2,7]. Platelet-rich plasma induces cell signaling molecules' release, for example, nerve growth factor, vascular endothelial growth factor, and fibronectin [8]. These biomarkers are known to be involved in the modulation of stem cell–like myelinating Schwann cell activation, resolution of inflammation, angiogenesis, and fibrogenesis; hence, the recovery of nerve function can be enhanced [9].

Platelets contain more than 1,100 proteins, for example, enzymes, enzyme inhibitors, growth factors, immune messengers, and other bioactive compounds that play a role in tissue repair and wound healing [10–13]. Platelet-derived angiogenesis factors can stimulate new capillary growth through the enhanced migration of endothelial cells. It has been suggested that this is the mechanism by which platelet factors influence the process of angiogenesis and revascularization [14]. Based upon these findings, we have built our hypothesis, which suspects an improvement of nerve conduction, through revascularization and regeneration, leading to alleviation of DPN symptoms.

The primary end point of this study focused on the quality of pain alleviation after perineural PRP injection over six months' follow-up. The secondary end points included the improvement of numbness, nerve conduction studies, and modified Toronto Clinical Neuropathy Score (mTCNS) [15].

Methods

This is a prospective randomized outcome-assessor blinded clinical trial. The study was approved by the local research ethics committee of the Faculty of Medicine, Assiut University, Egypt, and it was registered at ClinicalTrials.gov (NCT03601494). It was conducted in accordance with the Declaration of Helsinki [16] in the pain clinic of the Anesthesia Department and the electrodiagnosis unit of the Rheumatology and Rehabilitation Department.

Sixty adult diabetic patients (type II DM) were enrolled from the diabetes care clinic of the Internal Medicine Department. All the participants had clinically symptomatized DPN (painful neuropathy for six or more months). They were clinically evaluated using the mTCNS, and then the problem was confirmed through nerve conduction studies. Written informed consent was obtained from each participant.

Based on the Toronto Expert Panel on Diabetic Neuropathy, we have developed the diagnosis of diabetic neuropathy (neuropathic symptoms or decreased distal sensation) [1,17]. Neuropathy was evidenced in the presence of decreased sensation and numbness, or prickling, burning, and/or aching sensation in the affected area. Motor weakness was mostly subclinical and was detected through the electro-diagnostic study.

Exclusion criteria included patients with other causes of neuropathy (e.g., vitamin B12 deficiency), hereditary neuropathies and entrapment neuropathies, overt neuropathy with foot ulcers and/or amputation, peripheral vascular diseases, vertebral pathologies (e.g., previous surgery, foraminal stenosis, spinal canal stenosis, and/or vertebral disc herniation), connective tissue diseases, thyroid disorders, significant renal or hepatic dysfunction, platelet dysfunction syndrome, critical thrombocytopenia, hemodynamic instability, septicemia, and local infection at the site of the procedure. Relative contraindications included consistent use of nonsteroidal anti-inflammatory drugs within the last two weeks, systemic corticosteroid administration or local injection at the suspected treatment site within the last month, recent fever or illness, hemoglobin level <10 g/dL, platelet count $<105 \times 10^9$/L, and/or tobacco use.

Randomization of the patients into two groups was done through the web-based randomizer (https://www.randomizer.org/). The grouping process was as follows:

Group I (intervention group) underwent perineural PRP injection under ultrasound guidance in addition to the medical treatment.

Group II (control group) received the medical treatment only.

The medical treatment included optimal glycemic control, vitamin B complex, α lipoic acid, selective serotonin reuptake inhibitors, and pregabalin. The outcome-assessing physician was kept blind to the grouping.

A diagnostic nerve conduction study (NCS) was done at room temperature (25–29°C) using the Nihon Kohden Neuropack M1 MEB-9200 EMG/EP/IOM System. Studies involved motor and sensory median, ulnar, radial, superficial and deep peroneal, posterior tibial (medial planter branch), saphenous, and sural nerves. Polyneuropathy types were described as demyelinating, axonal, or mixed [18,19].

PRP Preparation

Thirty milliliters of blood was withdrawn from the median cubital vein (22-gauge, one-inch needle) and used for the preparation of PRP (5–6 mL), depending on the baseline platelet count, and was not used if produced at a concentration $<300\%$ of the individual blood level. Under strict aseptic precautions, the process was carried out at 22–26°C, and the blood was collected in centrifuge test tubes, labeled with identification data (name and age), and gently mixed with acid citrate dextrose (ACD) as an anticoagulant in the ratio of 10:1.5, then divided into 15 tubes (2 mL for each). The tubes then underwent the first centrifugation for separation (at the rate of 3,500 rpm over 10 minutes). When the blood was separated into plasma-buffy coat and upper layers of red blood cells, the plasma was pipetted into other sterile

tubes (without anticoagulant) and subjected to the second centrifugation for activation of the platelets (at the rate of 4,000 rpm over seven minutes). Lastly, platelets were settled down as PRP, the upper third/fourth supernatant was discarded, and the lower PRP was obtained, which was then activated just before its injection by the addition of 10% calcium chloride in a ratio of 1:10 and agitation through vigorous shaking [20].

An ultrasound-guided PRP injection technique was performed in the pain clinic of the Anesthesia Department using MyLab 7 (Esaote, Europe B.V., Maastricht, the Netherlands) ultrasonography device. The 10–19-MHz high-frequency linear transducer was used to scan superficial nerves. The needle (22-gauge, one-inch) was introduced from the lateral side toward the midline using the in-plane approach to target the desired nerve. A freehand one-man technique was used by the physician, who was simultaneously holding the syringe with one hand and scanning the nerve by moving the probe with the other hand. Visualization of the needle's tip advancing until reaching the perineural tissue was continuous. The PRP was injected in a volume of 1.5 mL for each nerve. Postinjection, any suspected paresthesia or bleeding was managed accordingly (Figures 1 and 2). The median nerve was visualized in the volar aspect of the forearm, between the flexor digitorum superficialis and the flexor digitorum profundus as a hyperechoic nodule. The ulnar nerve was visualized through the medial mobilization of the transducer from the previous position used for the medina nerve. The tibial nerve was visualized between the medial malleolus and the tendon Achilles, and if the transducer was mobilized just above the medial malleolus. The deep peroneal nerve can be detected as a hyperechoic structure lateral to the anterior tibial artery, midway between the medial malleolus and lateral malleolus. The superficial peroneal nerve has a honeycomb appearance and is located in a groove within the intermuscular septum 5–10 cm above the lateral malleolus. On the other hand, the sural nerve can be visualized by placing the transducer transversely between the lateral malleolus and the tendon Achilles. It has also a honeycomb appearance and is located posteriorly between the short saphenous vein and the tendon Achilles.

Data Collection

Baseline pain and numbness visual analog scale (VAS) and mTCNS scores were reported, then reassessed by the end of months 1, 3, and 6 after treatment. The maximal mTCNS score equals 33, which means extensive sensory tests indicating impairment and many symptoms. The lowest mTCNS score equals 0, which denotes normal sensory tests and an absence of symptoms (Table 3) [15]. Nerve conduction studies were done primarily for diagnosis (baseline values), then at the end of month 6 after treatment.

Statistical Analysis

A calculated sample size of 25 would have a power of 80% to detect a 20% difference in the pain VAS scale between groups (primary outcome variable) with a type I error of $\alpha = 0.05$ and a confidence level of 95%. The normality of the data distribution was first inspected using the Shapiro Wilk test. Data are presented as mean ± SD or SE, number, ratio, and/or median with interquartile range. Groups' categorical data were compared using the chi-square test. The continuous parametric data of the groups were compared using the independent *t* test, and the nonparametric data were compared using the Mann-Whitney test (between groups) and the Wilcoxon signed-rank test (within the same group). A *P* value <0.05 was considered statistically significant. Statistical analysis was conducted with IBM SPSS Statistics for Windows, version 23.0 (IBM Corp., Armonk, NY, USA).

Results

Sixty patients with type II DM and DPN were included in the study, as shown in the CONSORT flowchart (Figure 3). All patients had demyelinating neuropathy, and 31 of the participants had received PRP perineural injection. Table 1 demonstrates the demographic and medical status of the participants. No statistically significant difference was noticed between the two groups.

Pain VAS scales were significantly lower in the PRP group in comparison with the control group during the whole follow-up period. The pain VAS scale showed significant decreases during the follow-up period in comparison to the basal value in the PRP group. In the control group, the pain VAS scale was significantly higher than its basal value by the sixth month (Table 2).

The numbness VAS scale showed the same pattern of significant decreases in the PRP group as the other group by months 1, 3, and 6. A significant decrease within the same group was noticed in the PRP group during the study period in comparison with its corresponding basal value. In the control group, the month 6 numbness VAS value showed a significant increase (Table 2).

With regard to the mTCNS, it significantly improved (decreased) in group I in comparison with group II, with $P = 0.01$, 0.001, and <0.001 at months 1, 3, and 6, respectively. The PRP group showed significantly lower postinterventional mTCNS values during the whole six months of the study in comparison with their basal value within the same group (Table 3, Figure 4).

The confirmatory nerve conduction studies are shown in Tables 4 and 5. Normal values for each nerve are demonstrated [21–24]. Mean nerve conduction velocities in both the upper and lower limbs showed a significantly higher acceleration in group I patients than those in group II. However, no significant difference was found in distal motor latency (DML) in either the upper or lower limbs between the two groups.

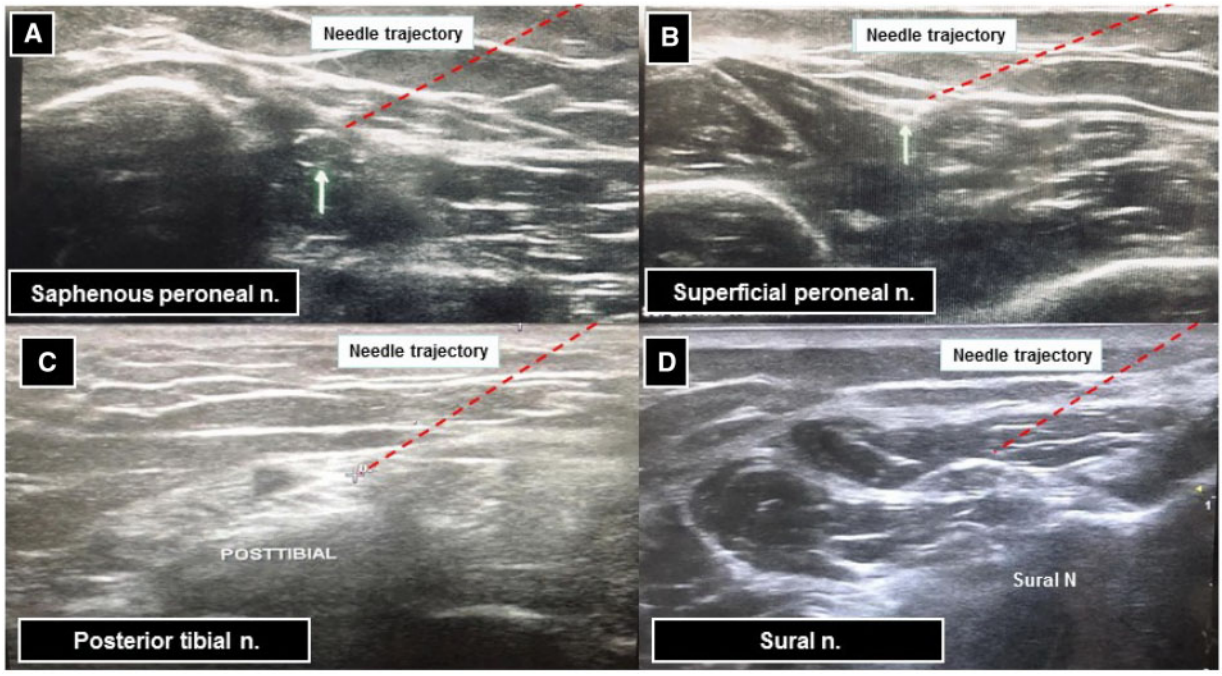

Figure 1. Ultrasonographic views of upper limb nerve injection.

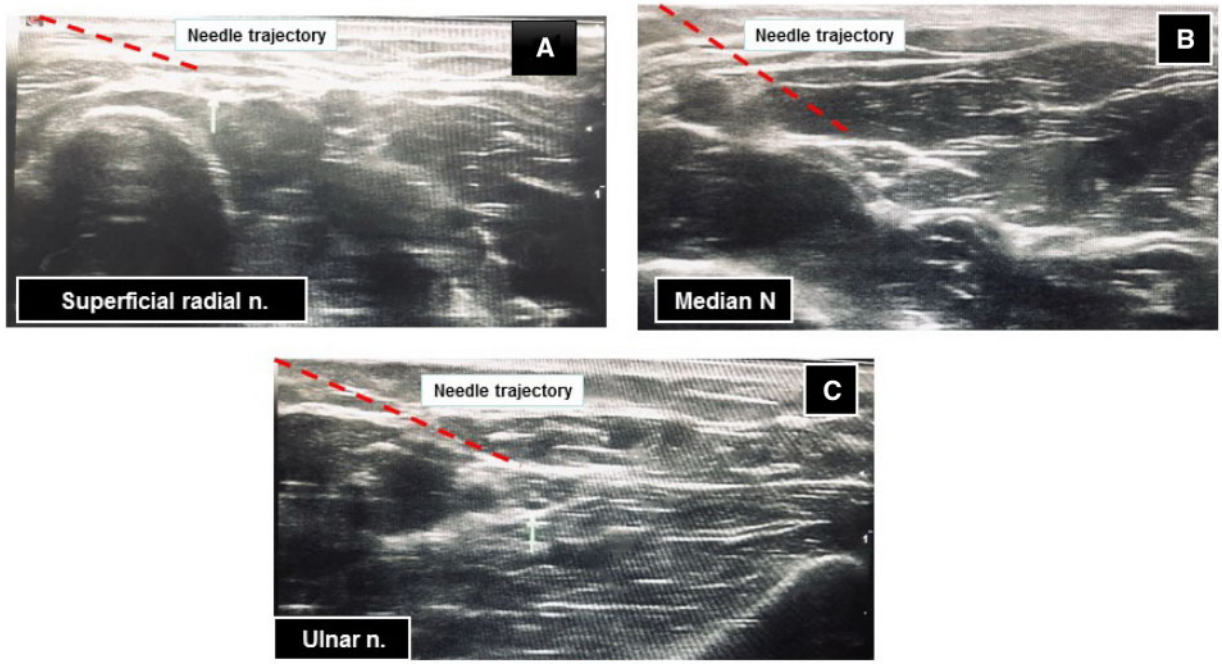

Figure 2. Ultrasonographic views of lower limb nerves injection.

Changes within the same group in comparison with the pretreatment value were significantly increased in the PRP group during the whole study period. On the other hand, the increase was significant in the mean motor nerve conduction velocity (NCV) of the deep peroneal and posterior tibial nerves only in the group II patients. Generally, all DML studies have shown significant decreases in six-month follow-up records in both groups.

Post-PRP injection complications in the form of pain and/or paresthesia were noticed in three patients, who responded to short-term (three days) vitamin B complex and/or paracetamol.

Discussion

To our knowledge, this is the first study that has investigated the efficacy of single-shot perineural injection of

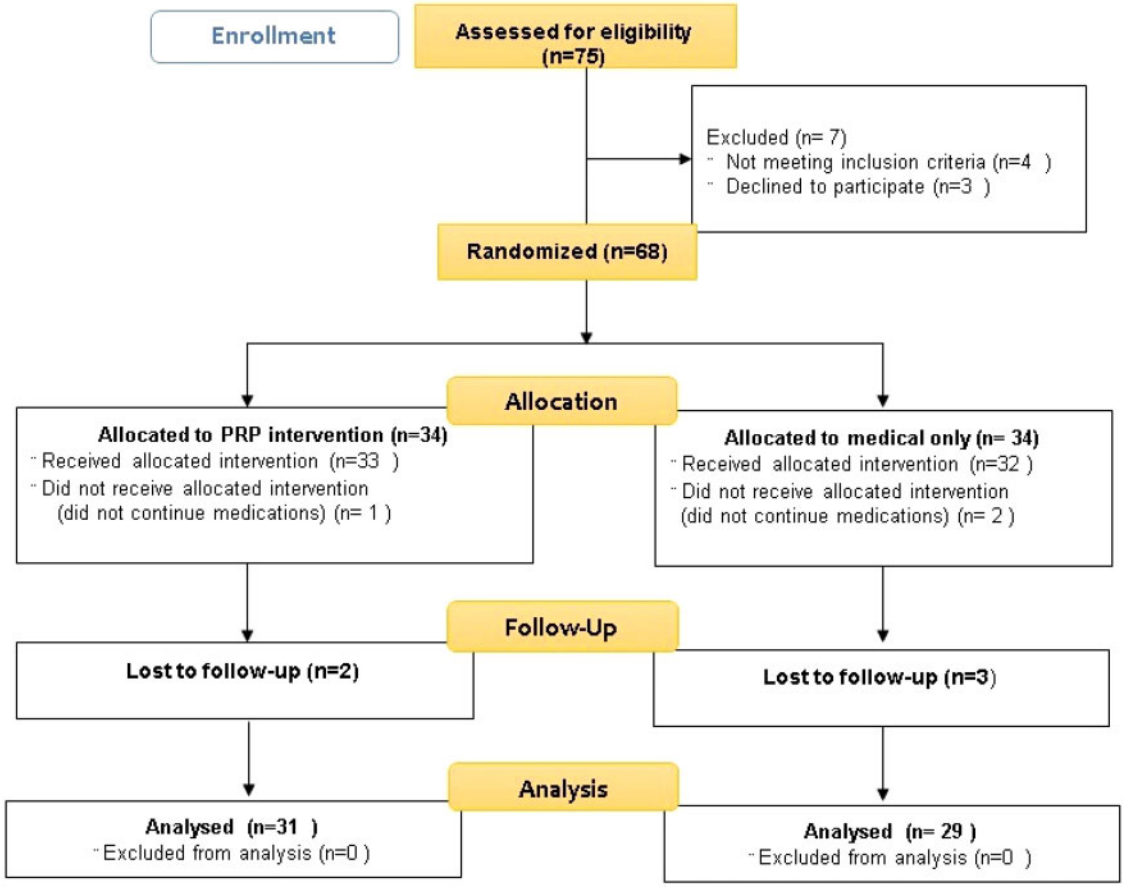

Figure 3. Participant CONSORT flow diagram.

Table 1. Demographic and clinical data

Variables	Group I (PRP) (N = 31)	Group II (Medical) (N = 29)	*P* Value
Age, y	39.7 ± 13.5	32.6 ± 18.2	0.2
Gender male/female	14/17	13/16	0.7
BMI, kg/m^2	34.7 ± 6.4	32.5 ± 3.2	0.5
Diabetes characteristics			
Duration, y	14.5 ± 5.4	12.5 ± 7.9	0.3
HbA1c %	8.24 ± 2.16	8.86 ± 1.75	0.8
Treatment			
On insulin	9 (29)	10 (34.5)	
On oral hypoglycemic	8 (25.8)	8 (27.6)	0.1
Combined therapy	14 (45.2)	11 (37.9)	
Comorbidities			
Hypertension	19 (61.3)	18 (62.1)	0.7
Retinopathy	17 (54.8)	9 (31)	0.9
Coronary artery disease	11 (35.5)	4 (13.7)	0.6
Dyslipidemia	20 (64.5)	21 (72.4)	0.2
Baseline nerve affection			
Lower limb (sensory)	31 (100)	29 (100)	–
Upper limb (sensory)	11 (35)	12 (41)	0.6
Lower limb (motor)	7 (22)	5 (17)	0.6
Upper limb (motor)	4 (12)	4 (13)	0.9

Data are expressed as mean ± SD, ratio, and number (percentage). $P < 0.05$ is considered statistically significant.

BMI = body mass index.

Table 2. Pain and numbness assessment VAS scales

Variables	Group I (PRP) (N = 31)	Group II (Medical) (N = 29)	*P* Value
Pain			
Baseline VAS	7 (2.5)	6 (2.5)	0.62
1st mo VAS	1 (0.3)*	5 (2)	<0.001
3rd mo VAS	1 (0.3)*	6 (1.3)	<0.001
6th mo VAS	1 (0)*	7 (2)*	<0.001
Numbness			
Baseline VAS	6.5 (3.3)	6 (3.3)	0.39
1st mo VAS	0 (1)*	5 (3)*	<0.001
3rd mo VAS	1 (0.3)*	5 (2)	<0.001
6th mo VAS	1 (0)*	7 (2)*	<0.001

Data are expressed as median and interquartile range. $P < 0.05$ is considered statistically significant.

VAS = visual analog scale.

*Significant change from the baseline value within the same group.

PRP as a novel therapy for the treatment of diabetic peripheral neuropathic pain and numbness. We have a high incidence of DPN patients in our country with variable degrees of neuropathy; at the same time, a lot of them are poorly responsive to the commonly available pharmacologic treatment. As evident from our results, there were

Table 3. The components of the modified Toronto Clinical Neuropathy Score

Symptom Scores	Sensory Test Scores
• Foot pain • Numbness • Tingling • Weakness • Ataxia • Upper limb symptoms	• Pinprick • Temperature • Light touch • Vibration • Position sense
Symptom scores graded as	Sensory test scores graded as
0 = absent	0 = normal
1 = present but no interference with sense of well-being or activities of daily living	1 = reduced at the toes only
2 = present, interferes with sense of well-being but not with activities of daily living	2 = reduced to a level above the toes, but only up to the ankles
3 = present and interferes with both sense of well-being and activities of daily living	3 = reduced to a level above the ankles and/or absent at the toes
Maximum mTCNS is 33.	
Symptoms and signs (sensory tests) are considered present if as a result of diabetic sensorimotor polyneuropathy in the opinion of the investigator.	

mTCNS = modified Toronto Clinical Neuropathy Score.

significant decreases in pain and numbness scales in the PRP group rather than the medical group, and this improvement was noticed early by the end of the first month and continued during the whole study period.

Platelet-rich plasma is an autologous, cheap, safe, and readily available preparation. Studies have highlighted its safety and efficacy upon the neuron's recovery in general [25,26]. Our study results are in agreement with the study of Anjayani et al., which showed that perineural injection of PRP (1 mL) improved pain VAS scores and scores on the two-point discrimination test in patients with Hansen's disease suffering from peripheral neuropathy, compared with platelet-poor plasma. They mentioned that improvement was noticed two weeks after the injection of both types of plasma [27]. Local injection of PRP has also shown a very promising effect upon nerve regeneration in comparison to platelet-poor plasma in a rat model, as demonstrated by Farrag and colleagues [25].

We are also in agreement with Wu and colleagues, who conducted a study with 60 patients suffering from carpal tunnel syndrome (CTS). The intervention was a sonographic local injection of PRP (3 mL) into the carpal tunnel vs a night splint in the control group. Follow-up of the patients showed significant pain alleviation (lower VAS values) in the PRP group. They concluded that the PRP injection can be considered a safe, effective modality of neuropathic pain alleviation in CTS [28].

In this study, we used mTCNS as a reliable sensitive score for the diagnosis and assessment of DPN progress. Nerve conduction studies have been done before treatment, then re-evaluated six months after treatment. Most of the PRP patients showed significant improvement in their NCS and mTCNS compared with the other group. We assume that this improvement is based upon the work of Anitua and colleagues. They mentioned that once PRP is perineurally injected, it enhances fibrinolysis and causes some sort of nerve liberation, in addition to the release of cell-signaling molecules from the platelets. The mediators that can be released include neurotrophic nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor 1 (IGF-1), platelet-derived growth factor (PDGF), hepatocyte growth factor (HGF), and neurotrophic factors (fibrin, fibronectin, and vitronectin), which have effects on nerve regeneration [29].

Navani et al. [30] documented the beneficial effects of PRP local injection in painful musculoskeletal diseases upon tissue healing; however, variations in the preparations and composition, as well as the anatomical and medical conditions, can affect the outcome in general. The effect of PRP on the recovery of nerve integrity has also been documented in previous studies. Two animal model studies on acute nerve injury in the guinea pig and rabbits applied PRP to Schwann cells and reported good effects on the number of nerve axons, myelination, and electrophysiological parameters [31,32].

Farrag et al. [25] reported that PRP may enhance myelin thickness and increase axon counts when the injured nerve is sutured and assisted with PRP. On the other hand, Sariguney et al. [33] found that sutured nerves assisted with PRP showed a better functional outcome, which was associated with improvement in myelin thickness and onset latency, but there was no positive effect on the nerve's axonal size. Uzun et al. revealed an insignificant improvement of sensory nerve conduction velocity (SNCV) and DML during a six-month follow-up period (except third-month SNCV) after PRP injection in patients with minimal to mild carpal tunnel syndrome, which contrasts with our findings [34].

Interestingly, we have found that medical therapy has offered some sort of NCV enhancement. This is in line with Zhao and coworkers' meta-analysis, which included 20 studies and demonstrated the value of combined α-lipoic acid plus epalrestat therapy in the treatment of diabetic peripheral neuropathy and improvement of NCV [35].

We cannot certify the definite mechanism of the patients' improvement in the PRP group, but the mechanism could be multifactorial. First, the local PRP could have enhanced angiogenesis, neurogenesis, and nerve regeneration; this is based upon the above-mentioned studies [25,26,31,33]. Second, PRP could have decreased the local inflammation and swelling around the nerves, as mentioned by the study by Takamura and co-workers. Such an improvement in the swelling, as well as the injection itself, may act like a hydro-dissection around the nerves and provide better blood supply and function

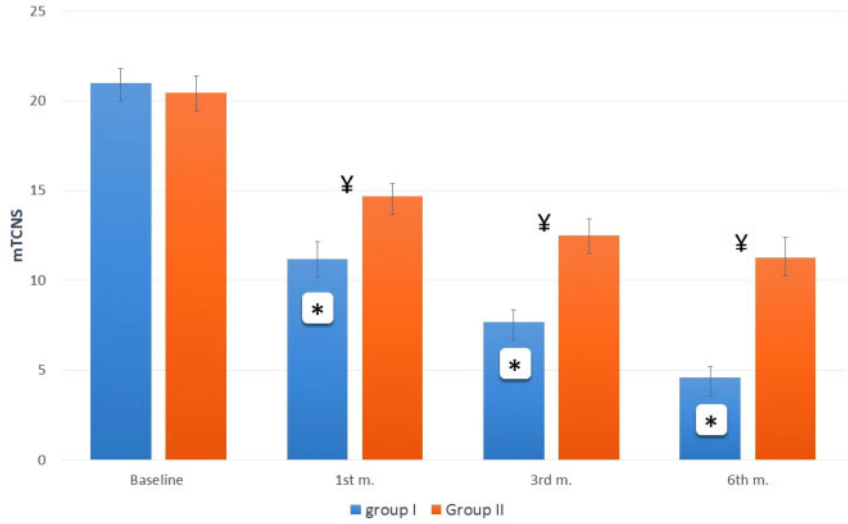

Figure 4. Modified Toronto Clinical Neuropathy Score changes. Data are expressed as mean ± SE. ¥Significant difference between groups. *Significant change from the baseline value within the same group. $P < 0.05$ is considered statistically significant.

Table 4. Nerve conduction study in the upper limb

Variables	Group I (PRP) (N = 31)	Group II (Medical) (N = 29)	*P* Value
Mean motor NCV (median n.) (normally 49–64 m/s)			
Baseline	35.6 ± 11.67	36.7 ± 11.35	0.08
6 mo	47.38 ± 6.68*	40.16 ± 12.67	0.005
Mean motor NCV (ulnar n.) (normally 49+ m/s)			
Baseline	36.7 ± 11.54	36.4 ± 10.68	0.2
6 mo	45.56 ± 8.02*	39.66 ± 11.34	0.005
Mean DML (median n.) (normally 4.4 m/s)			
Baseline	5.4 ± 1.2	5.6 ± 1.4	0.3
6 mo	4.8 ± 1.4*	4.9 ± 1.3*	0.09
Mean DML (ulnar n.) (normally 3.6 m/s)			
Baseline	4.8 ± 1.0	4.6 ± 1.5	0.1
6 mo	4.1 ± 1.6*	4.2 ± 1.2*	0.46
Mean sensory NCV (median n.) (normally 45–70 m/s)			
Baseline	16.00 ± 9.8	16.92 ± 9.4	0.7
6 mo	33.52 ± 3.5*	19.52 ± 9.0	0.01
Mean sensory NCV (ulnar n.) (normally 48–74 m/s)			
Baseline	18.42 ± 5.7	18.55 ± 9.2	0.5
6 mo	35.71 ± 5.5*	20.82 ± 10.3	0.01

Data are expressed as mean ± SD.

DML = distal motor latency; NCV = nerve conduction velocity; PRP = platelet-rich plasma.

*Significant change from the baseline value within the same group. $P < 0.05$ is considered statistically significant.

Table 5. Nerve conduction study in the lower limb

Variables	Group I (PRP) (N = 31)	Group II (Medical) (N = 29)	*P* Value
Mean motor NCV (posterior tibial n. medial planter branch) (normally 41+ m/s)			
Baseline	34.5 ± 8.3	33.5 ± 9.2	0.1
6 mo	48.2 ± 4.7*	40.7 ± 6.5*	0.05
Mean motor NCV (deep peroneal n.) (normally 44+ m/s)			
Baseline	35.4 ± 9.3	35.7 ± 10.3	0.5
6 mo	49.1 ± 3.5*	40.9 ± 6.3*	0.01
Mean DML (posterior tibial n. medial planter branch) (normally 6.1 m/s)			
Baseline	6.3 ± 0.22	6.2 ± 1.06	0.5
6 mo	5.6 ± 1.2*	5.8 ± 0.7*	0.07
Mean DML (deep peroneal n.) (normally 6.5 m/s)			
Baseline	6.2 ± 1.02	6.2 ± 1.25	0.8
6 mo	5.7 ± 1.0*	5.9 ± 0.9*	0.1
Mean sensory NCV (superficial peroneal n.) (normally 40+ m/s)			
Baseline	17.3 ± 9.8	17.6 ± 10.6	0.7
6 mo	37.05 ± 1.2*	18.6 ± 9.7	0.001
Mean sensory NCV (saphenous n.) (normally 40+ m/s)			
Baseline	20.4 ± 8.8	20.6 ± 8.6	0.6
6 mo	35.5 ± 2.2*	21.9 ± 8.2	0.001
Mean sensory NCV (posterior tibial n. medial planter branch) (normally 35+ m/s)			
Baseline	19.7 ± 9.1	19.6 ± 9.6	0.5
6 mo	37.4 ± 1.04*	20.2 ± 7.2	0.001
Sural n. NCV (normally 46–64 m/s)			
Baseline	17.00 ± 10.86	17.38 ± 12.36	0.7
6 mo	36.18 ± 3.21*	19.42 ± 11.34	≤0.001

Data are expressed as mean ± SD.

DML = distal motor latency; NCV = nerve conduction velocity; PRP = platelet-rich plasma.

*Significant change from the baseline value within the same group. $P < 0.05$ is considered statistically significant.

[36]. Lastly, we aimed to inject the PRP perineurally rather than intraneurally to avoid susceptibility to iatrogenic nerve damage.

Limitations

Electrodiagnostic studies are capable only of testing large myelinated nerve fibers, which can limit their sensitivity in detecting neuropathies of the small nerve fibers (i.e., pain, temperature, and autonomic functions). No monitoring of the HbA1c was done during the follow-up period. Finally, heterogeneity of the neuropathy pattern within participants in both groups can be considered a limitation, instead of the nonsignificant difference between the two groups in this regard.

Conclusions

Perineural platelet-rich plasma injection is an effective and safe modality for diabetic peripheral neuropathy. It can significantly alleviate neuropathic pain and numbness symptoms. Nerve conduction studies showed significant improvement after injection.

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