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ORIGINAL RESEARCH PAIN MANAGEMENT

# Effectiveness of platelet rich plasma (PRP) treatment and its comparison with pregabalin in painful diabetic polyneuropathy: A randomized controlled clinical trial

**Shahzad Anwar[1], Muhammad Waseem Hassan[2], Gull-a-Rukh Shaukat[3], Fatima Tirmzi[4], Muhammad Umer Saeed[5], Mudassar Aslam[6]**

**Author affiliations:**

1. Shahzad Anwar, Director School of Pain and Regenerative Medicine, The University of Lahore, CEO Iffat Anwar Medical Complex, Lahore Pakistan; E-mail: shahzadtirmzi@yahoo.com
2. Muhammad Waseem Hassan, Pain Physician & Acupuncturist, Iffat Anwar Medical Complex, Lahore Pakistan; E-mail: mainwaseem786@yahoo.com
3. Gull-a-Rukh Shaukat, Research Scientist & Biostatistician, Iffat Anwar Medical Complex, Lahore, Pakistan; E-mail: grukhkhan@gmail.com
4. Fatima Tirmzi, Medical Student, CMH Lahore Medical College, Lahore, Pakistan; E-mail: ispd.pk@gmail.com
5. Muhammad Umer Saeed, Interventional Pain Physician & Anesthetist, Iffat Anwar Medical Complex, Lahore, Pakistan; E-mail: umer444@hotmail.com
6. Mudassar Aslam, Prof. of Anesthesiology, Punjab Institute of Neurosciences (PINS), Lahore, Pakistan; E-mail: M.mudassar.aslam@gmail.com

**Correspondence:** Shahzad Anwar; E-mail: shahzadtirmzi@yahoo.com

## ABSTRACT

**Background & objective**: The most common consequence of diabetes mellitus (DM) is diabetic peripheral neuropathy (DPN), and it has serious clinical implications that can affect patients' quality of life. There is an urgent need to to discover new methods of treatment, as the medications currently in use for prevention and treatment of DPN are only partially effective and have frequent adverse effects. We aimed to determine and compare the effect of platelet rich plasma (PRP) injection on acupuncture points and pregabalin in painful DPN.

**Methodology:** A randomized controlled trial was conducted at Iffat Anwar Medical Complex. All the clinically diagnosed patients having neuropathic sign and symptoms of DPN, with type 2 DM diagnosed having an HbA1c level greater than 7.5, both genders aged between 40-70 y were enrolled in the study. After the written informed consent, a total of 60 patients were randomly divided into two groups in a 1:1 ratio. Group I received PRP injections on acupuncture points and Group II received 75 mg pregabalin PO twice daily. The PRP injection treatment was given once a month for three months. Follow up of all patients was conducted every month till three months and after one year for final assessment. All the data was entered and analyzed by SPSS 25.0. The difference among pain, SF-36, sleep quality scale among groups was compared by independent sample t test and before and after difference was observed by paired sample t-test. $P < 0.05$ was considered as significant.

**Results:** The VAS scores were significantly decreased in Group I (from 7.47 ± 1.27 to 3.67 ± 1.09; $P < 0.05$) as compared to Group II (7.30 ± 1.59 to 5.20 ± 1.58, $P < 0.05$). The neuropathic symptoms scale also showed significant improvement (Group I: 13.50 ± 50 to 8.50 ± 2.30 vs. Group II: 14.93 ± 2.55 to 9.83 ± 2.17, $P < 0.05$), as well as the quality of life (Group I: 67.77 to 31.50 ± 9.24 vs. Group II:69.37 ± 11.7to 41.20 ± 12.16, $P < 0.05$) and sleep quality scale (Group I:49.53 ± 12.4 to 27.30 ± 8.03 vs. Group II: 52.13 ± 10.9to 32.60 ± 7.103, $P < 0.05$).

**Conclusion:** We conclude that the treatment of diabetic peripheral neuropathy with platelet rich plasma injections at acupuncture points significantly improves the pain scores, quality of sleep and neuropathic symptoms as compared to conventional treatment with 75 mg pregabalin PO twice daily.

**Abbreviations:** DM- Diabetes Mellitus; DPN- Diabetic Polyneuropathy; LANSS- Leeds Assessment of Neuropathic Symptoms and Signs; PRP- Platelet Rich Plasma; QoL- Quality of Life; SQS- Sleep Quality Scale

 

**Key words:** Acupuncture; Diabetic Poly Neuropathy; Pain; PRP injections; Quality of Life

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# 1. INTRODUCTION

The most frequent microvascular complication of diabetes mellitus (DM) is diabetic peripheral neuropathy (DPN), and 50% of diabetic individual's experience neuropathy at some point throughout their illness.[1,2] Individuals with DPN typically experience numbness, tingling, discomfort, or weakness that begins at the distal ends of the limbs and proceeds to the proximal ends, with the classic stocking-glove distribution.[3] DPN is the most prevalent kind of neuropathy in the world, and it is thought to affect almost half of diabetics.[4] It significantly raises mortality, reduces quality of life (QoL), and causes significant morbidity.[5] In fact, DPN accounts for almost one-fourth of American healthcare spending on diabetes.[6]

DPN is now treated through prevention, blood sugar control, and pain and symptom management.[7] Drug therapy is currently the primary form of treatment for DPN, and many patients do not obtain efficient therapies.[8] There is an urgent need to perform in-depth research to discover new methods because the medications now used for the prevention and treatment of DPN are ineffective and frequently have adverse effects. These symptoms have a significant impact on a patient's QoL since they make it harder for them to carry out daily tasks, participate in social and professional activities, maintain a healthy lifestyle, and preserve their independence.[9]

Due to the absence of numbness treatment, it has been claimed that the medications' ability to reduce the symptoms of DPN is insufficient. Moreover, all available medication carries a relevant risk of side effects and medication interactions.[10] While there are few effective treatments for neuropathy, researchers are investigating complementary therapy, such as acupuncture.[11] The treatment of painful DPN is made possible by the approval of three non-opioid oral medications, e.g., duloxetine, pregabalin, and gabapentin, in the United States and the European Union.[12] But only approximately one-third of patients have pain relief of at least by 50%, and may have adverse effects. Widely used drugs frequently have adverse effects that affect the central nervous system, rather than stopping pain signals at the site of origin in the periphery.[13]

Axonal or demyelinating diabetic neuropathy can affect both small and large neurons. The most prevalent glial cells, called Schwann cells, have a function in metabolic maintenance and injury prevention as well as acting as nerve axon insulators and neurobiological modulators.[13] Church cells' normal function is compromised in diabetic patients, which impairs glial-axon communication and nerve homeostasis and causes fiber loss, neurodegeneration, and pain.[14]

In such circumstances, the literature demonstrates the efficacy of local platelet-rich plasma (PRP) injection for long-term pain relief. According to the studies, local PRP could promote local tissue remodeling, healing, and nerve axonal regeneration. Release of cell signaling molecules such as nerve growth factor, vascular endothelial growth factor, and fibronectin is induced by PRP.[15,16]

Chronic neuropathic pain has received considerable attention in recent studies, focusing on the potential efficacy of local injections of PRP for long-term relief. These studies hypothesize that administration of PRP directly into the affected area holds promise for alleviating persistent pain by facilitating enhanced local healing, promoting tissue remodeling, and supporting axonal regeneration of nerves.[15,17]

PRP has evolved over the past few decades into an empirically supported adjunct therapy for DPN. The underlying assumption is that the administration of PRP at the site of pain can trigger a cascade of positive biological responses that ultimately contribute to sustained relief of neuropathic pain symptoms. Platelet-derived angiogenesis factors can stimulate the development of new capillaries by enhancing endothelial cell migration. These data have served as the foundation for our hypothesis, which predicts that revascularization and regeneration will improve nerve conduction and reduce DPN symptoms. Therefore, this study was conducted to determine the effect of PRP injections at the acupuncture points and compare the effects with the use of pregabalin in painful diabetic poly neuropathy.

# 2. METHODOLOGY

A randomized controlled trail was conducted at Iffat Anwar Medical Complex after the approval from Ethical Review committee of School of Pain and Regenerative Medicine, The University of Lahore (IRB/SPRM/2020-

 

1). The duration of study was March 2020 to April 2021. We enrolled clinically diagnosed patients having neuropathic signs and symptoms of DPN, such as numbness, pain in hands and feet, muscle weakness, burning sensation etc. with type 2 diabetes with an HbA1c level greater than 7.5, of both genders, and aged between 40-70 y in the study. The exclusion criteria were patients having comorbidities like chronic liver or kidney disease, ischemic heart disease, and the patients who were on antiepileptics or antidepressants.

The sample size was calculated by the power of an earlier study equal to 80% and level of significance equal to 5% the sample of subjects by incidence of pain at 6 month in PRP group was 3.2% and in medicine group was 24%.[18] After the written and informed consent total of 60 patients were randomly divided into two groups in a 1:1 ratio. Group I (treatment group), received PRP injections (0.3 ml on each point) on specific acupuncture points (DU14, 20, ST36, 40, 41, SP6, SP10, GB39, P6 and R6); and Group II (control group) received standard treatment. In Group II patients were given 75 mg pregabalin twice daily for two weeks. Follow up was done every 2 weeks for 3 months consecutively and dose was titrated according to the symptoms of the patients which was increased gradually from 100 mg to 300 mg twice a day.

With a 22-gauge, one-inch needle, 30 ml of blood were taken from the median cubital vein to prepare PRP (5–6 mL), The procedure was carried out at a temperature of 22 to 26 °C under stringent aseptic guidelines, and the blood was collected in centrifuge test tubes. When the blood's serum coat and upper layers of red blood cells were separated, the plasma was pipetted into additional sterile tubes and spun again to activate the platelets. After retrieving, the PRP injection was performed at the points DU14, 20, ST36,40,41, SP6. SP10, GB39, P6 and R6. The selected points were based on traditional Chinese medicine diagnoses for diabetes and neuropathy.[19] The physician employed a freehand one-man approach, moving the probe while holding the syringe in one hand and examining the nerve with the other. A 1.5 mL dose of PRP was injected into each nerve.

The PRP treatment was given once a month till 3 months. Follow up of all patients was conducted every month till three months and after completion of treatment patients were followed up after three months, at 6th month and at 1 year. At 1 year final assessment of patients was done, which included pain intensity measured by Visual Analog Scale (VAS), assessment of DNP was carried out by using Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score >12 showed predominantly neuropathic pain),[20] QoL was measured by Short Form 36 Health Survey (SF-36), low score showed less impaired QoL,[21] and the sleeping problem was measured by Sleep Quality Scale (SQS), it ranges from 0-84, higher score indicates acute sleep deprivation.[22]

During the follow up period patients were monitored at each follow up for any the adverse effects. Patients were asked to report the adverse effect during the treatment period.

All the data was entered and analyzed by SPSS 25.0. The difference among pain, QoL, SQS among groups were compared by independent sample t test, and before and after difference was observed by paired sample t test. $P < 0.05$ was considered as significant.

## 3. RESULTS

Sixty patients were enrolled in the current study. The patients were randomly divided into two equal groups. Group I received PRP injections treatment on acupuncture point and Group II received standard treatment (75 mg pregabalin twice daily). The demographic data and the pain parameters are given in Table 1. The mean age of patients in both groups as statistically equivalent ($P = 0.729$). There were 17 females in Group I and 12 in Group II. The baseline VAS score among both groups was equally severe ($P = 0.655$), the LANSS also showed neuropathic pain among participants of both groups ($P = 0.035$), The QoL was also measured by Short Form 36 Health Survey (SF-36)

**Table 1: Baseline characteristics of patients**

| Groups | Group I (n = 30) | Group II (n = 30) | P-value |
|---|---|---|---|
| Gender (M/F) | 13/17 | 18/12 | 0.196 |
| Age (y) | 55.17 ± 8.87 | 54.37 ± 8.90 | 0.729 |
| BMI (kg/m$^2$) | 25.37 ± 4.64 | 24.8 ± 4.73 | 0.642 |
| VAS Score at Baseline | 7.47 ± 1.27 | 7.30 ± 1.59 | 0.655 |
| LANSS score at Baseline | 13.50 ± 50 | 14.93 ± 2.55 | 0.035 |
| SF-36 at baseline | 67.77 ± 12.2` | 69.37 ± 11.7 | 0.607 |
| SQS score at baseline | 49.53 ± 12.4 | 52.13 ± 10.9 | 0.394 |

*Data presented as mean ± SD; P < 0.05 considered as significant*

*SQS- Sleep Quality scale; LANSS- Leeds Assessment of Neuropathic Symptoms and Signs; Sf-36- Short Form 36 Health Survey*

 

**Table 2: Difference among outcome variables before and after treatment (Treatment Group 1)**

| Outcome Variables | Mean score before treatment | Mean Score after treatment (at follow up) | P-value |
|---|---|---|---|
| VAS score | 7.38 ± 1.42 | 4.43 ± 1.55 | 0.000 |
| LANSS Pain Score | 14.22 ± 2.65 | 9.17 ± 2.33 | 0.000 |
| SF-36 | 68.57 ± 11.9 | 36.35 ± 11.7 | 0.000 |
| SQS score | 50.83 ± 11.6 | 29.95 ± 7.97 | 0.000 |

*Data presented as mean ± SD; P < 0.05 considered as significant*

*SQS- Sleep Quality scale; LANSS- Leeds Assessment of Neuropathic Symptoms and Signs; Sf-36- Short Form 36 Health Survey*

**Table 3: Difference among outcome variables between study groups**

| Variables | Group I | Group II | t test | P-value |
|---|---|---|---|---|
| VAS score after treatment | 3.67 ± 1.093 | 5.20 ± 1.584 | 4.363 | 0.000** |
| LANSS score after treatment | 8.50 ± 2.306 | 9.83 ± 2.193 | 2.95 | 0.025** |
| Sf-36 after treatment | 31.50 ± 9.247 | 41.20 ± 12.161 | 3.47 | 0.001* |
| SQS score after treatment | 27.30 ± 8.026 | 32.60 ± 7.103 | 2.708 | 0.009* |

*Data presented as mean ± SD; P < 0.05 considered as significant*

*SQS- Sleep Quality scale; LANSS- Leeds Assessment of Neuropathic Symptoms and Signs; Sf-36- Short Form 36 Health Survey*

which shows that the patients had impaired QoL (P = 0.607) , and SQS showed impaired sleep deprivation among both groups (P = 394). LANSS, QoL was measured by SF-36 and SQS.

Table 2 shows the effect among the measuring parameters before and after treatment in Group I. The VAS score shows significantly decrease from 7.38 to 4.43 with a significant improvement (P < 0.05). The patient's LANSS scores also reported decrease which shows that the patients recovered from neuropathic pain, their overall QoL and SQS scores with both treatment (P < 0.05).

LANSS, QoL was measured by SF-36, and SQS.

The outcome variables were compared in both groups. The VAS score significantly decreased in Group I; 3.67 ± 1.09 compared to 5.20 ± 1.58 in Group II. There was significant difference among both groups (P = 0.000).

LANSS scale also showed significant improvement; 8.50 ± 2.30 vs. 9.83 ± 2.17 in Group I vs. II (P = 0.025), as well as the QoL, the difference in the two groups being significant (P = 0.001) and SQS (P = 0.009). The PRP group showed better results as compared to the conventional therapy group.

## 4. DISCUSSION

The most common consequence of diabetes mellitus, diabetic peripheral neuropathy (DPN), has serious clinical implications that can affect patients' QoL. Despite improved knowledge of the disease and available treatments, the prevalence of DM has increased over the past 20 years. We conducted this study to determine the effect of injecting PRP at specific acupuncture points as compared to pregabalin in painful diabetic poly neuropathy.

The findings of current study revealed that the PRP Group showed more improvement in sign and symptoms as compared to the conventional group. The VAS score significantly improved in Group I as compared to Group II. The neuropathic symptoms also showed significant improvement, as well as the QoL and SQS in the patients receiving PRP. The PRP Group showed more promising results as compared to conventional therapy.

The findings of the recent study were compared by another research, in which the study participants were divided into two groups, the intervention group consisted of sonographic local injection of PRP (3 mL) into the carpal tunnel, while a night splint served as the control. Those who received PRP demonstrated a significant reduction in pain using VAS during follow-up. They came to the conclusion that PRP injections can be used safely and effectively to treat carpal tunnel syndrome patients with neuropathic pain.[23]

According to research by Farrag and colleagues, local PRP injection offers a very promising effect on nerve regeneration when compared to platelet-poor plasma in a rat model.[24] In another study it was found that sutured nerves assisted with PRP demonstrated an improved functional outcome, which was associated with improvement in myelin thickness and onset response time.[25] The findings of the current study were compared with another research with the objective to determine the effectiveness of perineural PRP injection for pain and numbness relief. The study proved perineural PRP

 

injection as an effective treatment for reducing the pain and numbness of diabetic neuropathy and improving peripheral nerve function.[26]

The positive effects of local injection of PRP in painful musculoskeletal conditions have been documented by Navani et al. who particularly emphasized the effects on tissue recovery. It is important to recognize that the overall efficacy of PRP may be subject to variations in its production and composition, in addition to elements related to specific medical conditions and anatomy.[27]

The results of our study are consistent with the research findings of Anjayani et al. who showed that perineural injection of one ml of PRP in patients with Hansen's disease suffering from peripheral neuropathy led to an improvement in VAS pain scores and two-point discrimination test scores. Compared to platelet-poor plasma, the positive effects were observed two weeks after injection of both types of plasma, underscoring the superiority of PRP in promoting positive outcomes for individuals with peripheral neuropathy associated with Hansen's disease.[28]

# 5. CONCLUSION

The results of our study conclude that the treatment of diabetic peripheral neuropathy with platelet rich plasma injections at acupuncture points significantly improves the pain scores, quality of sleep and neuropathic symptoms as compared to conventional treatment with 75 mg pregabalin PO twice daily.

## 6. Learning point

Pain is a universal problem and although with constant improvement in the existing treatment modalities and innovating new technology, the pain specialist has a wide and bigger armamentarium now, yet he needs to choose wisely.

## 7. Data availability

The numerical data generated during this research is available with the authors.

## 8. Acknowledgement

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## 9. Conflict of interest

The study utilized the hospital resources only, and no external or industry funding was involved.

## 10. Authors' contribution

SA: Research idea, planning and manuscript preparation

MWH: Critical Review

GRS, FT: Data collection and analysis

MUM: Results writing and reporting

MA: Patient management, Bibliography review and editing

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