Brief Report

Possible Role of Platelet-Rich Plasma in the Treatment of Patients with Postherpetic Neuralgia: A Prospective, Single-Arm, Open-Label Clinical Study

Mohammed Abu El-Hamd, Shereen G. Abd Elaa, Ashraf Abdelwahab

Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag, Egypt

Abstract

Background: Currently, no treatment can fully and finally treat postherpetic neuralgia (PHN). **Aim and Objectives:** This study aimed to evaluate the possible efficacy of autologous intralesional platelet-rich plasma (PRP) injection in treating patients with PHN. **Materials and Methods:** A prospective, single-arm, open-label clinical study was conducted on 45 patients with PHN attending the Dermatology Outpatient Clinics of Sohag University Hospital, Egypt, between November 2019 and November 2021. Patients were subjected to full clinical general and dermatologic examinations. Patient's assessment included severity of pain through visual analogue scale (VAS), numerical rating scale (NRS), and verbal rating scale (VRS), in addition to Medical Outcomes Study 36 Item Short-Form (SF-36). Patients were treated by autologous PRP injection every 2 weeks for 2 months (4 sessions). Patients were evaluated before every session and 3- months after the last session. **Results:** There was a significantly decreased VAS, NRS, VRS, and SF-36 questionnaire values in the last session and three months after the last session. There was a highly significant moderate correlation between both scales (VAS and VRS) and patient's age in years and who have aggravating factors. Likewise, there was a significant moderate positive correlation between scales (VAS and VRS) and the disease duration, medical co-morbidities, and associated myalgia. **Limitations:** These findings require further confirmations on more inclusive large-sized multicenter, randomized, placebo-controlled, clinical trials with longer follow-up. **Conclusion:** This clinical pilot study concluded that autologous intralesional PRP injection was an effective therapeutic option for patients with PHN.

Keywords: *Herpes zoster, platelet-rich plasma, postherpetic neuralgia*

Introduction

Postherpetic neuralgia (PHN) is a neuropathic pain (NP) which characterized by pain that persists for months to years after the resolution of the herpes zoster (HZ) rash. PHN is the most prevalent HZ complication.[1]

The pathophysiology of PHN is poorly understood; numerous pathophysiologic processes may explain the development of PHN.[2] It may affect both peripheral and central mechanisms.[3] Damaged peripheral nerves lose the ability to inhibit nociception pain signals. This lowers the threshold for nociceptive pain activation and produces spontaneous ectopic discharges. The result generates disproportionate pain with non-painful stimuli (peripheral sensitization). The HZ virus-induced nerve inflammation also impairs the descending inhibitory pain pathways, secondary to compromise of the dorsal horns (central sensitization).[4]

Unlike other neuropathic conditions; the diagnosis of PHN is relatively straightforward. Detailed medical history and careful physical examination in qualifying the pain and its effect on the quality of life are very important.[5] Patients with PHN report decreased quality of life and interference with activities of daily living that may affect physical, psychological, and social aspects of their lives as well as their ability to function.[6] Psychologically, patients report anxiety and depression primarily from the fear of recurrent pain.[7]

Currently, no treatment can fully and finally treat PHN. The available treatments for managing PHN give only temporary relief of pain and sometimes are not effective at all. Furthermore, several medications have serious adverse effects and sometimes can lead to serious disability in the patients.[8]

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Address for correspondence:
Prof. Mohammed Abu El-Hamd, Dermatology, Venereology, and Andrology, Faculty of Medicine, Sohag University, Sohag University Street, Sohag City - 82524, Sohag, Egypt. E-mail: mohammedadva@yahoo.com

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The platelet-rich plasma (PRP) is a biological product defined as a portion of the plasma fraction of autologous blood with a platelet concentration above the baseline. It is enriched by a range of growth factors (GFs), chemokines, cytokines, and other plasma proteins. Numerous GFs are released from alphagranules of the activated platelets including platelet-derived growth factor (PDGF), transforming growth factor (TGF), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), epidermal growth factor (EGF), and interleukin (IL)-1.[9]

This clinical study aimed to evaluate the possible efficacy of autologous intralesional PRP injection in the treatment of patients with PHN.

Patients and Methods

A prospective, single-arm, open-label clinical study was conducted on 45 patients with PHN attending the Dermatology Outpatient Clinics of Sohag University Hospital, Egypt, between November 2019 and November 2021.

Inclusion criteria: Patients of both sex aged 18–80 with PHN were included. PHN was defined as pain that remained 3 months or more after the shingles rash went away.

Exclusion criteria: Patients with one or more of the following criteria was excluded from this study; other causes of NP, patient refusal, platelet dysfunction syndrome, and critical thrombocytopenia (less than 100,000/ml), hemoglobin less than 10 gm/dl, local infection, and coagulopathy.

Methods: All patients in this study were subjected to clinical assessment as follows:

A) Medical history taking: (1) Personal history included: age, sex, marital status, residence, occupation, education, and special habits. (2) History of present illness included: Pain (a) Onset, course, duration, distribution, radiation, diurnal variation, aggravating and relieving factors of the pain. (b) Sensory descriptors included pain qualities as hot, burning, sharp, stabbing, cold, allodynia, and common non-painful sensations as tingling, prickling, itching, numbness. Associated symptoms; symptoms of concurrent motor or autonomic nerve involvement may be present. (3) Medical history included: Any history suggestive immunosuppression as in individuals with acquired immunodeficiency syndrome, cancer, organ transplant recipients, diabetes mellitus (DM), chronic liver or kidney disease, systemic corticosteroids, or chemotherapeutic agents.

B) Clinical examinations included; (1) General examination was done to exclude any systemic affection. (2) Local examinations were done as follows: (a) Skin examination included; dermatomal distribution, pigmentary changes, residual dermatomal scar, alternation in temperature, sweating, and hair growth. (b) The sensory examination included: (1) Touch sensation which may be diminished or absent in the involved dermatome, (2) Dynamic allodynia (pain due to cotton wool lightly moving across the skin), (3) Thermal allodynia (burning sensation in response to ice cube on the skin), (4) Hyperalgesia (exaggerated pain response), and (5) Dysesthesia (unpleasant and abnormal sensation).

Patient's assessment included:

1. Severity of pain

Visual Analogue Scale (VAS): A straight line with the endpoints defining extreme limits such as "no pain at all" and "worst possible pain". The patient is asked to mark his pain level on the line between the two endpoints. The distance between "no pain at all" and the mark then defines the subject's pain. In several studies, VAS has been demonstrated to be sensitive to treatment effects.[10]

Numerical Rating Scale (NRS): Patients were asked to circle the number between 0 and 10, 0 and 20, or 0 and 100 that fits best to their pain intensity. Zero usually represents "no pain at all" whereas the upper limit represents "the worst pain ever possible". In contrast to the VAS, only the numbers themselves are valuable answers, meaning that there are only 11 possible answers in a 0–10, 21 in a 0-20, and 101 in a 0-100 point NRS, it has shown high correlations with other pain assessment tools in several studies.[10] The feasibility of its use and good compliance has also been proven.[11]

Verbal Rating Scale (VRS): Adjectives were used to describe different levels of pain. The respondent was asked to mark the adjective which fits best to the pain intensity. As in the VAS, two endpoints such as "no pain at all" and "extremely intense pain" should be defined. Between these extremes, different adjectives that describe different pain-intensity levels are placed in the order of pain severity. Like VAS, VRS has been shown to correlate strongly with other pain assessment tools.[10] Compared to other instruments, the respondent's compliance is often as good or even better even though the subjects must read the entire list before answering, which is time-consuming.[11]

2. Quality of life included SF-36 questionnaire: One of the most widely used measures of Health-related quality of life (HRQ) is the Medical Outcomes Study 36 Item Short-Form (SF-36).[12] As chronic pain affects all aspects of life and health including physical, psychological, and social well-being that is that which is defined as HRQ, the SF-36 has been used to describe the impact of chronic pain in the community and measure treatment effects, with improvements in both physical and mental health observed in randomized trials for the treatment of patients with NP conditions.[13,14] A lower score indicates better health status.

3. Patients were assessed before every session and 3 months after the last session.

4. Investigations before treatment included complete blood count and coagulation profile.

Method of treatment

Forty-five patients were treated by autologous PRP injection every 2 weeks for 2 months (4 sessions). 10 cc of the blood was collected under a complete aseptic condition in ordinary tubes then centrifuged at 1000 rpm (revolution per minute) for 10 minutes to separate the plasma and platelets from red and white cells. The lower 1-2 cc of the plasma was yielded as PRP concentrate after centrifugation.

Topical anesthetic cream was applied to the treated area, and 0.1 cc of PRP was injected per point with an insulin syringe intradermally with a space of 1 cm in between different points of injections.

Ethical consideration: This study was approved by the Ethical and Scientific Research Committees at the Faculty of Medicine, Sohag University. Informed written consent was obtained from all participants.

Statistical analysis

The collected data were verified, coded by the researcher, and analyzed using the Statistical Package for the Social Sciences (SPSS) program, version 24 (IBM Corporation, New Orchad Road, Armonk, New York, USA).

Results

The present study was conducted on 45 patients with PHN; 36 (80%) patients completed the study and received 4 sessions of autologous PRP injection every 2 weeks for 2 months and came for follow-up after 3 months of the last session. Five (11.11%) patients received 3 sessions and 4 (8.88%) patients received 2 sessions.

The mean ± SD age of the included patients was (56.73 ± 12.2) years; 23 (51.1%) patients were female patients. The mean ± SD of duration of PHN was 16.09 ± 19.5 months and 26 (57.8%) patients had a progressive course. The clinical characteristics of the patients are shown in Table 1.

In this study, most patients with PHN (30, 66.7%) had thoracic dermatomal distribution, followed by lumbar, trigeminal, and cervical dermatomal distribution in (8, 17.8%), (5, 11.1%), (2, 4.4%); %); respectively. 3 (6.7%) patients presented with scar. None of the patients showed alternation in temperature, hair growth, or sweating.

The mean baseline VAS, NRS and VRS levels in the first session were 6.36 ± 1.4, 6.25 ± 1.5, and 2.53 ± 0.9, significantly decreased to 2.86 ± 0.9, 2.83 ± 0.7, and 1.33 ± 0.4 in the last session; respectively (P value < 0.001) and significantly decreased to 2.50 ± 0.6, 2.50 ± 0.4, and 1.17 ± 0.1 three months after the last session; respectively (P value < 0.001). The effects of PRP on VAS, NRS, and VRS levels are shown in Table 2.

In current study; significant improvement was evident for all domains of SF-36 questionnaire through reduction of patient dissatisfaction. Different domains of the SF-36 questionnaire of the studied populations are shown in Table 3.

Table 1: Clinical characteristics of the studied population (n=45)

Variable	Category	n=45
Course of disease	Progressive	26 (57.8%)
	Regressive	4 (8.9%)
	Stationary	15 (33.3%)
Disease duration/ months	Mean±SD	16.09±19.5
	Median (Range)	3 (1-120)
Pain radiation	No	43 (95.6%)
	Radiant	2 (4.4%)
Pain diurnal variation	No	29 (64.4%)
	Nocturnal Accentuation	16 (35.6%)
Pain aggravating factors	No	34 (75.6%)
	Emotional Stress	4 (8.9%)
	Physical Activity	7 (15.5%)
Pain relieving factors	No	31 (68.9%)
	Rest	8 (17.8%)
	Medication	4 (8.9%)
	Psychological Stability	2 (4.4%)
Type of pain	Hotness	4 (8.9%)
	Burning Sensation	40 (88.9%)
	Stabbing Pain	1 (2.2%)
Associated symptoms	No	33 (73.3%)
	Myalgia	12 (26.7%)
Co-morbidity	No	25 (55.6%)
	DM	7 (15.6%)
	HTN	5 (11.1%)
	CRD	1 (2.2%)
	DM & HTN	5 (11.1%)
	DM & HTN & IHD	1 (2.2%)
Response to previous treatment	No	8 (17.8%)
	Mild	26 (57.8%)
	Good then recurrence	11 (24.4%)
Number of treatment sessions	Uncompleted (2 & 3)	9 (20%)
	Completed (4)	36 (80%)

DM: Diabetes Mellitus, HTN: Hypertension, CRD: Chronic Renal Disease, IHD: Ischemic Heart Disease

Table 2: Effect of PRP on the VAS, NRS, and VRS scores of the studied population (n=45)

Session	VAS score	NRS score	VRS score
	Mean±standard deviation		
Before 1st session	6.36±1.4	6.25±1.5	2.53±0.9
Before 2nd session	4.64±1.2	4.72±1.1	1.97±0.7
Before 3rd session	3.50±1.1	3.56±1.0	1.58±0.7
Before 4th session	2.86±0.9	2.83±0.7	1.33±0.4
3- months after last session	2.50±0.6	2.50±0.4	1.17±0.1
*P	<0.001	<0.001	<0.001

*One-way RM-ANOVA test was used to compare Means over time. *P<0.05 is significant. PRP: Platelet Rich Plasma. VAS: Visual Analogue Scale. NRS: Numeric Rating Scale. VRS: Verbal Rating Scale

The relationships between the response of treatment (VAS and VRS change at the end of treatment) and determinants of PHN are shown in Table 4. The correlations between treatment response and determinants of PHN are shown in Table 5.

Discussion

To the best of our knowledge; no previous reports are available about the possible efficacy of autologous intralesional PRP injection in the treatment of patients with PHN. In this study; the efficacy was evaluated by VAS, NRS, VRS, and SF-36 questionnaire. The baseline VAS, NRS, and VRS levels significantly decreased in the last session and three months after the last session.

Some previous studies demonstrated the efficacy of PRP in the treatment of NP. One study concluded that PRP was more effective than PPP in treatment of neuritis in patients with leprosy.[15] In another prospective study on 45 patients

Table 3: Effect of PRP on the different parameters of SF-36 questionnaire of the studied population (*n*=45)

Domain	Before 1st session	Before 2nd session	Before 3rd session	Before 4th session	3 months after last session	*P**
	Mean±standard deviation					
Physical function	46.25%±14.1	32.10%±11.6	38.89%±5.9	13.89%±4.2	28.61%±7.5	<0.001
Role limitation due to physical function	58.33%±12.9	38.89%±11.7	36.11%±4.4	36.39%±6.1	23.94%±4.1	<0.001
Role limitation due to emotional function	55.56%±14.4	36.11%±10.2	46.67%±14.1	30.22%±7.5	23.01%±4.8	<0.001
Energy/fatigue	58.89%±12.9	46.67%±10.4	39.50%±10.1	31.69%±8.1	29.94%±6.2	<0.001
Emotional well-being	50.28%±15.5	39.50%±10.6	41.97%±13.1	38.19%±11.2	38.06%±10.9	<0.001
Social functioning	58.36%±14.5	41.92%±12.9	50.00%±15.1	40.83%±12.8	36.81%±9.9	<0.001
Pain	64.76%±17.3	49.93%±13.7	47.78%±12.1	43.06%±11.2	13.47%±1.2	<0.001
General health	55.00%±13.1	47.78%±11.8	58.33%±14.1	14.72%±2.9	13.89%±3.4	<0.001
Health change	75.00%±19.2	58.33%±14.1	20.69%±3.6	13.89%±1.9	11.11%±2.2	<0.001

*One-way RM-ANOVA test was used to compare Means over time. **P*<0.05 is significant. PRP: Platelet Rich Plasma

Table 4: Relationship between response to treatment (VAS and VRS Changes) and determinants of PHN

	VAS Change after PRP Treatment			VRS Change after PRP Treatment		
	No Change (*n*=8)	Improved (*n*=37)	*P*	No Change (*n*=13)	Improved (*n*=32)	*P*
Age (year)	68.00±9.3	54.30±11.4	=0.003*	65.08±8.8	53.34±11.8	=0.002*
Sex						
• Female	3 (37.5%)	20 (54.1%)	=0.495**	8 (61.5%)	15 (46.9%)	=0.372#
• Male	5 (62.5%)	17 (45.9%)		5 (38.5%)	17 (53.1%)	
Disease course						
• Progressive	4 (50%)	22 (59.5%)	=0.272***	6 (46.2%)	20 (62.5%)	=0.174***
• Regressive	0 (0%)	4 (10.8%)		1 (7.7%)	3 (9.4%)	
• Stationary	4 (50%)	11 (29.7%)		6 (46.2%)	9 (28.1%)	
Duration (months)	26.63±2.6	13.81±2.8	=0.012*	21.23±2.7	14.01±3.8	=0.033*
Pain diurnal variation	4 (50%)	12 (32.4%)	=0.291**	5 (38.5%)	11 (34.4%)	=0.528#
Pain aggravating factor	5 (62.5%)	6 (16.2%)	=0.013**	5 (38.5%)	6 (18.8%)	=0.251#
Pain relieving factor	3 (37.5%)	11 (29.7%)	=0.689**	5 (38.5%)	9 (28.1%)	=0.502#
Associated myalgia	4 (50%)	8 (21.6%)	=0.094**	5 (38.5%)	7 (21.9%)	=0.254#
Co-morbidity	5 (62.5%)	16 (43.2%)	=0.322**	8 (61.5%)	13 (40.6%)	=0.202#
Pain radiation	0 (0%)	2 (5.4%)	=0.501**	0 (0%)	2 (6.3%)	=0.356#
Dermatological distribution						
• Trigeminal	0 (0%)	5 (13.5%)	=0.231***	2 (15.4%)	3 (9.4%)	=0.407***
• Thoracic	6 (75%)	24 (64.9%)		9 (69.2%)	21 (65.6%)	
• Lumbar	1 (12.5%)	7 (18.9%)		1 (7.7%)	7 (21.9%)	
• Cervical	1 (12.5%)	(2.7%)		1 (7.7%)	(3.1%)	
Type of pain						
• Hotness	1 (12.5%)	3 (8.1%)	=0.467***	1 (7.7%)	3 (9.4%)	=0.555***
• Burning Sensation	7 (87.5%)	33 (89.2%)		12 (92.3%)	28 (87.5%)	
• Stabbing Pain	0 (0%)	1 (2.7%)		0 (0%)	1 (3.1%)	

*Independent *t*-test was used to compare the mean difference between groups. **Fisher's Exact test was used to compare the proportion difference between groups. ***Monte Carlo Exact test was used to compare the proportion difference between groups. #Chi-square test was used to compare the proportion difference between groups. *P*<0.05 is significant

Table 5: Correlation between treatment response and determinants of PHN

	VAS score	VRS score
	r (*P*)*	
Age (years)	0.465 (*P*=0.001)	0.457 (*P*=0.001)
Disease duration (months)	0.311 (*P*=0.019)	0.270 (*P*=0.037)
Aggravating factors	0.403 (*P*=0.003)**	0.366 (*P*=0.007)**
Associated symptoms	0.350 (*P*=0.009)**	0.359 (*P*=0.008)**
Co-morbidity	0.258 (*P*=0.044)**	0.166 (*P*=0.138)**

*Pearson's correlation coefficient. **Spearman's Rank correlation coefficient. *P*<0.05 is significant

with peripheral neuropathy with a refractory multimodal approach to pharmacologic treatment for more than 3 months; of the patients received a sonographic-guided injection of PRP at the affected dermatome sites; at the end of three-month follow-up, the pain score was reduced up to 70% in 39 of the patients, with improved their quality of life.[16] Also, it has been found that perineural injection of PRP in patients with diabetic peripheral neuropathy was an effective adjunct therapy as it significantly improved neuropathic symptoms.[17]

It could be explained as autologous PRP could effectively control neuroinflammation and contribute to the relief of NP, similar to lidocaine or even better, not only by blocking noxious inputs and avoiding the subsequent neural tissue damage but through its anti-inflammatory effect and its important role in nerve healing and regeneration.[18,19] In addition, PRP contain several platelet-released factors that promote axon regeneration; these GFs include EGF, VEGF, IGF-1, PDAF, and others.[20] Mesenchymal stem cells (MSCs) in PRP can differentiate into proliferating Schwann cells that synthesize and release axon regeneration-promoting neurotrophic factor,[21] that increase axon regeneration and neurological recovery.[22]

From the previous studies assessed efficacy of PRP on PN, we suggested that the efficacy of autologous intralesional PRP in the treatment of PHN; could be due to blocking noxious inputs and preventing the subsequent neural tissue damage through its anti-inflammatory effect and its pivotal role in nerve healing and regeneration, because it contain several GFs as (EGF, VEGF, IGF-1, PDAF) and MSCs which differentiate into proliferating Schwann cells that synthesize and release axon regeneration-promoting neurotrophic factors.

In the current study; The SF-36 questionnaire was used to assess the quality of life (QoL). PRP treatment resulted in improved patient QoL as assessed by SF-36 scores. Significant improvements were evident for all domains through the reduction of patient dissatisfaction. This is explained as patients with NP report substantially low levels of health-related quality of life, and pain severity is a primary predictor of negative health impact[23]; so the greatest improvement in SF-36 domain scores was reported by patients achieving substantial pain relief.[24]

In the current study; age was significantly affected the response of treatment; as the better response was with younger age of the patients. It has been found that in elderly patients with PHN; pain is severe and debilitating, and dissatisfaction with treatment is high.[25] It could be explained by impairment of inhibitory descending pain pathways due to age and PHN-induced central sensitization may play role in resistance to pain relief.[26]

This study revealed that there was a statistically significant correlation between patients response to treatment and duration of PHN; the less duration PHN the more response to treatment. There is evidence to suggest that initiating appropriate treatment prior to central sensitization can minimize the likelihood of neuropathic pain developing.[27] However; Pérez *et al*.[28] postulated that once a peripheral NP condition is established, there is no clear evidence that it becomes more difficult to treat over time.

In the current study; there was a statistically significant correlation between patient's response to treatment (VAS and VRS at the end of follow-up) and emotional stress; as poor response was reported in patients with stressful conditions. These results are supported by previous findings that repeated or chronic exposure to stress typically causes stress-induced hyperalgesia.[29,30]

Regarding physical activities; there was a statistically significant correlation between patient's response to treatment (VAS and VRS at the end of follow-up) and physical activities, patients with physical activities recorded poor responses. However; a previous showed that exercise may be a particularly important treatment option for patients with NP; due to its wide array of established health benefits; such as reduced risk of chronic diseases including cardiovascular disease, type 2 DM, and cancer; reduced depression and anxiety and improved sleep, cognition, bone health, and physical function.[31]

There was a highly significant moderate positive correlation between both scales (VAS and VRS) and patient's age in years. In other words; with one-year increase in age, there was an increase in the score of both scales.

Likewise; there was a significant moderate positive correlation between both scales (VAS and VRS) and the disease duration in months. Namely; with one-month increase in disease duration, there was an increase in the score of both scales.

Moreover; there was a highly significant moderate/moderate positive correlation between both scales (VAS and VRS) and aggravating factors. i.e., having aggravating factors was associated with higher scores of both scales. As well; there was a significant moderate positive correlation between both scales (VAS and VRS) and having myalgia. i.e., having myalgia was linked with higher scores of both scales. Further; there was a significant moderate positive correlation between VAS and having co-morbidity.

Expressly; having chronic diseases was related to higher VAS scores.

Limitations

However, these findings require further confirmations on more inclusive large-sized multicenter, randomized, placebo-controlled, clinical trials with longer follow-up periods to establish the efficacy and safety of autologous intralesional PRP injections in PHN patients.

Conclusion

In conclusion, this clinical study concluded that autologous intralesional PRP injection was an effective therapeutic option for patients with PHN.

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Conflicts of interest

There are no conflicts of interest.

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