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Platelet-Rich Plasma Gel Phonophoresis for Chronic Diabetic Foot Ulcers

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ABSTRACT

The purpose of the study: To explore the therapeutic effect of Platelet-Rich Plasma Gel Phonophoresis on wound healing in chronic diabetic foot ulcers.

Subjects and methods: Seventy-five patients suffering from chronic diabetic foot ulcers were randomly assigned into three equal groups, each group had 25 patients; their ages ranged from 45-65 years. The study group (A) received plasma gel phonophoresis in addition to the ordinary physical therapy program (offloading techniques, range of motion exercises, strengthening exercises as tolerated, balance and proprioception training, gait training, vascular/neuromuscular stimulation and patient education and self-care training) and medical treatment (glycemic control, wound care and infection prevention and management). Group B received ultrasound followed by applying topical platelet rich plasma (PRP) in addition to the ordinary physical therapy program and medical treatment. Group C received ultrasound in addition to the ordinary physical therapy program and medical treatment. Each patient received two sessions per week for six weeks. Evaluation procedures were carried out to evaluate ulcer area and depth using Image J software and cotton tip applicator respectively. The data were collected before and after the period of treatment for all groups.

Results: There was a significant decrease in ulcer surface area post treatment compared with pre-treatment in all groups ($p < 0.001$), with the greatest reduction observed in group A (MD=62.77%), followed by group B (MD=46.36%) and group C (MD=25.58%). Similarly, ulcer depth showed a significant decrease in post treatment compared with pre-treatment across all groups ($p < 0.001$). Group A demonstrated the largest improvement (MD=52.89%), followed by group B (MD=31.25%) and group C (MD=12.61%). There was a significant decrease in ulcer surface area and depth in group A and group B compared with group C post treatment ($p < 0.01$). In addition, there was a significant decrease in ulcer surface area and depth in group A compared with group B ($p < 0.01$).

Conclusion: Platelet-rich plasma gel phonophoresis was considered to be an effective modality for improving wound healing in subjects suffering from chronic diabetic foot ulcers.

KEYWORDS: Diabetic foot, Ulcers, Platelet-rich plasma gel, Ultrasound, Phonophoresis.

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INTRODUCTION

A metabolic disorder defined by persistently high blood sugar levels, diabetes mellitus (DM) [1]. The research findings predicted the global incidence of diabetes mellitus to be around 436 million people in 2019. The global population affected by diabetes mellitus is anticipated to reach 700 million by 2045 [2].

Diabetes mellitus is an escalating global issue, now impacting around 5%-15% of the total population in several industrialized and emerging nations. Diabetes can result in consequences across all organ systems, with foot ulceration being recognized as one of the most prevalent and severe sequelae. Approximately 12%-25% of individuals with diabetes will seek medical attention for a foot issue at some point in their lives. These are mostly ulcers resulting from peripheral neuropathy and, to a lesser extent, peripheral arterial disease. Diabetic foot ulcers (DFUs) can lead to grave consequences, including severe infections, hospitalization, and lower limb amputations, which are linked to a five-year death rate of almost 50% [3].

Diabetic foot ulcers (DFU) can be ascribed to several sources, including poor blood glucose control, anatomical foot abnormalities, neurological deficits, impaired circulation, and physical trauma. Upon the formation of the DFU, it can readily progress into a chronic refractory wound, ultimately resulting in amputation or mortality. Moreover, owing to the enduring presence of ulcerogenic elements, even after effective wound healing, ulcers are prone to reemergence within a little timeframe [4].

Platelet-rich plasma (PRP) has been offered as a novel adjunctive therapy for patients with chronic wounds. It is a platelet concentration derived from centrifuging the patient's own blood. It comprises fibrin and elevated levels of growth factors, which are recognized for facilitating the repair of diverse organs. This therapy was initially documented in the mid-1980s. Since that

time, its application has surged significantly in reconstructive plastic surgery, spine surgery, orthopedics, and oral and maxillofacial surgery. Its initial proposal for application in chronic wound management occurred in the early 1990s. Nonetheless, its application in wound management is not as prevalent as in other domains, and presently, only a restricted number of institutions provide this treatment [5].

Platelets play an important role in wound healing due to their hemostatic action and the presence of cytokines and growth factors. Several growth factors, including PDGF, EGF, FGF, IGF1, IGF2, VEGF, TGF-β, and KGF, play a role in wound healing [6].

Phonophoresis is the use of ultrasound to improve the transdermal administration of medicines. This treatment is most commonly utilized in physical therapy and dates back to the late 1950s. Anti-inflammatory, corticosteroid, and analgesic medications were administered. In early research, high-frequency ultrasound (0.7 to 16 MHz) was employed. In the mid-1990s, it was demonstrated that low-frequency ultrasound (20-100 kHz) was more successful in improving skin permeability; research over the following 20 years has concentrated mostly on low frequency ultrasound for transdermal drug administration [7, 8]. So, the study's goal was to determine the therapeutic efficacy of plasma gel phonophoresis on wound healing in diabetic foot ulcers.

PATIENTS

The patients of the current study were recruited and selected from Al Kasr Al Ainy Teaching Hospital and the National Institute of Diabetes and Endocrinology. Seventy-five patients who have chronic of at least 12 weeks' duration diabetic foot ulcers were participated in this study. Inclusion Criteria included patients between 45 and 65 years of age and both males and females had chronic diabetic foot ulcers of 12 to 20 weeks, with either grade 1 or 2 on Wagner Ulcer Classification System. All ulcers were confined to one anatomical site with no evidence of gangrene in the ulcer or on any other part of the foot. All patients had controlled blood glucose levels with the appropriate medical treatment along the time of the study. We excluded patients with blood diseases, with iron deficiency anemia, with blood anemia, with other types of ulcers, with eczema, edema, infection, autoimmune disease, bone marrow disease, chemotherapy, renal disease and ulcers exposing bones. All participants were informed about the nature and the effect of measurement and treatment methods and were asked to sign the informed consent which included their agreement to participate in the study. They were instructed to report any side effects during the management. This work was done after approval of the ethical committee number "P.T.REC/012/004824" on 03/09/2023.

The study started in January 2024 and lasted for 15 months. The study was implemented in the same recruitment places. In this study the patients were randomly assigned into three equal groups (25 patients for each group), group A (study group) included 25 chronic diabetic foot ulcer patients who were received plasma gel phonophoresis in addition to the ordinary physical therapy program and medical treatment, group B (Control group 1) included 25 chronic diabetic foot ulcer patients who were received ultrasound followed by topical PRP without phonophoresis in addition to the ordinary physical therapy program and medical treatment and group C (Control group 2) included 25 chronic diabetic foot ulcer patients who were received therapeutic ultrasound in addition to the ordinary physical therapy program medical treatment.

METHODS

Sample size calculation and randomization process:

Participants were randomly assigned to one of three groups (A, B, or C) using block randomization with a block size of 6 to ensure balanced group sizes throughout the study. The randomization sequence was generated using the RAND function in Microsoft Excel. The randomization sequence was generated by an independent statistician who was not involved in participant recruitment or data collection. Allocation concealment was maintained using sequentially numbered, opaque, sealed envelopes prepared by a research coordinator. The envelopes were opened only after participant enrollment. Outcome assessors were blinded to group allocation to minimize bias.

To avoid a type II error, a preliminary power analysis was conducted considering depth of the wound as a primary outcome with the following parameters: [two tailed statistical analysis, actual power $(1-\beta)$ =81.8, $\alpha = 0.05$, large effect size = 0.4] [9]. The calculation determined a sample size of 22 for each group which was increased by 13 % up to 25 for each group to overcome the expected dropout. G*power software (3.1.9.2) was used for sample size calculation.

Measurement intervention

Patient assessment was performed before and after treatment. The maximum treatment duration was limited to six weeks because studies had reported that the mean duration of healing of ulcers using platelet rich plasma (PRP) was 6 weeks. Measurement tools included image J software for measuring wound surface area [10], and cotton tip applicator to measure wound depth [11].

Ulcer area:

Photographs were taken placing a ruler next to the wound in parallel with the healthy skin. The digital photographs were visualized with Image J 1.45s software. All the pictures included in this study were taken with the iPhone 13 pro max, which has a camera of 12 megapixels using the flash.

Ulcer depth:

Wound depth can be measured using a sterile cotton-tipped applicator, a simple and widely accepted method in both clinical and research settings. To begin, the wound should be gently cleansed with sterile normal saline to remove any debris or exudate that might interfere with accurate measurement. Wearing sterile gloves, a sterile cotton-tipped applicator is inserted perpendicularly into the deepest part of the wound bed without applying excessive force. Once resistance is felt, indicating the base of the wound has been reached, the clinician uses their fingers to mark the level at which the applicator flushed with the surrounding intact skin. In all cases, care should be taken not to disturb granulating tissue or force the applicator into resistant areas, especially in painful or infected wounds. For added documentation, wound photographs with a visible scale bar may be used alongside depth measurements to track healing over time.

Treatment intervention:

Preparation of platelet-rich plasma (PRP) gel:

Obtaining PRP required a skilled lab technician to take blood samples, spin them, and then degranulate the platelets using thrombin. Following a single centrifugation, the following components were isolated: red blood cells (RBCs), white blood cells (WBCs), and two plasma fractions: GFs (GF-poor) (upper 60%) and PRGF (lower 40%). The repeated freeze-thaw process activates the PRP, which may be produced from around 10 mL of whole blood, often resulting in 2-3 mL. Every week until the healing period for each patient had passed, the PRP treatment (2mL/cm2) of the ulcers would be administered. The PRP gel was created by combining the plasma with calcium gluconate and thrombin. Proteins like thrombin trigger platelet degranulation, which in turn releases a plethora of factors called coagulation factors, platelet thrombo-plastin, thrombospondin, transforming growth factor-ß (TGF-ß), fibrinogen, platelet-derived growth factor (PDGF), epidermal growth factor (EGF), transforming growth factor- (TGF-), vascular endothelial growth factor (VEGF), calcium, serotonin, histamine, and hydrolytic enzymes [12].

Platelet-rich plasma (PRP) gel has theoretical potential to act as a coupling medium for therapeutic ultrasound in the treatment of chronic diabetic foot ulcers, particularly when applied directly to the wound bed. PRP gel is aqueous and viscous, which allows it to conduct ultrasonic energy in a manner similar to traditional ultrasound gels. More importantly, in the context of chronic ulcers where the skin barrier (particularly the stratum corneum) is compromised or absent, the need to transmit ultrasound energy through intact skin is eliminated. This creates a favorable environment for both ultrasound propagation and the delivery of PRP's bioactive factors directly to the tissue [13].

Ulcer area preparation:

All ulcers were debrided before the onset of this study to freshen the wounds and to remove necrotic tissues. The wound and surrounding skin are gently cleansed with sterile normal saline to remove debris, exudate, or contaminants that might hinder the transmission of ultrasound waves.

Treatment in Group A (phonophoresis):

Ulcer area in group A received a thin and even layer of freshly prepared PRP gel activated using calcium gluconate and/or thrombin was applied directly to the wound bed. The PRP gel acts as both a therapeutic agent and a coupling medium for ultrasound application. A sterile ultrasound transducer was then applied over the wound area using the following ultrasound parameters: 1 MHz, probe size of 5 cm2, 1.0 W/cm2, pulsed 1:1 duty cycle, 7:10 minutes/session, with care taken to maintain full contact with the PRP-covered surface. In addition to phonophoresis treatment, the ordinary physical therapy program (offloading techniques, range of motion exercises, strengthening exercises as tolerated, balance and proprioception training, gait training,

vascular/neuromuscular stimulation and patient education and self-care training) and medical treatment (glycemic control, wound care and infection prevention and management) were received by the group.

Treatment in Group B:

Ulcer area in group B received a thin layer of sonic gel applied directly to the wound bed as a coupling medium for ultrasound application. A therapeutic ultrasound device was then applied over the wound area using a sterile ultrasound transducer, with the same parameters used in group A. then after the ultrasound time, sonic was removed and a thin and even layer of freshly prepared PRP gel activated using calcium gluconate and/or thrombin was applied directly to the wound bed and maintained on wound bed for time equal to ultrasound application time. The group received an ordinary physical therapy program and medical treatment.

Treatment in Group C:

Ulcer area in group C received a thin layer of sonic gel applied directly to the wound bed as a coupling medium for ultrasound application. A therapeutic ultrasound device was then applied over the wound area using a sterile ultrasound transducer, with the same parameters used in group A. The group also received an ordinary physical therapy program and medical treatment.

The treatment was repeated two times per week for all groups.

Patient Safety Precautions:

To minimize any potential adverse health effects, the operator used the minimum patient exposure required to achieve the desired benefit. The operator was present all the time during an ultrasound exposure, so the intensity was reduced, or the treatment can be terminated if the patient shows the least any sign of distress. Records were kept of each patient, noting the exposure levels, times, and couplant used. Maintaining well documented, reproducible exposure conditions, was helped minimize unnecessary exposure. Since ultrasound is almost totally reflected at an air-tissue interface, coupling media (gel pads) were always used between the applicator surface and the patient to ensure maximum energy transmission and minimize to prevent infection (Badr 2025).

Statistical Analysis

We used analysis of variance (ANOVA) to compare the groups according to age, and a chi-squared test to compare the groups according to sex. The Shapiro-Wilk test was used to ensure that the data followed a normal distribution. To ensure consistency across categories, we used Levene's test for variance homogeneity. The effects on ulcer surface area and depth were compared within and between groups using mixed MANOVA. For following multiple comparison, post hoc tests were conducted using the Bonferroni correction. A significant level of $p<0.05$ was established for all statistical tests. Windows version 25 of the Statistical Package for the Social Sciences (SPSS) (IBM SPSS, Chicago, IL, USA) was used for all statistical analysis.

RESULTS

Table (1) shows the subject characteristics of group A, B and C. There was no significant difference between groups in age and sex distribution ($p > 0.05$).

Mixed MANOVA revealed that there was a significant interaction of treatment and time (Wilk's A=0.24, F=36.08, p=0.001, $\eta 2$=0.50). There was a significant main effect of time (Wilk's A=0.06, F=489.25, p=0.001, $\eta 2$=0.93). There was no significant main effect of treatment (Wilk's A=0.92, F=1.49, p=0.21, $\eta 2$=0.04). There was a significant decrease in ulcer surface area post treatment compared with pre-treatment in all groups ($p < 0.001$), with the greatest reduction observed in group A (MD=6.34 cm^2, % change=62.77%), followed by group B (MD=4.65 cm^2, % change=46.36%) and group C (MD=2.33 cm^2, % change=25.58%). Similarly, ulcer depth showed a significant decrease in post treatment compared with pretreatment across all groups ($p < 0.001$). Group A demonstrated the largest improvement (MD=0.64 cm, % change=52.89%), followed by group B (MD=0.35 cm, %

change=31.25%) and group C (MD=0.14 cm, % change=12.61%) (Table 2).

There was a significant decrease in ulcer surface area and depth in group A and group B compared with group C post treatment ($p < 0.01$). In addition, there was a significant decrease in ulcer surface area and depth in group A compared with group B ($p < 0.01$) (Table 3).

Table (1): Basic characteristics of participants

	Group A	Group B	Group C	p-value
	mean ± SD	mean ± SD	mean ± SD	
Age (years)	56.72 ± 5.86	55.32 ± 5.34	56.60 ± 5.91	0.63
Sex, n (%)				
Females	13 (52%)	12 (48%)	15 (60%)	0.69
Males	12 (48%)	13 (52%)	10 (40%)	

SD, standard deviation; p-value, Probability value

Table (2): Mean ulcer surface area and depth pre and post treatment of group A, B and C

	Group A	Group B	Group C
	mean ± SD	mean ± SD	mean ± SD
Ulcer surface area (cm²)			
Pre treatment	10.10 ± 3.03	10.03 ± 2.67	9.11 ± 2.52
Post treatment	3.76 ± 1.23	5.38 ± 1.56	6.78 ± 1.91
MD	6.34	4.65	2.33
95% CI	(5.67: 7.00)	(3.98: 5.32)	(1.67: 3.00)
% of change	62.77	46.36	25.58
	p=0.001	***p=0.001***	***p=0.001***
Ulcer depth (cm)			
Pre treatment	1.21 ± 0.38	1.12 ± 0.34	1.11 ± 0.34
Post treatment	0.57 ± 0.22	0.77 ± 0.24	0.97 ± 0.30
MD	0.64	0.35	0.14
95% CI	(0.59: 0.70)	(0.29: 0.40)	(0.09: 0.20)
% of change	52.89	31.25	12.61
	p=0.001	***p=0.001***	***p=0.001***

SD, Standard deviation; MD, Mean difference; CI, Confidence interval; p value, Probability value

Table (3): Comparison of ulcer surface area and depth between group A, B and C post treatment.

Outcome	Group A vs B		Group A vs C		Group B vs C			
	MD (95% CI)	p value	MD (95% CI)	p value	MD (95% CI)	p value	F-value	partial η^2
Ulcer surface area (cm²)	-1.62 (-2.70: -0.54)	0.002	-3.02 (-4.09: -1.94)	0.001	-1.4 (-2.47: -0.32)	0.008	22.49	0.38
Ulcer depth (cm)	-0.2 (-0.37: -0.03)	0.01	-0.4 (-0.57: -0.23)	0.001	-0.2 (-0.37: -0.03)	0.01	15.37	0.29

MD, Mean difference; CI, Confidence interval; p value, Probability value; η², Eta Squared

DISCUSSION

This study investigated the therapeutic efficacy of plasma gel phonophoresis in enhancing wound healing in patients with chronic diabetic foot ulcers (DFUs). The findings demonstrated that plasma gel phonophoresis (Group A) significantly outperformed both topical PRP application without ultrasound (Group B) and standard ultrasound therapy alone (Group C) in reducing wound surface area and depth over a six-week treatment period. These outcomes not only confirm the therapeutic value of PRP in wound healing but also introduce ultrasound-mediated PRP delivery (phonophoresis) as a potentially superior intervention for DFU management.

Post-treatment results, however, revealed a highly significant improvement in wound surface area (P=0.0001), with Group A achieving the greatest reduction (mean±SD: 3.76 ±1.23), followed by Group B (5.38 ±1.56) and Group C (6.79 ±2.27). Similarly, wound depth was significantly reduced (P=0.0001) in Group A (0.57 ±0.21), compared to Group B (0.77 ±0.24) and Group C (0.97 ±0.3).

The superior performance of Group A can be attributed to the synergistic effect of phonophoresis, which uses ultrasound to enhance transdermal delivery of plasma gel into the wound bed. This method likely facilitated deeper penetration of the bioactive components within PRP, such as growth factors and cytokines, which are known to stimulate angiogenesis, fibroblast proliferation, and tissue regeneration. This is in agreement with previous studies suggesting that ultrasound-mediated drug delivery can significantly enhance the permeability of biological tissues, thereby amplifying therapeutic outcomes [8].

In contrast, while Group B benefited from topical PRP application, its therapeutic impact may have been limited by the natural barrier function of the skin, which restricts the depth of penetration of topically applied agents. Group C, receiving ultrasound therapy alone, showed the least improvement, indicating that while ultrasound may support wound healing through mechanical stimulation and improved microcirculation, its effect is less pronounced without the addition of bioactive agents [14, 15].

Consistent with what Kakagia et al. [15] found in a randomised study on 51 patients with persistent diabetic foot ulcers, we found that a combination of PRP and protease-modulating matrix statistically increased the healing rate compared to protease-modulating matrix alone.

On the 20th week after therapy with platelet releasates, a statistically significant greater rate of healing was observed in 26 599 patients with diabetic foot ulcers, according to retrospective controlled research conducted by Margolis et al. [16] (50 vs. 41%; P<0.05). According to a 2010 meta-analysis and systematic review by Villela and Santos [16], there is scientific evidence that PRP is useful in treating diabetic ulcers, particularly in terms of the healing rate in the PRP group.

In a randomized controlled experiment, Ahmed et al. [19] examined the efficacy of platelet-rich plasma (PRP) in treating diabetic foot ulcers in 56 patients. They discovered a statistically significant difference in the rate of full healing following PRP therapy (86 vs. 68%, P<0.05). Blood components such as hemoglobin, hematocrit, platelet counts, and albumin were not reduced despite the frequent little quantities of blood collected (≤20 ml) at each visit, according to the periodic laboratory tests conducted on patients in this study.

The use of platelet-rich plasma (PRP) therapy improved wound healing and reduced risk of complications in patients with diabetic foot ulcers, according to research by Qu et al. [18]. The authors also noted the need for care, such as wearing the right shoes to avoid ulcer recurrence, and the necessity for an interdisciplinary approach to the correct therapy of DFU.

Both our results and those of Hirase et al. [14] are in agreement with one another, as we discovered that using PRP in DFU increased the cure rate and decreased the complication rate compared to regular therapy.

Ahmed et al. (2017)[19] and Li et al. (2015)[20] described fewer complications in the group using PRP than in the control group. Hu et al. (2019)[19], concluded that PRP can be an effective therapy for the treatment of DFU and is not associated with a significant increase in risk for adverse effects.

While no previous studies have directly evaluated PRP phonophoresis in DFU, existing research supports the underlying mechanisms of this combined modality. Ultrasound particularly in therapeutic frequencies (1–3 MHz) has been shown to increase transdermal drug absorption by temporarily disrupting the stratum corneum, enhancing tissue permeability, and facilitating deeper penetration of macromolecules [20, 21].

In contrast, a randomized clinical trial by Elsaid et al. (2020)[22] reported that only 25% of patients in the PRP gel group achieved complete ulcer healing, whereas none in the control group saw full closure. The remaining PRP-treated participants experienced partial healing, but the trial was limited to only 24 patients, raising concerns about sample power and generalizability.

By the conclusion of the eighth week, Ahmed et al. [19] found that the pace of healing utilizing PRP was noticeably slower. The authors hypothesized that this is because of the biphasic effects of the extraordinarily high concentration of growth hormones, which negatively regulate receptors. To back up this discovery, nevertheless, more research with bigger patient groups are required. Furthermore, the authors recommended using PRP for 8 weeks to hasten the healing process, followed by the traditional dressing, until full healing has taken place. As shown before, PRP may have additional antibacterial functions, as the infection rate was reduced in the PRP group.

We found no clinical or statistically significant changes in the chemistry tests for sodium, potassium, chloride, bicarbonate, creatinine, or albumin; however, Driver et al. [24] found the opposite. More individuals in the PRP gel group transitioned to high glycosylated hemoglobin or serum glucose levels at endpoint compared to the control group. Neither the statistical nor the therapeutic implications of these changes were noteworthy.

In addition, a meta-analysis of 15 RCTs (n=1,100 across PRP and control groups) found a significantly higher odds ratio (OR=3.23; $p < 0.0001$) for healing with PRP but noted persistent inconsistency in ulcer area reduction and risk of infection or amputation outcomes across trials [24]. Some individual trials revealed no statistically significant difference in ulcer size reduction despite marginally faster closure rates, implying that PRP may accelerate healing onset but not always improve final wound dimensions.

LIMITATIONS

Despite the promising outcomes demonstrated in this study, several limitations should be acknowledged. First, the relatively small sample size may limit the statistical power and generalizability of the findings. Larger multicenter studies are needed to validate these results across diverse populations and clinical settings. Second, the follow-up period was limited to the short-term post-treatment phase, which restricts the ability to assess long-term healing sustainability, recurrence rates, or potential delayed complications. Third, although efforts were made to standardize procedures, the study lacked blinding of both participants and evaluators, which may introduce performance and detection bias. The absence of a placebo control group also restricts the ability to attribute observed effects solely to the intervention rather than to natural wound healing or other external factors.

CONCLUSION

Overall, the study underscored the clinical value of advanced wound care approaches particularly those that involve biologically active agents (PRP) and enhanced delivery methods (phonophoresis) in significantly improving wound healing outcomes. These results advocate for broader clinical adoption of combination therapies such as PRP with phonophoresis in managing diabetic foot ulcers. Further long-term studies with larger sample sizes are recommended to validate these findings and optimize treatment protocols for widespread clinical use.

CONFLICT OF INTEREST

All authors have no conflicts of interest that are directly relevant to the content of this review.

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