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Original Research Article

Comparative analysis of autologous platelet-rich plasma and topical insulin injections on wound healing outcomes in patients with diabetic foot ulcers: a retrospective study

Sridhar Jaganathan*, Dharaneesh Selvaraja Sangeethapriya, Baddam Nikhil Reddy

Department of General Surgery, Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Salem, Tamil Nadu, India

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***Correspondence:**
Dr. Sridhar Jaganathan,
E-mail: ssdharaneesh@gmail.com

ABSTRACT

Background: Diabetes mellitus is a chronic condition leading to high blood sugar due to pancreatic dysfunction, insulin resistance, or decreased insulin production. Among diabetics, 4–10% develop diabetic foot ulcers (DFUs), with elderly patients at higher risk. A cost-effective and efficient treatment approach is needed for prolonged ulcers. Insulin promotes wound healing through molecular mechanisms involving AKT and ERK pathways. Platelet-rich plasma (PRP) contains high concentrations of platelets and growth factors that accelerate healing.
Methods: A randomized clinical study of 100 patients with post-debridement DFUs (<10×10 cm²) divided into two groups: Group A received PRP injections, and Group B received topical insulin. Wound healing was assessed on days 3, 7, 14, and 21 based on ulcer size reduction, granulation tissue formation, and need for further intervention. Data were analyzed using Statistical Software, with $p<0.05$ considered significant.
Results: The PRP group had a mean age of 57.18 years, and the Topical Insulin group, 56.28 years ($p=0.36$). PRP showed superior granulation tissue formation (59.88±1.30 vs. 44.48±1.71 at day 21), shorter hospital stays (21.34 vs. 30.94 days, $p=0.0001$), and fewer re-interventions (36% vs. 62%, $p=0.009$).
Conclusion: The findings consistently show that PRP outperforms Topical Insulin in key areas such as reducing ulcer size, promoting granulation tissue growth, shortening hospital stays, reduced need for re-interventions.

Keywords: Diabetic foot ulcer, Wound healing, Autologous platelet-rich plasma, Topical insulin, Granulation tissue, Re-intervention rate

INTRODUCTION

Diabetes is a chronic condition characterized by an increase in sugar concentration due to pancreatic dysfunction, the production or resistance of insulin has decreased in peripheral tissues.[1] One of the most frequent complications of trauma or infection and subsequent effects is the diabetic leg ulcers, which affects the end of most organs where diabetes has a low vascular effect.[2] Among the diabetic community, diabetes foot ulcers develop in 4–10% of patients; Elderly patients are more likely to develop the disease.[3,4] The lifelong probability of developing the foot ulcers is fifteen percent of patients with diabetes, and it is estimated that five percent of diabetes had organ ulcers.[3,4]

In addition to financially taxing patients, the management of diabetic foot ulcers is an important issue for surgeons.[5] Management of diabetes ulcers includes appropriate therapeutic footwear, betadine dressing, hydrocolloid dressing, and an important step to unload the wound with the help of skin grafts. Many topical drugs and gels are advocated for ulcer care and treatment.[1,2,6] Despite their high cost, the safety of recent treatment techniques,

including development factor and application of pluripotent cells, is yet to be evaluated.[1] It is mandatory for patients with long-term ulcers to consider a less complex and economically beneficial clinical approach. There is a role in healing insulin wounds, which is important in controlling metabolic activity, protein, cellular spread and development. Insulin affects fibroblast, endothelial cell, and proliferation of keratinocyte, migratory and secreted activities among other cell types, and plays a role in their development and progress.[6,7]

Insulin contains various molecular mechanisms that increase wound healing in individuals with diabetes. Proteins stuck in early stages of insulin action can be important, given the important effects of AKT and ERK on growth and development. In addition, the application of obstructions in these routes reduces the effect of insulin, indicating that insulin increases the process of healing the wound using both routes. Wound healing can be greatly affected by at least two important AKT substrates: eNOS (endothelial nitric oxide synthes 3) and GSK3β (Glycogen Synthez 3 beta).

When AKT phosphorylate GSK3β, its activity decreases. Even in the presence of ischemia, AKT can phosphorylate the eNOS and stimulate the production of nitric oxide (NO), angiogenesis, morphogenesis, blood flow, and improve cell survival.[8] "Autologous platelets rich plasma" blood received after blood has a platelet suspension, which is centrifuged and divided into three layers: plasma poor in platelets, platelet rich plasma and erythrocyte layer. PRP has more platelets per two to six folds than full blood, which is rich in hemodynamically active protein that promotes wound healing. Platelet derivative growth factor, vascular endothelial growth factor, growth factor-β, epithelial growth factor, fibronectin, fibrinogen, vitronectin are among those molecules that are especially present in platelet alpha-granules.

In addition, dopamine, serotonin, histamine, calcium, and adenosine platelets are found in delta granules. These substances interact with the first mentioned growth factors to control the treatment of lesions. As our understanding of pathophysiology of the refractory deep-pocket ulcers increases, the local effects of platelet-rich plasma can be rapidly important in reducing the sickness related to these persistent wounds.[4]

The biological processes required for tissue repair and regeneration are triggered by growth factors found in platelets. These mechanisms include angiogenesis, cellular distinctions, guided chemotaxis and cellular proliferation. Furthermore, several research studies have been published regarding the efficacy of platelet-rich plasma in the treatment of non-healing wounds. The current study compares the effects of autologous platelets rich plasma and topical insulin injections when the wound healing in diabetic foot ulcers.

METHODS

A randomized clinical study conducted over a period of January 2024 to June 2024 at Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, Salem, Tamil Nadu, India, with a sample size of 100 patients with post-debridement healing diabetic foot ulcers of area less than 10×10 cm^2, was approved by the Institutional Ethics Committee of Vinayaka Mission's Kirupananda Variyar Medical College and Hospital, reference number VMKVMC&H/IEC/22/77. These patients are randomly divided into 2 groups A & B by lot method. Group A were given autologous platelet rich plasma injection and group B were given topical insulin injections. Wound healing was recorded on day 3, 7, 10, 14,18, 21st day on the basis of reduction in size of ulcer, granulation tissue, need of any other intervention like debridement. Average mean days to heal were calculated for both groups. And chi square value was calculated, to find the noteworthy distinction in recovery of ulcer by using autologous "platelet rich plasma" and topical insulin injections.

"Platelet rich plasma" is platelet suspension in plasma obtained after blood is centrifuged which divides in to three layers: plasma poor in platelets, plasma rich with platelet, and erythrocyte layer. The upper and middle layers are collected mixed and used. Firstly, the ulcer was carefully washed using povidone solution after which any debris or infected tissues present was removed by debriding the lesion. Depending on the size of ulcer, 5-6 ml prepared platelet rich plasma solution was injected into floor and edges of the ulcer and covered with a dressing. The procedure is repeated on day 3,7,10, 14, 18, 21 days. The effect of treatment is measured by decrease in ulcer size, appearance of granulation tissue, need for re-intervention like debridement, presence of discharge and mean hospital stay.

Post debrided diabetic foot ulcers were injected with insulin adjusted from main correction (1cm=1 unit of human insulin) in the edges and on the floor of the ulcer and a dressing is done. The procedure is repeated on day 3 and checked for any infection or improvement. The same process was repeated on day 7, 10, 14, 18, 21 days. The effect of the procedure is measured by decrease in ulcer size, appearance of granulation tissue, need for re-intervention like debridement, presence of discharge and mean hospital stay.

Inclusion criteria

This study will include patients aged over 35 years with non-infected diabetic foot ulcers classified as Grade 2 or 3, featuring sloping edges and measuring between 1 cm and 10 cm. Ulcers may be located on the dorsum of the foot, medial or lateral side of the leg, plantar surface, or toes. Eligible patients must have well-controlled diabetes managed with regular oral hypoglycemic agents or

injectable insulin, a hemoglobin level above 9 g/dl, and willingness to undergo treatment.

Exclusion criteria

Patients Had infected ulcers extending to tendons or bone, uncontrolled diabetes, anemia with hemoglobin levels below 8 g/dl, or if they are unwilling to participate in the treatment were excluded.

Statistical analysis

Data was Entered in to Microsoft excel 2013 and analyzing was done using Statistical Software. Frequencies and percentages were used to describe data that was qualitative, whereas mean±standard deviation were used to express quantitative data. Parametric tests include Un-paired t tests and independent sample t-tests was used for intergroup comparisons of continuous variables, while non-parametric test include Chi square test was used for categorical data. A p value of <0.05 was considered statistically significant.

The receiver operating characteristic (ROC) curve analysis was conducted to assess the diagnostic accuracy of PRP and Topical Insulin in wound healing. Ethical clearance was obtained before commencing the study.

RESULTS

Table 1 presented the baseline characteristics of patients before treatment initiation, showing no significant differences between the PRP and topical insulin groups in age (p=0.777), sex distribution (p=0.205), or ulcer laterality (p=0.546), indicating that both groups had comparable demographic and clinical profiles. However, a statistically significant difference was observed in ulcer duration (p=0.025), with the topical insulin group exhibiting a wider range, suggesting greater variability in chronicity. This difference in ulcer duration may have influenced treatment outcomes, emphasizing the need for careful interpretation of healing responses. Overall, the comparable baseline characteristics strengthened the validity of the study's comparative analysis of PRP and topical insulin efficacy.

Table 2 summarized the clinical characteristics of patients before treatment initiation. The mean HbA1c levels were slightly higher in the PRP group (10.5±1.6) compared to the Topical Insulin group (10.4±1.1), with a statistically significant difference (p=0.030), suggesting a marginally greater degree of glycemic variability in the PRP group. Hemoglobin levels showed no significant difference (p=0.209), indicating similar baseline anemia status. The ulcer size at admission was comparable between the groups (p=0.862), ensuring an unbiased assessment of treatment efficacy. These findings demonstrated that both groups had largely similar baseline clinical parameters, enhancing the reliability of the study outcomes. Table 3 presented the outcomes and VAS scores after treatment. The PRP group exhibited a significantly smaller ulcer size at the end of treatment (p=0.000) and a greater reduction in ulcer size (p=0.009), indicating superior wound healing. Granulation tissue formation was consistently higher in the PRP group across all time points, with statistically significant differences.

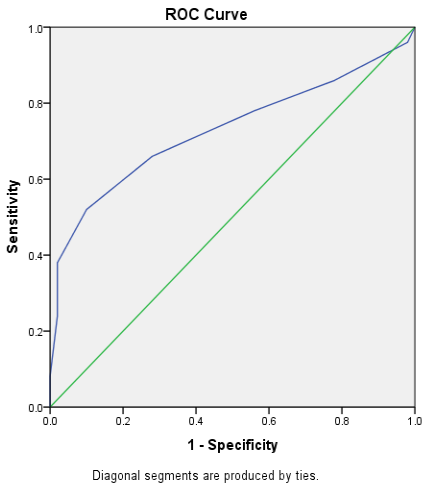

Figure 1: Receiver operating characteristic curve of autologous platelet rich plasma.

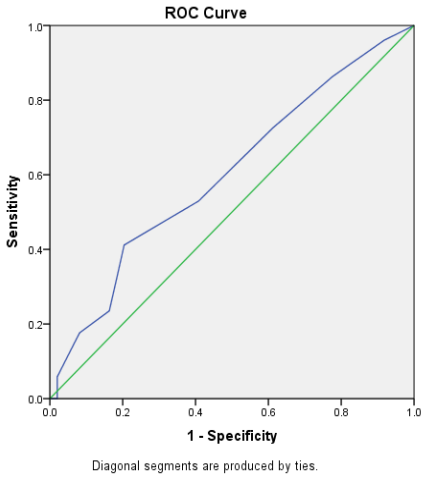

Figure 2: Receiver operating characteristic curve of topical insulin.

Hospital stay was significantly shorter for PRP-treated patients (p=0.003), and the need for re-intervention was lower (p=0.009), emphasizing PRP's efficacy. VAS scores showed no significant difference (p=0.762), suggesting comparable pain levels between both groups. Overall, PRP demonstrated enhanced healing outcomes. Table 4 presented the ROC curve analysis comparing the effectiveness of autologous platelet-rich plasma (PRP) and topical insulin injections in wound healing among patients with diabetic foot ulcers. The area under the curve (AUC) for PRP was 0.729, indicating a strong predictive value for wound healing, with statistical

significance (p=0.000). The 95% confidence interval (CI) ranged from 0.627 to 0.831, further supporting PRP's effectiveness. In contrast, topical insulin showed a lower AUC of 0.601, with a p value of 0.081, suggesting a weaker and statistically non-significant predictive ability. The confidence interval (0.490–0.712) indicated considerable variability in its efficacy. These results highlighted that PRP was significantly more effective in promoting wound healing than topical insulin. The higher AUC value for PRP suggested better diagnostic accuracy in predicting successful healing outcomes, reinforcing its superiority as a therapeutic approach for diabetic foot ulcers. This analysis supported PRP as a more reliable treatment modality. The ROC curves in Figures 1 and 2 illustrate the diagnostic performance of autologous platelet rich plasma (PRP) and Topical Insulin in wound healing for diabetic foot ulcers. Figure 1 shows the ROC curve for PRP, with an AUC (Area Under the Curve) of 0.729, indicating a good predictive value for wound healing. The curve deviates significantly from the diagonal reference line, signifying a strong ability to differentiate between healing and non-healing ulcers. In contrast, Figure 2 represents the ROC curve for topical insulin, with an AUC of 0.601, suggesting a weaker predictive ability compared to PRP. The curve remains closer to the diagonal line, indicating limited discriminatory power. The difference in AUC values suggests that PRP is more effective in promoting wound healing than Topical Insulin. These findings reinforce the advantage of PRP in clinical decision-making and support its use as a superior treatment modality for diabetic foot ulcers.

Table 1: Baseline characteristics of patients in before initiation of treatment.

Variables	PRP	Topical Insulin	P value
Age (in years)	57.1±9.9	56.3±9.7	0.777
Sex			0.205
Male	36 (72.0)	30 (60.0)	
Female	14 (28.0)	20 (40.0)	
Side of ulcer			0.546
Right	29 (58.0)	26 (52.0)	
Left	21 (42.0)	24 (48.0)	
Duration of ulcer	27.9±28.4	31.8±110.0	0.025**

* Significant at the 0.01 level (2-tailed); ** Significant at the 0.05 level (2-tailed)

Table 2: Clinical characteristics of patients in before initiation of treatment.

Variables	PRP	Topical insulin	P value
HBA1C	10.5±1.6	10.4±1.1	0.030**
HB level	6.4±0.6	6.6±0.4	0.209
Size of ulcer at admission (cm^2)	17.4±8.9	19.3±8.9	0.862

* Significant at the 0.01 level (2-tailed); ** Significant at the 0.05 level (2-tailed)

Table 3: Outcome and VAS score of patients in after treatment.

Variables	PRP	Topical Insulin	P value
Size of ulcer at end of treatment (cm^2)	11.4±6.7	13.8±7.5	0.000*
Decrease in size at the end of treatment (cm^2)	6.0±3.2	5.5±5.1	0.009*
Granulation tissue appearance			
Day 0	7.3±0.3	7.1±0.2	0.001*
Day 7	18.8±1.3	24.4±1.6	0.004*
Day 14	44.8±1.4	23.1±1.4	0.007*
Day 21	59.9±1.3	44.5±1.7	0.005*
Duration of hospital stay	21.3±2.3	30.9±2.1	0.003*
Need for re-intervention			
Yes	18 (36.0)	31 (62.0)	0.009*
No	32 (64.0)	19 (38.0)	
VAS			
No pain	26 (52.0)	23 (46.0)	0.762
Mild	19 (38.0)	20 (40.0)	
Moderate	5 (10.0)	7 (14.0)	

*Significant at the 0.01 level (2-tailed); ** Significant at the 0.05 level (2-tailed)

Table 4: ROC curve analysis for autologous platelet rich plasma vs topical insulin injections on wound healing in patients with diabetic foot ulcer.

Variables	AUC	SE	P value	95% CL	
				LB	UB
Autologous platelet rich plasma	0.729	0.052	0.000	0.627	0.831
Topical insulin	0.601	0.057	0.081	0.490	0.712

DISCUSSION

The age distribution in this study ranged from 31 to 80 years, with the majority between 51 and 60 years old. The mean ages were 57.18 years for the PRP group and 56.28 years for the Topical Insulin group, with no significant difference (p=0.36). This aligns with other studies, such as Rao et al, where the insulin group had a mean age of 53.94 years and the saline group 55.92 years.[11]

Older adults tend to heal more slowly due to reduced cellular regeneration and comorbidities like diabetes and poor circulation. Understanding the age distribution helps assess the effectiveness of PRP and topical insulin in different age groups. PRP's growth factors may provide added benefits for older patients, enhancing healing where natural processes are slower. In terms of gender distribution, 74% of the PRP group and 60% of the topical insulin group were male, with an overall male representation of 67% (p=0.13). Rao et al reported similar trends, with male dominance in both insulin and saline groups. Men are more prone to diabetic foot ulcers due to occupational hazards and delayed medical attention. Gender differences in wound healing suggest that men may benefit more from PRP's growth factors, which accelerate tissue repair. The findings also highlight the need for gender-specific approaches in wound care research.[12]

The location of ulcers showed no significant differences between groups (p=0.54). In the PRP group, 58% of ulcers were on the right side, while 52% were on the right side in the topical insulin group. The distribution suggests that ulcer site did not impact treatment effectiveness prior research by Li et al.[13] Regardless of the location, PRP supports the overall efficacy in healing. Ulcers on weight-bearing areas might require different management strategies, but the nearly equal distribution in this study indicates that both PRP and topical insulin are practical across various ulcer sites. Ulcer duration differed significantly between groups, with the PRP group averaging 39.10 days compared to 31.82 days in the Topical Insulin group (p=0.001). Longer-standing ulcers are harder to heal, making effective treatments crucial. Li et al found PRP to accelerate healing, particularly in chronic ulcers.[13] PRP's prolonged release of growth factors helps repair long-standing wounds by stimulating tissue regeneration. Shortening healing time is crucial in preventing complications such as infections and amputation. HbA1c levels were significantly different between groups (p=0.02). About 70% of the PRP group had HbA1c levels between 5.5 and 6.5, compared to 54% in the topical insulin group. This suggests that better glycemic control is linked to improved wound healing. Although Rao et al did not focus on HbA1c levels, their study emphasized glycemic control as essential in treating diabetic ulcers. PRP may offer additional benefits for patients with well-managed diabetes, reinforcing the importance of a holistic approach to wound care.[12] Hemoglobin levels showed no significant difference between groups (p=0.73), indicating that oxygen transport capacity did not directly impact treatment outcomes. While prior studies did not extensively analyze hemoglobin levels, adequate oxygenation remains essential for cellular repair. However, the findings suggest that PRP and topical insulin are equally effective regardless of hemoglobin status.

The size of the initial ulcers was the same between groups, mostly larger than 9 cm. At the end of treatment, the PRP group had a mean ulcer size of 11.38 cm^2, compared to 13.80 cm^2 in the Topical Insulin group, with a borderline significance (p=0.09). Li et al found that PRP significantly reduced wound dimensions, likely due to its high concentration of growth factors that enhance tissue repair.[13] A reduction in ulcer size is a key indicator of healing progress, supporting PRP's potential in managing chronic wounds effectively. PRP group (0.71 cm^2) had a significant decrease in ulcer size compared to the topical insulin group (0.45 cm2, p = 0.0006). This aligns with Li et al, who reported that PRP promoted faster healing. Growth factors such as VEGF and PDGF in PRP stimulate angiogenesis and cell proliferation, leading to faster wound closure. This significant reduction in ulcer size is clinically relevant as it lowers the risk of complications and facilitates faster recovery.[14]

Both groups showed increased granulation tissue, but the PRP group had slightly better growth. Ali et al reported similar findings, highlighting PRP's role in enhancing granulation tissue formation, a critical step in wound healing.[15] PRP's long-term stimulation of angiogenesis and fibroblast activity contributes to sustained tissue development, making it a valuable option for chronic wounds. Hospital stay was significantly shorter for the PRP group (21.34 days) than the topical insulin group (30.94 days, p=0.0001). Li et al also found PRP to reduce treatment time. A shorter hospital stay lowers healthcare costs, reduces infection risk, and improves patient quality of life. PRP's ability to accelerate healing contributes to better resource utilization in healthcare settings.[13] PRP group (36%) had a re-intervention rate lower compared to topical insulin group (62%, p=0.009). Fewer additional procedures, such as debridement or amputation, indicate

a more sustained healing response with PRP. This finding aligns with previous research showing PRP's long-term benefits in reducing wound recurrence and complications. Fewer interventions translate to reduced healthcare burden and improved patient outcomes.

Overall, the study findings reinforce PRP's superiority over topical insulin in accelerating wound healing, reducing ulcer size, promoting granulation tissue, and shortening hospital stays. The results are consistent with previous research, supporting the broader application of PRP in clinical wound management.

CONCLUSION

This study provides strong evidence for the efficacy of PRP in diabetic foot ulcer management. PRP significantly outperforms topical insulin in reducing ulcer size, enhancing granulation tissue growth, shortening hospital stays, and minimizing re-interventions. These benefits translate into faster healing, improved patient comfort, and better quality of life. PRP's high concentration of growth factors accelerates wound healing by promoting cell proliferation, angiogenesis, and tissue remodeling. The observed reduction in hospital stays highlights PRP's potential to optimize healthcare resource utilization, reducing complications and costs. Its ability to minimize re-interventions and control infection further establishes PRP as a valuable treatment option. Incorporating PRP into clinical practice can enhance healing outcomes, reduce treatment duration, and improve patient care efficiency.

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