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Original Research Article

A comparative study of efficacy of platelet rich fibrin and conventional saline dressing in chronic non-healing ulcers: A randomized controlled trial in a tertiary care centre, Chengalpattu, Tamil Nadu

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ABSTRACT

Introduction: Non-healing ulcers pose a significant risk for deformities and platelet-rich fibrin (PRF) emerges as a promising treatment modality with feasible, easy, cost-effective day care therapy for chronic non-healing ulcers, exhibiting notable improvement in these chronic conditions.
Aims: This study aims at demonstrating the efficacy of PRF (platelet rich fibrin) dressing in chronic non-healing ulcers.
Materials and Methods: A prospective study with Forty patients of chronic non-healing ulcer aged more than 18 years are recruited, treated with PRF dressing and normal saline dressing. PRF dressing is repeated every week for 4 weeks and for normal saline dressing it is done every alternate days for the same period. Photographs were taken before treatment and at every subsequent session and sizes are measured in baseline (1) and 2,3,4 weeks. Each patient was followed up after four weeks from the last visit.
Result: In this study, excellent improvement was seen in 57% of total ulcers, 15% have showed moderate improvement. PRF dressing have shown significant improvement with >75% improvement in the size of the ulcer in visit 3 where as normal saline have shown only 34% improvement in 3^{rd} visit. Depth of the ulcer improved to 100% and 35% in visit 3 for PRF and normal saline dressing respectively.
Conclusion: This study have found that PRF dressing has shown significant reduction in the overall size of the ulcer and quality of life with minimal visits and without any adverse events.

1. Introduction

An ulcer is characterized by the loss of tissue integrity in the skin or mucous membrane, resulting from cell death. If the ulcer persists without improvement after appropriate treatment for over three months, it is termed a non-healing ulcer.[1,2]

The normal wound healing process involves inflammation, tissue formation, and tissue remodeling. Disruption of this process can lead to the development of chronic wounds.[3] Platelets, plays a key role in wound healing. Platelet-rich fibrin (PRF), a second-generation platelet concentrate, is an autologous blood preparation.[4] PRF forms a fibrin matrix trapping cytokines (leukocytes) and growth factors (platelets), normalizing metabolic processes, promoting neo-angiogenesis, and activating local immunity.[4]

Non-healing ulcers, associated with high morbidity and requiring expensive and prolonged treatment, can result from various causes like venous ulcers, traumatic, tropic ulcers etc. PRF, an easily prepared and safe platelet concentrate, has shown effectiveness in certain specific

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etiologies of non-healing ulcers.[4–9]

2. Materials and Methods

Forty-two patients with chronic non-healing ulcer aged more than 18 years who gave written informed consent are recruited from the dermatology department in our institute from June 2023 - October 2023.This study was approved by Institutional Ethical Committee ref: KIMS/PG/2022/43 and registered in Clinical Trial Registry - India CTRI/2023/06/054409.

2.1. Inclusion criteria

1. Patients with trophic ulcers due to Hansen disease or diabetes mellitus.
2. Patients with stasis dermatitis.
3. Venous ulcer.
4. Traumatic ulcer.
5. Age group > 18 years.

2.2. Exclusion criteria

1. Patients with a history of bleeding disorders.
2. Anemia and other hematological disorders.
3. Platelet count <1 5 lakhs/cu mm.
4. Patients on anticoagulant medications (aspirin, warfarin, heparin.
5. Patients with malignant ulcers, pregnant and lactating females.

Subjects in the study were assigned randomly to either of two groups A and B using a computer generated randomization chart, each group consist of 21 patients with chronic non-healing ulcer. For each of the patients, details collected are as follows: demographic profile, detailed evaluation of ulcer, co-morbid conditions and laboratory parameter like serology for HIV, HBSAG, hemoglobin, platelet count, bleeding time and clotting time. Ulcer area in cm (length, breadth and depth) were measured accordingly at the maximum area of each dimension at baseline and end of each week/visit for 4 weeks (1(baseline), 2, 3, 4) using a toothpick. Last measurement was done after 4 weeks of the treatment. Photographs were taken at each visit.

Improvement was assessed by area - calculation by the formula at baseline and at each visit

Area of the ulcer L*B (%) =Area of the ulcer at baseline – Area of the ulcer at the end /Area of the ulcer at baseline * 100= %

Improvement was measured and classified as following

1. <25%- mild improvement
2. 25-50%- moderate improvement
3. 50-75%- good improvement
4. >75%- excellent improvement

Treatment protocol:

RCT
N = 40

Group A (PRF dressing) N=20 | Group B (Saline dressing) N=20

2.2.1. PRF preparation

About 10 to 15 ml of patient's blood was collected in sterile conical plastic test tubes without any anticoagulant and tubes were centrifuged with 2800rpm for 15 minutes.After centrifugation, three layers were formed with lower part containing red blood cells and the upper part with plasma and the middle part of fibrin clot. The clot was separated placed inside the ulcer and dressing was done.

2.2.2. Group A (PRF dressing)

PRF dressing was applied over the wound surface as a thin layer and covered with a saline gauze (primary dressing) followed by cotton pad and roller bandage (secondary dressing). The dressing was left in place for a week.

2.2.3. Group B (saline dressing)

Patients wound/ ulcer was cleaned and dressing was done with normal saline gauze followed by cotton pad and roller bandage. A total of 14 sessions at alternate days were given for a total duration of 4 weeks. Ulcer size and depth were measured at the baseline and at 2, 3, 4^{th} weeks and followed up after 4 weeks.

Data was tabulated in excel and analyzed by SPSS 20. The descriptive statistics of the age, and gender, Comparisons of both groups are analyzed by chi-square test

3. Results

Total 48 patients were diagnosed to have non-healing ulcer were screened for the study. Out of 48 patients, 42 were included in the study and the rest 6 patients were excluded, as they were not meeting the eligibility criteria while others were randomized into two groups (Figure 1).

Out of 42 patients, 37 were males and 5 were females with minimum age of 35 to maximum age of 72 years. Two dropouts in the study. The duration of ulcer in the study, 60% (n=24) had ulcers more than 6 months whereas 40% (n=16) had less than 6 months duration.

In this study, the site of ulcer was taken as above and below ankle - below ankle ulcers were 27(67.5%) and above ankle ulcers were 13 (32.5%). By occupation, in our study we had 25% of semiprofessional followed by 20 % clerk/farm/shop.

Associated co-morbidity includes 22.5% had diabetes and 15% had diabetes with hypertension, and 40% without any co- morbidity.

Stasis ulcer was implicated as a causative in 30% cases whereas other causes contribute to 70%.

Figure 1: A: Centrifuge; **B** & **D:** Sample after centrifuge; **C:** Blood sample; **E:** PRF; **F:** Fibrin kept inside the wound.

There is no significant variation in both the groups in terms of age (Table 3), sex (Table 1), site of lesion(Table 5), duration of ulcer (Table 2) and co morbidity. (Table 1)

Ulcer size are measured using length x breadth in which the largest ulcer 63.35 cm^2 in terms of area and depth in PRF group (A) whereas in normal saline Group (B)it was 26.25 cm^2.

The smallest size of ulcer in Group A and B were 3.5 cm and 0.96 cm respectively. Depth of ulcer in PRF group varies from 0.3cm to 5.2 cm and in saline group it was 0.3 to 1.5cm.

In the baseline, the PRF dressing group had a significantly higher median size of ulcer, 12.73 cm, than the normal saline dressing group, which was 7.13cm. Even though in the 1^{st} visit the higher median size of the ulcer was seen in the PRF dressing group, due to the treatment effect, subsequently during the follow-up, it significantly reduced to 7.84, 3.86, 0.9, and 0.0 cm from 12.73 cm. While coming to the Normal Saline group, the size of reduction in each subsequent visit was 6.3, 5.36, 4.45, and 2.87 cm from 7.13 cm. The mean size reduction of ulcers in Group A with respect to baseline was 5.022 cm^2 after one week of treatment, and it was 13.38 cm^2 after 4^{th} sitting, which completely healed in 8 weeks. When compared with mean size of reduction of ulcers in Group B from baseline, 0.75cm^2 after one week of treatment and 2.60cm^2in four weeks but not healed in 8 weeks.(Figure 2)

In the baseline, the PRF dressing group had a median depth of ulcer of 0.9 cm and the normal saline dressing had 1.050cm. Median depth of the ulcer in PRF dressing group significantly reduced to 0.35, 0.0 cm from 0.9 cm, reduced completely within visit 3. Normal Saline group, the depth reduction in each subsequent visit was 0.90, 0.70, 0.5, and 0.15 cm from 1.05 cm, size of reduction is nearly 0.25cm in each subsequent visit but not comparable with PRF group. The mean depth reduction of ulcer in group A with respect to baseline was 0.6100cm after one week of treatment, it was 1.08cm in four weeks.when compared with the mean depth of reduction of ulcers in Group B from baseline,this showed 0.2 cm after one week of treatment,0.54cm in four weeks. The mean depth of reduction in Group A was more statistically significant at visit 3 when compared with Group B (Figure 3)

In Group A out of 20 ulcers, 6 ulcers completely healed within 3 weeks, 5 ulcers in 8 weeks whereas remaining 9 ulcers, 6 showed >90 % and 3 showed >50 % improvement at the end of 8weeks.

In Group B, 5 ulcers completely healed in eight weeks, only 2 ulcers showed >80% improvement while others showed 4 (<40%), 5 (>40%), 4 (>60%). Comparing the healing process Group A had shown significant results than Group B.

With the improvement scale 17 out of 20 ulcers in Group A have shown excellent (>75%)improvement and 3 ulcers have shown good improvements (>50%) whereas normal saline dressing only 7 out of 20 ulcers shown excellent improvement, remaining ulcers have only mild to moderate improvement.(Table 6)

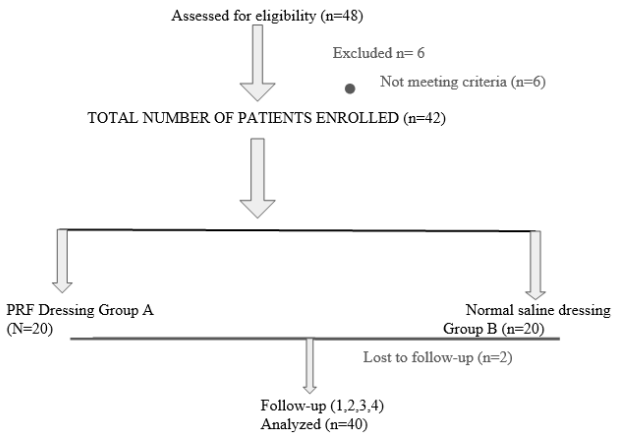


Chart 1: Patients are randomized into two groups

4. Discussion

Wound healing is a dynamic process involving three interconnected phases: inflammation to control damage, proliferation to rebuild the tissues and maturation to strengthen and remodel the healed tissue. Each phase plays a crucial role in the overall recovery process. [10]

Table 1: No significant variation in both the groups in terms of sex

Sex	PRF Dressing (n=20)		Normal Saline Dressing (n=20)		Total (n=40)		P value
	n	%	n	%	n	%	
F	3	15.0%	0	0.0%	3	7.5%	0.231
M	17	85.0%	20	100.0%	37	92.5%	

Table 2: Duration of ulcer in both groups

Duration	PRF Dressing (n=20)		Normal Saline Dressing (n=20)		Total (n=40)		P value
	n	%	n	%	n	%	
<6months	8	40.0%	8	40.0%	16	40.0%	1.0
>6months	12	60.0%	12	60.0%	24	60.0%	

Table 3: No significant variation in both the groups in terms of age

Variables	Group	N	Mean	STD. Deviation	P value
Age	Prf dressing	20	57.45	8.101	0.564
	Normal saline dressing	20	58.85	7.058	

Table 4: Comparing the co-morbidity associated in both groups

CO Morbidity	PRF Dressing (N=20)		Normal Saline Dressing (N=20)		Total (N=40)		P value
	N	%	N	%	N	%	
CAD	1	5.0%	1	5.0%	2	5.0%	0.527
DM	4	20.0%	5	25.0%	9	22.5%	
HTN	1	5.0%	1	5.0%	2	5.0%	
DM/CAD	1	5.0%	0	0.0%	1	2.5%	
DM/HANSEN'S	1	5.0%	0	0.0%	1	2.5%	
DM/HTN	2	10.0%	6	30.0%	8	20.0%	
DM/HTN/CAD	0	0.0%	1	5.0%	1	2.5%	
NIL	10	50.0%	6	30.0%	16	40.0%	

Table 5: Level of the ulcer is compared in both groups

Site	PRF Dressing (n=20)		Normal Saline Dressing (n=20)		Total (n=40)		P value
	n	%	n	%	n	%	
Above ankle	8	40.0%	5	25.0%	13	32.5%	0.501
Below ankle	12	60.0%	15	75.0%	27	67.5%	

Table 6: Improvement scale in PRF and Normal saline dressing

Improvement noted	In PRF	percentage of patients	In normal saline	Percentage of patients
Excellent	17	85%	7	35%
Good	3	15%	6	30%
Moderate	0	-	7	35%
Mild	0	-	0	-

Platelet rich fibrin (PRF) - a second generation concentrate, consists of fibrin plug. The cytokines identified in platelets are transforming growth factor-β (TGF-β), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I & II), fibroblast growth factor (FGF), epidermal growth factor, vascular endothelial growth factor (VEGF) and endothelial cell growth factor. These cytokines play important role in cell proliferation, chemotaxis, cell differentiation and angiogenesis. The histamine and serotonin released by the platelets increase capillary permeability, which in turn gives the inflammatory leukocytes and macrophages, an improved access to the wound site resulting in macrophage activation.[11]

PRF has shown promising result as a cost-effective method for ulcer treatment, leveraging the regenerative properties of platelets. Research in this area continues to

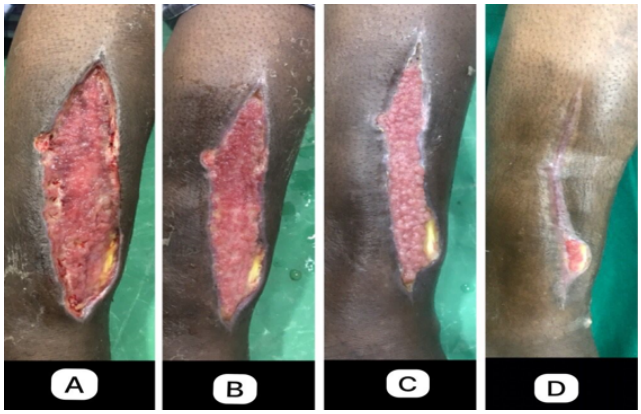


Figure 2: Patient 1 -shows significant improvements and decrease in the dimension of the ulcer

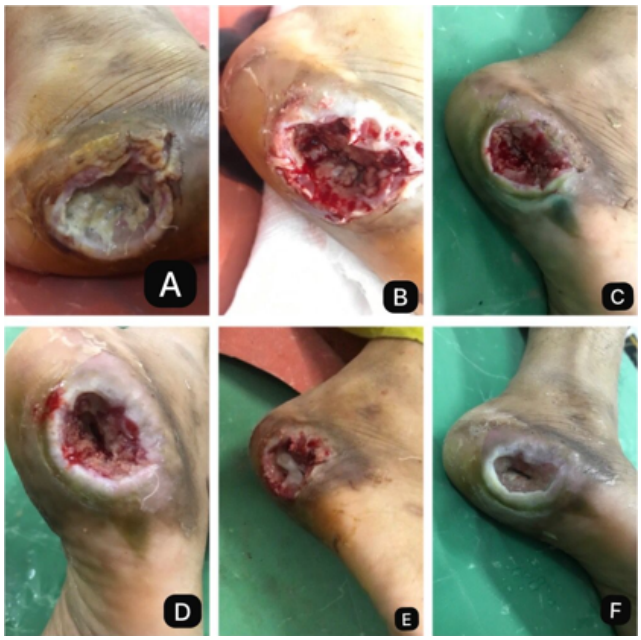


Figure 3: Patient 2 **A):** Ulcer before treatment **F**): Ulcer after 4weeks of treatment with prf

explore its efficacy and practical applications.[12] It was first developed in France by Choukroun et al.[13] Since then PRF has been used for non-healing ulcers of various etiologies.[11,14]

Dohan Ehrenfest et al.[15] compared PRP and PRF in ulcer management and significant differences were observed in the in vitro biological behavior of the two products. PRF has shown to be superior to PRP in non-healing ulcers. In vitro studies have indeed demonstrated that Platelet-Rich Fibrin (PRF) can release a variety of growth factors from its fibrin matrix for an extended period, up to at least 7 days. These growth factors contribute to the stimulation of cellular activities crucial for tissue repair and regeneration.[15–22]

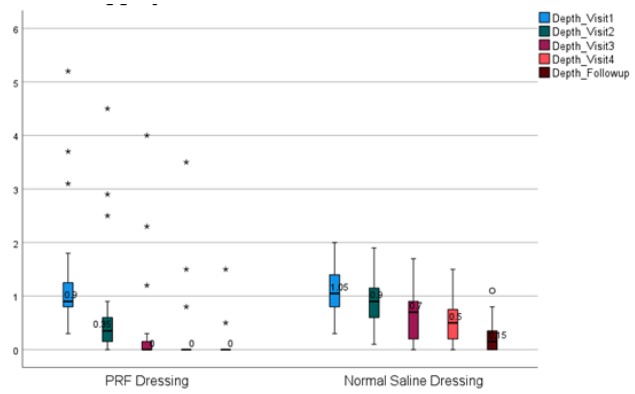
Figure 4: Patient 3 with one session of prf treatment

Figure 5: Patient 4 before and after treatment with prf at 2 session

In the study conducted by Nagaraju et al,[23] Autologous PRF Matrix in non-healing trophic ulcers in patients with Hansen's disease showed 93.52% and 97.74% improvement in respect to area and volume.

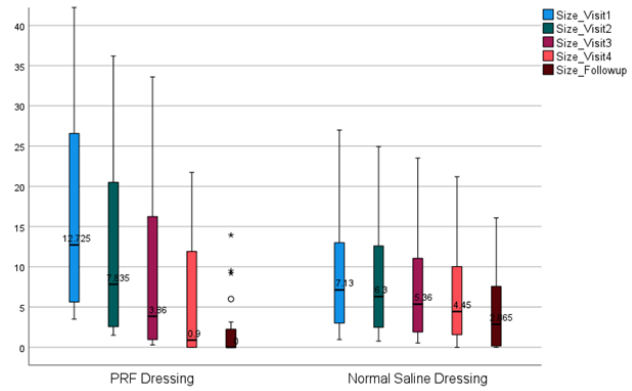
Similarly, Varma et al.[24] used Autologous PRF which showed average percentage improvement of area and volume by 97.12% and 98.72% respectively.

We have compared the results of our study with other studies in the table. From these studies it is found that PRF is found to be an effective modality when compared with



Graph 2: The below box and whisker graph are showing the summarizing of the data for the PRF and Normal saline Dressing groups.

Figure 6: Patient 5 before and after treatment with prf in one session



Graph 1: The below box and whisker graph are showing the summarizing of the data for the PRF and Normal saline Dressing groups.

Unna's paste, normal saline and PRP.

The mean reduction in size of ulcer varies from 73.3% to 86.03% in other studies whereas it is 92.15% in our study. Ulcer depth reduction was not compared in other studies, in our study, the depth reduction was found to be 97.1% with PRF treatment.

In our study, in the normal saline group the mean reduction in the size of ulcer was 65% and the depth of ulcer was 70% from the baseline. Whereas in the PRF group, the mean reduction in size of ulcer was 92.15% and depth of ulcer reduced by 97.1% from the baseline. With the improvement scale, 17 out of 20 ulcers in PRF group have shown excellent (>75%)improvement and 3 ulcers have shown good improvement(>50%) whereas in normal saline dressing only 7 out of 20 ulcers have shown excellent improvement, remaining ulcers have only mild to moderate improvement.

To conclude, the mean percentage of wound reduction was higher in the PRF group (92.3%) than the saline group (65%), which was statistically significant.(P <0.0001).

5. Conclusions

PRF treatment resulted in a notable decrease in the size of non-healing ulcers compared to those treated with standard normal saline dressing. This is attributed to the release of various growth factors and cytokines by PRF, promoting and expediting the wound healing process.

Platelet-rich fibrin is emerging as a promising therapy for treatment of chronic non-healing ulcers, which is showing better clinical efficacy, cost effective, easily available, less time consuming and without any adverse effects.

6. Limitations

Limitation of our study was its small sample size. Inclusion of large sample size, will give us a better validation of results.

7. Source of Funding

None.

8. Conflict of Interest

None.

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