# **Original Research Article**

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# Efficacy of autologous platelet rich fibrin matrix in the management of non-healing ulcers

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### **ABSTRACT**

**Background:** Non healing ulcers have a worldwide prevalence of 1.9%-13.1% with lower extremity being the commonest site. They are difficult to manage for the physician and frustrating for the patient due longer duration of treatment, cost, unsatisfactory outcomes and impairment caused due to them. Standard conventional management may fail at times and hence growth factors derived from platelets have been tried in the management of these ulcers. The purpose of our study was to evaluate the efficacy of platelet rich fibrin matrix (PRFM) in treatment of these ulcers. **Methods:** Twelve patients with fifteen non-healing ulcers more than 3 months duration were included in the study. 10cc of venous blood was withdrawn in plain tube without anti-coagulants and centrifuged at 1500 rpm for 14 minutes as early as possible as per advanced PRF protocol. Middle layer of PRFM was applied to the clean ulcer followed by a secondary dressing. All patients received PRFM sittings every 7-10 days or till ulcer healed. Baseline photographs and measurements of length, breadth and depth were taken to calculate the area of ulcer at every sitting. **Results:** The average percentage reduction in area and volume of the ulcer was 95.84% and 98.18% respectively at the end of six sittings. Twelve out of fifteen ulcers showed complete healing by 6 weeks, while three ulcers showed significant improvement but did not heal completely. The procedure was safe, well tolerated without any side effects. **Conclusions:** Platelet rich fibrin matrix is a novel modality and an ideal, safe, affordable therapeutic option for nonhealing wounds of varied causes.

Keywords: Non healing ulcers, Platelet rich plasma, Platelet rich fibrin matrix, Growth factors

#### INTRODUCTION

Chronic non-healing ulcers are defined as lesions which fail to heal in a defined period of time or persist despite of standard conventional treatment. These wounds have a worldwide prevalence of 1.9-13.1%. These ulcers not only impair the quality of life and productivity of the person, but also increase the cost burden on health system.<sup>3</sup>

Lower limb is a common site for these ulcers, the majority of causes being venous, arterial, neuropathic,

vasculopathic and traumatic. The treatment of these ulcers depends upon the etiology of ulcers, but lack of growth factors in these ulcers is one of the major causes for delayed healing. Measures to hasten healing of these wounds will not only improve the quality of life of these patients, but also decrease the long-term cost involved in treatment.

Recently platelets, which are one of the blood components, have been shown to produce growth factors with varied applications in the medical field. Platelet rich plasma (PRP) and platelet rich fibrin matrix (PRFM) are

such newer modalities to hasten wound healing. Fibrin matrix in PRFM acts as a drug delivery system for sustained release of growth factors making it more superior than PRP for treatment of non-healing ulcers.

The objective of our study is to evaluate the efficacy of platelet rich fibrin matrix in the treatment of non-healing ulcers, to compare the percentage reduction in area and volume following treatment with platelet rich fibrin matrix and to study the time required for ulcer healing.

#### **METHODS**

A prospective non-randomized uncontrolled interventional study was conducted in dermatology department of Seth G S Medical College and KEM Hospital. The study duration was 1 year from December 2017 to January 2019 during which 12 patients with 15 non healing ulcers were included in the study. PRFM was applied to non-infected ulcers every weekly till ulcer healed or maximum 6 sittings.

#### Inclusion criteria

Inclusion criteria were patients with non-healing ulcers which have failed to respond to conventional therapies for at least 12 weeks; patients above the age group of 18

years; patients willing to participate in the study and have given written informed consent.

#### Exclusion criteria

Exclusion criteria were patients not willing to give written informed consent for participation in the study; active infection or malignant ulcers; uncontrolled diabetes; history of bleeding disorder or thrombocytopenia; patients on anti-coagulants or anti platelet agents; pregnant and lactating females.

#### Procedure

#### Preparation of PRFM

With strict aseptic precautions, 10 cc of venous blood was withdrawn in plain tube without anti-coagulants and centrifuged at 1500 rpm for 14 minutes as early as possible as per advanced PRF protocol. In the absence of anti-coagulants, platelet activation starts immediately after blood comes in contact with glass tubes. Centrifugation concentrates fibrinogen in the upper part of the tube between serum and red blood cell (RBC) layer. Fibrinogen gets converted to fibrin by the action of thrombin and platelets and growth factors are entrapped within the fibrin matrix.<sup>4</sup>

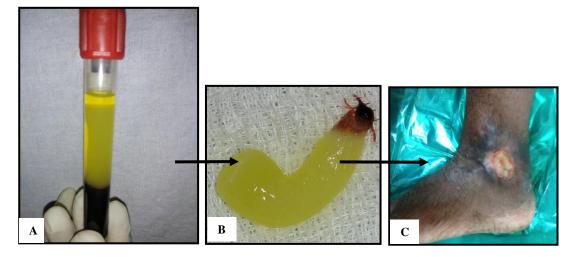


Figure 1: (A) Three layers after centrifugation, (B and C) middle layer of PRFM.

Three layers were obtained after centrifugation (Figure 1A). Upper straw colored (platelet poor plasma)- which was discarded. Middle PRFM layer (Figure 1B)-separated and placed on the ulcer (Figure 1C). Lowest layer (RBC clot) - which was discarded.

Pus cultures were sent from all ulcers to rule out any infection and only clean ulcers were treated with PRFM. The middle layer of PRFM was separated with the help of forceps along with 1 mm of RBC layer and immediately placed on clean ulcer. Blotting of middle PRFM layer showed decrease in growth factors and hence it was avoided.<sup>4</sup>

It was covered with secondary dressing which was changed every 7-10 days. The procedure was repeated every weekly for 6 weeks or till ulcer heals whichever is earlier. The standard conventional management of ulcer was continued along with sittings of PRFM according to the etiology.

#### Measurements

All the ulcers were clinically examined at each visit with the help of sterile polydrape, marker pen and measuring scale. Area (cm<sup>2</sup>) and volume (cm<sup>3</sup>) were measured from readings. Serial photographs of ulcers were taken at baseline and each sitting post PRFM.

The data was collected and statistical analysis was done using SPSS software to calculate percentage reduction in the area and volume of ulcers.

#### **RESULTS**

A total of 13 patients with 15 ulcers were included in the study. The age of patients ranged from 13 years to 62 years with mean age being 46.06 years. There were 10 males and 5 females with male preponderance (66.67%) noted in our study.

The etiology of ulcers included were trophic ulcers (26.67%), venous ulcers (40%) and post infective or

traumatic (33.33%). Sites of trophic ulcers included sole of feet, for venous ulcers were lower third of legs with medial malleoli while post infective ulcers were seen on the upper aspect of the leg and lower thigh.

The average duration of ulcers ranged from 3 months to 2 years. The average duration of trophic ulcer was 8.58 months, venous ulcer was 6.86 months and that of post-infective ulcer was 6.83 months.

Table 1 shows the average reduction in area at the end of 2<sup>nd</sup>, 4<sup>th</sup> and 6<sup>th</sup> sitting which was 48.13%, 79.21% and 95.84% respectively.

The average reduction in volume of ulcers at the end of  $2^{\text{nd}}$ ,  $4^{\text{th}}$  and  $6^{\text{th}}$  sitting was 59.30%, 89.55% and 98.18% respectively as seen in Table 2.

Table 1: Percentage reduction in the area of ulcer after PRFM sittings.

S. no.	Etiology of ulcer	Post 2nd PRFM (%)	Post 4th PRFM (%)	Post 6th PRFM (%)
1	Trophic ulcer	93.75	100.00	100.00
2	Venous	4.26	93.92	100.00
3	Traumatic	56.52	100.00	100.00
4	Venous	60.95	100.00	100.00
5	Venous	36.53	82.97	100.00
6	Venous	33.61	81.97	100.00
7	Post infective	53.30	100.00	100.00
8	Post infective	57.53	86.61	100.00
9	Traumatic	86.36	100.00	100.00
10	Trophic	28.57	58.44	79.00
11	Trophic	33.33	58.33	70.50
12	Trophic	18.92	67.57	88.11
13	Venous	56.46	75.00	100.00
14	Post infective	76.84	100.00	100.00
15	Venous	25.05	83.35	100.00

Table 2: Percentage reduction in the volume of the ulcer after PRFM sittings.

S. no.	Etiology of ulcer	Post 2nd PRFM (%)	Post 4th PRFM (%)	Post 6th PRFM (%)
1	Trophic	68.75	100.00	100.00
2	Venous	4.26	93.92	100.00
3	Traumatic	86.82	100.00	100.00
4	Venous	90.48	100.00	100.00
5	Venous	22.60	91.49	100.00
6	Venous	47.54	78.69	100.00
7	Post infective	76.65	100.00	100.00
8	Post infective	57.91	86.61	100.00
9	Traumatic	93.18	100.00	100.00
10	Trophic	64.29	94.81	96.25
11	Trophic	77.78	77.50	90.00
12	Trophic	59.46	67.57	86.49
13	Venous	12.92	58.33	100.00
14	Post infective	76.84	100.00	100.00
15	Venous	50.04	94.45	100.00



Figure 2: (A) Traumatic ulcer- baseline; (B) traumatic ulcer-post 4th PRFM.

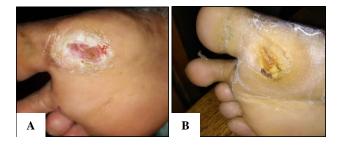


Figure 3: (A) Trophic ulcer-baseline; (B) trophic ulcer-post 3rd sitting.



Figure 4: (A) Venous ulcer-baseline; (B) venous ulcerpost 6th PRFM.

There was complete healing of six ulcers by the end of fourth sitting of PRFM, while 6 more ulcers healed completely by of six weeks. None of the ulcers had healed completely after 2 sittings of PRFM. Post infective or traumatic ulcers showed the best response followed by venous ulcers and trophic ulcers. Three trophic ulcers failed to heal completely at the end of 6 sittings though they showed significant improvement.

#### **DISCUSSION**

Non-healing ulcers pose a major therapeutic challenge to the treating physician. Standard conventional therapies may fail to accelerate healing in many cases. Topical platelet derived growth factors are FDA approved for wound healing, but their cost makes it unaffordable for use in developing countries.<sup>5</sup>

Platelets are known to have a significant role in thrombus formation and hemostasis. But recently various studies have shown that these cells release cytokines, growth factors which promote wound healing and repair of damaged tissue. <sup>6,7</sup>

Both platelet rich plasma (PRP) and platelet rich fibrin matrix (PRFM) are new generation platelet concentrates which accelerate wound healing through the release of growth factors like platelet derived growth factors, transforming growth factor, vascular endothelial growth factor, epidermal growth factor, insulin like growth factor, interleukin-1, fibrinogen, fibronectin etc.

Choukroun et al first used PRFM in oral and maxillofacial surgery to improve bone healing. Since then PRFM has been widely used with few modifications in the preparation protocol and also there have been few comparative studies between PRP and PRFM.

Various protocols for PRF have been tried with modifications in centrifugation time and rate per minute (rpm) in order to get the best yield of PRF.

- 1) Choukroun's standard PRFM- 2700 rpm for 12 min.
- 2) Advanced PRFM (A-PRF)- 1500 rpm for 14 min.

When the time of centrifugation was increased and rpm were decreased, more number of neutrophilic granulocytes was seen in the distal part of the clot near PRFM, while in standard PRF they were concentrated more proximally near RBC layer. These cells not only add to the amount of growth factors released but also promote differentiation of monocytes to macrophages resulting in improved tissue regeneration. Studies have shown that the clot forms with A-PRF is loose, more cellular and with even distribution of cells.

PRP releases significantly higher amount of growth factors at earlier point of time as compared to PRFM. Comparative studies have revealed that PRP is better suited for faster release of growth factors while PRFM is superior for wound healing. <sup>10</sup> This is due to the fact that PRFM has about 3 times higher concentration of growth factors and these are released in a slow and sustained manner over a week. <sup>10-12</sup> Hence we repeated the sittings of PRFM every 7-10 days in our study.

Alsoa modified protocol for PRF which is A-PRF released total higher quantity of growth factors up to 10 days as compared to traditional PRF. 10

The mean age of patients in our study was 46.06 years as compared to 38.33 years in the study by Nagaraju et al. 13

The average duration of ulcers was 3 months to 2 years in our study which was similar to 2 months to 1 year in another study.<sup>13</sup>

The average percentage reduction in area and volume of ulcers after two sittings of PRFM was 48.13% and 59.30% which was lesser than 94.52% and 97.74% in the

study by Nagaraju et al.<sup>13</sup> This may be due to varied etiologies of ulcers and longer duration of some ulcers included in the study.

The mean percentage reduction in area and volume of ulcer was 94.7% and 95.6% at the end of 6 sittings in a study by Sarvajnamurthy et al and 95.84% and 98.18% respectively in our study which was comparable.<sup>14</sup>

In a study by Nagaraju et al and Sarvajnamurthy et al, all the ulcers healed by 5 weeks, while in our study 12 out of 15 ulcers healed at the end of 6 weeks. <sup>13,14</sup>

## Limitations

The limitations of our study were small sample size and uncontrolled study. Also, we suggest more studies with larger sample size are required to confirm our results.

#### **CONCLUSION**

The procedure is simple, cheap, safe day care using autologous blood without anticoagulants. <sup>15,16</sup> It can be done single handedly, without any downtime, without much training and assistance and no downtime required for the patient. Also, it can be practiced in small to large scale clinics with minimum equipment's even by beginners. All these advantages make it an ideal and affordable option for chronic non- healing wounds of varied causes.

A word of caution needs to be mentioned that though faster healing can be achieved, it does not address to the cause of ulcer and hence recurrences cannot be prevented. Measures to prevent recurrences should be continued along with treatment of causative factors.

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