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Clinico-Etiological Study of Efficacy of Autologous Platelet Rich Fibrin in Chronic Non Healing Ulcers.

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Abstract:
Background: *Chronic ulcers,often disguised as a comorbid condition, are presenting as a silent epidemic affecting a large fraction of the world population and posing as a major and gathering threat to the public health and economy. Autologous Platelet-rich fibrin (PRF) is one of the cost effective, easy, newer modalities for chronic ulcers and it contains fibroblast growth factor (FGF), vascular endothelial GF, angiopoietin and platelet-derived GF which enhances the wound healing.*
Aim: *The aims of the present study are to determine the efficacy of autologous platelet-rich fibrin for non-healing ulcers and to compare the rate of healing of different ulcers based on aetiology, taking care of the primary disease.*
Methods: *A nonrandomized, uncontrolled study was performed on 30 patients with 30 non-healing ulcers of various aetiologies with healthy granulation tissue. Uncontrolled diabetics, seropositive individuals were excluded. All patients were treated with PRF at weekly intervals for a maximum of 6 treatments. Area and volume were calculated and photographs were taken. Final assessment of reduction in the size of the ulcer was determined in percentage .*
Results*: The mean age of the patients observed was 43.3 years. Mean duration of healing observed was 4.5 weeks. The total Mean percentage improvement in the area and volume observed was 95.8%,100% respectively by 6thsitting. No significant statistical correlation is observed between the age of the patient, sex of the patient and site of the ulcer and aetiology of ulcer with the rate of healing of healing of the ulcer. All ulcers closed by a maximum of six sittings. No adverse events were noted*
Conclusion: *In comparison to conventional dressings, autologous platelet rich fibrin provides necessary growth factors for wound healing and it is a safe, affordable, biocompatible, and simple procedure for the treatment of chronic non-healing ulcers*
Keywords-*chronic ulcer, platelet rich fibrin, platelet rich plasma*

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I. Introduction

Chronic ulcers[1]are those that do not progress through the healing process in a timely manner to produce anatomical and functional integrity of the injured site. Often disguised as a comorbid condition, chronic wounds are presenting as a silent epidemic affecting a large fraction of the world population and posing as a major and gathering threat to the public health and economy. Chronic ulcers occur in many with vascular disease or diabetes and are attributed to chronic venous insufficiency, arterial disease, prolonged pressure, or neuropathy.

Common features shared by each of these wounds include prolonged or excessive inflammation, persistent infections, the formation of drug-resistant microbial biofilms, and the inability of dermal and/or epidermal cells to respond to reparative stimuli. In aggregate, these pathophysiologic phenomena result in the failure of these wounds to heal. The underlying pathologies, however, differ among various types of chronic wounds.

Overcoming the factors that contribute to delayed healing is a part of the comprehensive approach to wound care and presents the primary challenges to the treatment of chronic wounds.

In the developed countries, it has been estimated that 1-2% of the population will experience a chronic wound during their lifetime.[2] An Indian study by Shukla et al[3]estimated the prevalence as 4.5 per 1000

population. It is estimated that 10% of the population would develop a chronic wound in the course of time with a wound-related mortality rate of 2.5%.[4]

Chronic wounds are defined as wounds that fail to proceed through the normal phases of wound healing in an orderly and timely manner[1]. Often, chronic wounds stall in the inflammation phase of healing. They lack the necessary growth factors (GF"s) and hence do not heal well. Conventional therapies for non-healing ulcers basically includes wound cleansing, tissue debridement, prevention, and treatment of infection, mechanical off-loading, adjustment of blood glucose levels and local care with dressing application may not always be effective and requires strict medical care

Platelets play a crucial role not only in haemostasis[5]but also in the wound healing process. Platelets release a variety of cytokines and growth factors[6],which control and enhance the migration, proliferation, and functions of keratinocytes, fibroblasts, and endothelial cells

Under these conditions, the application of platelet- rich-derived therapies gives ground for optimism. Platelet Rich Fibrin (PRF) is being used in reconstructive, cosmetic, orthopaedic, cardiovascular, oral maxillofacial and dermatologic surgery in an attempt to improve tissue healing.[7]

In comparison to conventional dressings, autologous platelet rich fibrin provides necessary growth factors for wound healing and it is a safe, affordable, biocompatible, and simple procedure for the treatment of chronic non-healing ulcers. Hence, the present study aims to determine the efficacy and to compare the rate of healing of different ulcers based on aetiology taking care of the primary disease.

II. Materials and Methods

This was a nonrandomized, uncontrolled study conducted from December 2016 to October 2018 at a tertiary hospital in Kurnool medical college. Ethical clearance was obtained before beginning of the study from Ethical Clearance Committee. A total of 30 patients with 30 nonhealing ulcers of various aetiologies were included in this study. Inclusion criteria were ulcers of more than 6 weeks duration. Patients with a bleeding disorder, uncontrolled sugar levels and ulcers with active infection were excluded.

A detailed history was elicited with reference to onset, duration, type of lesion, predisposing factors, genetic, occupational and systemic factors if any. Disease history - age of onset of ulcer and progression, Treatment history, Past medical and surgical history was noted. A thorough local and systemic examination was carried out. Patients were thoroughly examined, and ulcer size (length, breadth, and width) was measured by the "clock-face" method described by Sussman et al[8]using a cotton tip applicator and paper ruler.

After obtaining consent, under aseptic precautions 10 ml of the patient's own blood was drawn into the vacutainer without any anticoagulant and immediately centrifuged (centrifuge machine used is table centrifuge and no- REMI R C 8) at 2700 rotations per minute for 12 min. After 12 min, a fibrin gel appears in the centre of the vacutainer, in between the red blood cells (RBCs) which are settled at the base and acellular plasma above.

Three layers were obtained. Upperstraw-colouredplateletpoorplasma(PPP), a red-coloured lower fraction containing red blood cells (RBCs) , andthemiddlefractioncontainingthePRFM.

The upper straw-coloured layer (PPP) was discarded. PRFM was separated from red corpuscles at the base using a sterile forceps and scissors, preserving a small RBC layer measuring around two mm in length, which was transferred onto a sterile gauze. The membrane does not tear when manipulated with forceps and scissors. However, excess force should not be applied. Middle membrane so obtained was compressed between two gauze pieces gently and applied on a healthy wound. On an average 10 ml of whole blood yields about 2.5 ml of the clot

Dressings and follow-up: A secondary non-absorbable dressing was secured directly over the PRFM with gauze wrap. The primary dressing was left in place for 7 days and was changed only by site personnel at weekly intervals. Care was taken not to disturb the wound bed (including the PRFM) unless there was concern about possible infection Adequate rest was ensured during the treatment course

The procedure was repeated every week up to a maximum of six sittings as per requirement. At the beginning and every week, healing of the ulcer was assessed, area and volume were calculated and photographs were taken. Follow-up visits were also scheduled at 4 weeks after closure. Wound area was calculated using the formula for an ellipse: Length × width × 0.7854 (an ellipse is close to a wound shape than a square or rectangle). The use of an ellipse for calculating wound measurement has been used in randomized controlled trials in wound healing literature[9-11]. Volume was calculated using the formula (length × width × 0.7854) × depth[10-11]. Statistical analysis was performed using simple statistical methods using the statistical programme for social sciences 19 (SPSS, Inc, Chicago, Illinois).

III. Results

In this study, Out of 30 patients included in the study, majority of patients are in between 41- 50 years (36.66%). The mean age of the patients observed was 43.3 years. Out of 30 patients, majority of patients were males (63.3%) compared to females (11/36.6%)(Chart1). Majority of ulcers are due to Hansen'sdisease (16/53.3%) followed by diabetic ulcers (6/20%), venous (4/13.3%), traumatic (3/10%)(Chart 2). Majority of patients in the study had ulcer duration of 3-6 months (93.3%). The baseline line mean area and volume is 345.88(cm^2),527.76 cm^3. The declining trend in the reduction of sum of the area and volume of the ulcers is shown (chart 3 and 4).The total mean percentage improvement in the area observed was 95.8% by 6^{th}sitting and mean percentage improvement in volume observed was 100% by 6^{th}sitting (Chart 5 and 6).

Out of 30 patients, 95.3%achieved complete healing by the 6^{th}week. There was no significant statistical correlation observed between the age of the patient (P=0.46), sex of the patient (0.46) and site of the ulcer (P=0.40) with the rate of healing of the ulcer. The aetiology of the ulcer (P=0.749) has not shown any significant statistical difference in the process of healing of the ulcer. We had not encountered any complications during the period of study, and there were no recurrences till today. The before and after PRF therapy photographs are shown (figures1-4)

chart1: Age and sex wise distribution of cases

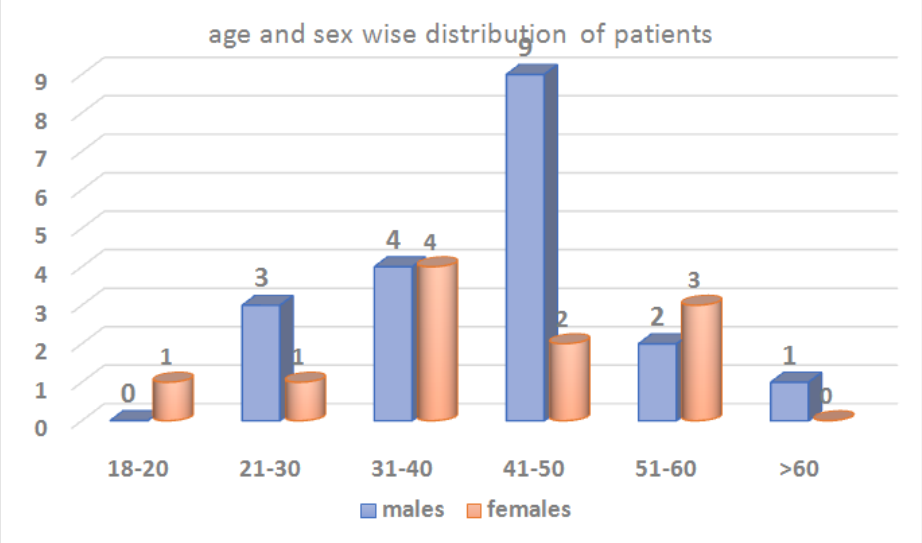


Chart 2: Etiological distribution of ulcers

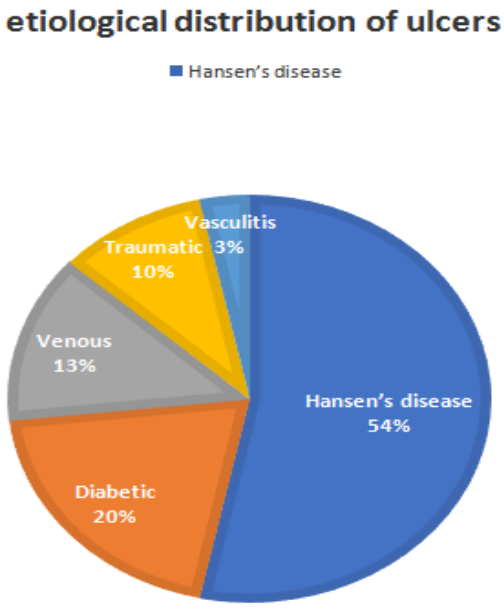


Chart 3: The sum of the mean area reduction

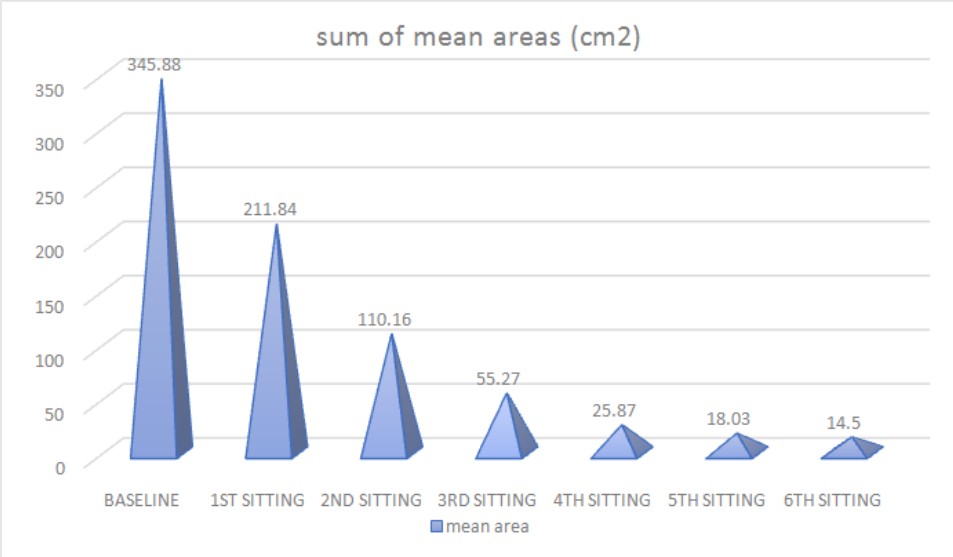


Chart 4: The sum of the mean volume reduction

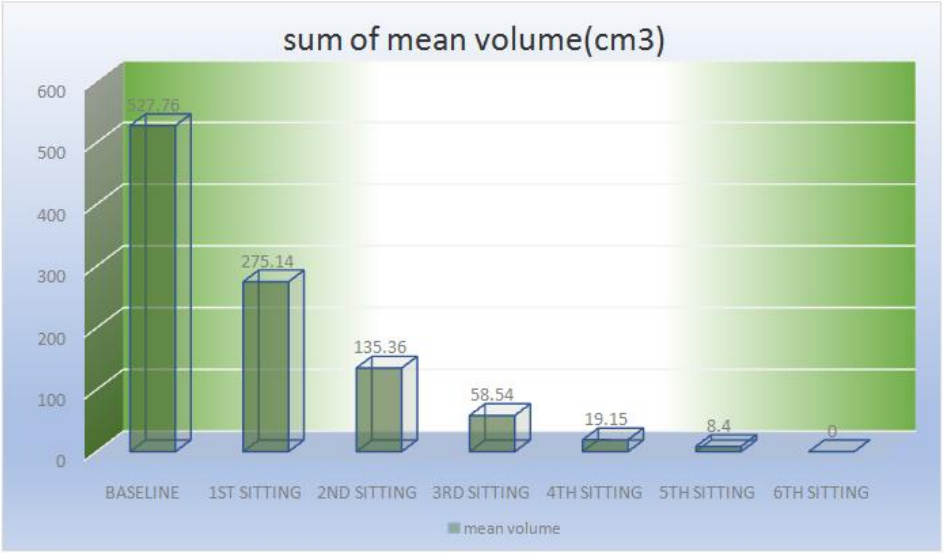


Chart 5- percentage improvement of mean area in each sitting

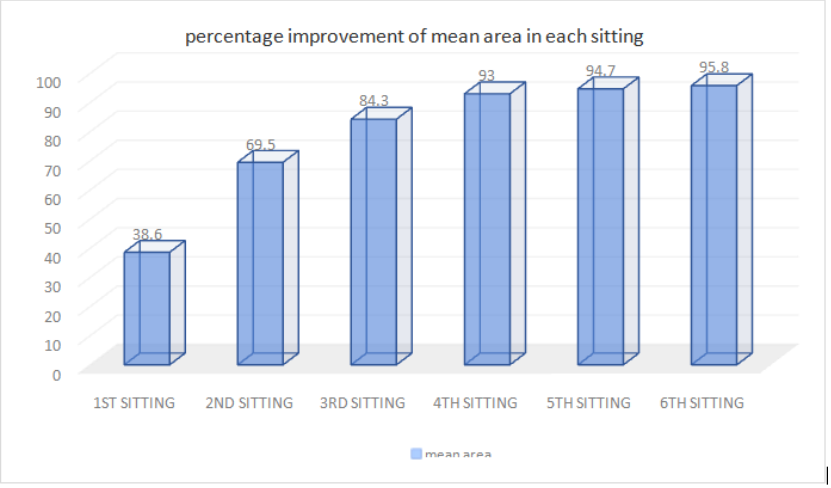


Chart 6- percentage improvement of mean area in each sitting

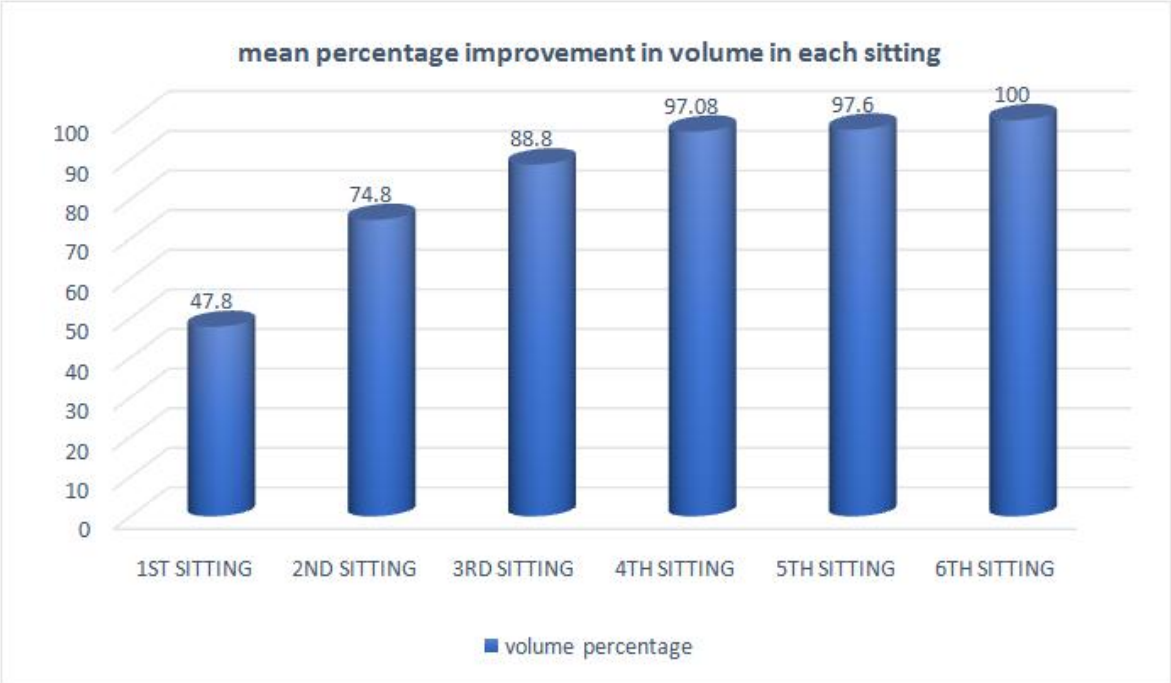


Figure 1: before and after therapy

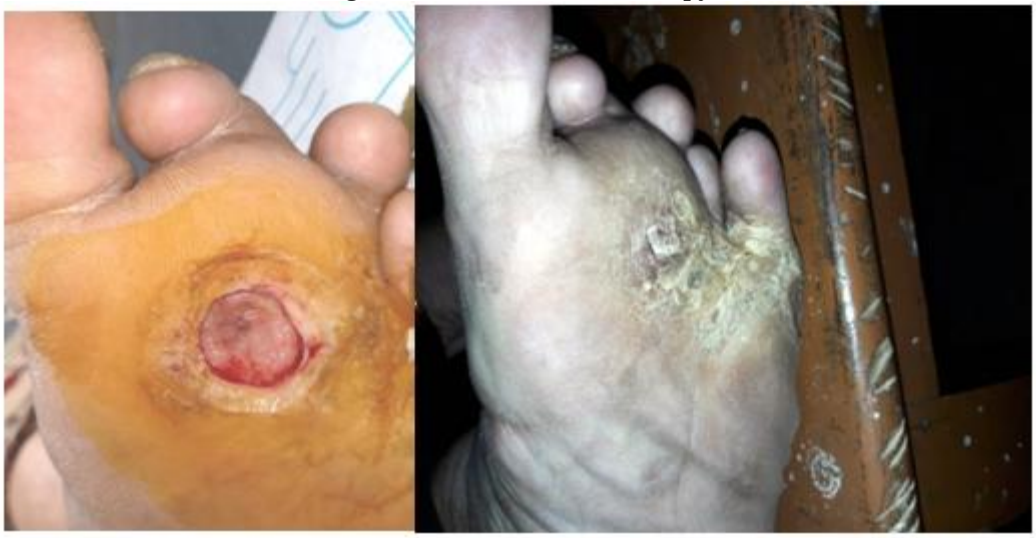


Figure 2: before and after

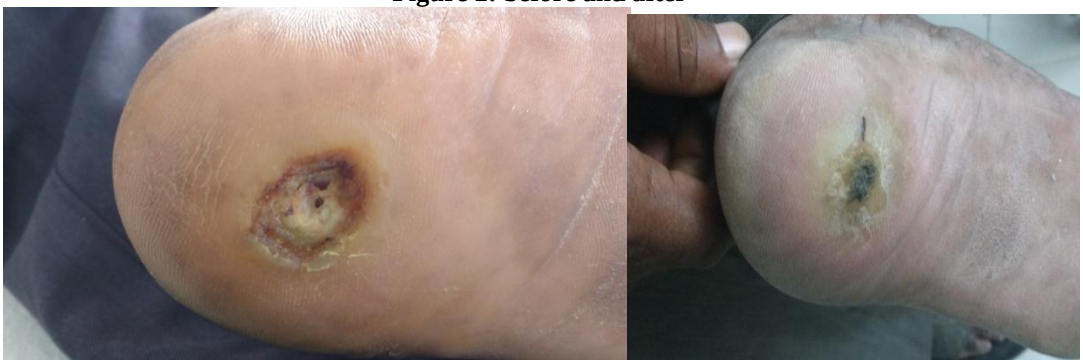


Figure 3: before and after therapy

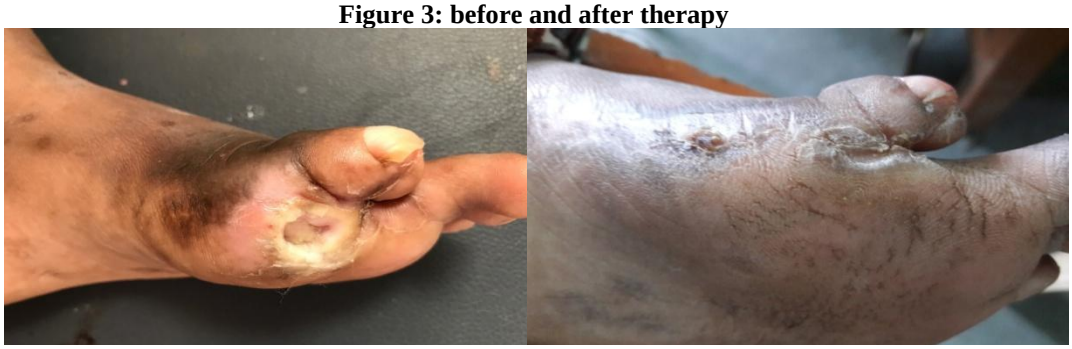
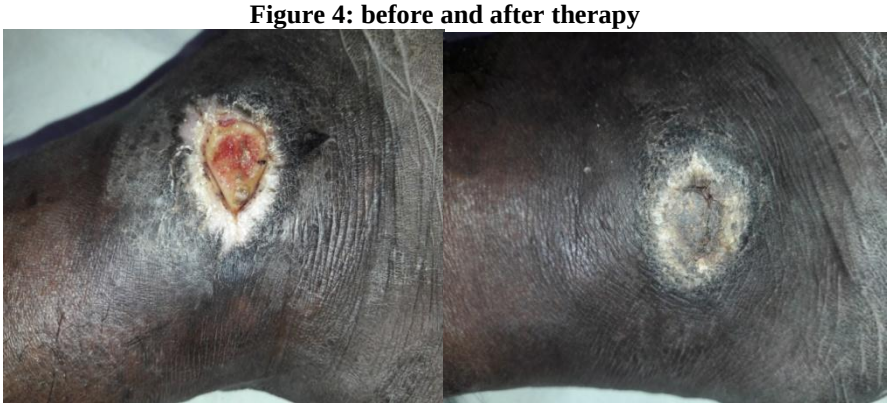


Figure 4: before and after therapy



IV. Discussion

Chronic wounds do not respond to standard wound care, the longevity of care alone becomes very expensive. Additional events such as infection, hospitalization, and amputation add significantly to the cost.

These stalled wounds have consistently high levels of MMP'S and proinflammatory cytokines (i.e., TNF-a) and consistently low levels of TIMMP'S and GF's (i.e., PDGF etc.).

Platelets contain these growth factors, cytokines, and chemokines, which are all crucial in the early stages of wound healing. Harnessing factors from platelets and applying them to a non- healing wound, as well as providing the anti-inflammatory properties of the plasma, could restart the healing process, moving the wound out of the inflammatory cycle into the proliferative phase of healing.

Fibrin is the activated form of Fibrinogen[12]. Fibrinogen is transformed into insoluble fibrin by thrombin and plays an important decisive role in platelet aggregation during haemostasis. Fibrin glue was first described in 1970 by Matras et al. Because of the risk of transmitting hepatitis, the fibrin adhesives were removed from the market, and the focus was shifted on to the production of autologous fibrin. Second-generation platelet concentrates which doesn't utilize anti- coagulation factors was developed. A platelet concentrates lacking coagulation factors, later termed platelet-rich fibrin (PRF) was developed due to its anticipated properties in tissue regeneration and wound healing. It was first developed by Choukranet al.[13] 2001 in France.

The mechanism involved in this is; the fibrinogen concentrated in an upper part of the tube combines with circulating thrombin due to centrifugation to form fibrin.

There is a gradual and fast release of growth factors from PRF clot. The release of these factors commences 5- 10 min after clotting and continues for at least 60-300 min. Resistant autologous fibrin membranes are prepared by driving out the fluids trapped in a fibrin matrix.

The conversion of fibrinogen to fibrin takes place slowly with small quantities ofphysiologically available thrombin present in the blood sample itself which is similar to the physiological architecture due to slow polymerization. The fibrin network which is generated is similar to a natural one and has more efficient cell migration and proliferation causing cicatrisation[14].

The active secretion of these growth factors by platelets begins within 10 min after activation, with more than 95% of the pre synthesized growth factors secreted within 1 hour and stimulation for the proliferation of endothelial cells peak at 1.25×10^6platelets/mL, respectively[15].

The difference between a natural blood clot and PRF is that the latter is more homogeneous and stable and easy to handle and place. The number of platelets in blood is approximately $0.2 \times 10^6/\mu l$. The platelet concentration can be raised to $>1.0 \times 10^6/\mu l$ using purification techniques[16].

Normal PRF membrane has rapid degradability (12 weeks), but the cross-linked fibre's provide resistance against enzymatic degradation and could be more stable during the healing time[4].

Clinical studies regarding the role of PRF in chronic ulcers are increasing in number. In a study conducted by UmasankarNagaraju et al[17] on PRF in trophic ulcers in Hansen's disease, all ulcers healed by maximum of 5 sittings with mean percentage improvement in area of 93.52% and 97.74% by second sitting.

Another study conducted by Anirudh Somani et al[18],comparing PRF vs saline dressings in leg ulcers, mean reduction in area of 85.5% was observed as compared to saline group.They concluded that PRF is more efficacious than saline dressings.Similar study was conducted by NabhaSrinivas Shreyas et al [19]. In this studyPRF dressings were compared to conventional dressings. The median time to healing observed in PRF group was 3.5 weeks compared to 4.19 weeks observed in conventional dressing group.Median 100% healing was seen earlier in PRF group(4^{th} week) compared to 7weeks in conventional group and concluded that PRF dressings had faster rate of healing in comparison to conventional dressings.

In a randomised controlled study of 30 patients conducted by Azariah et al[20],the efficacy of PRP was compared to PRF. They observed that the mean duration of healing observed in PRP group was 6.5 weeks compared to 5.7 weeks in PRF and 100 % resolution of ulcers by 6^{th} sitting was observed in 73.3% of patients in PRF group ,where as it was 53.3% in PRP group. Hence, he concluded PRF is more efficacious with quick healing rate when compared to PRP.

In a study conducted by Gui-Qui-shan et al [21]on 21 patients with non-healing ulcers, no correlation between rate of healing andtype and site of ulcer was observed. Similar results were observed in Saad setta et al[22] study, where, sex, age of the patient and platelet concentration had no correlation with rate of healing. In another similar study conducted by Mohmmad Raslan et al[23] on PRP in 24 non healing ulcers,also concluded that no correlation existed between rate of healing in relation to age, sex, type and site of ulcer. This supports the results in our study

We could not compare the efficacy of PRP and PRF, but we achieved almost comparable results when compared to studyby Sarvajnamurthy*et al.* [24] which took six weeks to achieve it.

V. Conclusion

Hence, this study demonstrates that the application of an enhanced formulation of a near-physiological concentration of platelet-rich fibrin, which provides a rapid and consistent improvement in the healing of chronic wounds and highlights the use of autologous PRF in various healthcare settings to restart the healing process in complex nonhealing wounds, even wounds recalcitrant to other treatments, and those of patients with advanced age, compromised laboratory values, and comorbidities.Autologous platelet rich fibrin provides necessary growth factors for wound healing and it is a safe, affordable, biocompatible, and simple procedure for the treatment of chronic non-healing ulcers

Limitations: Our study was limited its small sample size, single institution setting and limited follow up

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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