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EFFICACY OF PLATELET-RICH FIBRIN MATRIX (PRFM) IN THE TREATMENT OF CHRONIC NON-HEALING ULCERS: A PROSPECTIVE CLINICAL STUDY

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ABSTRACT
Chronic non-healing ulcers present a significant clinical challenge due to their resistance to conventional treatments. This study aimed to evaluate the efficacy of Platelet-Rich Fibrin Matrix (PRFM) in treating chronic non-healing ulcers of various etiologies. A prospective, non-randomized interventional trial was conducted at G.K. General Hospital, Bhuj, from January 2019 to January 2020. A total of 25 patients, aged 18 to 70 years, with 28 non-healing ulcers persisting for more than six weeks, were enrolled. Patients were treated with PRFM at weekly intervals, with a maximum of six sessions. The PRFM was prepared from the patients' venous blood through centrifugation, and the resultant matrix was applied to the wound site. Wound healing was assessed by measuring changes in ulcer area and volume. The results demonstrated a significant reduction in both the area and volume of ulcers. The mean baseline area and volume of the ulcers were 9.32 cm^2 and 4.01 cm^3, respectively. By the end of the fifth treatment session, the mean area decreased to 0.32 cm^2, and the mean volume reduced to 0.001 cm^3. Ulcers caused by Hansen's disease showed a faster healing response compared to other etiologies. PRFM treatment was completed within 40 minutes in all cases, highlighting its efficiency and practicality. These findings suggest that PRFM is an effective, safe, and cost-effective treatment for chronic non-healing ulcers. However, the study's small sample size indicates the need for further research with larger populations to validate these results and assess long-term efficacy and safety. Future studies should also aim to standardize PRFM treatment protocols for broader clinical application.

Key words: Chronic non-healing ulcers, Platelet-Rich Fibrin Matrix (PRFM), wound healing, Growth factors, Platelet-Rich Plasma (PRP), Cost-effective treatment, Hansen's disease, Ulcer management.

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INTRODUCTION

Chronic non-healing ulcers, defined as spontaneous or traumatic lesions that do not respond to initial therapy or persist despite appropriate care, pose a significant challenge in clinical practice. These ulcers fail to heal within a defined period due to an underlying etiology, which may be related to systemic diseases or local disorders [1, 2].

The pathophysiology of chronic non-healing ulcers is complex, often involving a multifactorial process that hinders the normal stages of wound healing: inflammation, tissue regeneration, and tissue remodeling. When these stages are disrupted, either due to systemic conditions such as diabetes or local factors like chronic venous insufficiency, the ulcer becomes chronic and resistant to conventional treatments.

The causes of chronic non-healing ulcers are diverse and include chronic venous disease, peripheral vascular disease, diabetes mellitus, Hansen's disease, trophic ulcers, and trauma [3].

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Among these, chronic venous disease, arterial insufficiency, and diabetes are the most prevalent causes, particularly in lower extremities. These conditions lead to impaired blood flow and nutrient delivery, which are essential for tissue repair, thus contributing to delayed wound healing.

The prevalence of chronic non-healing ulcers varies globally, with estimates ranging from 1.9% to 13.1% [4, 5]. In India, the prevalence is reported to be around 4.5 per 1,000 population, according to a study by Shukla et al. [6]. This prevalence is expected to rise due to the increasing incidence of risk factors such as smoking, obesity, aging, and diabetes. Indeed, it is estimated that up to 10% of the population may develop a chronic ulcer during their lifetime, and the mortality rate associated with chronic wounds is approximately 2.5% [7].

Traditional treatment modalities for chronic non-healing ulcers involve a multifaceted approach aimed at addressing both local and systemic factors. Initial treatment typically includes wound cleaning, debridement of necrotic tissue, infection control through antibiotics and antiseptics, and the application of topical antibacterial agents [8, 9]. For diabetic patients, maintaining blood glucose levels within a normal range is crucial for optimizing wound healing. Local care often involves the use of various types of dressings designed to maintain a moist wound environment, which is conducive to healing.

However, despite these conventional methods, many chronic ulcers remain refractory to treatment, necessitating more advanced therapeutic approaches. Skin grafting, hyperbaric oxygen therapy, vacuum-assisted closure (VAC), angioplasty, and reconstructive surgery are some of the advanced methods that have been employed to enhance wound healing in cases of chronic ulcers [10,11]. These techniques aim to improve blood supply, reduce bacterial load, and promote tissue regeneration.

The role of growth factors in wound healing has also been increasingly recognized, particularly in chronic ulcers where a deficiency in growth factors and cytokines is often implicated in the failure of wound closure. Topical application of growth factors, such as platelet-derived growth factor (becaplermin) and epidermal growth factor, has shown promise in accelerating the healing process [12]. These growth factors act by promoting cellular proliferation, migration, and angiogenesis, all of which are essential for wound repair.

In recent years, a novel treatment modality known as autologous platelet-rich fibrin matrix (PRFM) has emerged as a promising option for the management of chronic non-healing ulcers. PRFM is derived from the patient's own blood and contains a high concentration of platelets, growth factors, and cytokines. When applied topically, PRFM delivers these bioactive substances directly to the wound site, stimulating the healing process. This technique is gaining popularity due to its simplicity, safety, cost-effectiveness, and ability to accelerate wound healing in chronic ulcers that are otherwise resistant to treatment [13]. PRFM represents a less invasive, time-saving alternative to more complex procedures, making it an attractive option in clinical practice.

In conclusion, chronic non-healing ulcers represent a significant clinical burden, particularly in populations with a high prevalence of risk factors such as diabetes and vascular disease. While conventional treatment methods remain the cornerstone of management, advanced therapies, including the use of growth factors and PRFM, offer new hope for patients with refractory ulcers. Further research and clinical trials are necessary to optimize these treatments and establish standardized protocols for their use in chronic ulcer management.

MATERIALS AND METHODS

This prospective, non-randomized interventional trial was conducted at Sri Lakshmi Narayana Institute of Medical Sciences, Pondichery, India and Sree Balaji Medical College & Hospital, Chrompet, Chennai, Tamil Nadu, India, focusing on patients presenting with chronic non-healing ulcers of various etiologies. The study period spanned from January 2008 to January 2009. A total of 25 patients, aged 18 to 70 years, were enrolled in the study, with a total of 28 non-healing ulcers being evaluated.

Inclusion Criteria

- Patients with chronic non-healing ulcers persisting for more than 6 weeks.
- Patients who were willing to participate in the study and provide written informed consent.
- Patients aged 18 years and above.

Exclusion Criteria:

- Patients under 18 years of age.
- Patients unwilling to participate or unable to provide informed consent.
- Patients with bleeding disorders, those on anticoagulant therapy, those with thrombocytopenia, uncontrolled diabetes, active infections at the ulcer site, malignant ulcers, and pregnant or lactating women.

Study Procedure

A detailed history was taken from each patient, including demographic information such as name, age,

sex, occupation, and address, as well as a record of any medications being used. Both general and local examinations were conducted, with particular attention paid to the ulcer. Measurements of the ulcer's length, width, and depth were recorded. Routine laboratory investigations, including a complete blood count (CBC), HIV, and HbsAg tests, were performed. After obtaining written informed consent, the procedure for preparing autologous platelet-rich fibrin matrix (PRFM) was initiated. For the preparation of PRFM, 10 ml of venous blood was drawn from each patient under strict aseptic conditions into a plain vacutainer (without anticoagulant). The blood was then centrifuged at 3000 rpm for 7 minutes, resulting in a three-layered solution. The uppermost layer, consisting of straw-colored platelet-poor plasma (PPP), was discarded. The middle layer, containing PRFM, was carefully separated from the bottom layer, which consisted of red blood cells (RBCs), using sterile forceps. The PRFM was then applied directly to the wound, and a dressing was applied using Coloplast. This procedure was repeated weekly for up to six sessions. During each session, photographs of the ulcer were taken to document progress, and the healing was assessed by measuring changes in the ulcer's dimensions and volume. Wound area was calculated using the ellipse formula, which is more accurate for irregularly shaped wounds than square or rectangular approximations [12]. The formula for calculating the area of an ellipse is (length * width * 0.7854), and the volume of the wound was calculated as (area * depth). This approach allowed for consistent monitoring of ulcer healing and provided a standardized method for evaluating the efficacy of PRFM treatment in chronic non-healing ulcers.

RESULTS

A total of 25 patients with non-healing ulcers of various etiologies, as outlined in Table 1, were treated with platelet-rich fibrin matrix (PRFM) at weekly intervals, with a maximum of six treatment sessions. Of these 25 patients, 17 were male and 8 were female, with a mean age of 40.48 years. The duration of the ulcers varied, ranging from 1 month to 1 year. The mean duration of healing for the ulcers was 3.96 weeks. At the baseline, the mean area of the ulcers was 9.32 cm^2, and the mean volume was 4.01 cm^3. By the end of the fifth treatment session, the mean area had decreased to 0.32 cm^2, and the mean volume had reduced to 0.001 cm^3. Notably, the volume of the ulcers improved more rapidly than the area, indicating a significant reduction in the depth of the ulcers during the treatment process. Ulcers resulting from Hansen's disease showed a faster healing response compared to those caused by other conditions. In all cases, the PRFM treatment procedure was completed within 40 minutes, demonstrating its efficiency and practicality in a clinical setting. These results suggest that PRFM is an effective treatment for chronic non-healing ulcers, with a notable reduction in both ulcer area and volume over the course of treatment.

Tables 1: According to aetiology

Cause of ulcer	No. Of ulcer
Leprosy	9(36%)
Venous ulcer	3(12%)
Alcoholic neuropathy	2(8%)
Diabetes mellitus	11(44%)
Total	25

Table 2: According to age and sex

Age	Male	Female	No. of ulcers
21-40	10	5	15(60%)
41-60	5	3	8(32%)
>60	2	0	2(8%)
Total	17	8	25

Table 3: According to duration.

Duration of ulcer (in months)	No. of ulcers
<3months	15(60%)
3-6 months	7 (28%)
>6 months	3(12%)
Total	25

DISCUSSION

Chronic non-healing ulcers present a significant challenge in clinical practice due to their resistance to conventional treatments. Various modalities, including regular dressings, vacuum-assisted closure (VAC), hyperbaric oxygen therapy, reconstructive surgery, and surgical debridement, have been employed with varying degrees of success. However, these treatments can be costly, time-consuming, and, in some cases, inaccessible, particularly in developing countries [13]. The use of topical platelet-derived growth factors, an FDA-approved treatment for chronic ulcers, has shown promise but is often prohibitively expensive in resource-limited settings [14]. In this context, Platelet-Rich Fibrin Matrix (PRFM) emerges as a cost-effective, safe, and simple alternative.

The potential of growth factors in wound healing was first demonstrated in 1986 by Knighton et al. [15]. Platelets, which contain a high concentration of growth factors, cytokines, and chemokines, play a crucial role in the early stages of wound healing by promoting inflammation and tissue repair [16, 17]. This understanding led to the concept of utilizing platelets as a therapeutic tool for non-healing wounds. By isolating platelets from the blood and applying them to chronic ulcers, PRFM can shift the wound from the inflammatory phase to the proliferative phase, leveraging its anti-inflammatory properties.

PRFM was first developed by Choukroun et al. [18] for use in oral and maxillofacial surgery. The preparation of PRFM is straightforward and does not require anticoagulants, differentiating it from Platelet-Rich Plasma (PRP). The absence of anticoagulants in PRFM preparation allows the platelets to be naturally activated upon contact with the walls of the centrifuge tube, initiating the coagulation cascade. This process results in three distinct layers: the red blood cell base layer, the acellular plasma top layer, and a PRF clot in the middle [19]. Unlike PRP, which dissolves quickly, PRFM forms a strong fibrin matrix that is slowly remodeled, mimicking a natural blood clot [20]. A study conducted by Yazawa et al. [21] demonstrated that PRFM could yield superior results compared to PRP. When used in drug delivery systems like fibrin, the concentration of growth factors in PRFM was found to be three times higher than in conventional PRP [22-23]. The growth factors in PRFM are released in a controlled manner over a period of one week, which contributes to more effective wound healing compared to PRP [24-25]. This sustained release of growth factors allows for continuous stimulation of the wound healing process, resulting in better outcomes.

CONCLUSION

PRFM represents a promising therapy for the treatment of chronic non-healing ulcers. It is a safe, simple, effective, and inexpensive option that has shown to accelerate wound healing without significant complications or side effects. However, the main limitation of this study is the small sample size, which underscores the need for further research. Larger-scale studies are required to assess the long-term efficacy and safety of PRFM in the treatment of chronic non-healing ulcers. Future research should focus on validating these findings and establishing standardized protocols for the clinical use of PRFM in diverse patient populations.

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