e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(8); 315-319

Original Research Article

Assessing Efficacy of Autologous Platelet Rich Fibrin Matrix versus Zinc Oxide and Phenytoin Paste in Non-Healing Ulcers: A Comparative Study

Birendra Prasad

Associate Professor and HOD, Department of Skin and VD, Sri Krishna Medical College and Hospital, Muzaffarpur, Bihar, India

Received: 10-01-2023 Revised: 20-02-2023 / Accepted: 25-03-2023
Corresponding author: Dr. Birendra Prasad
Conflict of interest: Nil

Abstract

Aim: The aim of the present study was to compare the therapeutic efficacy of autologous PRFM versus triple combination paste (zinc oxide, phenytoin, and mupirocin ointment) in non-healing ulcers.

Methods: The present clinical trial was conducted in the Department of Skin and VD, for December 2019 to November 2020. A total of 60 patients were included in the study with the age range 20–70 years. Patients with non-healing ulcers were selected from the outpatient department.

Results: A total of 60 cases of non-healing ulcers of varying etiologies were treated using autologous platelet rich fibrin (PRF) at weekly intervals for maximum frequency of 6 sittings respectively. Most of the patients belonged to the age group 40-50 years. The mean age of the patients was 36.4 ± 12.08 years. Out of 30 ulcers in group A, there were 10 (33.34%) venous ulcers, 4 (13.33%) traumatic ulcers, 9 (30%) diabetic ulcers and 7 (23.33%) trophic ulcers. Out of 30 ulcers in group B, there were 9 (30%) venous ulcers, 6 (20%) traumatic ulcers, 10 (33.34%) diabetic ulcers and 5 (16.66%) trophic ulcers. The length of non-healing ulcer ranged from 3 months to 14 months with a mean of 6.54±1.78 months. Group A showed a mean reduction in the ulcer area by 8.23 mm^2 which was highly significant (P-value = 0.0002). Group B showed a mean reduction in the ulcer area by 4.79 mm^2 which was also significant (P-value = 0.015).

Conclusion: This procedure is simple, patient-friendly, cost-effective, painless and can be performed as an outpatient procedure. We concluded that autologous platelet-rich fibrin matrix is much more effective than the triple combination paste (zinc oxide, phenytoin, and mupirocin ointment) in the treatment of non-healing ulcers.

Keywords: Non-Healing Ulcer, Phenytoin, PRF, Zinc.

Introduction

A non-healing ulcer is defined as an ulcer that does not heal even after 3 months of constant treatment. It is highly common among adult males and possesses major health problems and has a great impact on the quality of life due to distressing symptoms like pain, difficulty in walking, and impaired sleep. They can result secondary to arterial disease, venous disease, and diabetic neuropathy, metabolic disorders, hematological disorders, and infective diseases. The autologous platelet-rich fibrin (PRF) is a simple and cost-effective method for the treatment of non-healing ulcers. It provides the necessary polypeptide growth factors that enhance tissue healing. One of them is transforming growth factor beta (TGF)-beta which is profibrotic and highly potent. These factors stimulate fibrosis and subcutaneous collagen deposition, increase biomechanical strength, and epithelial resurfacing and differentiation. The recent literature shows autologous platelet-rich fibrin matrix (PRFM) being rich in growth factors. It is effective in the treatment of chronic non-healing ulcers. [1,2]

Phenytoin sodium causes hyperplasia of the gingiva [3] following its constant use; this is attributed to inflammation and/or fibrosis. This finding has prompted exploration of its role in wound healing. [4-6] Phenytoin increases fibroblast activity, decreases collagenase activity with the formation of granulation tissue. Mupirocin ointment possesses antibacterial action. Various modalities of treatment for venous ulcers include compression stockings, good wound care and sometimes surgical therapies. The treatment is often difficult and is generally associated with high recurrence rate. [7-9] Dressings play a major role in healing of these ulcers. Moist occlusive dressings with saline are known to improve wound healing. Platelet concentrates have been widely used in regenerative medicine to promote wound healing as they contain transforming growth factor (GF) F, platelet-derived

GF, vascular-endothelial GF, platelet derived epidermal GF, insulin-like GF-I and basic fibroblast GF.

Tissue engineering has demonstrated regeneration potentiality without any permanent sequelae. Many researchers have proven that human skin has the ability to regenerate through available stem cell populations. Stem cell has the ability of self-renewal and ability to differentiate into function specific daughter cells. Regenerative medicine has a definite role in regulating these stem cell populations for promoting skin regeneration. [10]

The aim of the present study was to compare the therapeutic efficacy of autologous PRFM versus triple combination paste (zinc oxide, phenytoin, and mupirocin ointment) in non-healing ulcers.

Methods

The present clinical trial was conducted in the Department of Skin and VD, Sri Krishna Medical College and Hospital , Muzaffarpur, Bihar, India for December 2019 to November 2020. A total of 60 patients were included in the study with the age range 20–70 years. Patients with non-healing ulcers were selected from the outpatient department of Skin and VD.

Inclusion Criteria

- Patients with trophic ulcers due to Hansen disease or diabetes mellitus
- Patients with stasis dermatitis
- Pyoderma gangrenosum
- Venous ulcer
- Traumatic ulcer
- Age group 18–85 years

Exclusion criteria

- Patients with age group below 18 years
- Patients with a history of bleeding disorders
- Anemia and other hematological disorders
- Platelet count <1.5 lakhs/cu mm
- Patients on anticoagulant medications (aspirin, warfarin, heparin)
- Patients with malignant ulcers, pregnant and lactating females

The study population was randomized into two groups, i.e.,

Group A consisted of 30 patients on autologous PRFM.

Group B consisted of 30 patients on triple combination paste (zinc oxide, phenytoin, and mupirocin ointment).

Preparation of PRFM

After taking informed consent, the length and breadth of the ulcer were measured. Under aseptic conditions, 10 mL of venous blood was collected from the median cubital vein and added to a sterile centrifugation tube without any anticoagulant. The tube was rotated at 3,000 rpm for 10 min. Three layers were obtained following this topmost a cellular layer which is the platelet-poor plasma (PPP), the lowermost layer containing red blood cells (RBCs), and the middle layer containing the PRFM. The upper layer (PPP) was discarded. The PRFM was separated from the RBCs at the base with the help of sterile forceps and scissors in a clean and sterile petri-dish. The matrix was then placed onto sterile gauze and applied over the ulcer followed by the application of a secondary non-absorbable dressing. The patient was advised to take adequate rest. The dressing was removed after a period of minimum of 5 days. The procedure was repeated every week for up to five sittings. The healing of the ulcer was assessed, the area was calculated, and photographs were taken at the beginning and end of every week. The wound area was calculated using the formula for an ellipse: Length × width × 0.7854 (an ellipse is closer to a wound shape than a square or rectangle). The use of an ellipse for calculating the wound measurement has been used in randomized controlled trials in wound healing literature.[11,12]

Preparation of triple combination paste (zinc oxide, phenytoin, and mupirocin ointment)

Under aseptic conditions, 10 phenytoin tablets (100 mg) were crushed finely in mortar and pestle. These were mixed with 10 g of zinc oxide powder and mupirocin ointment until a smooth paste was obtained. The patient was asked to apply it twice daily. At the beginning and every week, the healing of the ulcer was assessed, the area was calculated and photographs were taken The wound area was calculated using the formula for an ellipse: Length × width × 0.7854 as done in the preparation of the PRF matrix.

Results

Table 1: Demographic details of patients

Age group (in years)	Group A N (%)	Group B N (%)
20-30	5 (16.66)	6 (20)
30-40	4 (13.34)	4 (13.34)
40-50	12 (40)	15 (50)
50-60	6 (20)	3 (10)
60-70	3 (10)	2 (6.66)
Total	30	30

Ulcers		
Venous ulcers	10 (33.34)	9 (30)
Traumatic ulcers	4 (13.33)	6 (20)
Diabetic ulcers	9 (30)	10 (33.34)
Trophic ulcers	7 (23.33)	5 (16.66)

A total of 60 cases of non-healing ulcers of varying etiologies were treated using autologous platelet rich fibrin (PRF) at weekly intervals for maximum frequency of 6 sittings respectively. Most of the patients belonged to the age group 40-50 years. The mean age of the patients was 36.4 ± 12.08 years. Out of 30 ulcers in group A, there were 10 (33.34%) venous ulcers, 4 (13.33%) traumatic ulcers, 9 (30%) diabetic ulcers and 7 (23.33%) trophic ulcers. Out of 30 ulcers in group B, there were 9 (30%) venous ulcers, 6 (20%) traumatic ulcers, 10 (33.34%) diabetic ulcers and 5 (16.66%) trophic ulcers. The length of non-healing ulcer ranged from 3 months to 14 months with a mean of 6.54 ± 1.78 months.

Table 2: Improvement in both groups

Groups	**Initial Size (mean ±SD)**	**Final Size (mean± SD)**	**P**
Group A	10.845±5.150	2.615±1.630	0.0002
Group B	10.055±4.850	5.265±3.170	0.015

Group A showed a mean reduction in the ulcer area by 8.23 mm^2 which was highly significant (P-value = 0.0002). Group B showed a mean reduction in the ulcer area by 4.79 mm^2 which was also significant (P-value = 0.015).

Discussion

Chronic non-healing ulcers due to various etiologies have become cumbersome and add morbidity for patients and society. These wounds pose a greater challenge for healthcare personnel to treat. These usually present with exposed underlying tissues and further complicates the process of granulation tissue whilst simple dressing. Additionally, at the same time it presents with an equivocal challenge to maintain the viability of surrounding tissue. These non-healing ulcers need a multimodal approach for treating by ascertaining the underlying pathology and the systemic condition of the individual. Conventional approach of treatments were not able to provide growth factors to induce neovascularization at the ulcer site to initiate the healing process. [13]

PRF is an autologous platelet and leucocyte-rich fibrin material and is an important advancement in regenerative medicine. It forms an organised network where the platelets and leucocytes are concentrated leading to the sustained release of various GFs, resulting in wound healing. Hence, it can also be used for the treatment of venous ulcers. [14] A study conducted by Margolis et al. which included 26,599 patients, concluded that patients who were treated with products derived from platelets, tend to heal faster than patients who were treated without the products derived from platelets. He also concluded that even though the ulcers that were treated with these derivatives were bigger and deeper than the other groups these showed better improvement at the end of 12 weeks. [15]

A total of 60 cases of non-healing ulcers of varying etiologies were treated using autologous platelet rich fibrin (PRF) at weekly intervals for maximum frequency of 6 sittings respectively. Most of the patients belonged to the age group 40-50 years. The mean age of the patients was 36.4 ± 12.08 years. Out of 30 ulcers in group A, there were 10 (33.34%) venous ulcers, 4 (13.33%) traumatic ulcers, 9 (30%) diabetic ulcers and 7 (23.33%) trophic ulcers. Out of 30 ulcers in group B, there were 9 (30%) venous ulcers, 6 (20%) traumatic ulcers, 10 (33.34%) diabetic ulcers and 5 (16.66%) trophic ulcers. The length of non-healing ulcer ranged from 3 months to 14 months with a mean of 6.54 ± 1.78 months. Group A showed a mean reduction in the ulcer area by 8.23 mm^2 which was highly significant (P-value = 0.0002). Group B showed a mean reduction in the ulcer area by 4.79 mm^2 which was also significant (P-value = 0.015). In a similar study by Anirudh Somani and Reena Rai, [16] the improvement was 80% which is much higher than the present study. According to a study by G. Yuvasri, [17] the mean reduction in the area of the ulcer size observed was 86.03%. In the present study, the improvement in the ulcer size is 45% using triple combination paste (zinc oxide, phenytoin, and mupirocin ointment). In a study by Sehgal et al. [18] zinc oxide and phenytoin paste were used in the treatment of trophic ulcers of leprosy. Complete resolution was seen in 55% of the patients. In a study by Shafer et al., [19] granulation tissue was formed in 50–90% of his patients.

PRF contains enormous platelets with fibrin. Once alpha granules in the platelets start degranulation, it releases various growth factors (transforming growth factor β, platelet derived growth factor, epidermal growth factor, nerve growth factor) along with vitronectin, fibronectin and sphingosine 1-phosphate which helps in enhancement of wound

healing and microenvironment homeostasis. This unique organization in the form of the 3-dimentional fibrin matrix provides a binding site for platelets as well as growth factors. This flexible mesh serves as scaffold to promote cellular migration in micro-environment and perquisite in repairing and regenerating tissue. Overall, in PRF preparation, leukocyte and fibrin acts as mutual stimulatory actors by imitating the physiological process of wound healing and boosting angiogenic, osteogenic and antimicrobial activities. [20,21] Suryanarayan S., et al. showed the mean duration of ulcer healing with PRP was 5.6 weeks. [22] Kim SA., et al. showed 90 - 100% epithelization after 15.18 days of treatment with PRP for non-healing ulcers. [23] Frykberg., et al. showed that 63 of 65 ulcers responded with a reduction in area, volume and undermining of the ulcers in a mean duration of 2.8 weeks with PRP treatments. [24]

Conclusion

This procedure is simple, patient-friendly, cost-effective, painless and can be performed as an outpatient procedure. We concluded that autologous platelet-rich fibrin matrix is much more effective than the triple combination paste (zinc oxide, phenytoin, and mupirocin ointment) in the treatment of non-healing ulcers. The results of our series should encourage future prospective studies to assess the efficacy of PRF dressing in ulcers. Its distinctive advantages include use of autologous blood and low cost and limited resource requirement in its preparation. However, it's wide spread application is still limited due to poor accessibility of health care facilities by leprosy patients, disease stigmatisation and lack of manpower resources.

References

1. O'Connell SM, Hessler K, Dardik H. Cascade® Autologous System Platelet-Rich Fibrin Matrix in the Treatment of Chronic Leg Ulcers. Adv Wound Care (New Rochelle). 2012 Feb;1(1):52-55.
2. Steenvoorde P, van Doorn LP, Naves C, Oskam J. Use of autologous platelet-rich fibrin on hard-to-heal wounds. J Wound Care. 2008 Feb;17(2):60-3.
3. SHAPIRO M. Acceleration of gingival wound healing in non-epileptic patients receiving diphenylhydantoin sodium (dilantin, epanutin). Exp Med Surg. 1958;16(1):41-53.
4. SHAFER WG, BEATTY RE, DAVIS WB. Effect of dilantin sodium on tensile strength of healing wounds. Proc Soc Exp Biol Med. 1958 Jun;98(2):348-50.
5. SHAFER WG. Effect of dilantin sodium on various cell lines in tissue culture. Proc Soc Exp Biol Med. 1961 Dec; 108:694-6.
6. el Zayat SG. Preliminary experience with topical phenytoin in wound healing in a war zone. Mil Med. 1989 Apr;154(4):178-80.
7. Bergqvist D, Lindholm C, Nelzén O. Chronic leg ulcers: the impact of venous disease. Journal of vascular surgery. 1999 Apr 1;29(4):752-5.
8. Evans CJ, Fowkes FG, Ruckley CV, Lee AJ. Prevalence of varicose veins and chronic venous insufficiency in men and women in the general population: Edinburgh Vein Study. Journal of Epidemiology & Community Health. 1999 Mar 1;53(3):149-53.
9. Mayer W, Jochmann W, Partsch H. Varicose ulcer: healing in conservative therapy. A prospective study. Wiener medizinische Wochenschrift (1946). 1994 Jan 1;144(10-11):250-2.
10. van Gent WB, Wilschut ED, Wittens C. Management of venous ulcer disease. Bmj. 2010 Nov 12;341.
11. Margolis DJ, Kantor J, Berlin JA. Healing of diabetic neuropathic foot ulcers receiving standard treatment. A meta-analysis. Diabetes care. 1999 May 1;22(5):692-5.
12. Blume PA, Walters J, Payne W, Ayala J, Lantis J. Comparison of negative pressure wound therapy using vacuum-assisted closure with advanced moist wound therapy in the treatment of diabetic foot ulcers: a multicenter randomized controlled trial. Diabetes care. 2008 Apr 1;31(4):631-6.
13. Rahman GA, Adigun JA, Fadeyi A. Epidemiology, etiology and treatment of chronic leg ulcer: experience with sixty patients. Annals of African Medicine. 2010;9(1).
14. O'CONNELL SM. Autologous platelet-rich fibrin matrix as a stimulator of healing of chronic lower extremity ulcers. Wound Rep Regen. 2006;14:A76.
15. Margolis DJ, Kantor J, Santanna J, Strom BL, Berlin JA. Effectiveness of platelet releasate for the treatment of diabetic neuropathic foot ulcers. Diabetes care. 2001 Mar 1;24(3):483-8.
16. Somani A, Rai R. Comparison of efficacy of autologous platelet-rich fibrin versus saline dressing in chronic venous leg ulcers: A randomised controlled trial. Journal of cutaneous and aesthetic surgery. 2017 Jan;10(1):8.
17. Yuvasri G, Rai R. Comparison of efficacy of autologous platelet-rich fibrin versus Unna's paste dressing in chronic venous leg ulcers: A comparative study. Indian Dermatology Online Journal. 2020 Jan;11(1):58.
18. Sehgal VN, Prasad PV, Kaviarasan PK, Rajan D. Trophic skin ulceration in leprosy: evaluation of the efficacy of topical phenytoin

sodium zinc oxide paste. International Journal of Dermatology. 2014 Jul;53(7):873-8.
19. Shafer WG. Effect of dilantin sodium on various cell lines in tissue culture. Proceedings of the Society for Experimental Biology and Medicine. 1961 Dec;108(3):694-6.
20. Tunalı M, Özdemir H, Küçükodacı Z, Akman S, Fıratlı E. In vivo evaluation of titanium-prepared platelet-rich fibrin (T-PRF): a new platelet concentrate. British Journal of Oral and Maxillofacial Surgery. 2013 Jul 1;51(5):438-43.
21. Caruana A, Savina D, Macedo JP, Soares SC. From platelet-rich plasma to advanced platelet-rich fibrin: biological achievements and clinical advances in modern surgery. European journal of dentistry. 2018 May;13(02):280-6.
22. Suryanarayan S, Budamakuntla L, Khadri SI, Sarvajnamurthy S. Efficacy of autologous platelet-rich plasma in the treatment of chronic nonhealing leg ulcers. Plastic and Aesthetic Research. 2014 Aug 28; 1:65-9.
23. Kim S, Ryu HW, Lee KS, Cho JW. Application of platelet-rich plasma accelerates the wound healing process in acute and chronic ulcers through rapid migration and upregulation of cyclin A and CDK4 in HaCaT cells. Molecular medicine reports. 2013 Feb 1;7(2):476-80.
24. Frykberg RG, Driver VR, Carman D, Lucero B, Borris-Hale C, Fylling CP, Rappl LM, Clausen PA. Chronic wounds treated with a physiologically relevant concentration of platelet-rich plasma gel: a prospective case series. Ostomy/wound management. 2010 Jun 1;56(6):36.