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SHORT REPORT

Platelet rich fibrin dressings in the treatment of non-healing trophic ulcers of leprosy

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Summary

Introduction: Trophic ulcers in leprosy are a therapeutic challenge. Various treatment options have been tried, but none is found to be universally effective. The search for better treatment continues.

Methods: Leprosy patients with long standing trophic ulcers treated with platelet rich fibrin (PRF) dressings were identified in this retrospective review. PRF was prepared by centrifuging autologous blood at 2800 rpm for 15 minutes. The PRF dressings were repeated at weekly intervals and treatment response was assessed using the National Pressure Ulcer Advisory Panel (NPUAP) staging.

Results: Ten patients (7 males) treated with PRF dressings were identified. The mean age of the study patients was 45·4 years. Three patients had NPUAP stage II, six patients had NPUAP stage III and one patient had NPUAP stage IV ulcers. Eight patients showed complete healing after 2–4 PRF dressing sessions. Complications were limited to localised infection in one patient.

Conclusion: PRF dressings are a promising therapeutic option for treatment of non-healing trophic ulcers in leprosy patients.

Keywords: Dressing, Leprosy, Platelet rich fibrin, Trophic ulcers

Introduction

Leprosy is a complex and multi-faceted disease responsible for various chronic disabilities. Foot ulceration is one of the common sequelae of the sensory-deficient foot, and its chronicity is perpetuated by repeated inadvertent trauma.[1] However, little research has been published

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on its management. Treatment strategies are based on protection of the foot, in addition to varied medical and surgical measures;[2] but nothing seems to be universally effective and the search for a better treatment options continues.

Tissue growth factors, platelet derived growth factor (PDGF) and epidermal growth factor (EGF) are reported to be useful in treating neuropathic ulcers by expediting wound healing and tissue regeneration.[3,4] Platelet derived autologous products, platelets rich fibrin (PRF) and platelet rich plasma (PRP) are a rich source of these growth factors and they have been previously shown to be effective in treating non-healing, chronic leg ulcers, including neuropathic ulcers.[5,6,7] In this study we evaluated the role of weekly PRF dressings in the treatment of non-healing, trophic leprosy ulcers.

Material and methods

STUDY DESIGN

This was a retrospective review of clinical charts of leprosy patients treated with PRF dressings for non-healing trophic ulcers from July 2015 to June 2016. The study was performed in accordance with the declaration of Helsinki and Institute Ethics Committee approval was waived for this retrospective review.

Patients

Leprosy patients with non-healing trophic ulcers attending the leprosy clinic of our tertiary care centre were offered treatment with PRF dressings. Non-healing was arbitrarily defined as failure to show signs of healing after 12 weeks of treatment with complete rest and sterile dressings. Patients with concurrent diabetes mellitus, hypertension, varicose veins, infection and other secondary causes contributing to the chronicity of the leg ulcer were excluded from this review. All patients were treated for leprosy and its complications with standard of care at the leprosy clinic of our institute.

Platelet rich fibrin preparation

PRF was prepared as per the published literature.[8] Briefly, under aseptic precautions 5 ml of blood was collected in a sterile vial without anticoagulant. It was then immediately centrifuged at 2800 rpm for 15 minutes. At the end of centrifugation a natural fibrin matrix gel was obtained at the middle of the tube with RBC's below and a cellular plasma at the top (Figure 1a). The fibrin gel was then placed over the ulcer base and covered with a sterile dressing to be left in-situ for 7 days (Figure 1b).

Follow-up and treatment assessment

All patients received weekly PRF dressings for a maximum of 5 weeks or until complete epithelization of the ulcer, whichever was earlier. At each visit, the clinical assessment was done using the National Pressure Ulcer Advisory Panel (NPUAP) staging and its modification.[9] During the intervening period, patients were educated on foot care practices, to avoid prolonged standing, to continue taking multi-drug therapy and to use appropriate microcellular rubber footwear. Clinical images were obtained under standard conditions at each visit. Post-treatment, all patients were followed until completion of multi-drug therapy.

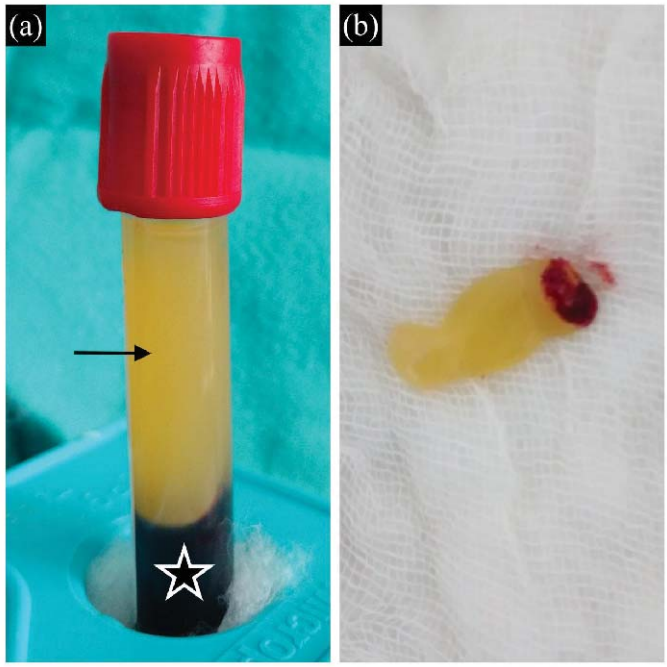

Figure 1. (a) Preparation of platelet rich fibrin matrix showing fibrin matrix gel at the middle of the tube (arrow) with RBC's below (star) and acellular plasma at the top (b) The fibrin gel was then placed over the ulcer base and covered with a sterile dressing to be left in-situ for 7 days.

Results

Ten leprosy patients (four with borderline lepromatous and six with lepromatous leprosy) with trophic ulcers who were treated with PRF dressings were identified. They included seven males and three females with a mean age 45·4 years (range, 34 to 60 years) and the mean ulcer duration was 39·4 months (range: 14 to 58 months). Three patients had NPUAP stage II, six patients had NPUAP stage III and one patient had NPUAP stage IV ulcer (Figure 2a).

All ten patients had a glove and stocking pattern of anaesthesia of the extremities. The demographics and disease characteristics are summarised in Table 1.

Eight patients showed complete healing of the trophic ulcers after 2–4 PRF dressing sessions (Figure 2b). Improvement (but not complete healing) was noted in two patients at the end of five treatment sessions. Complications were limited to localised infection in one patient, who required oral antibiotics and local debridement. One patient (patient 6) with NPUAP stage IV ulcer healed upto stage 1 with five sessions of PRF. However, he relapsed after 4 months of treatment.

Discussion

Deformity and disabilities are preventable sequelae of leprosy and are strongly associated with social stigma. The recently launched WHO 5-year global leprosy strategy aims at a

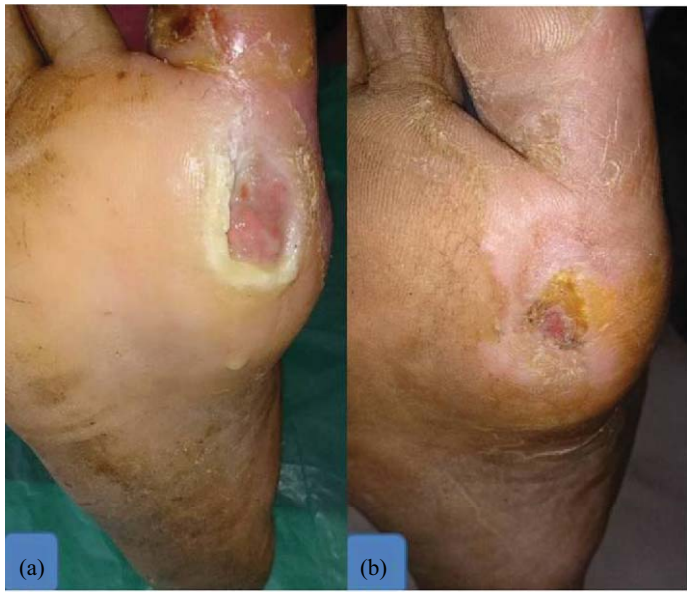

Figure 2. (a) Pre-treatment clinical photograph (patient 6) showing NPUAP stage 3 ulcer. (b) Post-treatment clinical photograph showing complete healing after 2 sessions with PRF dressings.

reduction in the disease burden of leprosy as assessed by a decline in the number of visible deformities (Grade 2 disability, G2D) among new cases.[10] One of the set targets to achieve this goal is a reduction in the rate of new G2D cases to <1 case per million population. However, the current G2D rate stands at 1·7 per million population, with India accounting for 39·8% of cases (5098 in absolute numbers).[10] Trophic ulcers, one of the dreaded presentations of G2D, significantly impairs patients' activities and is associated with considerable morbidity. The treatment strategies observed are broadly conservative and include protection of the foot and resting the affected limb for prolonged periods. However, these measures are not universally effective and there is a need for better treatment options to hasten recovery and healing.

PRP and PRF have been found useful in treating chronic ulcers of sclerodema, venous leg ulcers, diabetic foot ulcers and neuropathic ulcers.[6,7] However, there is limited evidence on use of PRP and PRF in trophic leprosy ulcers. Anandan *et al.* reported healing of 92% of leprosy trophic ulcer when dressed with activated PRP at weekly intervals.[11] Nagaraju *et al.* reported more than 90% improvement in seven leprosy patients treated with weekly PRF dressings for non-healing trophic ulcers. In the current study, 80% of patients showed complete healing of trophic ulcers. Two patients showed improvement in their NPUAP ulcer stage. The improvement was apparent as early as week two and most of the ulcers re-epithelised by 3 weeks. The healing was also supported by educational interventions on wound care practices and care of anaesthetic limbs. The relapse in one patient after five sessions of treatment was probably due to inappropriate foot-care practices following the procedure. Educational interventions on foot care practices are essential for prevention of relapses as the primary risk factor for trophic ulcer (anaesthetic limbs) persists in these patients.

Table 1. Demographics and disease characteristics of the study patient

Patient no	Age	Sex	Diagnosis	Duration of Ulcer (months)	Location	Ulcer size, cm (baseline)	Ulcer size, cm (end)	NPUAP stage (baseline)	NPUAP stage (end)	No of sessions	Multidrug therapy
1	48	Male	BL	24	Right great toe	2	0	2	0	3	On therapy
2	54	Male	LL	18	Left sole	4	0	3	0	4	On therapy
3	46	Male	LL	48	Right malleoli	1·5	0	3	0	4	On therapy
4	34	Male	LL	20	Right sole	2	1	3	2	5	Completed
5	60	Male	LL	14	Right toe	2	0	3	0	2	On therapy
6	36	Male	BL	50	Left sole fore foot	3	1	4	1	5	On therapy
7	56	Male	BL	52	Left great toe	3·5	1·5	2	0	3	Completed
8	42	Female	LL	54	Left malleoli	2	0	2	0	2	On therapy
9	38	Female	LL	56	Right sole fore foot	1	0	3	0	4	On therapy
10	40	Female	BL	58	Right sole fore foot	2	1	3	0	4	Completed

BL, borderline lepromatous leprosy; LL, lepromatous leprosy.

The mechanism of wound healing with PRF/PRP is an area of intense scientific study. Platelets and platelets derived products have been explored for their various healing, regenerative and aesthetics properties in many surgical fields.[12] The growth factors released from the α-granules of activated platelets, along with fibrin, fibronectin and vitronectin play a pivotal role in modulation of tissue repair and regeneration. These growth factors include vascular endothelial growth factor (VEGF), fibroblast growth factor-β (FGFβ), PDGF, hepatocyte growth factor (HGF), EGF, and angiopoietin-I (Ang-I) among others.[5] The growth factors, through their autocrine and paracrine action, promote angiogenesis, tissue remodelling, recruitment of keratinocytes and mesenchymal stem cells and synthesis of the extracellular matrix.[5,13]

PRF is a second-generation platelet concentrate consisting of a fibrin matrix gel polymerized in a tetra molecular structure, with incorporation of platelets, leucocytes, cytokines, and circulating stem cells.[14] PRF has some distinct advantages over PRP. The technique of PRF preparation is simpler, involves minimal handling, does not require anti-coagulant or a thrombin activator. The consumables required for PRF preparation (sterile test tubes, forceps and centrifuge machine) are easily available in a hospital setup. Further, the gel formulation of PRF is easy to apply on a raw wound compared to a liquid formulation of PRP.[15] Studies have also shown that the concentration of growth factors is significantly higher in PRF compared to PRP and whole blood.[15] The effects of PRP are not limited to their growth factor content alone, but many factors of healing act in complex synergy, such as leukocytes, fibrin matrix, and circulating progenitor cells. The biologic activity of the autologous growth factors along with biomechanical stiffness of plasmatic proteins after fibrin mesh formation has shown to offer a unique physiologic architecture that is very favourable to the healing process.[5]

Our study was limited by its small sample size, retrospective study design and lack of follow-up of treated patients. Educational interventions on wound care practices and care of anaesthetic limbs would have added to the efficacy of PRF in hastening wound healing. However, our patients had previously failed these supportive measures for at least 12 weeks and the rapidity of wound healing after PRF dressings points to its definitive role. The results of our series should encourage future prospective studies to assess the efficacy of PRF dressing in trophic leprosy ulcers. Its distinctive advantages include use of autologous blood and low cost and limited resource requirement in its preparation. However, its 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] Sehgal VN, Prasad PVS, Kaviarasan PK, Rajan D. Trophic skin ulceration in leprosy: evaluation of the efficacy of topical phenytoin sodium zinc oxide paste. *Int J Dermatol*, 2014; **53**: 873–878.

[2] Chauhan VS, Pandey SS, Shukla VK. Management of plantar ulcers in Hansen's disease. *Int J Low Extrem Wounds*, 2003; **2**: 164–167.

[3] Wieman TJ, Smiell JM, Su Y. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. A phase III randomized placebo-controlled double-blind study. *Diabetes Care*, 1998; **21**: 822–827.

[4] Tiaka EK, Papanas N, Manolakis AC, Georgiadis GS. Epidermal growth factor in the treatment of diabetic foot ulcers: an update. *Perspect Vasc Surg Endovasc Ther*, 2012; **24**: 37–44.

[5] Anitua E, Pino A, Orive G. Opening new horizons in regenerative dermatology using platelet-based autologous therapies. *Int J Dermatol*, 2017; **56**: 247–251.

[6] Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I *et al.* Autologous platelet-rich plasma for treating chronic wounds. In: Martinez-Zapata MJ (ed). *Cochrane database of systematic reviews*, Chichester, UK: John Wiley & Sons, Ltd, 2016. doi:10.1002/14651858.CD006899.pub3.

[7] Pinto NR, Ubilla M, Zamora Y *et al.* Leucocyte- and platelet-rich fibrin (L-PRF) as a regenerative medicine strategy for the treatment of refractory leg ulcers: a prospective cohort study. *Platelets*, 2017; DOI. 10.1080/09537104.2017.1327654. [Epub ahead of print].

[8] Dohan DM, Choukroun J, Diss A *et al.* Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part I: technological concepts and evolution. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*, 2006; **101**: e37–e44.

[9] Edsberg LE, Black JM, Goldberg M *et al.* Revised National Pressure Ulcer Advisory Panel Pressure Injury Staging System. *J Wound Ostomy Cont Nurs*, 2016; **43**: 585–597.

[10] Global leprosy update, 2016: accelerating reduction of disease burden. *Relev Epidemiol Hebd*, 2017; **92**: 501–519.

[11] Anandan V. Platelet Rich Plasma: Efficacy in Treating Trophic Ulcers in Leprosy. *J Clin Diagn Res*, 2016; doi:10.7860/JCDR/2016/21899.8758.

[12] De Pascale MR, Sommese L, Casamassimi A, Napoli C. Platelet derivatives in regenerative medicine: an update. *Transfus Med Rev*, 2015; **29**: 52–61.

[13] Houdek MT, Wyles CC, Stalboerger PG *et al.* Collagen and Fractionated Platelet-Rich Plasma Scaffold for Dermal Regeneration. *Plast Reconstr Surg*, 2016; **137**: 1498–1506.

[14] Choukroun J, Diss A, Simonpieri A *et al.* Platelet-rich fibrin (PRF): A second-generation platelet concentrate. Part IV: Clinical effects on tissue healing. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology*, 2006; **101**: e56–e60.

[15] Nishimoto S, Fujita K, Sotsuka Y *et al.* Growth Factor Measurement and Histological Analysis in Platelet Rich Fibrin: A Pilot Study. *J Maxillofac Oral Surg*, 2015; **14**: 907–913.