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Original Research Paper

Dermatology

ASSESSMENT OF EFFICACY OF ACTIVATED AUTOLOGOUS PLATELET RICH PLASMA THERAPY IN CHRONIC NON-HEALING LEG ULCERS USING PERCENTAGE REDUCTION IN SURFACE AREA AND PHOTOGRAPHIC WOUND ASSESSMENT TOOL SCORE – AN INTERVENTIONAL STUDY FROM SOUTH INDIA

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ABSTRACT

Introduction: Chronic non-healing leg ulcers are a misery for the patients and a challenge for the treating doctor. They pose considerable morbidity, financial and social burden on the affected person. The lack of response to conventional treatments makes it a difficult problem to tackle. Platelet rich plasma (PRP) has been a major breakthrough in the treatment of chronic non-healing ulcers as it provides various growth factors that enhance wound healing. The aim of our study was to evaluate the efficacy of activated autologous PRP in chronic non-healing leg ulcers of varying aetiologies.

Methods: Activated autologous PRP was injected to the ulcer borders at definite intervals according to the protocol to 50 patients with chronic non-healing ulcers of varying aetiologies. Treatment outcome was assessed by percentage reduction in ulcer surface area and photographic wound assessment tool (PWAT) score.

Results: Among 50 patients, 46% had diabetic ulcers, 28% had venous ulcers, 20% had leprosy ulcers and 6% had post traumatic ulcers. After PRP therapy, 76% of patients showed excellent response, while 8% patients showed good and 16% patients showed moderate response. None of the patients showed poor response.

Conclusion: Autologous PRP is a safe and effective treatment modality for recalcitrant non-healing leg ulcers of varying aetiologies. However formulations of universal guidelines for preparation and administration of PRP may help in better treatment outcome.

KEYWORDS :

INTRODUCTION

Chronic non-healing leg ulcers are defined as spontaneous or traumatic lesions that are unresponsive to initial therapy and do not heal in a defined time period with underlying systemic or local aetiological factors [1]. Chronicity of ulcers is contributed by factors like lack of rest, pressure, diabetes mellitus, venous and arterial insufficiency.It is a major health problem with a global prevalence of 9 to 13.1% [2]. In India about 4.5person/1000 population is affected by chronic leg ulcers [3]. These lower the quality of life (QoL) and productivity of the patientleading to substantial financial burden on the patient and the healthcare system [4].

Autologous PRP therapy for chronic leg ulcers has been a breakthrough in the stimulation and acceleration of soft-tissue healing [1]. PRP provides numerous signalling cytokines and growth factorswhich regulates inflammation, angiogenesis, synthesis and remodelling of new tissue [1]. Our study was formulated to examine to efficacy of PRP therapy in chronic leg ulcers of varying aetiologies.

MATERIALS AND METHODS

This is an interventional, non-randomised, uncontrolled, prospective study conducted over a period of 18months ina teaching hospital in South India. After institutional ethical committee approval, 50 patients with chronic leg ulcers of different aetiologies were treated with autologous PRP injections. Patients ≥18 yearswith ulcer duration ≥4 weeks were included in the study. Exclusion criteria included patients with haemoglobin<11gm%, platelet count <150000cells/mm^3, pregnancy, lactation, uncontrolled diabetes, local and/or systemic infections, patients on anticoagulants and immunosuppressive drugs. All the patients were screened for HIV, HBV and HCV infections. Ulcer swab for culture and sensitivity was done and appropriate antibiotics were given before the procedure.

Autologous PRP was prepared by Manual double spin method [5] in a test tube coated with Acid Citrate Dextrose (ACD-A) with 15ml blood. After the first spin of 2000rpm for 10minutes, the supernatant excluding the RBCs was subjected to second spin of 3000rpm for 10 minutes. PRP which has settled down was harvested from the test tube.Calcium Chloride 10% in a ratio of 10:2(PRP: $CaCl_2$) was added to make it activated. After thorough cleansing of ulcer area, 0.1ml/cm^2 of activated PRP was injected to ulcer borders and the rest was smeared over the ulcer surface. Sterile, non-absorbent saline dressing was given. Ulcer was inspected on day 3 and alternate day dressing was given till the next sitting. A total of 6 sittings were plannedweekly for the first 2 sittings and once in 2 weeks for the next 4 sittings with follow up period for 3months. On complete healing of the ulcer, injections were suspended.Percentage reduction in wound surface area was calculated by the formula - (Initial surface area – final surface area) x 100 / Initial surface area [5] . Ulcer was also assessed by photographic wound assessment tool (PWAT) which scores-edges, necrotic tissue- amount and tissue type, granulation tissue, surrounding skin colourand epithelialization [6].The response was graded as excellent(>90%), good(71-90%), moderate(30-70%) and poor (<30%). Student's paired t test was used to calculate statistical significance.

RESULTS

A total of 50 patients were treated with mean age of 52.58±7.97 years. The male to female ratio was 3.16:1. The duration of the ulcer ranged from 6 weeks to 2years (mean - 6.34±5.52 months). After PRP therapy, excellent response was noted in 76%, good response in 8%, moderate response in 16% and poor response in no patients. Overall mean duration of ulcer healing was found to be 4.74±2.81 weeks.All the 14 patients with venous ulcer showed excellent response (fig. 1).

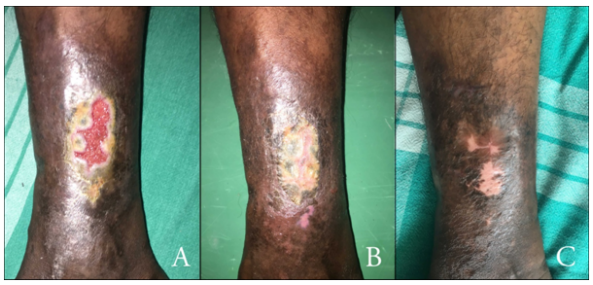

Figure 1: A) chronic venous ulcer over right leg before treatment. B) complete closure after one session of PRP. C) 3months after PRP therapy

Diabetic ulcer was the commonest (48%) of which 69.6% showed excellent response (fig. 2).

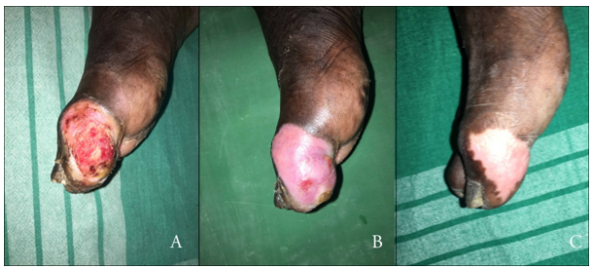

Figure 2A) chronic diabtetic ulcer over right great toe. B) complete re-epithelialisation after first PRP injection. B) Follow up picture

In case of leprosy ulcers, 60% showed excellent response (fig. 3)

Figure 3A) chronic ulcer over left sole due to leprosy. B) complete healing after 4 sitting of PRP injections

and 2out of 3 patients with post traumatic ulcers (fig.4) had excellent response.Out of 50 patients, complete healing was noted in 68% by 4 weeks and 84% by the end of the PRP therapy.

Figure 4A) post traumatic ulcer over left foot – dorsal aspect. B) after 3 sitting of PRP injections. C) complete closure after 4 weeks of PRP therapy.

The remaining 16% cases had complete healing during follow up period (Table.1).

No specific local or systemic complications were noted in any patients during treatment period. All the patients were followed up for 3months after the final PRP session. During that period there was no evidence of recurrence of the ulcers.

Table.1:Details of response to PRP therapy

Causes of ulcer	No. of patients (n%)	Mean duration of treatment (weeks)	Mean No. of PRP injections	No. of patients with complete re-epithelialisation (weeks)			
				<4 n(%)	4-6 n(%)	6-8 n(%)	>8 n(%)
Diabetes	23(46)	5.35±3.08	3.61±1.58	15(65.2)	0	2(8.6)	6(26.1)
Venous	14(28)	3.21±1.18	2.50±0.76	14(100)	0	0	0
Leprosy	10(20)	5.50±3.24	3.70±1.70	4(40)	3(30)	1(10)	2(20)
Traumatic	3(6)	4.67±3.05	3.33±1.53	1(33.3)	1(33.3)	1(33.3)	0
Total	50(100)	4.74±2.81	3.30±1.47	34(68)	4(8)	4(8)	8(16)

DISCUSSION

Being one of the common causes for lower limb amputations, management of non-healing leg ulcers continues to be a challenge for treating doctors. The mechanism of action of PRP is thought to be initiation of wound repair by releasing growth factors like platelet derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor(TGF) etc., via alpha granules degranulation upon activation[7]. It also triggers cell division and produces signalling protein which attracts macrophages and antimicrobial and homeostatic properties by producing fibrin[7].

In our study, among 50 patients, diabetes was the commonest aetiological factor which is in contrast to venous ulcer being reported as the most common cause for chronic leg ulcers in the literature [2]. The response to PRP in diabetic ulcers was comparable to the available published data[8].All the patients with venous ulcers in our study (n=14) showed excellent response and the mean duration of healing was 3.21 weeks which was shorter than what is reported in available literature[9,10].Among leprosy ulcers, 70% showed complete healing in 6weeks duration which comparable with the study conducted by Anandan et al[5] (n=50) which showed that mean duration of ulcer healing was 4.38 weeks with 88% of patients showing complete healing.

Maximum size of the ulcer treated in our study was 10cm^2 which is in accordance with available data [5]. According to Prabhu et al [11], 12.5% required skin grafting for complete healing inspite of PRP therapy. The cause for this may be increased size of the ulcer and other local/systemic factors.Ulcers over plantar area showed delayed wound healing. No correlation between duration of ulcer and duration of ulcer healing was noted. All the types of ulcers showed improvement with statistically significant reduction in surface area ($p<0.05$). Overallas well as all the types of ulcers except post traumatic ulcer showed statistically significant reduction in PWAT score (Table.2).

Table.2: Comparison of ulcer surface area and PWAT score before and after PRP

Types of ulcer	Mean surface area (cm^2)			Mean PWAT score		
	Initial	Final	P value	Initial	Final	P value
Diabetic (n=23)	6.70	0.65	<0.05	10.22	1.09	<0.05

Venous (n=14)	5.21	0.00	<0.05	9.57	0.29	<0.05
Leprosy (n=10)	5.60	0.60	<0.05	11.00	1.0	<0.05
Traumatic (n=3)	6.00	0.67	<0.05	9.67	0.67	–
All ulcers (n=50)	6.02	0.46	<0.05	10.16	0.82	<0.05

As universally accepted protocol for PRP preparation was not available, we formulated manual double spin method referring the available literature. As the methods of PRP preparation and administration have a significant impact on efficacy, the response to therapy by different methods may not be comparable. A comparison between different parameters of our study with available literature is given in table.3

Table.3: Comparison of present study with available literature.

Parameters	Present study	Chandramouli N et al[12]	Deshmukh NS et al[13]	Prabhu et al[11]	Anandan et al [5]	Raslan et al [14]
Mean Age	52 years	54.5 years	36.5 years	52.34 years	41.9years	41 years
Mean duration	6.34 months	19weeks	9.1 months	9months	11.62 weeks	NA
Type of study	Pr UnC	Pr RnC	Pr UnC	Pr Rn UnC	Pr Rn UnC	Pr UnC
Aetiology	Various aetiology	Various aetiology	Various aetiology	Various aetiology	Leprosy	Various aetiology
PRP therapy	I/L Inj.	Top A	I/L Inj.	Top A	Top S	I/L Inj.
Number of ulcers	50	15	10	104	50	24
No. of PRP applications	6 / till complete healing	4	4	10	6	Biweekly inj upto complete healing
Reduction in surface area	93.02%	81.58%	69.38%	81.73%	NA	NA

Key – Pr – Prospective, Rn – Randomised, NRn – Non randomised, UnC – Uncontrolled, C- case controlled, I/L Inj. – Intra lesional injection, TopA – Topical application, TopS – Topical spraying.

CONCLUSION

Activated autologous PRP therapy is a safe and cost effective procedure for non-healing leg ulcers. It shortens the in-patient stay and improves the overall QoL of the patients. A statistically significant clinical response in wound healing was obtained for all who underwent PRP therapy. But ulcers with $>10cm^2$ surface area may require procedures like skin grafting in addition to PRP therapy. Statistically Significant correlation was not found between duration of ulcers and healing time.

Limitations

The major limitation of our study was lack of control group. Due to inadequate number of post traumatic ulcers,the statistical significance could not be ascertained even though it had a good response with PRP therapy. Bigger sample size with traumatic ulcers should be evaluated for PRP therapy to find the correlation.

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