Original Research Article

The effects of autologous platelet rich plasma in Chronic non- healing ulcers

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Received: 03-12-2020 / Revised: 23-12-2020 / Accepted: 01-11-2021

Abstract

Introduction: Chronic non healing ulcers are those which do not heal by 4-6 weeks .and are characterized by a long inflammatory phase that hinders regenerative wound healing. They are the major cause of chronic wounds occurring in 70% to 90% of leg ulcers cases. Chronic non healing ulcers include venous ulcers, pressure ulcers, traumatic ulcers and diabetic ulcers. Autologous platelet rich plasma (PRP) is a safe, simple and inexpensive procedure in the treatment of chronic non healing ulcers. **Objectives: 1.** To determine the efficacy of autologous PRP in the management of chronic non healing ulcers and the time taken for complete healing of chronic non healing ulcers. **2.** To determine the duration and the rate of healing with the application of autologous platelet rich plasma. **Methods:** 63 Patients with complaints of long standing chronic non healing ulcers were included with the following inclusion and exclusion criteria attending OPDs or getting admitted in the Department of General Surgery, Victoria Hospitals and Bowring & Lady Curzon Hospitals, Bangalore during the period from November 2014 to August 2016. Sixty three non-healing ulcers of various etiologies were treated with autologous PRP at weekly intervals for a maximum of 6 sittings/weeks. At the end of 6 weeks, the reduction in size of the ulcers (area and volume) was assessed.**Results:** The mean age of the patients was 47.89 years (SD 14.09). Among 63 patients, 43 (68.3%) were males & 20 (31.7%) were females. The mean duration of healing of the ulcers was in 3.9 weeks (SD 1.06). The mean percentage improvement in the area & volume of the ulcer at 3rd week was 79.38% (SD 16.01) & 89.49% (SD 8.99). Similarly, at 6th week was 99.67% (SD 1.87) & 99.83% (SD 0.94) respectively.**Conclusion:** Chronic non healing ulcers are often difficult to heal because they lack the necessary growth factors to maintain the healing process. Conventional therapies do not provide satisfactory healing, since these treatments are not able to provide the necessary growth factors (PDGF, EGF, VGEF etc.) which are essential for the healing process. PRP is a safe, affordable, biocompatible and simple office based procedure for the treatment of non-healing ulcers.

Keywords: Platelet rich plasma, PRP, leg ulcers, growth factors, non-healing ulcers.

Introduction

Chronic non healing ulcer is defined as the ―loss of skin and subcutaneous tissue usually on the leg or foot, which takes more than 4-6 weeks to heal. The prevalence of leg ulcers is well documented to be varying between 0.18% to 1%.[1] Epidemiological studies have shown that the prevalence of leg ulceration in the adult population, either active or healed, is about 1% – 2%. The three major causes of lower extremity ulcers are venous, arterial and neuropathic. Venous ulcers account for more than 70% of these ulcers.[2] Chronic non healing ulcers include venous ulcers, pressure ulcers, traumatic ulcers and diabetic ulcers. Chronic wounds, especially in patients with diabetes mellitus (DM), are a major health challenge. The standard treatment algorithm includes a complete patient and wound assessment, history, physical examination and a variety of diagnostic tests that determine the need for infection control intervention, revascularization, excision and debridement, skin graft/flap, wound protection, and education.[3]Chronic non healing ulcers lack the necessary growth factors1 (GFs) and hence do not heal well. Conventional recombinant GF products, becaplermin[4] (recombinant platelet derived GF) have been approved by Food and Drug Administration for the treatment of chronic wounds.[5] However the medication is in a liquid form and therefore easily dissipates following wound application. In addition, it is very expensive and is unaffordable in developing countries such as India. Autologous platelet rich plasma (PRP) is a simple office based procedure which helps in enhancing wound healing[6] by releasing many GFs like platelet derived growth factors (PDGFs), fibroblast derived growth factors (FDGFs) and epidermal growth factors (EGFs). PRP is an autologous product derived from whole blood through the process of gradient density centrifugation. Autologous PRP4 is a safe, easy and cost effective method with good results in the management of chronic non healing ulcers.

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Materials and Methods

This is a prospective study involving 63 patients who presented with chronic non healing leg ulcers to General Surgery department of Victoria and Bowring and Lady Curzon Hospitals attached to Bangalore Medical College and Research Institute, Bangalore during November 2014 to August 2016. Ethical clearance was obtained

before starting the study from Ethical Clearance Committee of Bangalore Medical College and Research Institute.

Inclusion criteria: Patients in the age group of 18 to 80 years with long standing chronic non healing ulcers. 1. Ulcer > 4weeks duration and patients who had received conventional therapies for at least 4weeks. 2. Ulcer size < 5cms (25cm2). 3. Hb > 10gms

Exclusion Criteria: 1. Patients with platelet count < 100 X 104 /L. 2. Patients with known or suspected osteomyelitis/malignancies/ bleeding disorders. 3. Ulcer with active infection (presence of visible pus or copious wound exudates). 4. Presence of cellulitis, inadequate perfusion, ischemia or gangrene. 5. Ulcer size > 5cms. 6. Uncontrolled sugar levels. 7. Patients with serum creatinine > 1.5mg/dl. 8. Lipodermatosclerosis.

Methodology

Written informed consent was taken before their participation in the study. Detailed history including name, age, sex, address, contact number, occupation and history of medication was noted. Photographs of the ulcers before and after the dressings were taken, along with culture and sensitivity of the ulcers. After undergoing a detailed clinical examination and relevant investigations, the initial wound area was recorded after sharp debridement by Measuring length x width using metric tape. Patients were thoroughly examined and ulcer size (length, breadth & width) was measured by _clock-face' method described by Sussman using a cotton tip applicator and ruler. The outcome that is the area of the target ulcer was measured by using a metric tape. Results were subjected to statistical analysis.

Under aseptic precautions 20ml of venous blood was drawn and added to a test tube containing acid citrate dextrose in a ratio of 9:1 (blood: acid citrate dextrose). It was centrifuged at 5000rpm for 10-15 minutes to separate the red blood cells from platelet and plasma. Then the supernatant which composed of platelets and plasma was collected and centrifuged again at 2000rpm for 5-10minutes in order to pellet the platelets. Thus the PRP was obtained and 5-10% calcium chloride was added in the ratio 0.3:1 (0.3ml for 1ml of PRP). PRP was applied onto the wound after proper surgical debridement. After applying PRP, ulcer was dressed with a non-absorbent dressing. After 1 week the dressing was removed with 54 normal saline and assessed for the improvement. The procedure was repeated once weekly for 6 weeks. The wound area and volume was calculated by length×width×0.7854 and length×width×depth×0.7854 respectively with photographs at every sitting. The treatment outcome was defined as a percentage in change of area and volume of the ulcer and was calculated as initial measurement minus assessment day measurement divided by initial measurement.

Statistical Analysis: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale with in each group. SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs & table.

Results

Table 1: Age and Gender-wise distribution of Study participants

Gender	No. of Participants	Percentage (%)
Male	43	68.3
Females	20	31.7
Total	63	100

According to table 1 The age of these patients ranged from 19 years to 78 years with a mean of 47.89 years (SD 14.09). Among the 63 patients, 43 (68%) were males and 20 (32%) were females. Incidence of chronic lower limb ulcers were more in males compared to females.

Table 2: Duration and Onset of the Ulcers

Duration (weeks)	No. of Participants	Percentage (%)
1-4	16	25.4
5-8	47	74.6
>8	0	0
Onset of Ulcer		
Spontaneous	39	61.9
Traumatic	24	38.1

As per table 2 The duration of the ulcer ranged from 4 weeks to 8 weeks with a mean duration of 5.25 weeks. 16 (25.4%) patients had duration less than 4 weeks, 47 (74.6%) patients had duration of 5-8 weeks. Traumatic ulcers were 38 % (24 ulcers) and spontaneous ulcers were 62% (39 ulcers). It was observed spontaneous ulcers were more in the study. With Medial Malleolus was the most common site.

Table 3: Initial Platelet Count Distribution of Patients with Culture and sensitivity

Initial Platelet Count	No. of Participants	Percentage (%)
<2.5	18	28.6
2.5-3.5	27	42.8
>3.5	18	28.6

As per table 3 culture yields no growth in 50 ulcers (79.4%), 7 ulcers (11.1%) had staphylococcus aureus organisms, 18 patients (26.8%) had initial platelet count of less than 2.5 lakhs/cu mm, 27 patients (42.9%) had between 2.5-3.5 lakhs/cu mm and another 18 patients (26.8%) had more than 3.5 lakhs/cu mm, with mean platelet count of 2.95 lakhs/cu mm.

Table 4: Assessment at Different Time Periods- Area

Area	Min-Max	Mean ± SD	Difference-	t value-	P value-
Baseline	3.12-15.45	11.02±3.31			
@ 1st week	1.24-12.82	8.30±3.31	2.722	20.573	<0.001**
@ 2nd week	0.00-19.42	5.55±3.39	5.468	22.555	<0.001**
@ 3rd week	0.00-7.56	2.68±2.23	8.343	30.988	<0.001**
@ 4th week	0.00-5.36	0.66±1.27	10.360	27.653	<0.001**
@ 5th week	0.00-3.21	0.14±0.59	10.876	26.379	<0.001**
@ 6th week	0.00-1.26	0.04±0.22	10.981	26.354	<0.001**
Last visit	0.00-0.64	0.01±0.08	11.010	26.336	<0.001**

As per table 4 the area involved showed at different time periods with baseline being reference. It was at all weeks from 1st to last week the p-value was highly significant (p<0.05). this clearly show the importance of PRP and the ability of healing of ulcers.

Table 5: Weeks of Complete Healing

Weeks of healing	No. of Participants	Percentage (%)
1	0	0
2	5	7.9
3	15	23.8
4	30	47.6
5	9	14.3
6	2	3.2
7	2	3.2

As per table 5 The mean duration of healing of the ulcers was in 3.9 weeks (SD 1.06). The mean percentage improvement in the area & volume of the ulcer at 3rd week was 79.38% (SD 16.01) & 89.49% (SD 8.99). Similarly, at 6th week was 99.67% (SD 1.87) & 99.83% (SD 0.94) respectively.

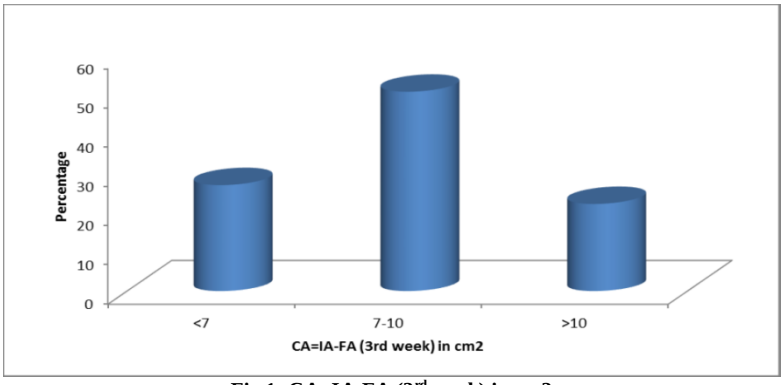

Fig 1: CA=IA-FA (3rd week) in cm2

Figure 1 shows In this study, ulcers treated with PRP had better wound contraction of Mean ± SD 8.34 ± 2.14 at 3rd week. These were found to be statistically significant P<0.001**, significant, on Student t test.

Discussion

Chronic non healing ulcers management is still challenging in this advanced medical era because it depends upon multiple factors. The idea of wound dressing to keep the wound moist and to provide the environment for healing and to prevent the wound from getting infected. Chronic wounds have been managed with different type of dressings. The present study conducted at Bowring & Lady Curzon Hospitals, BMCRI. Platelet rich plasma, it has been used also in periodontal, maxillofacial surgery, orthopedics and trauma surgery. No adverse reaction or complication has been reported. In this study we selected chronic non healing ulcers and used platelet rich plasma for wound dressings. A total of 63 patients were selected in this study based on study inclusion and exclusion criteria. In this study, Incidence of chronic lower limb ulcers was more in males as compared to females. The mean age in the study was 47.89 years.

In this study, spontaneous ulcers were 61.9 % and Traumatic ulcers were 38.1%. It was observed spontaneous ulcers were more. In this study, ulcers around medial malleolus of the foot being most common site constituting 34.9%. On dorsum constituting 30.2%. Plantar aspect making 19.0%, followed by lateral malleolus making 14.3% and only one patient (1.6%) had an ulcer on great toe. In this study, mean fasting blood sugar was 108.06 (SD 17.57). Similar study were done with nearly similar results.[7-11]In our study it was observed that patients receiving Platelet rich plasma dressing had better mean wound contraction of 8.34 ± 2.14 in cm2 (50.8%). These were found to be statistically significant on Student T test (p<0.001) suggesting that Platelet rich plasma enhances wound healing in chronic Lower Limb ulcers. In this study no adverse reaction or complications has occurred. Slightly different results in some studies.[12-14]In this study the mean time taken for complete healing of the ulcers were 3.90 weeks (SD 1.06). The overall mean percentage improvement in the area & volume of the ulcer at 3rd week was 79.38% (SD 16.01) & 89.49% (SD 8.99). Similarly, at 6th week was 99.67% (SD 1.87) & 99.83% (SD 0.94) respectively. From our study, we can say that platelet rich plasma dressing therapy facilitates wound healing in patients suffering from chronic lower limb ulcers.

Conclusion

Chronic wounds are a frequent problem in developing countries and are often difficult to heal because they lack the growth factors necessary for the healing process, and are frequently complicated by super infection. Conventional therapies such as dressings, surgical debridement, and even skin graft cannot provide satisfactory healing since these treatments are not able to provide enough necessary growth factors to modulate the healing process. Patients with chronic ulcers frequently have to undergo long-term dressing regimens and repetitive painful debridement without a definitive outcome. PRP contains various growth factors that are necessary in wound healing. Moreover, it also has some other advantages. After blending with calcium and thrombin, PRP turns into gel, which prevents growth factors and leukocytes from releasing, and maintains their activity for a longer time within the wound. Additionally, a high concentration of leukocytes present in PRP is also helpful in preventing infections.

Currently there is a paucity of critical scientific data regarding the beneficial effects of platelet rich plasma in clinical procedures. There have been animal and human studies both purporting and refuting its adjunctive positive effect. In theory, PRP has many beneficial effects such as autologous supply of growth factors and improved wound healing. However, from the current available literature, there is great variability in study design, clinical and radiographic parameters that were measured, and clinical outcome. Many studies claiming a positive beneficial effect suffer from a poor study design. Many have no controls or a limited sample size. Platelet rich plasma dressing is

an effective modality to facilitate wound contraction in patients suffering from lower limb ulcers and can be used as an adjunct to conventional mode of treatment (conventional dressings) for healing of Lower Limb ulcers. In general, PRP is a safe, affordable, biocompatible and simple office based procedure for the treatment of non-healing ulcers.

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Conflict of Interest: Nil
Source of support:Nil