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Efficacy of autologous platelet gel versus conventional dressing in chronic wounds-comparative study using PWAT

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Abstract
Introduction: Chronic wounds are a frequent problem in developing countries and represent a heavy burden to the patient. Platelet extract is known to release various growth factors which include Platelet Derived Growth Factor (PDGF) and Epidermal Growth Factor (EGF), which act locally on the wound and hasten the healing process.
Methods: The source of data were patients attending the outpatient on a regular basis or those admitted as inpatients for the management of chronic wounds to the Department of General Surgery, J.S.S.H., Mysore from September 2014 to September 2016. Total of 60 patients were studied;
Results: Autologous platelet gel showed faster and better healing rates. The mean area reduction was statistically significant in the study group. There were no adverse effects or reactions seen with the use of autologous platelet gel among the study group.
Conclusion: This evaluation provides strong evidence that autologous platelet gel dressings provide safe and cost effective method of enhancing the healing rates of chronic wounds, reducing the overall hospital stay and morbidity.

Keywords: Chronic ulcer, platelet dressing, granulation tissue, bio-engineering

Introduction
Wound healing is a complex process of cellular, immunological and hormonal components interacting to result in a healed wound. For most patients this proceeds unabated and without sequelae, but for millions of others, wound healing is not so simple. Studies on chronic wound fluid suggest that growth factor levels are reduced and perhaps the levels of proteases are high [1]. There may thus be an intrinsic molecular defect in chronic wounds which prevents their healing. This opened a new window of treatment by stimulating healing of chronic wounds by therapeutic manipulation of the required growth factors.
Platelet extract has shown to enhance and accelerate both soft tissue and hard tissue healing [2]. Its effectiveness is based on its high level of growth factors such as platelet derived growth factor (PDGF), transforming growth factor-β (TGF-β), epidermal growth factor (EGF), Vascular endothelial growth factor (VEGF) and insulin like growth factor (IGF) [3].
Platelet extract can be made using recombinant technology, using blood bank platelet concentrate or by using autologous blood.
Since not all patients can afford commercially available recombinant platelet gel or blood bank platelet for dressing, autologous platelet gel promises a simple and cost

Methodology
This a prospective randomized controlled study, to test the efficacy of autologous platelet gel in epithelialization and wound reduction in chronic wounds. The study was conducted in the department of surgery, JSS Medical College, Mysore for a period of one year from September 2014 to September 2016.
The source of data were patients attending the outpatient on a regular basis or those admitted as inpatients for the management of chronic wounds. 60 patients were studied. 30 cases were randomly chosen for study with autologous platelet gel and 30 cases received conventional dressing for the chronic wounds.

Sample size: 60 cases, 30 patients received autologous platelet gel and 30 patients received conventional dressings.

Inclusion criteria: Age group – 18-80 yrs, Ulcer ≥ 8 weeks, Hb > 10 g%,FBS ≤ 110mg% and PPBS ≤140 mg% if diabetic

Exclusion criteria: Ulcers with evidence of malignancy, Active infection with pus discharge, slough, Indexed ulcer has exposed tendons, ligaments or bone, Evidence of gangrene in the ulcer or on any other part of limb, Patient is currently receiving or has received radiation or chemotherapy within the last 3 months, Patient has known or suspected osteomyelitis, Patient with active cancer, decompensated liver disease, or on renal dialysis, Patient on steroids for another illness

Method of Collection of data: Detailed history was taken in all cases regarding the duration, mode of onset, progression and associated symptoms. The etiological factor that might be responsible for chronicity was also elicited.
Ulcer examination was done in all cases and wound assessed of its characteristics. 4 dressings were done 3-4 days apart for each patient (Day 1, 4, 7, 10). Size of ulcer was plotted over a graph and a photograph was taken of the wound, at the beginning and at the end of study (Day 1 and Day 14) and photographic wound assessment tool (PWAT) used in this comparison

Statistical analysis: Unpaired students "t" test and paired "t" test were used to find out the statistical significance. A '*P*'<0.05 was taken as significant.

Step 1: Collection of Blood: Under all aseptic precautions, 12 ml of blood was drawn intravenously from the antecubital region into 2 bulbs containing CPDA (0.7 ml) each. The bulbs were shaken thoroughly to ensure mixing of anticoagulant with drawn blood

Step 2: Preparation of Platelet Poor plasma: The blood centrifuged at 3000 rpm for 10 mins. The supernatant formed is Platelet Poor Plasma (PPP) and buffy coat. 2 ml of PPP was aspirated and kept aside for use in the preparation of autologous thrombin (see step 4)

Step 3: Preparation of Platelet rich plasma: Remaining PPP, Buffy coat (upper 1 mm of RBC) layer is collected in another vacutainer and again centrifuged at 1000 rpm for 10 mins. The upper half is discarded and the lower half yields concentrated platelet rich plasma.

Step 4: Preparation of autologous thrombin: 2 ml of PPP which was kept aside is thoroughly mixed with 0.08 ml of 10% Calcium gluconate. This resulted in clot formation and a supernatant which is the autologous thrombin, after 20 mins.

Step 4: Preparation of PRP gel: 0.5 ml of the autologous thrombin is added to the concentrated PRP which forms a transparent PRP gel after a few minutes.

Results

The present study was conducted in JSS Medical College, Mysore and the findings are tabulated below. During the study year from September 2014 to September 2016, 60 patients with chronic ulcers were randomized into study (PDGF) and control (conventional dressing) group. These groups were studied for the effect of conventional dressing versus PDGF on epithelialization and wound reduction.
Analysis was done using Fischer's Exact Test for categorical data and students paired 't' test for continuous variables within the groups and unpaired 't' test for continuous variables between cases and controls
In this study, the age of the patients ranged from 18 years to 78 years. 53% in the 40-60 yeas group. This includes 53% in the cases and 53% in the control group (table 1).
The mean age of cases was 47.93 ± 15.86 years and the mean age of controls was 47.20 ± 14.45 years. The difference in mean age between cases and controls was not statistically significant (p = 0.896) (table 2).
In this study, 50% of the wounds were of non-specific traumatic etiology. The next most common wounds were pressure sores at 16.6%. There is no statistical difference between cases and controls with regard to the etiology of the wounds (p = 0.797) (table 3).
The mean duration of wound in cases was 103.73 ± 130.75 weeks and 52 ± 98.2 weeks in the control group. The difference of mean duration of wound in cases and controls was not statistically significant (table 5 and graph 1).
The mean area at the beginning of the study was 518.73 ± 383.02 mm^2 in the cases and 517.73 ± 506.91 mm^2 in the controls. There was no statistical difference between the two groups (p = 0.995) before initiation of treatment (table 6 and graph 2).
There was a statistically significant difference between the area before the treatment and after the treatment among the cases (*P*<0.001) whereas no statistical difference between the area before the treatment and after the treatment was present for the controls (p = 0.067) (table 7 and graph 3).
Mean reduction in area of ulcer, 237.67 mm^2 for the cases was more than that of controls, 17.04 mm^2 after the initiation of treatment and the difference was statistically significant (*p*<0.001) (table 8 and graph 4). The percentage reduction in cases was 46.95% ± 15.16% and 2.28% ± 2.54% in controls which was statistically significant (p = 0.000).

Discussion

Autologous platelet rich plasma for the treatment of chronic wounds has been under development as a theory and for clinical application since 1986 when Knighton *et al.* demonstrated for the first time its use in stimulating repair of non healing human wounds. Since then there have been many case reports and case studies but few randomized control trials (RCT) demonstrating its efficacy.
The recent Cochrane review lists 9 eligible RCTS comparing autologous platelet rich plasma with placebo or alternative treatments for chronic wounds in adults, and concludes that currently there is no evidence that autologous PRP is of any value. However, current evidence is based on a small number of RCTS.

Comparison with 9 other RCTS

Study	No of Patients	Type of wounds	Duration of treatment	Demonstrated Efficacy of PRP
Weed 2004	26	Mixed wounds	24 wks	No
Driver 2006	72	Diabetic foot ulcers	24 wks	Yes
Kakagia 2007	51	Diabetic foot ulcers	8 wks	Yes
Planinsek 2007	10	Venous ulcers	-	Yes
Anitua 2008	15	Mixed wounds	8 wks	Yes
Present Study	60	Mixed wounds	2 wks	Yes

In comparison with 4 of the above trials which studied mixed chronic wounds, the mean age of the cases and controls were largely in 60-70 yr age group as compared to the present study, where the mean age was in the 40-50 yr age group. In Weed 2004, the cases were older than the controls. Anitua 2008 reported that participants in the control group were older than those in the experimental group. In the remaining studies including the present study, the difference in age between cases and controls was not statistically significant.

Theoretically, the leading causes of delayed wound healing include diabetes, peripheral vascular disease, venous disease and pressure sores followed by a host of local and systemic causes. Stadelman has stated that hypoxia is a significant contributing factor in the formation and failure of healing of vascular ulcers.

Experimentally, it has been demonstrated that growth factors can be ineffective in augmenting wound repair in ischemic, hypoxic wounds. These observations led Zhao *et al.*, to suggest that growth factors may need to be used with supplemental hyperbaric oxygen to achieve optimal benefit in ischemic wounds.[23] In view of the above findings, patients with peripheral vascular disease were excluded from the present study. Wounds of arterial origin were also excluded in the Anitua study.

Unlike the other studies, the present study had a sizable proportion of the wounds of nonspecific traumatic etiology – nearly 50% in both cases and controls. 2 of the wounds in each group were due to snake bites, the chronicity a sequelae of the local toxin.

Knighton, Krupski and Weed studied wounds only of the lower limb. Anitua included wounds in the pelvic region which made up 25% of the cases and 29% of the controls. The present study also included wounds in the pelvic region which made up 20% of the cases and 13% of the controls.

In the Knighton study, the experimental group had a longer duration than the control group (119 weeks compared to 47 weeks) whereas in the Anitua study, the wound duration was longer in the control group (110 weeks versus 68 weeks). The remaining studies including the present study had no statistical difference of wound duration between cases and controls

Comparison of mean ulcer size and duration

Study	Ulcer size Case (cm^2)	Ulcer size Control (cm^2)	Duration of ulcer Case (wks)	Duration of ulcer Control (wks)
Knighton 1990	11.6	22.0	119.0	47.0
Krupski 1991	13.0	28.9	22.0	24.8
Weed 2004	6.7	5.7	51.3	54.4
Anitua 2008	5.5	8.9	68.0	110.0
Present study	51.9	51.7	106	52

The mean size of the wounds in the present study was 51.7 cm^2 which is much higher than in the other studies being 4 times more than the next largest in the series, 13 cm^2 of the Krupski study. In the Krupski study, the control group presented with a larger wound area than the experimental group (29 cm^2 versus 13 cm^2). The remaining studies showed comparable wound size between cases and controls.

Although the initial area of the wounds (in mm^2) were similar in both groups, the final area of the wounds was significantly reduced in the platelet group as compared to the control group at the end of the study. The platelet group showed filling up of wound bed with granulation, epithelialization and wound contraction.

In the Krupski trial, the rate of healing in cm^2/week was studied as a secondary outcome. The rate of healing in the control group was 1.9 ± 2.7 cm^2/week. In contrast, the wounds in the platelet group increased in size and thus the values are recorded as negative numbers -4.3 ±12.2 cm^2/week. In the present study the rate of healing in the control group was.85 ± 1.67 cm^2/week and in the platelet group was 11.87 ± 9.71cm^2/week (p<0.05)

Two trials reported the percentage of wound area healed as a secondary outcome. Knighton reported a mean percentage of surface healed to be 93% ± 17% for the PRP group and 41% ± 39% for the control group at the end of the study of 8 weeks. In the Anitua study, at the end of 8 weeks, the mean percentage of surface healed in the PRP group was 72.94% ± 22.25% whereas it was 21.48% ± 33.56% in the control group (p<0.05). In the present study, the Platelet group showed 46.95% ± 15.16% percentage reduction whereas the control group showed 2.28% ± 2.54% at the end of two weeks.

Comparison of Percentage Reduction of wounds

	% Reduction Cases (cm^2/wk)	% Reduction Controls (cm^2/wk)	p
Knighton 1990	93% ± 17%	41% ± 39%	<0.001
Anitua 2008	72.94% ± 22.25%	21.48% ± 33.56%	<0.01
Present Study	46.95% ± 15.16%	2.28% ± 2.54%	<0.001

The time taken per platelet dressing was 30-40 mins. No cost was incurred by the patient as all materials required were available as hospital supply. No adverse effects were seen with platelet dressing. The growth factors present in platelets are the individual patient's natural growth factors in their biologically determined ratio. Because it is autologous, it presents no risk of immunogenic reactions or human to human disease transmission like HIV or Hepatitis B, thus making it a safe modality of treatment.

The study, inspite of its shortcomings, does indicate that topical application of autologous platelet is more effective than standard therapy in helping a chronic ulcer to heal and that it has the potential to be a useful, safe and cost effective adjunct to wound healing.

Conclusion

With the use of autologous Platelet Derived Growth Factor (PDGF) dressings in comparison with the control group for the treatment of chronic ulcers, the following conclusions were derived.

- PDGF showed faster and better healing rates among the study group
- Area reduction was statistically significant in the study group
- There were no adverse effects or reactions seen when autologous Platelet derived growth factors (platelet gel) were applied over the ulcer.

It is a cost effective procedure, helps in early skin grafting and reduced hospital stay.

Tables and graphs

Table 1: Age at Presentation

Age Group (in yrs)	No of Patients	Percentage (%)	Cases n= 30(%)	Controls n= 30 (%)
<20	2	3	0(0)	2(6)
20-40	14	23%	8(26)	6(20)
40-60	32	53	16(53)	16(53)
60-80	12	20	6(20)	6(20)

Table 2: Distribution of study subjects according to Gender

Sex	No of patients	Percentage (%)	Cases n =30(%)	Controls n=30 (%)
Male	54	90	28 (93.3)	26(86.7)
Female	6	10	2(6.7)	4(13.3)

Table 3: Showing Various Etiologies of Wounds

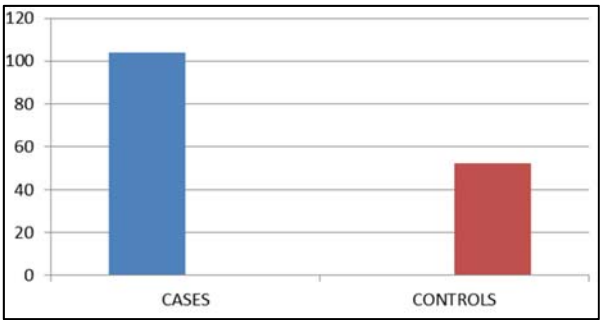
Etiology	Cases (%)	Controls (%)	Total (%)
Non Specific Traumatic	16(53.3)	14(46.6)	30(50)
Pressure Sore	6(20)	4(13.3)	10(16.6)
Diabetes	2(6.7)	6(20)	8(13.3)
Other Infected Ulcers	4(13.3)	4(13.3)	8(13.3)
Varicose Veins	2(6.7)	2(6.7)	4(6.7)

Table 4: Showing side of wound

Side	Cases (%)	Controls (%)	Total (%)
Left Lower Limb	14(46.7)	12(40)	26(43.3)
Right Lower Limb	14(46.7)	16(53.3)	30(50)

Table 5: Showing Duration of wound

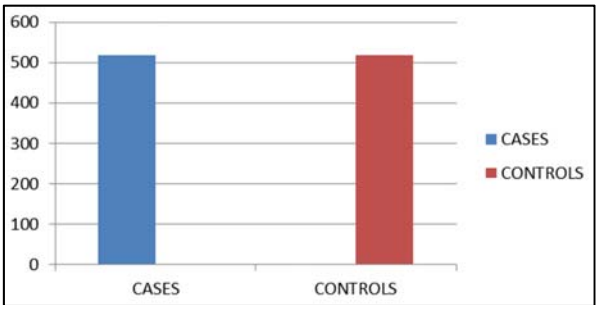
	Duration In Weeks		P
	Mean	Sd	
Cases	103.73	130.75	0.231
Controls	52	98.2	



Graph 1: Duration in weeks

Table 6: Showing Initial Wound Area In mm^2

	Before		P
	Mean	Sd	
Cases	518.73	383.02	0.995
Controls	517.73	506.91	



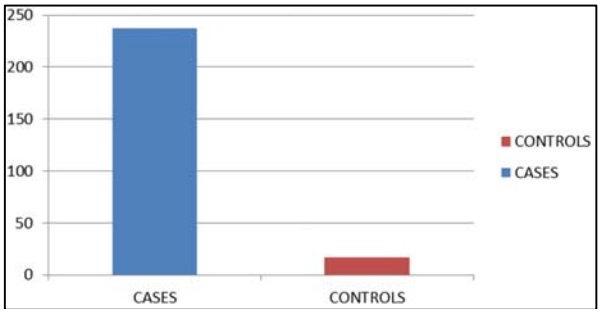
Graph 2: Initial wound area in mm^2

Table 7: Showing Comparison of before and after Area In mm^2

	Area Before		Area After		P
	Mean	Sd	Mean	Sd	
Cases	518.73	383.02	281.07	225.18	<0.001
Controls	517.73	506.91	500.67	485.86	0.067

Table 8: Showing Reduction of Mean Area of Ulcer of Cases and Controls after Treatment

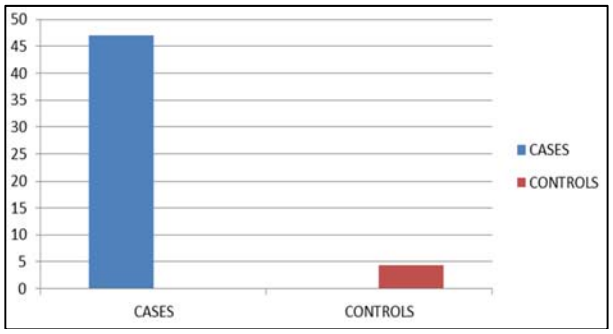
	Mean Area Reduced In Mm^2	Sd	P
Cases	237.67	194.02	<0.001
Controls	17.07	33.30	



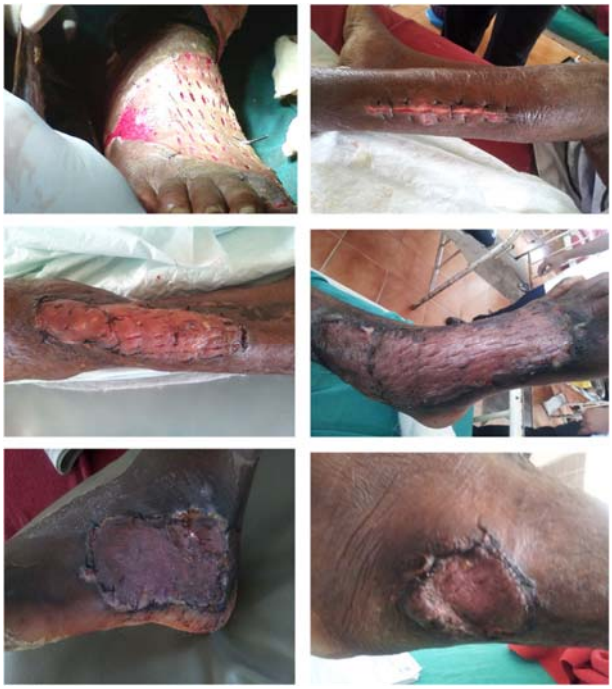
Graph 3: Area Reduced In mm^2

Table 9: Showing Percentage Reduction of Wounds

	Percentage Reduction		p
	Mean	SD	
Cases	46.95	15.16	0.000
Controls	2.28	2.54	



Graph 4: Percentage Reduction



Photos: Final outcome of PDF Dressing

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