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Original Research Article

Treatment of Ulcers with Platelet Rich Plasma Impregnated Dressings

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Abstract: Ulcers, especially in the lower limb are a frequent problem encountered in our hospitals and are often difficult to heal because they lack the necessary growth factors to maintain the healing process, and are frequently complicated by superinfection. Conventional therapies such as dressings and surgical debridement cannot provide satisfactory healing since these treatments are not able to provide enough necessary growth factors to modulate the healing process. Platelet-rich plasma (PRP), as a concentrate of platelets, releases a high concentration of multiple growth factors that can modulate healing processes. Furthermore, PRP also contains a high level of leukocytes, which can inhibit infection. PRP has been widely used in many clinical applications. The objective is to study the effect of PRP dressing in comparison to regular saline dressing on ulcers and its influence in wound healing. A prospective randomized trial of platelet rich plasma dressing and regular saline dressing was done. Two comparative studies were done, one under the setting of the presence of diabetes as comorbidity and the other without it. Both the studies compare the efficacy of platelet rich plasma versus regular saline dressing in terms of duration of stay in hospital. A total of 114 case were taken for study. Duration of stay in hospital was less in case of wounds treated with PRP dressings than that of Saline dressings. The results were similar for both diabetic and nondiabetic ulcers with PRP dressings having a shorter duration of stay in hospital irrespective of diabetes as comorbidity.
Keywords: Ulcers, platelet rich plasma, diabetes.

INTRODUCTION

The term ulcer is used to refer to spontaneous or traumatic lesions, typically in the lower extremities, which do not heal in a reasonable time, with an underlying etiology that may be related to systemic disease or local disorders. The healing process is complex and dynamic. Once ulcers start to be treated, they eventually heal completely in most cases. However, due to some risk factors associated with the patient (comorbidities) or to the ulcer (infection), acute ulcers can become chronic.

At present ulcers are treated with antibiotics first empirical and then according to the culture sensitivity results along with wound debridement with Betadine wash and saline dressing. Once healthy granulation tissue is formed the ulcer is treated with split skin graft if large, if small it is allowed to heal with secondary intention. Using platelet-rich plasma (PRP) is one of the new treatments for ulcers. Platelet-rich plasma (PRP) is a platelet concentrate that has been widely used in a variety of clinical applications. A number of studies show that PRP enhances and accelerates both soft tissue and hard tissue healing.

The effectiveness of PRP 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).

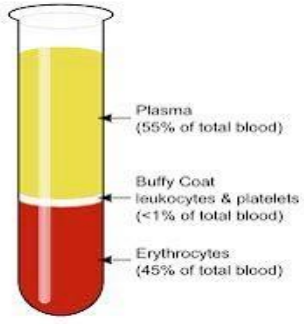

Fig-1: PRP (Buffy Coat)

PRP also includes three proteins in blood known to act as cell adhesion molecules: fibrin,

fibronectin and vitronectin.

PRP also contains a high level of leukocytes, which can inhibit infection. Platelets also secrete TGF-Beta and MCP-1 that would attract monocytes and neutrophils to the wound site thus reducing local sepsis.

The growth factors are important in modulating mesenchymal cell recruitment, proliferation, and extracellular matrix synthesis during the healing process. Chronic cutaneous 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 superinfection. 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 ulcers frequently have to undergo long-term dressing regimens and repetitive 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. The calcium and thrombin also activate the alpha granules to release the above mentioned growth factors. Additionally, a high concentration of leukocytes contained in PRP is also helpful in inhibiting infections. The preparation of PRP is simple. Only two centrifugations of autologous whole blood and a total of 20 to 30 minutes is required. PRP is biocompatible and safe, and does not carry an infection risk.

AIMS AND OBJECTIVES

To study the efficacy of Platelet-rich plasma (PRP) in the treatment of ulcers over regular dressing in setting of diabetic and non-diabetic conditions.

The outcome of the patients with an ulcer depends on the following conditions

1. Age: Elderly patients tend to have significant comorbidities and are more likely to be on multiple medications, which impact on healing. Ageing itself also affects both the rate and quality of the healing process.
2. Comorbidities: diabetic patients with hard-to-heal wounds may have a number of comorbid conditions that affect the healing process. Diabetes is a significant factor and can affect healing.
3. Ischaemia: As described, wound healing is dependent on cell replication, the formation of a new supporting matrix and the elimination of damaged, necrotic, foreign or infecting material. All of these processes are energy dependent and only occur effectively in the presence of an adequate blood supply and the delivery of nutrients and oxygen to the wounded area. This process is impaired in the presence of systemic disease (cardiac and respiratory failure), regional ischaemia (peripheral vascular disease) and local ischaemia within the wound, secondary to poor neo- vascularisation and angiogenesis.
4. Infection and Inflammation: Inflammation is a necessary component of the healing process, but is detrimental if it continues at an inappropriate level beyond the initial phases of healing, or is stimulated by other events such as infection within a wound. Diseases such as rheumatoid arthritis and medication (eg steroids) alter the inflammatory process. This can have a detrimental effect on healing.

In the following situations Platelet-rich plasma (PRP) can be of much help because of the supply of growth factors and leukocytes at local level.

MATERIALS AND METHOD OF STUDY

Patient Selection:

Written informed consent was obtained from all patients undergoing PRP application. Full-thickness skin or soft tissue defects were present in these patients. There was no necrotic tissue in the wound, for which the risk of infection was assumed to be low or removed by wound debridement. Ulcer types were divided into diabetic and non diabetic. The haemoglobin of the patient must not be below 11gms% and heamtocrit not below 35% which was checked before autologous transfusion. The patient should not have consumed Acetaminophen, aspirin or alcohol for 48 hrs before transfusion.

Ulcer Assessment:

After ulcer grading into diabetic or non-diabetic also taking age into consideration, all ulcers with slough or necrotic tissue were surgically debrided of necrotic tissues by a surgeon. Then, ulcer depth and surface area were measured. Debridement if excessive was done under spinal anaesthesia else if small and in the peripheral region local anaesthesia was preferred. After wound debridement betadine and peroxide wash was given to remove the remnant slough or necrotic tissue. Usually wound healing starts in the few first days after debridement and granulation tissue appears in 5 to 10 days.

Intervention:

After debridement, the wounds of the control group were irrigated with normal saline and dressed with sterile gauzes. However, in the

intervention group, the debrided ulcers were dressed with sterile gauzes impregnated with PRP. For this purpose, a piece of sterile gauze impregnated with PRP was placed on the ulcer surface and supported by two pieces of dry sterile gauzes and fixed using cotton bands. In an interval of 5 days this method was used 3 times and regular saline dressing was applied on the other days as the shelf life of PRP is 5-7 days. PRP dressing was performed only at the beginning of study in the 5 day interval and subsequent dressings in both groups were performed similarly using normal saline and ordinary sterile cotton gauzes. To avoid confounding factors, all patients were advised not to use any other material on the ulcer and avoid any dressing change without informing the researcher. All patients were also instructed about the signs of ulcer infection and asked to inform the researcher if any signs of infection occurred. All dressing changes during the study were performed by the first researcher in hospital.

Preparation of Platelet-Rich Plasma (PRP):

The patient's phlebotomization consisted of 350 mL of whole blood and was drawn from the median cubital vein with a 21-gauge needle in a blood bag with anticoagulant added. Blood was drawn at a slow and steady phase, mixing the anticoagulant with the blood to prevent the formation of clots. Blood was processed by centrifuging it and plasma separated from packed cells. The packed cells are transfused back into the patient. The plasma is again centrifuged to obtain platelet rich plasma. The total yield of platelet rich plasma was 50ml. This was stored at a temperature of 22-24 with platelet agitator. This platelet rich plasma was used for dressing by soaking the gauze in the platelet rich plasma and covering the wound. In an interval of 5 days this method was used 3 times and regular saline dressing was applied on the other days.

Fig 2: Phlebotomization

Fig 3: Plasma Separator

Fig 4: Centrifuge

METHOD OF STUDY

A total of 114 cases of ulcers which were treated at our hospital from 2015 -2016 were included in the study with 41 cases using platelet rich plasma dressing. A prospective randomized trial of platelet rich plasma dressing and regular saline dressing was done. Two comparative studies were done, one under the setting of the presence of diabetes as comorbidity and the other without it. Both the studies compared the efficacy of platelet rich plasma versus regular saline dressing in terms of duration of stay in hospital.

Fig -5 & 6: Preparation of PRP dressing

Fig 7&8: Ulcer being dressed with PRP

RESULTS/DATA ANALYSIS

A total of 114 cases were studied including both diabetic and nondiabetic ulcers, preferably of the foot. PRP dressing was done in 41 cases and saline dressings for the remaining 73 cases. Rate of wound healing,epithelisation and wound contracture/reduction in size of raw area were observed for all cases. Duration of stay in the hospital was analysed for statistical purposes. Statistical analysis was done amongst the two groups under study.

Fig 9: Ulcer after PRP dressing showing granulation tissue with contracted width and depth of the wound

Table 1: Age wise distribution

AGE		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	21TO 40	18	15.8	15.8	15.8
	41TO 60	47	41.2	41.2	57.0
	61 ABOVE	49	43.0	43.0	100.0
Total		114	100.0	100.0	

Table 2: Sex wise distribution

SEX		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	MALE	64	56.1	56.1	56.1
	FEMALE	50	43.9	43.9	100.0
	Total	114	100.0	100.0	

Table 3: Diabetic Vs Non-Diabetic Ulcer

Ulcer		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	DIABETICULCER	85	74.6	74.6	74.6
	NONDIABETICULCER	29	25.4	25.4	100.0
	Total	114	100.0	100.0	

Table 4: Saline Vs PRP dressing

Dressing		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	DRESSING	73	64.0	64.0	64.0
	DRESSING WITH PRP	41	36.0	36.0	100.0
	Total	114	100.0	100.0	

Table 5

Duration of stay in Hospital		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	1 TO 10DAYS	1	.9	.9	.9
	11TO 20DAYS	56	49.1	49.1	50.0
	21 TO 30DAYS	57	50.0	50.0	100.0
Total		114	100.0	100.0	

Table 6

Case Processing Summary	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
AGEt * DOS	114	100.0%	0	.0%	114	100.0%
SEX * DOS	114	100.0%	0	.0%	114	100.0%
ULCER * DOS	114	100.0%	0	.0%	114	100.0%
DRESSING * DOS	114	100.0%	0	.0%	114	100.0%

Table 7: AGE vs DOS

	DOS			Total
ageact	1TO10DAYS	11TO20DAYS	21TO30DAYS	
21TO 40	0	12	6	18
41TO 60	0	29	18	47
61ABOVE	1	15	33	49
Total	1	56	57	114

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.622(a)	4	.013
Likelihood Ratio	13.247	4	.010
Linear-by-Linear Association	7.342	1	.007
N of Valid Cases	114		

a 3 cells (33.3%) have expected count less than 5. The minimum expected count is .16.

Table 8: SEX vs DOS

		DOS			Total
		1TO10DAYS	11TO20DAYS	21TO30DAYS	
SEX	MALE	1	30	33	64
	FEMALE	0	26	24	50
	Total	1	56	57	114

Chi-Square Tests

			Asymp. Sig. (2-sided)
Pearson Chi-Square	1.003(a)	2	.606
Likelihood Ratio	1.376	2	.503
Linear-by-Linear Association	.042		
N of Valid Cases		1	.838

a 2 cells (33.3%) have expected count less than 5. The minimum expected count is .44.

Table 9: DIABETIC Vs NON-DIABETIC ULCER

	DOS			Total
	1TO10DAYS	11TO20DAYS	21TO30DAYS	
DIABETICULCER	0	35	50	85
NONDIABETICULCER	1	21	7	29
Total	1	56	57	114

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	12.429(a)	2	.002
Likelihood Ratio	12.741	2	.002
Linear-by-Linear Association	11.653	1	.001
N of Valid Cases	114		

a 2 cells (33.3%) have expected count less than 5. The minimum expected count is .25.

Table 8: DRESSING vs DOS

		DOS			Total
		1TO10DAYS	11TO20DAYS	21TO30DAYS	
DRESSING	DRESSING	0	18	55	73
	PRP DRESSING	1	38	2	41
Total		1	56	57	114

Chi-Square Tests

	Value	Df	Asymp. Sig. (2-sided)
Pearson Chi-Square	52.584(a)	2	.000
Likelihood Ratio	61.275	2	.000
Linear-by-Linear Association	51.713	1	.000
N of Valid Cases	114		

a 2 cells (33.3%) have expected count less than 5. The minimum expected count is .36.

Duration of stay in hospital was less in case of wounds treated with PRP dressings than that of Saline dressings. Among 41 cases of PRP dressings, duration of stay was less than 10 days for 1 case,10-20 days for 38 cases and 20 days or more for 2 cases whereas for 73 cases of saline dressings, none had duration of stay less than 10 days,18 cases had duration of stay 10-20 days and remaining 55 cases had a stay of 20-30 days. The results were similar for both diabetic and nondiabetic ulcers with PRP dressings having a shorter duration of stay in hospital irrespective of diabetes as comorbidity.

The above results were statistically significant.

DISCUSSION

The ideal dressing removes excess exudate, maintains a moist environment, protects against contamination, does not cause trauma when removed, and leaves no debris on wound bed. Dressings that retain moisture are less likely to be associated with infections than conventional dressings. There is no evidence to support one type of dressing over another, and no single dressing is appropriate for every type and location of ulcer. Moist saline or hydrocolloid dressings create a moist wound bed that enhances the healing process and prevents desiccation of the wound.

This study showed that PRP dressing could significantly increase the rate of healing of ulcers, so that the outcome which was duration of stay was significantly decreased. Our results are consistent with the findings of Driver *et al*. [2]. Who studied the effect of autologous PRP gel in the treatment of ulcers. Driver *et al.* [2] carried out the first reported prospective, randomized, controlled multicenter trial in the United States regarding the use of autologous PRP for the treatment of diabetic foot ulcers [2]. McAleer *et al*. [4] found that the use of autologous PRP was successful in healing a chronic lower extremity wound in a case study of a 57-year-old man with type 2 diabetes and a wound of six months duration. Salemi *et al.* [3] was a more recent case study evaluating the effectiveness of a combination of autologous adipose tissue and PRP in a lower extremity ulcer of three years duration in a non-diabetic 65-year-old male patient. This study differed from previous studies due to the investigators' use of autologous adipose tissue in addition to PRP for the treatment of a chronic lower extremity ulcer [3].

Margolis *et al*. [5, 8] was a retrospective cohort study devised to estimate the effectiveness of platelet releasate (PR) in the treatment of diabetic neuropathic foot ulcers. Crovetti *et al*. [6] published a prospective non-blinded study regarding the efficacy of platelet gel (PG) in healing cutaneous chronic wounds. O'Connell *et al*. [7] presented promising findings from a pilot study involving the treatment of chronic lower-extremity ulcers with autologous platelet-rich fibrin matrix membrane (PRFM). Although this study is limited as a small-scale pilot, it suggests that platelet-rich substances such as PRFM have the potential to

heal chronic lower-extremity ulcers that have failed to heal by conventional methods.PRP has been used effectively in several conditions such as dental and oral surgeries and in the treatment of musculoskeletal injuries [9] and treatment of androgenic alopecia [10].

Despite controversies, the present study confirmed the effectiveness of PRP in the treatment of ulcers. Despite many advances in the treatment of ulcers, many patients' especially diabetic patients are yet living with this destructive complication. Lack and malfunction of some growth factors disrupt the natural healing process in diabetic patients, which leads to non healing ulcers. It seems that PRP provides the growth factors [1] needed for healing. It is reported that fundamental protein growth factors that are actively secreted by platelet initiate wound healing process. PRP also includes three proteins [1] in blood known to act as cell adhesion molecules: fibrin, fibronectin and vitronectin. Platelets also secrete TGF-Beta and MCP-1 that would attract monocytes and neutrophils to the wound site. Our findings supported that PRP can facilitate healing of ulcers and therefore can reduce the risk of amputation or septicaemia.

Autologous PRP can be prepared easily. Therefore, its usage is economical and affordable, and as it is autologous, the risk of transmission of blood borne diseases is diminished. PRP preparation in the present study did not change biochemical composition of plasma, which is considered as its advantage. Moreover, PRP dressing used in the present study is a noninvasive method and seems to be more safe and affordable than methods used in previous studies (i.e. PRP gel or injection method). PRP gel [2] is usually prepared from bovine plasma and therefore may cause allergic reactions. PRP injection method may also put patients at risk of injection related complications.

In our study PRP dressing influenced the rate of healing by decreasing the size and depth of wound without any notable change in epithelisation. Lack of control over some confounding factors such as patients' nutrition, activities and their level of adherence to their medical treatments can be considered as some limitations of the present study. This study revealed that PRP dressing could significantly decrease the duration of stay by accelerating the healing process in ulcers. None of the patients receiving PRP developed any side effects. Therefore, using PRP in the treatment of ulcers is recommended.

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