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A Study Of Platelet-Derived Growth Factor In Wound Healing Of Diabetic Foot Ulcers In Indian Population.

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ABSTRACT

The majority of the cost associated with the care of diabetics is attributable to chronic or non-healing lower extremity ulcerations, which are a substantial source of morbidity and mortality in diabetics. Several growth factors, some of which have numerous effects on various cell types, are involved in the complicated process of healing wounds. One important growth factor, platelet-derived growth factor (PDGF), is present throughout the entire healing process. PDGF application is better than good wound care alone. However, the evidence to demonstrate the safety profile and efficacy of PDGF in diabetic foot ulcers is minimal. To evaluate the efficacy of PDGF over saline dressing in the healing of Diabetic ulcers of the foot. A comparative and analytic study of age, sex, and location of the ulcers plantar or dorsum. This Retrospective study was done with Patients with Diabetic foot ulcers admitted to surgery wards at Panimalar Medical College Hospital and Research Institute over 10 months from March 2020 to January 2021. Out of the 88 patients, 44 took the conventional Saline dressings and 44 took rh-PDGF dressing once a day. Glycemic control and adequate control of infection were maintained in both groups. If the culture grows organisms in both control and study groups would be treated with antibiotics as per the culture sensitivity report. X-ray foot was taken for all patients and bony involvement was excluded. The initial area measurement was taken on day 01 and the final measurement on day 15 was taken on a transparent sheet. Planimetry was used to measure the outcome which is the target ulcer area using a transparent graph sheet. In our study, it was observed that the Mean % of area reduction was higher in the study group (38.55%) as compared to the controls (12.79%). Diabetic foot ulcers in the study group had a better mean % of wound contraction of 38.55% as compared to the control group which had a mean % of wound contraction of 12.79 %, the difference in the mean 25.76% of area reduction of the two groups where studied using unpaired student t-test was found to be significant ($p<0.001$). Rh-PDGF dressing is found to be a more effective, safe promoter of wound healing and can be used as an adjunct to saline dressing for healing diabetic wounds. Healing of ulcers receiving PDGF was significantly faster as compared to ulcers receiving saline dressing.

Keywords: Diabetes, Wound Healing, Diabetic Foot Ulcer (DFU), Rh-PDGF.

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INTRODUCTION

DM is a state of chronic hyperglycemia producing complications like neuropathy, nephropathy, and retinopathy. It is also a strong co-factor in causing atherosclerotic disease and dyslipidemia. The microvascular and macrovascular complication prevalence is 46% and 64% respectively. Diabetes is the most common cause of non-traumatic lower extremity amputations [1]. It has been reported that annually, about 1 to 4 percent of those with diabetes develop a foot ulcer. Invariably diabetic foot ulcers are chronic ulcers that are resistant to heal because of multidrug-resistant organism growth and microvascular complications [2]. In the present era diabetic foot ulcers are treated with some physical therapies such as vacuum-assisted closure, high voltage pulsed current electrical stimulation, hyperbaric oxygen therapy (HBOT), and negative pressure wound therapy (NPWT), some biological therapies were also evaluated in diabetic foot ulcer treatment [3]. Some growth factors such as Epidermal growth factors [4]. granulocyte colony-stimulating factor, nerve growth factor, vascular endothelial growth factor, and activated platelet-rich plasma were evaluated in diabetic foot ulcers. Platelet-derived growth Factor (PDGF) is one of the growth factors important in angiogenesis and regeneration that is used in treating chronic ulcers. PDGF is derived from platelets that contain alpha and beta granules. The rh-PDGF is produced by recombinant DNA process by inserting the human gene for the B chain Platelet-derived growth factor (PDGF) is a dimeric protein, composed of2disulfide–linked polypeptide chains. It exists in 3 different isomers the heterodimer PDGF –ab consisting of an a and b chain, and 2 homodimers, consisting of 2a or 2b chains (pdgf –aa and pdgf –bb) it has been shown in preclinical and clinical studies to promote the formation of granulation tissue at the wound site and to stimulate wound healing [5]. Microscopic examination of the wounds treated with topical PDGF showed a marked increased intensity of the inflammation phase of the wound healing cascade characterized by an increased presence of neutrophils, monocytes, and fibroblasts. It is hypothesized that PDGF positively promotes angiogenesis indirectly through its activities on other inflammatory cells. There is a decrease in platelet function in patients with chronic diabetes. In type 2 diabetic individuals, the platelets adhere to the vascular endothelium and aggregate more easily in comparison to healthy individuals [6]. As the platelets here lose the sensitivity to normal restraint exerted by prostacyclin (PGI2) and nitric oxide (NO) produced by the vascular endothelium, it results in a decrease in the function of the platelet [7]. The Platelet Rich Fibrin containing platelets with the alpha granules trapped in fibrin is expected to release some growth factors. Irrespective of the fact that the platelets in Diabetic individuals will not have the usual efficacy of the function, the concentration of growth factors in PRF can still help in healing Diabetic Foot Ulcer (DFU) [8]. Encouraging results have shown that PDGF is better than good wound care alone. The average time for healing was shorter with a greater reduction in ulcer size. Clinical trials conducted in Western countries have demonstrated the safety and efficacy of PDGF in the management of diabetic foot ulcers but only a few trials are conducted in India hence the need for this study in our setup [9,10].

MATERIALS AND METHODS

This Retrospective study was done with Patients with Diabetic foot ulcers admitted to surgery wards at Panimalar Medical College Hospital and Research Institute over 10 months from March 2020 to January 2021. Out of the 88 patients, 44 took the conventional Saline dressings and 44 took rh-PDGF dressing once a day. Glycemic control and adequate control of infection were maintained in both groups. If the culture grows organisms in both control and study groups would be treated with antibiotics as per the culture sensitivity report. X-ray foot was taken for all patients and bony involvement was excluded. The initial area measurement was taken on day 01 and the final measurement on day 15 was taken on a transparent sheet. Planimetry was used to measure the outcome which is the target ulcer area using a transparent graph sheet. **Inclusion criteria:** Age between 20 to 80, Diabetic Ulcers Located below the Ankle, Diabetic Ulcers with Grade I & II, Size of the ulcer less than 10x10cm in length & breadth.**Exclusion criteria:** Patients will be excluded with Poor Sugar control (HBA1C more than 12%), Patients with severe Anemia will be excluded (Hb less than 7gm per dl), Diabetic Ulcers at grade –III, IV, and V (Wagner's Classification) will be excluded.

Statistical Analysis

Continual variables were compared using the independent sample t-test. Pearson chi-square test was used for the comparison of Categorical variables. Significance was defined by P values less than 0.05 using a two-tailed test. Data analysis was performed using IBM-SPSS version 21.0.

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RESULTS

In our study, it was observed that Diabetic foot was the most common in the age group between 51-60 years of age. In our study, it was observed that Diabetic foot was more common in males (68.00%) as compared to females (32.00%).

Table 1: Site of ulcer in the study

Site	No. of Cases	Percentage
Plantar	58	56.00%
Dorsum	29	44.00%
Total	88	100%

In our study, it was observed that diabetic foot more commonly occurs onthe plantar aspect (56%) of the foot as compared to the dorsal aspect (44%).

Table 2: Onset of Diabetic Foot Ulcers

Type of Onset	No of Patients	Percentage
Traumatic	50	64.00%
Spontaneous	33	36.00%
Total	88	100

Trauma is the most common cause of diabetic foot ulcer (64%) while only36 % were spontaneous in origin.

Table 3: Anti Diabetic Agents

Anti Diabetic	No. of cases	Percentage
OHA	18	18.00%
Insulin	70	82.00%
Total	88	100%

In our study, most of the participants were taking Insulin for glycaemic control.

Table 4: Distribution of wound surface area

Mean wound surface area	Control group (cm2)	Test group (cm2)
BASELINE	15.2	15.6
WEEK 1	14.8	13.2
WEEK 2	14.0	12.6
WEEK 3	13.7	11.8
WEEK 4	13.3	10.7
WEEK 5	13.1	9.8
WEEK 6	12.7	8.5
WEEK 7	12.4	7.7
WEEK 8	12.0	7.0

The mean wound surface area at baseline day was statistically not significant and was almost similar (15.2 cm2 in the control and 15.6 cm2 in the study group). But at the end of eight weeks mean WSA of control was 12.0 cm2 vs 7 cm2 in the study group which was statistically significant ($p<0.01$).

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Table 5: WSA- wound surface area.

Score	Percentage Of Granulation Tissue Cover
1	No granulation tissue
2	<25% OF WSA
3	25-74% OF WSA
4	75-100% OF WSA

There is no significant difference in the granulation of tissue at baseline between both groups.

Table 6: Granulation tissue cover at week 4

Granulation Tissue		Group			
		Study		Control	
		N	%	N	%
WEEK 4	1	0	-	8	4%
	2	16	32%	20	60%
	3	20	40%	10	24%
	4	8	28%	6	12%

The granulation of tissue at week six in the test group, < 25% of the wound in 2 (8%), 26-75% of the wound in 7(28%), and 76-100% of the wound in 16(32%) of patients. In the control group, no granulation in 1 < 25% of the wound in 8(4%), 26-75% of the wound in 20(60%), and 76-100% of the wound in 10 (24%) patients. At week six statistically significant granulation tissue cover was noted in the test group ($p<0.01$).

Table 7: Granulation tissue cover at week 8

Group	Mean area reduction%	S.D.	Median	P Value
Control	12.79%	2.55	11.81	P<0.01
Study	38.55%	2.52	37.58	P<0.001

In our study, it was observed that the Mean % of area reduction was higher in the study group(38.55%) as compared to the controls (12.79%). Diabetic foot ulcers in the study group had a better mean % of wound contraction of 38.55% as compared to the control group which had a mean % of wound contraction of 12.79 %, the difference in the mean 25.76% of area reduction of the two groups where studied using unpaired student T-test was found to be significant ($p<0.001$).

DISCUSSION

Diabetic foot ulcers are most commonly seen in 5th decade (38%), the next most common being in the sixth decade. While only 22% of the patients were in the fourth decade. The older the patient more the prevalence of having diabetic foot ulcer. In this study with vascular complications such as pulseless limb and patients were excluded. In this study, 64% of the ulcers were traumatic in origin, trauma being the triggering factor secondary to neuropathy 36% were spontaneous in origin secondary to blister rupture or unnoticed trivial trauma. More than half (56%) of the patients had ulcers on the plantar surface of the forefoot and the remaining (44%) had on the dorsum of the foot. Most of the patients (82%) were on insulin for control of sugar whereas only 18 % were on Oral Hypoglycemic Agents. In our study, it was observed that participants receiving rh-PDGF dressing had better wound contraction of 38.55 [11]. The group receiving only conventional dressing (normal saline dressing) in whom the mean wound contraction was 12.79% was found to be statistically significant on unpaired Student t-test ($p<0.001$) suggesting that rh-PDGF dressing enhances wound healing in diabetic wounds. We have found 12.79% (S.D; 2.55: Median; 11.81) contraction of wounds in the control groups as compared to 38.55% (S.D; 2.52, Median; 37.58) contraction of wounds in the study group. Therefore, the study group had 25.76 % more wound contraction as compared to the control group [12]. On applying unpaired student t- test $p<0.001$ which is Statistically significant. In our study, it was observed that participants receiving rh-PDGF dressing had better wound contraction. As compared to the group receiving only conventional dressing (normal saline dressing) it was found to be statistically significant

suggesting that rh-PDGF dressing enhances wound healing in diabetic wounds [13]. Due to their involvement in basically every phase of wound healing, as well as their general deregulation in chronic wounds, growth factors (including keratinocyte growth factor (KGF)-2, platelet-derived growth factor (PDGF), basic fibroblast growth factor (FGFb), epidermal growth factor (EGF), etc.) have long been considered as potential strategies in diabetic wound healing and have exhibited promise in small animal models of diabetic wound healing. Likewise, NGF supplementation has demonstrated some potential to promote healing after 5–14 weeks of treatment; however, these results came from a very small sample size [14]. The US Food and Drug Administration has approved only one topical-growth-factor (GF)--based therapeutic, Becaplermin (0.01% Regranex® gel), with efficacy in promoting the healing of DFUs. Although growth factor therapies exhibited promising results in vitro and in small animal models in vivo, all but one ultimately failed to achieve efficacy in accelerating diabetic wound closure for several reasons [15]. For one, locally prolonged bioavailability and hourly interaction of the ligand with the receptor are necessary for successful wound closure, but wounds are known to be a harsh microenvironment full of proteases and peptidases, making it hostile for local GF stability, chemical integrity, and bioavailability [16]. This has therefore rendered topical delivery of GF therapy futile without encapsulation into a protective delivery vehicle.Moreover, DFUs often exhibit deregulation and mislocalization of GF receptors as well compartmentalization within microdomains (i.e., caveolae), which prevent activation of downstream signaling events Therefore, even if GFs can be delivered to the wound, the lack of available and functional receptors precludes their ability to bind to the appropriate GF receptor and elicit a signaling cascade that will ultimately result in accelerated directional cell migration and subsequent wound closure [17]. Thus, unless these underlying problems are not corrected by future formulations that both encapsulate GFs and allow for their sustained slow release, as well as clear GF receptors from sequestration of specialized membrane microdomains, GF-based therapies will continue to be futile. For over 30 years, the use of autologous platelet-rich plasma (PRP) and platelet gel products has been reported to accelerate the healing of chronic wounds [18]. This results from the presence of several growth factors, including PDGF, TGF-β1, and EGF, as well as antimicrobial effects that stimulate tissue regeneration, cell proliferation, and differentiation, α-degranulation, and chemotaxis Interestingly, allogeneic-PRP is much less investigated than autologous-PRP, though it is an effective and safe treatment for diabetic chronic wounds [19]. Currently, PRP is combined with different activators and used either in injection therapies or gels—for instance, the use of platelet-enriched fibrin in combination with collagen-based dressings, thrombin/fibrinogen formulations or calcium gluconate The LeucoPatch® device, a PRP activated with fibrin embedded in a leukocyte wound dressing produced by the patient's blood, has shown significant improvement in healing outcomes. Moreover, because it is painless, platelet products have been reported to be more acceptable to patients with DFUs and have stimulated healing more than regular saline dressings that are standard care for non-healing DFUs [20].

CONCLUSION

The wounds in the study group treated with rh-PDGF dressing contracted more than the wounds in the control group (38.55% Vs. 12.79%; P = < 0.001- Statistically Significant) which indicates rh-PDGF dressing is an effective modality to facilitate wound contraction in patients suffering from diabetes. Rh-PDGF dressing is found to be a more effective, safe promoter of wound healing and can be used as an adjunct to saline dressings for the healing of diabetic wounds.

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