EFFICACY OF AUTOLOGOUS PLATELET RICH PLASMA FOR TREATMENT OF DIABETIC FOOT ULCER

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Abstract

Background: *Diabetic foot ulcer (DFU) is a common complication of long standing uncontrolled diabetes mellitus. There are different types of treatment commonly practiced among the clinicians to treat DFU. Among them, autologous platelet rich plasma (PRP) application is getting popularity day by day throughout the western world.*

Methodology: *It was a prospective, randomized, controlled study that was carried out among 40 DFU patients in the Department of Surgery, Dhaka Medical College Hospital. Among them, 20 patients were treated by autologous PRP and another 20 patients were treated by conventional method. They were followed up for 12 weeks period. Data collected from the participants were analyzed to compare the healing rate among two groups.*

Result: *In PRP treated ulcers, healing rate was significantly faster and better in comparison to conventionally treated ulcers. After 10th weeks follow up, in PRP group 14 ulcers were completely healed whereas in control group,4 ulcers were completely healed. On the contrary, 3 ulcers in control group showed further deterioration. At the end of 12th weeks follow up, 19 ulcers in PRP group were completely healed whereas 13 ulcers in control group were completely healed. In PRP group no patient showed any complication during treatment, whereas in control group 7 patients experienced local complications.*

Conclusion: *Treatment of diabetic foot ulcer with autologous platelet rich plasma results in faster and better ulcer healing in comparison to conventional treatment. PRP accelerates the healing rate and keep the ulcer area safe from external pathogens. Hence, autologous PRP is a better selection for DFU treatment.*

Key words: *Diabetic foot ulcer, ulcer healing, debridement, autologous platelet rich plasma*

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Introduction:

Diabetes is one of the four major types of non-communicable diseases that make the largest contribution to morbidity and mortality worldwide[1]. A recent scoping review (1994-2013) revealed that the prevalence of type 2 diabetes varied from 4.5% to 35% in Bangladesh. Neuropathy and peripheral vascular disease are two major factors causing foot ulcer in patients with diabetes[2]. The major problem with diabetic foot ulcers (DFUs) is the length of time they take to heal and it has been reported that the levels of metalloproteinases (MPs) and tissue inhibitors of metalloproteinase (TIMPs) can significantly contribute to a delay in healing (Muller et al. 2008). Due to the lack of oxygen and nutrients, epithelial cells at the ulcer site are unable to express essential factors for healing, such as vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF); almost all of the cells at the ulcer will change metabolism and activity[3]. These

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changes in the cells and other factors affecting DFUs such as the presence of infection, will delay the normal healing process. Platelet-rich plasma (PRP) has been proposed as an adjunct for the treatment of DFUs. The alpha granules of platelets contain growth factors that include molecules such as PDGF, VEGF and transforming growth factor (TGF-â) which stimulate cell proliferation and differentiation resulting in new tissue formation[4]. Platelet in PRP also play role in host defense mechanism at the ulcer site by producing signaling protein that attract macrophage; PRP may also contain a small number of leukocyte that synthesizes interleukin as a part of nonspecific immune response[5]. Foot problems in diabetic patients account for more hospital admissions than any other long-term complications of diabetes which results the potentially preventable end point amputation. The objective of this study was to determine the effectiveness of autologous PRP in the treatment of diabetic foot ulcer.

Methodology:

It was a prospective, randomized, controlled study done in the Department of surgery, DMCH from January, 2020 to December, 2020. Patients were selected by purposive sampling technique based on inclusion and exclusion criteria. Total sample size was 40. Initially, patients with diagnosis of DFU attended at Department of Surgery for treatment were enrolled in the study. All eligible patients were randomized into 2 groups. First patient was selected in PRP group by coin toss method and then every alternate patient was allotted in this group. Rests of the patients were allotted in control group. All the patients were informed vividly regarding the study procedure and written consent was obtained.

Inclusion Criteria:

- Ulcer of at least 2 weeks duration.
- HbA1c<12%
- Index ulcer located in medial, lateral, planter or dorsal aspect of foot but not exposing bone, tendon and ligament.
- Ulcer should not be associated with any foreign body, sinus tract, tunneling or undermining edge.
- Ulcer size 0.5 cm^2 to 20 cm^2
- Limb should have adequate perfusion (Ankle brachial pressure index >0.9)

Exclusion Criteria:

- Screening serum albumin level <2.5 gm/dl
- Screening Hb% <10 gm/dl
- Screening platelet count <100000/mm^3
- Patient who did not gave consent to participate in this study.

After selection sharp debridement of heavily infected ulcers or non-healing ulcers were performed. Debridement converted a chronic or a heavily infected ulcer to one that was acute by removing nonviable tissue that could stimulate excessive inflammation and bacterial growth. Adequate perfusion of the limb was ensured by ABPI. Before starting the intervention swab from ulcer were sent for culture to ensure that all the ulcers were free of pathogen. During the study period both groups were not under any systemic antibiotic coverage. After documenting the size and site of the wounds by using metric tape and photograph, the control group received conventional dressing by 10% povidone iodine solution and normal saline infiltration. And the intervention group received dressing by 10% povidone iodine solution and autologous PRP infiltration. Within half an hour after preparation of PRP, it was injected about 3/4^{th} of a cm within the margin of the ulcer at a distance of 3/4^{th} of a cm away from each injection site, followed by gauze dressing. Every ulcer was checked at an interval of three days.

The ulcer sizes (length, width) were measured every two weeks interval. At every visit ulcer was carefully checked for any evidence of infection. Every patient was followed up for maximum twelve weeks period or less if complete healing occurred earlier. If any evidence of infection was encountered, swab was sent for culture and sensitivity test. Also X ray of foot done if needed. Whenever any patient developed any complication, appropriate management was given with the help of respective department.

Results

Mean age of PRP group was 53.8±13.21 years and control group was 57.4±11.32 years. Among them majority of the patients were male. Regarding smoking habits, 40% patient in PRP group were smoker and 10% were nonsmoker whereas in control group 30% were smoker and 12% were nonsmoker. (Table-I)

After 4 weeks of treatment, difference between the treatments was significantly evident. In autologous PRP treated ulcers, healing rate was significantly faster and better than those of conventionally treated ulcers. At the end of 12th weeks follow up, only 1 ulcer in PRP group was not completely healed whereas 7 ulcers in control group were not completely healed (table II).

Table III shows in PRP group no patient showed any evidence of infection or any complication, whereas in control group 4 (20%) patients showed localized infection. These were suspected clinically by symptoms & signs and confirmed by culture of swab from ulcer. Each of them was treated by systemic antibiotic. Moreover, 2 patients developed osteomyelitis of great toe evident by X-ray, who needed amputation of distal phalanx. They were managed with collaboration of Department of Orthopedics. Progressive and extensive cellulitis encountered in 1 patient in control group and given intravenous antibiotic according to culture and sensitivity report.

At the end of 12th week, PRP group showed complete ulcer healing of 19 patients whereas control group showed complete ulcer healing of 13 patients. From Fisher exact test, p value was 0.04 which is significant. So it can be said that there is significant difference between the outcome of PRP group and control group. (Table IV)

Table-I

Baseline characteristics of the participants (N=40; 20 in each group)

Characteristics	PRP group (n1=20)	CONTROL group (n2=20)	P value
Age (in years) (mean±SD)	53.8±13.21	57.4±11.32	0.36
Age range (in years)	38 – 81	40 – 78	
Sex (n, %)			
Male/Female	18/2	16/4	0.38
Smoking status			
Smokers	8 (40%)	6 (30%)	
Non-smokers	7 (35%)	8 (40%)	0.8
Ex-smoker	5 (25%)	6 (30%)	

Table-II

Ulcer healing rate

Ulcer healing rate Ulcer area profile (cm^2)	PRP group (n1=20)	Control group (n2=20)	P-value
Baseline/index ulcer (mean±SD)	7.1±3.2	8.6±2.9	0.13^{NS}
2nd week follow up (mean±SD)	6.3±2.8	6.9±2.3	0.46^{NS}
4th week follow up (mean±SD)	4.5±1.2	6.3±2.1	$<0.002^{S}$
6th week follow up (mean±SD)	3.1±1.63	4.7±1.9	$<0.001^{S}$
8th week follow up (mean±SD)	1.9±1.3	2.5±0.7	$<0.04^{S}$
10th week follow up (mean±SD)	1.1±0.9	2.1±0.9	$<0.003^{S}$
12th week follow up (mean±SD)	0.5±0.3	1.9±0.7	$<0.001^{S}$

(S=Significant, NS= Not significant, P-value is significant at <0.05)

Table-III

Evidence of infection during treatment

Complications	PRP group (n1=20)	Control group (n2=20)	P value
Localized infection	0 (0%)	4 (20%)	0.03^{S}
Osteomyelitis	0 (0%)	2 (10%)	0.14^{NS}
Extensive cellulites	0 (0%)	1 (5%)	0.31^{NS}

(S= Significant, NS= Not significant)

Table-IV

Comparison of outcome between two groups

	Ulcer healed	Ulcer not healed	Marginal row total	P value
PRP group	19	1	20	
Control group	13	7	20	0.04^{S}
Marginal column total	32	8	40(Grand total)	

(S=Significant)

Discussion:

In this study, the mean healing time in PRP group was observed as 8.67 weeks that is also supported by a similar previous study [6]. A study conducted by Frykberg et al.[7] on 49 patients with 65 no healing ulcers showed that 63 of 65 ulcers responded with a reduction in area. Kakudo et al.[4] treated five cases of intractable skin ulcer with autologous PRP, among which three ulcers healed completely within 4 weeks and epithelialization of ulcer occurred within 6.6 weeks on average. We have treated 20 patients by autologous PRP among which 19 ulcers were completely healed after 10^{th} week offollow up. Unfortunately, only 1 ulcer was not completely healed after 12^{th} week of follow up that required more application of autologous PRP. Total 8.62 weeks were required on an average to heal the DFU in PRP group that is almost supported by all of the before-mentioned studies. Besides, the mean area of DFU treated by autologous PRP after each follow up in 4^{th}, 6^{th}, 8^{th}, 10^{th} and 12^{th} week showed far better statistically significant healing than those of treated by control. My findings were consistent with the findings of another previous study done by Suryanarayan et al[8].

Autologous PRP contains macrophage and interleukin which exert antimicrobial activity against some types of skin flora. Clinical data shows that the presence of infection is reduced in PRP-treated ulcers[9]. After completion of treatment no patient in PRP group was discovered with any sort of complication. On the contrary, 4(20%), 2(10%) and 1(5%) patients in control group experienced localized infection, osteomyelitis and extensive cellulitis respectively, who were managed appropriately with multidisciplinary team. End outcome of my study is complete healing occurred in 19 patients of PRP group and 13 patients in control group. Fisher Exact test shows p value is 0.04 which is significant. So there is significant difference between the outcome of PRP group and control group.

In the current study, autologous PRP was found to be useful in treating DFU. However, further controlled, randomized prospective clinical trials are necessary to definitively demonstrate its efficacy. Also a standard protocol for preparation and application of PRP is required, as currently there is no standardization of the procedure.

Conclusion:

Autologous PRP accelerates ulcer healing in diabetic patient in comparison to conventional treatment. Also PRP ulcers do not develop complications during the course of treatment. So there is scientific evidence regarding favorable outcome of autologous PRP in DFU treatment.

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