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Autologous Platelet-Rich Plasma In Diabetic Foot Ulcers, New Preparation Technique

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Abstract

Aim of work: To assess the healing of diabetic foot ulcers attributed to newly technique preparation of platelet-rich plasma (PRP) compared with that in the control group with conventional procedures.

Methods: A prospective study was carried out between January 2016 to July 2017 on 80 patients suffered from chronic diabetic foot ulcer not responding to the traditional treatment. Patients were classified into 2 groups:- group A; included 42 patients that were treated by application of autologous PRP prepared by minimal cost technique and group B; including 38 patients that were treated with the traditional methods of ulcer management.

Results: Mean ulcer area and ulcer volume in group (A) before treatment were 15.7 cm^2 and 14.1 cm^3 respectively while in group (B) were 16.49 cm^2 and 14.01 cm^3 respectively. Healing rate was (83.33%) in 35 patients in group (A) and (28.95%) in 11 patients in group (B). No patients suffered from any undesired effects that were directly related to PRP treatment apart from minimal skin irritation around the ulcer if the dressing was infrequently changed.

Conclusion: Autologous platelet-rich plasma combined with conventional treatment methods accelerates healing process of diabetic foot ulcers. Easily prepared PRP is safe and cost-effective with reasonable results.

Keywords: Platelet-Rich Plasma, Diabetic foot, Ulcers

Introduction

Lower extremity wounds constitute an important health problem disturbing patients' life especially when located in planter foot.(1) Chronic non-healing foot ulcers are defined for those that take more than 6 weeks to heal with prevalence in the world ranges from 1.9 - 13.1%. European guidelines stated that every 30 seconds approximately somewhere in the world, one patient has an amputation due to diabetes, leading to significant economic burden and affect the quality of life (QoL) (2) Diabetic foot ulcer (DFU) is multifactorial in origin and is known by its slow healing rate and high resistance to treatment and more liability for complications, such as recurrent infection, gangrene and subsequent amputation.(3) Management of these types of ulcers are still a challenge because of their complex pathophysiological process.(4) Autologous platelet-rich plasma is a blood derivative containing high concentrations of platelets and has been used for treatment of various chronic wounds including DFU because

PRP is rich in multiple growth factors that play an important role in the process of wound healing through its regulation of the inflammatory process and its role on cell proliferation.[5]

Not all wounds will respond to the standard wound management like surgical debridement of necrotic tissue, control of infection by antibiotics, wound dressing and off-loading devices. Recently, multiple varieties of advanced treatment e.g. hyperbaric oxygen therapy, maggot therapy, NPWT (negative pressure wound therapy) and reconstructive surgery are applied to enhance healing. Lastly, cellular therapies such as PRP has a considerable attention in regenerative medicine[6] and was found to be the most cost effective therapy compared to standard care using wet-to-moist dressings, offloading devices or other advanced therapies.[7]

Materials and Methods

This prospective study was carried out from January 2016 and July 2017 on 80 patients in Sohag University Hospitals suffering from chronic diabetic foot ulcer. Patients were classified into 2 groups:- group A; included 42 patients that were treated by application of autologous PRP prepared in new easier and minimal cost technique and group B; including 38 patients that were treated with the traditional methods of ulcer management. This series approved by ethical and medical committee in our faculty. All patients were admitted, given an idea about the planned procedure and then signed an informed consent before treatment. Inclusion and exclusion criteria of this study were:-

Inclusion criteria:

- Diabetic ulcers more than 6 weeks duration not responding to the traditional therapy of leg ulcer.
- Clean ulcer bed.
- Wounds did not show any clinical manifestations of active infection.
- Superficial ulcer with no exposure to bone, tendons or ligaments.

Exclusion criteria:

- Patients with flaring infection.
- Exposed bone or underlying osteomyelitis.
- Wounds with Charcot deformity.
- Current use of chemotherapy or radiotherapy.

All patients had full clinical assessment including detailed history taking and examination. Foot ulcers were subjected to thorough physical assessment regarding dimentions, depth, character of wound exudate, peri-wound maceration, wound duration and previous medications. X-ray foot and laboratory tests including hemoglobin, serum albumin and HBA1c were performed to all cases. Prior to treatment, all ulcers were inspected carefully for any necrotic tissues to be removed firstly. Wound swab cultures for antibiotics and sensitivity were taken.

Ulcer Measurements were performed using cotton-tipped applicators and sterile metal rulers to measure length, width, and depth of the ulcer. Ulcer area and ulcer volume were calculated using the “clock face” formula described by Sussman C. and Bates.[8] Wound area is calculated by (Length × width × 0.7854) while ulcer volume by (length × width × depth× 0.7854). Length was 12:00 to 6:00 with 12:00 toward the head, width was 3:00 to 9:00. Depth measurement was taken from the deepest point of ulcer bed to skin surface. Measurements were recorded before treatment and repeated routinely prior each PRP application session in patients in group (A) and weekly in patients in group (B).

Our protocol for management of group (A) patients was application of PRP inside the ulcer to enhance wound healing. In aseptic conditions, 9 ml of venous blood was collected from large vein e.g. antecubital vein and added into a 9:1 acid citrate dextrose tube. Blood was centrifuged at a rate of 1500-2000 r/min for 2-3 minutes to be separated into red blood cells, buffy coat and plasma. Then, plasma and thin white buffy coat was collected and centrifuged at a rate of 2000 r/min for 5 minutes to precipitate platelets collected as a pellet in bottom of the tube.

The bottom layer was collected as PRP. Calcium chloride 10% in a ratio of 0.3 ml / 1 ml PRP was added for activation as advised by Yilmaz et al in his series.[9] PRP was injected 2-5 mm deep into the wound immediately after its activation to make use of the largest amount of growth factors that released in early few minutes. Wound was covered with non- absorbant dressing e.g. paraffin gauze. Appropriate off-loading devices should be applied to avoid direct weight bearing .Antibiotics were prescribed according to culture and sensitivity test to control infection.

Wound dressing was changed on the 3rd day and the wound was irrigated with normal saline and assessed for the presence of any infection. Then, the dressing was frequently changed and patients were followed up for 13-16 weeks. PRP application was repeated once weekly. Every new session, wound healing was assessed by clinical improvement, appearance of islands of granulation tissues, measuring the ulcer volume and area and comparing the photography taken during each visit. Complete wound healing was defined as full skin epithelization. Beside application of PRP to the ulcer , all the traditional wound care was kept in mind regarding control of diabetes, anemia, correction of general condition of patient, guard against infection, keeping ulcer clean and application of off-loading braces.

Management protocol of group (B) patients was traditionally including ulcer debridement from any necrotic materials, control of infection by antibiotics according to culture and sensitivity, frequent dressing, off-loading devices as well as correction of general condition of patients e.g. anemia, and control of diabetes.

Study end point: Treatment was stopped when there was less than 20% reduction in ulcer area at the end of 3rd week in patients of both groups.

Study Outcome: The main variables were the difference in ulcer area and ulcer volume during treatment compared to the original ulcer prior to treatment strategy. These variables were expressed as a percentage in both PRP group and control group.

Statistical analysis:

All statistical analyses were performed using SPSS statistical software. Visual histograms and analytical methods (Shapiro-Wilk's test) were used for determination of normal distribution. Continuous variables were defined by the mean ± standard deviations. Paired values including wound area (cm^2) and wound volume (cm^3) were compared with paired samples t-test among consecutive times of study period.

(a) (b)

Figure (1): a: first centifuge separated blood into plasma , buffy coat and blood cells, , b: second centifuge showing platelet pellet in bottom of the tube.

(a)

(b)

(c)

(d)

(e)

Figure (2): a: large ulcer over later foot, b,c,d: follow up at 4^{th} , 8^{th} and 10^{th} weeks respectively, e: complete healing after 12 weeks.

(a) (b)

(c) (d)

Figure (3): a: chronic planter foot ulcer, b: after 2 sessions of PRP, c: after 4 weeks of treatment, d: complete ulcer healing after 6 weeks.

Results

This prospective study was performed on 80 patients with diabetic foot ulcers not responding to the traditional management for more than 6 weeks. Mean ulcer area and ulcer volume in group (A) before treatment were 15.7 cm^2 and 14.1 cm^3 respectively while in group (B) were 16.49 cm^2 and 14.01 cm^3 respectively. Site of ulcer was located commonly under the metatarsal head (38%) followed by heel ulcer and planter surface ulcer. Duration of ulcer before management in group (A) was 14-32 weeks with mean of 25 week while in group (B) was 19 weeks (10-22) weeks. All patients in group (A) were subjected to repeated sessions of autologous PRP (ranged from 8-16 sessions). All demographic data and patients' criteria were summarized in Table 1.

Table (1): Demographic data and patients' criteria:-

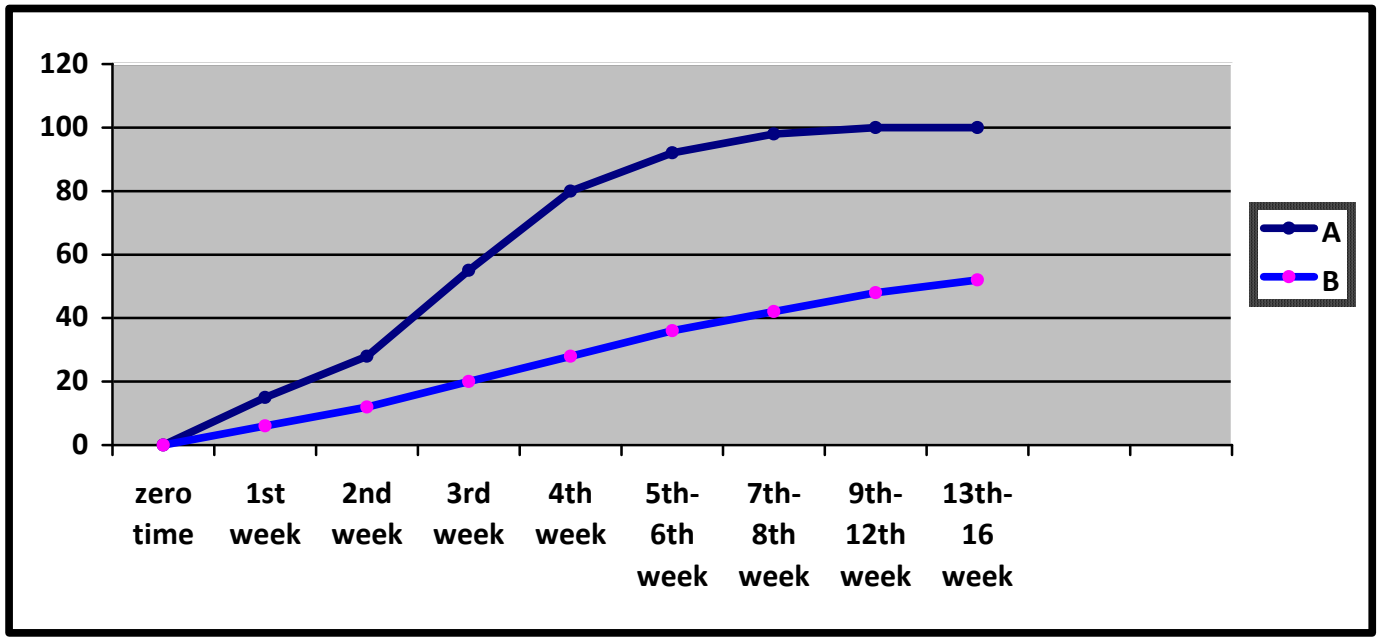
	Group (A) **NO. (42)**	Group (B) **NO. (38)**
Age /year	49 (40-65)	45 (41-68)
Sex	28 Males /14 females	22 male / 16 females
Ulcer area / cm^2	15.7 ± 4	16.49 ± 6
Ulcer volume/ cm^3	14.1 ± 2	14.01 ± 4
Site of ulcer	38 % ulcer under metatarsal head 32% heel ulcer 21% planter ulcer 9% other sites	
Duration of ulcer before treatment	25 (14-32) weeks	19 (10-22) weeks
No. of PRP sessions	8-16	00
Duration of treatment \ weeks	10 (8-16)	

Follow-up of ulcer healing was assessed during regular visits of application of PRP in patients with group (A) and during dressing and wound care for patients with group (B). Ulcer area and volume were checked and recorded routinely. Remarkable improvement and healing of ulcer was noticed around the 3^{rd} – 4^{th} week in group (A) by decrease in exudate, appearance of islands of granulation tissue inside its floor as well as decrease in its dimensions.(Table 2 & 3) Healing was achieved in 83.33% (35 patients) in group (A) and in 28.95% (11 patients) within 7^{th}-8^{th} week duration.(Table 4). The remaining 7 patients in group (A) and 27 patients in group (B) were treated classically by traditional wound care. 20 patients of them (5/42 of group (A) and 15/38 of group (B)) had ulcers under metatarsal head and developed chronic osteomyelites lesions proved by x ray finding during follow up that led to amputation of overlying toes and excision of the ulcer. 14 patients lost follow up visits after the 16^{th} week.

In paired comparisons that were performed between consecutive weeks, ulcer area and volume did not show significant reduction in first and 2^{nd} week follow-up whereas there were significant reductions among all consecutive measurements starting from 3^{rd} week. Then it became highly significant from 4^{th} week and thereafter (p- value < 0.0001). (Table 2 & 3)

Table (2): Healing rate of ulcer area:

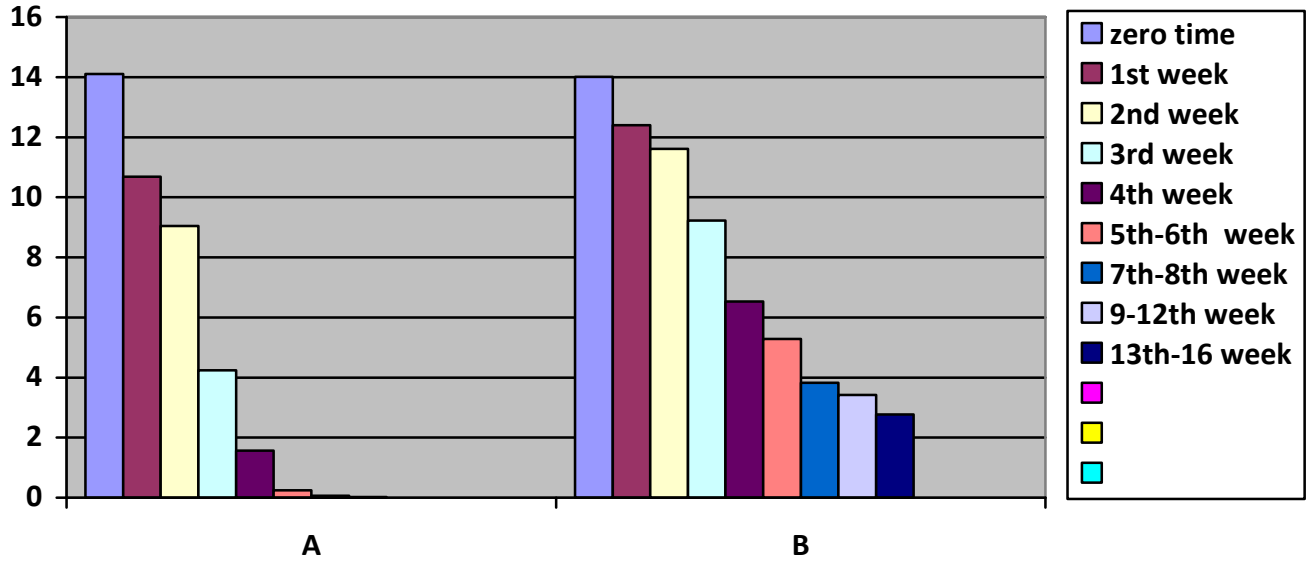
	Ulcer Area/ cm^2		
	Group (A) 15.7 cm^2	Group (B) 16.49 cm^2	P- *value*
1^{st}- week	13.35 (15%)	15.50 (6 %)	0.1705
2nd week	11.30 (28 %)	14.51 (12 %)	0.0125
3rd week	7.065 (55%)	13.19 (20 %)	0.0004
4th week	3.14 (80 %)	11.87 (28 %)	< 0.0001
5th- 6th week	1.26 (92%)	10.55 (36 %)	< 0.0001
7th- 8th Week	0.31 (98%)	9.56 (42 %)	< 0.0001
9th-12th week	0.16 (100%)	8.57 (48 %)	< 0.0001
13^{th} -16^{th} week	00 (100%)	7.92 (52 %)	< 0.0001



Graph (1): Healing Rate in ulcer area (percentage by weeks)

Table (3): Rate of regression in ulcer volume:

	Ulcer Volume/ cm^3		
	Group (A) 14.1 cm^3	Group (B) 14.01 cm^3	P- *value*
1st- week	10.68 (76%)	12.4 (89%)	0.1160
2nd week	9.04 (64%)	11.61 (83%)	0.0020
3rd week	4.24 (30%)	9.23 (66%)	< 0.0001
4th week	1.57 (11.13%)	6.53 (47%)	< 0.0001
5th- 6th week	0.25 (1.77%)	5.28 (38%)	< 0.0001
7th- 8th Week	0.06 (0.43%)	3.82 (27%)	< 0.0001
9th-12th week	0.02 (0.14%)	3.42 (24%)	< 0.0001
13th -16th week	00 (00%)	2.77 (20%)	< 0.0001



Graph (2): Rate of regression in ulcer volume (ulcer volume by weeks)

Table (4): Number of healed ulcers

	Group (A) No. (42)	Group (B) No. (38)	P-*value*
1st- week	4 (9.5%)	00 (00%)	0.007
2nd week	8 (19.04%)	00 (00%)	0.00
3rd week	27 (64.29%)	00 (00%)	0.00
4th week	31 (73.80%)	2 (5.26%)	0.0001
5th- 6th week	33 (78.57%)	5 (13.16%)	0.0001
7th- 8th Week	35 (83.33%)	11 (28.95%)	0.0001
9th-12th week	-	20 (52.63%)	0.00
13th -16th week	-	24 (63.16%)	0.00

Regarding complications of PRP, no patients suffered from any undesired effects that were directly related to PRP treatment apart from minimal skin irritation around the ulcer if the dressing was infrequently changed.

Discussion

Diabetic foot ulcer (DFU) is an unavoidable complication of DM and more than 25% of diabetics will suffer from foot ulcer during their life.[10] Chronic DFU is defined as ulcer not decreased to half of its actual size within one month. However, there is no consensus to define a certain time length to define chronicity.[11]

From the pathological aspect, diabetic foot can be attributed to autonomic & sensory neuropathy, tissue hypoxia, hyperglycemia related immunopathy and microvascular angiopathy. This leads to irregular pad of fat which make the metatarsal heads liable to more pressure and subsequently foot ulceration.[12]

Wound healing process is composed of coagulation, inflammation, migration / proliferation and remodeling phases. Chronic ulcers are known by its low proliferation rates. Inflammation is the initial phase which resolves within a few days and rendering wounds stop sending pro-inflammatory signals and starting new tissue synthesis.[13] In chronic wounds, the healing cycle was stucked in the inflammatory phase resulting in cellular senility.[14] Jacobson et al,.[15] found that growth factors released from activated platelets can restart the healing process by switching the wound from the inflammatory phase into the proliferative one.

PRP is a blood portion that has a platelet concentration above baseline and contains more than 30 bioactive proteins released from its α-granules including PDGF, TGF-β, VEGF, EGF and bFGF that play a vital role in wound healing. They are responsible for regulating cell migration, proliferation and differentiation as well as limition the inflammatory phase by suppressing cytokine release at the site of injury. PRP also has antimicrobial effects against *Candida albicans*, MRSA and *E. coli*. [5]

There are many methods to prepare PRP using blood centrifuge firstly to fractionate the blood followed by platelet activation by either thrombin, thrombin with calcium chloride or calcium chloride alone. These methods depend mainly on using special devices with variability in speed, timing, angulation or the radius of the rotator of the centrifuge e.g. Autogel system cytomedix dedices. Although, some of these methods are effective, they are expensive especially when this process is repeated weekly. Most of these methods nearly have the same principals of centrifuge velocity as 5000 r/min for about 15 min in first step and 2000 r/ min in second centrifuge step and used special tubes needed 20 ml blood.

In this series, several trials were made by using ordinary sterile tubes prepared manually by 1 ml acid dextrose to be added to 9 ml blood and centrifuged in two steps by changing in the speed and time of centrifugation until obtaining the optimum speed and time for this technique. This new technique of PRP preparation provided cheap tools instead of the previously ones and achieved also about 2-4 fold higher than basal platelet concentration of patients. Discrepancy between the previous techniques and this one in speed can be attributed by using of specific tubes containing large amount of blood (20 ml). These modifications allow physicians to repeat the procedure weekly with approximately no or minimal cost as well as using small amount of blood in each session that protect patient from more blood loss and anemia. Several authors commented on methods of PRP preparation and stated that variability in wound healing outcomes by PRP is due to differences in methods of its preparation while Marx et al,.[16] had confirmed that there is no standard method of PRP preparation and appreciated the double centrifugation technique rather than the single spin method as RBCs will interfere with their fine separation.

Adding calcium chloride 10% to the PRP has many advantages rather than activation of platelets as it counters act the effect of acid citrate used inside the tubes as an anticoagulant.[17]

In this series, it was advisable that PRP sessions should be repeated weekly and applicated immediately after its activation. That was appreciated with Shwetha et al,[18] who published in his series 70% of growth factors were released within the first 10 minutes and 90% within one hour. The remaining amounts continued their release for about 8 days until depletion.

Autologous PRP has more advantages over single recombinant growth factor as it doesn't have immunological reactions or share in blood transmitted infections. Nonetheless, it has multiple growth factors and inexpensive.[5]

In this study, a significant reduction in ulcer area and volume was obtained after 3-4 weeks of treatment with PRP and complete or nearly complete ulcer healing was obtained in the 7^{th}-8^{th} weeks (83.33%) 35 patients in comparison to (28.95%) 11 patients in group (B) patients (p-value: < 0.0001). Sheehan et al,.[19] achieved 53% reduction in wound area at 4th weeks led to 82% complete wound healing. Roubelakis et al.[20] reported in his study an average volume reduction of 34.1% within the first 8 weeks. Japanese wound care program provided 83% healing rate within 20 weeks in 40 patients with lower extremity chronic wounds of ischemic and diabetic etiology.[21] Driver et al,.[22] published their results of a prospective, multicenter, randomized, blinded, controlled trial of PRP in DFU and recorded success 81.3% and appreciated the use of autologous PRP for difficult to heal wounds.

Comparing limb salvage results from randomized trials, Lalla et al,.[23] showed that amputation rates was 45% in patients treated with standard wound care while it was significantly less 15% for those treated with growth factors. In this series, amputation rate was 12 % in group (A) and 39% in group (B) patients.

Pressure, sheer, and friction have been proved to delay wound healing, and thus, off-loading is important. Plaster cast or total contact casts is the ideal in off-loading but it interferes with frequent dressing so Millington and Norris [24] recommended removable contact walker as it has the same pressure reduction as total contact casts and can be removed for dressing when needed.

Chronic wounds are known by its multifactorial etiology and complex pathology. So they should be treated with combined modalities of treatment principals in a teamwork spirits to achieve healing. Autologous treatment of diabetic ulcer can reduce significantly the financial and social burden, liberating funds for the public health. [25]

Conclusion

Autologous platelet-rich plasma combined with conventional treatment methods accelerates healing process of diabetic foot ulcers. Newly technique of PRP preparation is easier and cost-effective method with reasonable results.

Recommendation for practice:

Management of DFU is a challenge. It is unwise and non practical to use a single therapy to achieve complete wound healing. It usually requires combined modalities in a teamwork spirits to achieve healing.

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