

## COMPARATIVE EFFECTIVENESS OF EXTRA-CORPOREAL SHOCK WAVE THERAPY, PLATELET RICH PLASMA THERAPY AND TOPICAL INSULIN THERAPY IN DIABETIC FOOT ULCER HEALING

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### Abstract

**Aim:** to compare the effectiveness of shock wave therapy, platelet rich plasma injection (PRP) and topical insulin therapy on healing of diabetic foot ulcer.

**Methods:** Sixty type II diabetic nonsmoker male patients with diabetic foot ulcer were recruited. The patients were randomly divided into four groups. All groups received standard care treatment. Fifteen patients received shockwave therapy (Group 1). Fifteen patients received PRP therapy (Group 2). Fifteen patients received topical insulin therapy (Group 3). Fifteen patients received standard care treatment only (Group 4). All patients were subjected to full history, general and local examination, also BMI, HbA1c were measured. PUSH score was assessed in all groups at zero, fourth and twelfth weeks.

**Results:** The four groups were matched as regards to age, BMI, HbA1c, and PUSH scores at zero weeks. There was statistically high significant decrease in the mean value of PUSH score at fourth and twelfth weeks of follow up compared to zero weeks in the four groups. At fourth and twelfth weeks of follow up there was statistically highly significant decrease in the mean value of PUSH score of Group 3 who received topical insulin compared to other groups. There was statistically significant correlation between PUSH score and each of BMI and HbA1c.

**Conclusion:** Diabetic foot ulcer in people with diabetes is common. Occurrence of ulceration, infection and gangrene are the most common causes of hospitalization. Appropriate and prompt management is necessary for successful treatment of DFU.

**Keywords:** DFU (Diabetic foot ulcer). PRP (Platelet Rich Plasma). HbA1c (Hemoglobin A1 c). BMI (body mass index). PUSH score (Pressure Ulcer Score of Healing).

### Introduction

Diabetes Mellitus (DM) is a global epidemic disease with a rapid increase in prevalence, morbidity and mortality (1). It is a major disease that causes pathological changes in multiple organs (2). Diabetic foot ulcers are a feature of detrimental multi-organ effect of DM (3). Diabetic foot ulceration is one of the most common long term consequences of DM as 25% of diabetic patients will develop diabetic foot ulcers in their lifetime (4).

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Etiology of diabetic foot ulcer (DFU) is multi-factorial, it is usually caused by microangiopathy associated with peripheral neuropathy and local infection (5). Standard care of DFU includes control of diabetes, adequate off loading, frequent debridement, proper wound care, treatment of infection and revascularization of ischemic limbs (6). Control of diabetes and proper shoe wear are key elements in management of DFU. Many adjunctive therapies are new, effective and non-invasive methods of treatment of chronic diabetic ulcers including extracorporeal shock wave therapy, PRP injection and topical insulin therapy (5).

Extracorporeal shock wave therapy (ESWT) has been recognized as a new adjuvant for wound healing. Physically, shockwave is described as propagation of acoustic energy that disperses in three dimensional spaces which may be transmitted, reflected or absorbed (7). ESWT can help in healing of wounds through up regulating angiogenesis related growth and proliferation factors and also helps to reduce pain by calcitonin gene related peptides and substance P (8).

Platelet rich plasma (PRP) is one of new adjuvant approaches in management of diabetic foot ulcer as healing process is modulated by growth factors and fibrin secreted by platelets (9).

Insulin is a peptide hormone and a growth factor that can restore damaged skin. Topical insulin in wound dressing can be desirable remedy to accelerate wound healing without changing blood glucose levels in diabetic and non-diabetic patients (10).

Our study aimed to compare the effectiveness of PRP injection, shock wave therapy and topical insulin therapy in healing of diabetic foot ulcer.

### Patients & Methods

#### Patients, Study Design

Sixty type II diabetic non-smoker male patients with diabetic foot ulcer were recruited from outpatient's clinics of Ain Shams University Hospitals. The patients were randomly divided into four groups. Fifteen patients received shockwave therapy (Group 1). Fifteen patients received PRP therapy (Group 2). Fifteen patients received topical insulin therapy (Group 3) and fifteen patients received standard care treatment (Group 4). Inclusion criteria in this study was patients  $\geq 50$  years old, the diabetic foot ulcer has to be clean located at or

below malleolar region more than 4 weeks, Grade 1 or 2 based on Wagner Classification and ulcer area  $\leq 20$  cm<sup>2</sup> (6). Patients with ulcer higher than Grade 1 and 2, ulcer located proximal to malleolous, history of smoking, bleeding disorders, positive history of antibiotic, anticoagulants, immunosuppressive drugs and patients with low platelet count were excluded from the study (6). Informed consent was obtained from all individuals in the study. The study was approved from Research ethics in Ain Shams University.

#### Clinical Assessment

All patients were subjected to full history, general and local examination. Body mass index (BMI) was measured. Diabetic foot ulcer was assessed at zero week, 4th and 12th weeks. Wound Margins were measured by sterile disposable ruler. Wound area was calculated by multiplying the two largest perpendicular diameters (11). HbA1c was measured by enzymatic assay. Pressure Ulcer Scale for Healing (PUSH) was assessed at 0, 4th and 12th weeks (4).

**Extra-corporal shock wave therapy:** The shockwave device (Technikwave GmbH & Co KG, China) uses a handheld probe to deliver high energy pulses similar to sound waves to wound surface. Shock wave device delivered waves with energy flux density 0.2mJ/mm<sup>2</sup> and frequency 5 Hz. Group (1) received 4 treatments of ESWT over 4 weeks (one session per week). Ulcer surface and perimeter of ulcer extending 1 cm in every direction was treated using 250 shocks/cm<sup>2</sup> and focal area 0-30 mm. Also 500 deep shocks were applied to anatomical location of arteries supplying ulcer location. Ulcers were covered with sterile film draping to prevent contamination. Standard ultrasound gel was used to couple between shock wave generator and film drape.

**PRP injection:** PRP was prepared using a platelet concentration system (centerion 2006 England). 20 ml of peripheral venous blood mixed with anticoagulant (citrate dextrose)- containing tube, was used to prepare autologous platelet concentrates via compact table-top centrifuge. Samples were centrifuged for 5 minutes at 1.5 rpm (soft spin step). After this step, three layers can be distinguished which are platelet poor plasma (PPP), PRP and red blood cell (RBC) layer from top to bottom. The upper two layers PPP and PRP were transferred to another anticoagulant-free tube. Plasma was again centrifuged for 5 minutes at 3.5 rpm (hard spin step). Platelet rich plasma (PRP) could be collected at the bottom of the tube as pellet which is diluted in 3ml plasma. This PRP is inactive; in order to prepare the end product, 0.2

ml thrombin was added for each ml of PRP and Calcium chloride was used to nullify the acid citrate's effect to form the fibrin matrix allowing the end product as a gel to be applied to the ulcer. The ulcer was covered by sterile non-absorbent dressing (non-absorbent sterile transparent dressing).Group (2) received one PRP therapy per week for 4 weeks.

**Topical Insulin Therapy**

Wounds were cleaned with sterile normal saline then irrigated with 4 units 0.1 ml of human soluble insulin (Lantus) in 1 ml saline for each 10 cm2 of wound. The prepared solution was sprayed on the wound surface with an insulin syringe twice daily for two days per week for 4 weeks .Each treatment was repeated twice in each day and the wound left to dry then treated with sterile treatment and covered with sterile gauze.

**Scoring and Healing Parameters**

Pressure Ulcer Scale for Healing (PUSH score) is a simple, accurate and useful wound assessment tool. Total score of PUSH score is 16. It is used to measure healing of wound through evaluation of the following wound characteristics: surface area, exudates amount and tissue type. The wound area scores were scored as area in cm2 =score): 0=0,<0.3=1,0.3-0.6=2,0.7-1=3,1.1-2=4,2.1-3=5, 1-4=6, 4.1-8=7, 8.1-12=8, 12.1-24=9.The exudates amount was scored as: none=0,light=1, moderate=2 and heavy=3. Tissue type scores were as follows: closed=0,epithelial tissue=1, granulation tissue =2, slough=3 and necrotic tissue=4. Each wound was given a sub score for each characteristic then theses sub scores were added to get overall score. The total score gives an indication of improvement or deterioration of wound healing (4).

- PUSH score was measured at 0, 4th and 12th weeks.

**Statistical Methods**

The collected data was revised, coded, tabulated and introduced to a PC using Statistical Package for Social Science version 20 (SPSS-V20) USA. Data was presented and suitable analysis was done according to type of data obtained for each parameter. Mean ±SD and range for numerical data, frequency and percentage for non-numerical data. Student T test was used to compare between two groups in quantitative data. Linear correlation coefficient used to assess the strength of association between non parametric variables in same group. ANOVA test was used for comparison among different times in the same group in quantitative data. Results were considered significant at p ≤ 0.05, highly significant at p ≤ 0.001.

**Results**

This study was conducted on sixty male non-smoker diabetic patients with diabetic foot ulcer. They were recruited from outpatient clinics of Ain Shams University Hospitals. The patients were randomly classified into four groups. Each group included 15 patients. Group 1 included patients whose ulcer was treated by extracorporeal shock wave therapy. Group 2 involved patients who received PRP therapy. Group 3 involved patients who were treated with topical insulin and Group 4 involved patients who were treated with standard care treatment and served as control group. Demographic, clinical, laboratory data and scoring parameters in each group are described in Table 1. The four groups were matched with respect to age, BMI and HbA1c.The mean value of PUSH score at zero weeks was matched in the four groups. There was statistically high significant decrease in the mean value of PUSH score at fourth and twelfth week of follow up compared to zero week in the four groups (Table 1).

As regards PUSH score, at fourth and twelfth week of follow up there was statistically significant decrease in the mean value of PUSH score of Group 3 who received topical insulin therapy compared to other groups (p< 0.053) (p< 0.025), (Table 2).

There was statistical significant positive correlation between PUSH score and each of BMI and HbA1c at zero, fourth and twelfth week in the four groups (Table 3).

**Discussion**

Diabetes is a chronic metabolic disorder of multiple etiologies. It is characterized by hyperglycemia, disturbance in carbohydrate, fat and protein metabolism which is due to defects in insulin action, secretion or both (12). The incidence of complication as impaired healing is increased as diabetes is the sixth most important cause of disability. Non healing wounds of diabetes constitute a major problem that diabetic patients face even with insulin treatment and controlled diet (12). Our study aimed to compare the effectiveness of PRP therapy, shock wave therapy and topical insulin therapy in healing of diabetic foot ulcer.

In our study the mean age was 65.33±7.43 in group 1, 67.73±7.93 in group 2, 65.8±6.25 in group 3 and 61.8±5.36 in group 4 which was in agreement with Radwa et al (4) who reported that the mean age of diabetic patients in their study was 55 years, also our results were in agreement with Bhattani et al (13) who showed that 61% of patients in their study were more than 55 years old. There was no statistical significant difference between the four groups as regards BMI which was in agreement with de Alencar F Santos et al (14) who showed no difference between patients as regards the pressure against ground but it was not in agreement with Jeffcoate et al (15) who showed notable difference in BMI as wound healing for patients whom BMI was more than 32 was lower than those with BMI was less than 32. Our study revealed no statistical significant difference as regards HbA1c which was agreement with de Alencar F Santos et al (14) who reported no difference between four groups although their study measured postprandial blood glucose which showed levels less than 140 mg/dl.

In our study the mean value of PUSH score showed statistically significant decrease at 4th and 12th week in comparison to those at zero weeks in each group which was in agreement with de Alencar F Santos et al (14) which revealed improvement in the parameters measured at 4<sup>th</sup> and 12<sup>th</sup> week. We found that the mean value of PUSH score showed statistically significant decrease in group 3 who received topical insulin in comparison to other groups. While in group 1 there was an improvement in mean value of PUSH score which was in agreement with Robert et al(6) who discussed that shockwave therapy increased perfusion, angiogenesis and growth factor up regulation which helps to regenerate skin, musculoskeletal and vascular structure in the wound bed and surrounding tissues. Also it was in agreement with Nasser et al (2) who showed increased expression of endothelial nitric oxide synthase, vascular endothelial growth factor and proliferation of cell nuclear antigen in patients treated with shock wave therapy. In addition Jeppesen et al (3) also showed that shock wave reduced the mean wound healing time by 19 days with remarkable reduction in risk as shockwave could function as a stimulator of microenvironment metabolism and promoter for growth of dermal cells through promoting collagen synthesis and fibroblast proliferation.

Our study revealed that Group 2 showed an improvement of ulcer healing in response to PRP therapy which was reported by Chi-Wen Lung et al (16) who explained the improvement of ulcer healing by PRP therapy through enhancing regeneration process by extra-physiological concentration of platelet derived growth factor, TGF β and VEGF. Also it improves ulcer healing, limit inflammation by suppression of cytokine release and interaction with macrophages. While Qiangru Huang et al (1) was not in agreement with our study as they used PRP dressing and concluded that PRP dressing was efficacious as normal saline dressing in management of diabetic foot ulcer, also they proved that there was no statistical significance in the final outcome during the follow up period(6 weeks)in their study.

**Table 1:** Demographic, clinical, laboratory data and scoring parameters in four groups.

	<b>Group1 (mean±SD)</b>	<b>Group2 (mean±SD)</b>	<b>Group3 (mean±SD)</b>	<b>Group4 (mean±SD)</b>
Age	50-75 65.33±7.432	52-77 67.73±7.93	51-7365.8±6.259	53-70 61.8±5.361
BMI	19-25 21.6±1.755	18-25 21.48±1.917	18-24 21.133±2.066	19-24 21.767±1.413
HbA1C	6.3-7.3 6.72±0.321	6-7 6.553±0.366	6.2-7.2 6.68±0.347	6-7.5 6.807±0.42
PUSH (0week)	5-15 9.4±2.72	6-16 11.133±3.09	5-16 9.2±3.098	6-15 10.133±2.615
PUSH (4thweek)	3-13 8.067±2.374	4-14 8.667±2.769	3-12 6.6±2.746	6-14 9.133±2.446
PUSH (12thweek)	3-11 6.467±2.669	3-12 6.267±3.011	2-11 4.8±2.678	5-13 7.933±2.463

BMI:Bodymassindex,HbA1c:HemoglobinA1c,PUSH:PressureUlcerHealingScale,SD:StandardDeviation

**Table 2:** Comparison between the four groups as regards PUSH score at zero, fourth and twelfth weeks.

	Group 1 Shockwave	Group 2 PRP	Group 3 Insulin	Group 4	P value	Sig
<b>PUSH (0 week)</b>	9.4±2.72	11.133±3.091	9.2±3.098	10.13±2.6	0.259	NS
<b>PUSH (4 weeks)</b>	8.067±2.374	8.667±2.769	6.6±2.74	9.13±2.44	0.053	S*
<b>PUSH (12 weeks)</b>	6.467±2.669	6.267±3.011	4.8±2.678	7.933±2.46	0.025	S*

PUSH: Pressure Ulcer Healing Scale, PRP: Platelet rich plasma, \*S: Significance (p<0.05), NS: Non significant, \*\*HS: Highly significant (p<0.001), ANOVA test.

**Table 3:** Correlation between PUSH score and each of BMI and HbA1c at 0, 4th, 12th week in the three groups.

PUSH score	Group 1		Group 2		Group 3		Group 4	
	P	Sig	P	Sig	P	Sig	P	Sig
<b>BMI</b>								
0 week	0.007	S	0.040	S	0.006	S	0.008	S
4th weeks	0.011	S	0.012	S	0.009	S	0.016	S
12th weeks	0.007	S	0.003	S	0.005	S	0.018	S
<b>HbA1c</b>								
0 week	0.004	S	0.008	NS	0.012	S	0.012	S
4th weeks	0.004	S	0.016	NS	0.006	S	0.019	S
12th weeks	0.003	S	0.018	NS	0.013	S	0.014	S

PUSH: Pressure Ulcer Healing Scale, BMI: Body mass index, HbA1c: Hemoglobin A1c \*S: Significance (p<0.05), NS: Non-significant, \*\*HS: Highly significant (p<0.001), Linear correlation coefficient test.

As regards topical insulin, we reported statistical significance difference in PUSH score at 4<sup>th</sup> and 12<sup>th</sup> week which was in agreement with Radwa et al(4) which revealed improvement in ulcer healing by administration of topical insulin to the ulcer.

In our study Group 3 who was treated with topical insulin showed statistically significant difference in PUSH score in comparison to other three groups. This is attributed to role of topical insulin which acts on human growth hormone receptors and enhances the reformation of the epithelium as well as collagen formation, granulation tissue and release of insulin like growth factor by fibroblast which was revealed by Cychoz et al (17). Also Zhang et al (18) showed that topical insulin formulation was used to control local hyperglycemia in peripheral tissue as well as acceleration of wound healing. Our study revealed that there was statistical significant correlation between PUSH score and each of BMI and HbA1c in all groups.

We found statistically significant positive correlation between BMI and HbA1C which was also described by Kostev K et al (19) who illustrated that risk factors for macrovascular complications such as obesity demonstrate the correlation between HbA1c and vascular complications.

### Conclusion

Diabetic foot ulcer in people with diabetes is common. Occurrence of ulceration, infection and gangrene are the most common causes of hospitalization. Appropriate and prompt management is necessary for successful treatment of DFU. Our study compared the effect of topical insulin, shock wave and PRP in healing of diabetic foot ulcer. There was statistically significant difference in healing rate and PUSH score among the three groups of our patients.

### Recommendations

From this study we recommend adding topical insulin as a basic therapy for treatment of diabetic foot ulcer wounds especially ulcers and wounds with complicated and delayed healing.

### Limitations of the Study

Limited sample size due to lack of fund and lack of long duration follow up due to poor compliance of the patients.

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