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Case Report Open Access

Extracorporeal Shock Wave Therapy in the Treatment of Non-Healing Diabetic Ulcer: A Pilot Study

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Abstract

15-20% of all diabetic patients develop a foot ulcer. Diabetic ulcer is the major cause of non-traumatic lower extremity amputation. Extracorporeal shock wave therapy (ESWT) has emerged as a promising therapy in the field of wound healing. In this study, Five patients with diabetic foot (mean age of 58.2 ± 19.63 years, mean ulcer duration: 1.6 years), received ESWT in 6-8 weekly sessions, at a flux density of 0.25 mJ/mm^2, delivered as 500 shocks at wound margin and 1000 shocks distal to the wound. All patients had evidence of peripheral vascular disease and neuropathy before treatment. A significant reduction in ulcer surface area was observed in four patients (mean reduction: 1.21 ± 0.82 cm2, p value=0.03). All patients showed improvement in the ankle brachial index and monofilament test after treatment. In sum, ESWT may be a promising adjunct in the treatment of chronic, non-healing diabetic ulcers.

Keywords: Diabetes complication; Ulcer; High-energy shockwave

Introduction

Diabetes affects 366 million people worldwide. Among patients with diabetes, 15-20% develops a foot ulcer, with 2-3% developing one or multiple foot ulcers every year [1]. Diabetic ulcer is the major cause of non-traumatic lower extremity amputation among people aged 20 years or older in the United States [2]. Diabetic ulcer occurs as a result of multiple etiologies including neuropathy, arterial disease, mechanical pressure, and foot deformity [3-5].

The management of diabetic foot ulcers often requires offloading the area of the ulcer, debridement, appropriate dressings, antibiotic therapy when necessary, and evaluation and correction of peripheral arterial insufficiency. However, only 30% of diabetic ulcers will heal within 20 weeks despite meticulous wound care [6]. Some novel therapeutic modalities have been used to enhance wound healing including growth factors, tissue-cultured skin substitutes, hyperbaric oxygen, and extracorporeal shock wave therapy (ESWT) [7,8].

Extracorporeal shock waves are defined as a sequence of sound waves that are generated by a vibration source and transported through tissues. These waves are characterized by high positive pressure, a rise time lower than 10 nanoseconds and a tensile wave .The positive pressure and the short rise time are responsible for the direct shock wave effect and the tensile wave for the cavitation or the indirect effect [9]. Originally used for lithotripsy and treatment of musculoskeletal disorders, ESWT has emerged as a promising therapy in the field of wound healing.

The objective of this pilot study was to evaluate the safety and efficacy of ESWT in patients with non-healing diabetic foot ulcer of complex underlying etiology including peripheral arterial disease and neuropathy.

Case Report

This study was performed at the wound clinic, Center for Research and Training in Skin Diseases and Leprosy (CTRSL), Tehran University of Medical Sciences. Diabetic patients (type 2), 18 years or older, with foot ulceration of at least 6 months duration who did not respond to standard wound care were selected. Patients were excluded if they were pregnant, breast-feeding, currently on anticoagulants, or had evidence of malignancy or venous thrombosis at the site to be treated. Microbial culture and smear was performed before including the patients and only wounds without evidence of infection or after reaching clean wound state and negative culture via appropriate antibiotic therapy were selected. Patients were strictly advised on off-loading, and ambulatory patients were instructed to use crutches. Local wound dressing was applied as necessary. All patients received ESWT in 6-8 weekly sessions, delivered as 500 shocks at wound margin and 1000 shocks distal to the wound (lower leg), spread over the entire muscle area at a flux density of 0.25 mJ/mm^2, using the C-actor hand piece of the Duolith SD1 device (STORZ MEDICAL AG, Tägerwilen, Switzerland).Treatment was delivered by "scanning" the treatment areas with slow hand piece movements. The sessions were performed outpatient under no anesthesia. The ulcer was covered with sterile cellulose barrier. The ultrasound gel was applied to the area of skin in contact with the shockwave tube. The patients were visited 2 weeks after the final session of treatment. Monofilament test, wound area measurement using digital photography, and calculation of the ankle brachial index (ABI) were done at each visit. Monofilaments test was performed as an indicator for neuropathy. Loss of the ability to detect this pressure on the plantar surface of the foot has been associated with loss of large-fiber nerve function and is highly predictive of subsequent ulceration [10]. Using nylon monofilaments, 10-g force was applied. The number of areas with loss of sensation was reported as the numerator of the fraction out of the 10 total points tested. We measured ABI according to the available guidelines [11]. Statistical analysis was performed using SPSS (Version 22, IBM).

Using Shapiro-Wilk test, all data were distributed normally. We employed paired sample T-test for comparing the means before and after the intervention.

Five patients, including four male, with a median age of 70 (interquartile range [IQR]: 36.5, mean: 58.2 ± 19.6) years and a median BMI of 29.2 (IQR: 3.05, mean: 29.2 ± 1.59) were enrolled (Table 1). The ulcer was located on plantar surface in 2 patients and on external malleolus, forefoot and heel in others. The median surface area and duration of ulcer were 6.25 (IQR: 7.73, mean: 7.54 ± 5.05) cm^2 and 1.5 (IQR: 1.75, mean: 1.6 ± 0.96) years, respectively. All patients showed evidence of peripheral vascular disease and neuropathy with a median ABI of 0.62 (IQR: 0.25, mean: 0.62 ± 0.13) and monofilament test score of 6/10, respectively before treatment. After 6-8 weekly sessions of ESWT, a significant reduction in ulcer surface area was observed in four patients with a mean post-treatment ulcer size of 6.33 cm^2 ± 5.00 (mean reduction: 1.21 ± 0.82 cm^2, p value=0.03) (Figure 1). All patients showed improvement in the ABI and monofilament test after treatment (mean ABI and monofilament test score of 0.9 ± 0.12, p value: 0.00 and 4/10 after treatment, respectively) (Table 1). No adverse events including pain, itching, burning, skin irritation, pigmentation, or infection was noted during the treatment and after 2 months of completion of treatment.

Patient Number	Sex	Age years	BMI	HbA1c	Ulcer Duration	Ulcer Location	ABI		Monofilament test score		Ulcer size (cm)		Dorsalis Pedis Pulse*		Posterior Tibial Pulse		Popliteal Pulse		Femoral Pusle	
							before	after	before	after	before	after	R	L	R	L	R	L	R	L
1	M	70	29.2	7.1	3(Years)	Plantar	0.5	0.8	6/10	3/10	2.5 × 2.5	2 × 2.2	+1	+1	+1	+1	+2	+2	+2	+2
2	M	72	28	8.9	1(Year)	Plantar	0.8	1.1	6/10	3/10	2.0 × 1.0	0.5 × 0.5	0	0	+1	0	+1	+1	+2	+2
3	M	75	31.3	9.7	1.5 (years)	External malleus	0.7	0.9	8/10	7/10	3.5 × 2.2	3.5 × 2.0	0	0	0	+1	+1	+1	+2	+2
4	M	41	27.4	6.5	6 (month)	forefoot	0.6	0.9	6/10	3/10	4.5 × 3.5	4 × 3.5	0	0	0	+1	+1	+1	+2	+2
5	F	33	30.2	7.4	2 (Years)	Heel	0.5	0.8	5/10	4/10	3 × 2	3 × 2	0	+1	0	+1	+1	+1	+2	+2

Table1: The characteristics and treatment response in patients with diabetic foot ulcer treated with ESWT (6-8 weekly session, 0.25 mj/mm 2.500 pulses on wound margin and 1000 on distal limb) R: Right; L: Left.

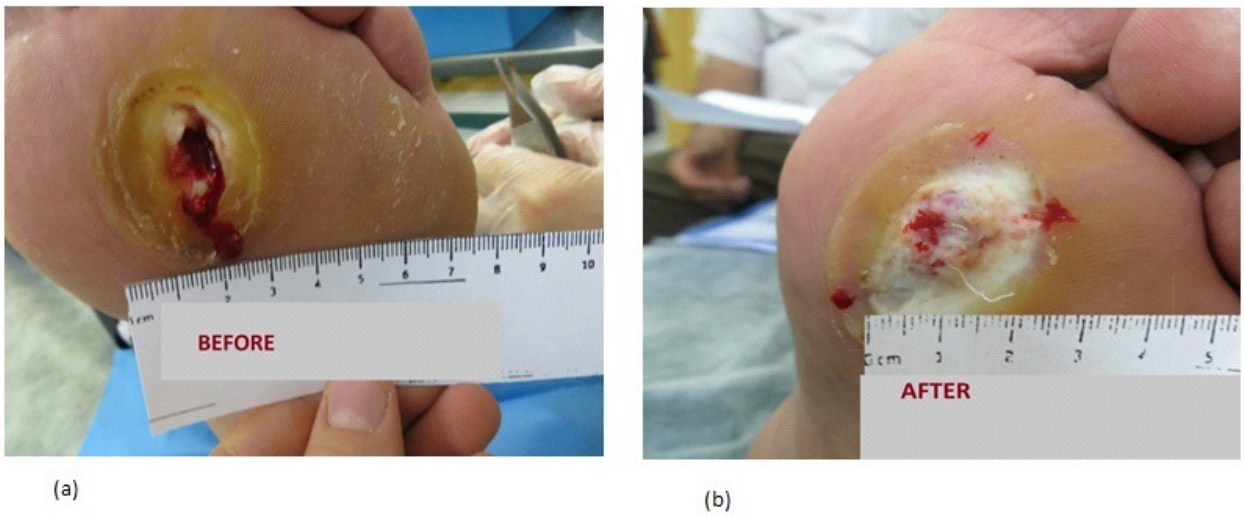

Figure 1: A 62 year-old male with a diabetic ulcer of one-year duration on plantar surface, measuring 2.0 × 1.0 cm before treatment **(a)**. Significant re-epithelialization was observed after ESWT with post-treatment ulcer size of 0.5 × 0.5 cm **(b)**.

Discussion

The delivery of shock waves has been shown to improve blood supply, increase cell proliferation and induce neovascularization via stimulation of endothelial nitric oxide synthase, vascular endothelial growth factor and proliferating cell nuclear antigen [12,13]. ESWT improves myocardial perfusion and cardiac function in a porcine model of chronic myocardial ischemia [14] and may help reduce the ischemic zone of flaps by increasing tissue perfusion and suppression of the inflammatory response [15]. In addition, shock wave stimulate the release of many mediators such as transforming growth factor beta-1 and insulin-like growth factor-1 leading to increased recruitment of skin fibroblasts and induction of a well-controlled inflammatory response enhancing the wound healing process especially of the chronic ones [16-18]. The effect of ESWT on neuropathic ulcers remains unclear. As suggested by Moretti et al, the anti-inflammatory effect, enhanced peripheral circulation, down-regulation of oxygen radicals, and release or neurotrophic cytokines have been proposed as possible mechanisms.

In this pilot study we evaluated the effect of ESWT on non-healing diabetic wound of very long duration and with complex underlying etiology including vascular insufficiency and neuropathy. None of our patients achieved complete re-epithelialization, however reduction in would surface area was notes in 4 of 5 patients. Importantly, an improvement in distal limb circulation and neuropathy was observed in all patients.

In a trial of neuropathic diabetic ulcers treated with 20 weeks of ESWT100 pulses per 1 cm^2 of wound delivered at a flux density of 0.03 mJ/mm^2, 53.33% of the patients had complete wound closure compared with 33.33% of the control patients [19]. Significant decrease in wound surface area and increase in the rate of epithelialization was seen in diabetic ulcer after treatment with 12 weeks of shock wave therapy 500 pulses/cm^2 at 0.1 mJ/mm^2 [20]. Our results in this small series of patients is inferior to the above trials as none of our patients achieved complete re-epithelialization and the reduction in ulcer size was not dramatic after treatment. However, it should be noted that in the previously mentioned studies diabetic patients with evidence of vascular insufficiency were excluded. Patients with diabetes have higher incidence of atherosclerosis, capillary basement membranes thickening and endothelial proliferation leading to peripheral arterial disease. Although severe limb ischemia and arterial insufficiency often requires invasive procedures such as angiography or bypass surgery for limb salvage, it is not uncommon for diabetic ulcers to have an underlying mild to moderate arterial disorder further complicating the healing process. Moreover, angioplasty or bypass surgery is generally ineffective in small-vessel disease and amputation becomes inevitable due to persistent critical limb ischemia, soft-tissue infection, and impaired wound healing with osteomyelitis [21].

Interestingly, patient number 2 (Figure 1) who had the best wound healing response after ESWT, had only mild arterial disease before treatment (ABI: 0.8) while the only non-responder (number 5) had the lowest pre-treatment ABI (0.5). It is possible that due to the localization of ulcer on external malleolus in patient 2, diabetic ulcer is less strong of an etiology and other contributing factors such as arterial insufficiency are more important.

The fact that ABI increased in all patients after treatment confirms the strong neovascularization effect of ESWT leading to enhanced limb perfusion. In addition, it is known that neuropathic diabetic ulcers of longer duration are less likely to undergo a timely healing process [6]. Therefore, the long duration of ulcer in our patients (mean: 1.6 years) could have contributed to the less favorable outcome. However, it should be noted that this small pilot study cannot provide conclusive evidence for such associations, and future larger studies are required. Another limitation is the variations in the described parameters of shock wave including frequency, energy flux and number of pulses for the treatment of diabetic ulcer. A prospective randomized clinical trial of ESWT in the treatment of chronic wound including diabetic is currently recruiting patient at our center.

In conclusion, ESWT may be a promising adjunct in the treatment of chronic, non-healing diabetic ulcers. Randomized trials are required to study the effect of ESWT on diabetic ulcers with complex underlying etiology and to determine the optimal shock waver parameters in this setting.

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