Efficacy of shock wave therapy on chronic diabetic foot ulcer: A single-blinded randomized controlled clinical trial

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\textbf{Abstract}

Objective: This study was conducted to evaluate the efficacy of extracorporeal shock wave therapy (ESWT) on the healing rate, wound surface area and wound bed preparation in chronic diabetic foot ulcers (DFU).

Methods: Thirty eight patients with 45 chronic DFU were randomly assigned into; the ESWT-group (19 patients/24 ulcers) and the control-group (19 patients/21 ulcers). Blinded therapist measured wound surface area (WSA), the percentage of reduction in the WSA, rate of healing and wound bed preparation at baseline, after the end of the interventions (W8), and at 20-week follow-up (W20). The ESWT group received shock wave therapy twice per week for a total of eight treatments. Each ulcer was received ESWT at a frequency of 100 pulse/cm\textsuperscript{2}, and energy flux density of 0.11 mJ/cm\textsuperscript{2}. All patients received standardized wound care consisting of debridement, blood-glucose control agents, and footwear modification for pressure reduction.

Results: The overall clinical results showed completely healed ulcers in 33.3% and 54% in ESWT-groups and 14.28% and 28.5% in the control group after intervention (W8), and at follow-up (W20) respectively. The average healing time was significantly lower (64.5 ± 8.06 days vs 81.17 ± 4.35 days, \(p < 0.05\)) in the ESWT-group compared with the control group.

Conclusion: ESWT-treated ulcers had a significant reduction in wound size and median time required for ulcer healing, with no adverse reactions. So, the ESWT is advocated as an adjunctive therapy in chronic diabetic wound.

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1. Introduction

Diabetic foot ulcer (DFU) is a major problem for modern healthcare providers. Research indicated that 15% of people with diabetes will develop foot ulceration in their lifetime, and 5–15% will end up with amputation [1,2].

There is a little research in Saudi Arabia on DFU prevalence, management or cost. However, survey suggested that the incidence of diabetes is 23.7%, and it is extremely high in urban areas [3]. The diabetic foot lesions constitute a major complication, with an overall prevalence of 10.4% [4,5]. Moreover, these lesions are linked with increased health, cost, diminished quality of life and prolong functional disability [6].

Many adjunctive therapies are designed for the care of DFU, involving hyperbaric oxygen therapy [7–9], vacuum-assisted wound closure [10,11], low level laser therapy [12] and electrical stimulation [13]. However, the results from these studies are inconsistent and reported limited success with no conclusive remark on its effect [7–13]. Therefore, the development of new effective noninvasive modalities for the management of diabetic wounds is extremely important to reduce both patients’ suffering from chronic wounds and the cost of treatment.

For the past 20 years, extracorporeal shockwave therapy (ESWT) has been used for musculoskeletal disorders [14–16]. Recently, ESWT was shown to be valuable for the treatment of chronic wound, such as bedsores [17], vascular and diabetic ulcers [18–20], burn wounds [21,22] and skin flaps [23]. However, these studies were limited clinical trials with low level of evidence [24]. Moreover, systematic review concluded that lack of evidence, and rigorous study design made it difficult for clinicians and therapists to support using of ESWT in wound healing [25]. Furthermore, clinical trials are required to assess the optimum ESWT treatment parameters, such as duration and frequency of therapy and types of wound remains.

Therefore, this single-blinded, randomized controlled study was conducted to evaluate the efficacy of ESWT on the healing rate, wound surface area and wound bed preparation in chronic diabetic foot ulcers.

Patients were excluded if they had: (1) evidence of local infection, acute cellulitis, osteomyelitis or gangrene anywhere in the affected extremity; (2) presence of renal, hepatic, neurologic or malignant diseases; (3) severe protein malnutrition (serum albumin < 2.0 g/dl) or severe anemia (Hgb < 7.0 g/dl) [13,28]; (4) an ankle-brachial index < 0.7, absence of the dorsalis pedis or posterior tibial artery pulse [20], and (5) pregnancy.

The study was approved by the Research Ethics Committee, King Saud Medical City. All subject signed informed consent form before participation in the study. The trial registration code of this study was ACTRN12613003557774.

Forty four patients with 52 chronic diabetic foot ulcers were assigned into; control-group (n = 22) and ESWT-group (n = 22).

Randomization was performed using the computer generator block labels describing the treatment groups. The sample size was estimated to be 38 in both groups and would be increased to 44 for possible dropout. This sample size was estimated to detect 20% difference in wound surface area between groups, with the probability level was set at 0.05 and power of 85%.

2.2. Clinical outcome measurements

Blinded therapist evaluated the patients and measured wound surface area (WSA), and percentage of WSA reduction, and wound bed preparation. These measurements were taken at baseline, after the end of the interventions (W8), and at 20-week follow-up (W20).

2.3. Wound surface area measurement

The percentage of decrease in WSA due to interventions was recorded. The therapist placed sterilized transparency sheet over the wound and traced the wound perimeter using a permanent marking pen [29]. Each wound was traced three times to ensure the reliability of measurement. The tracing was digitized using the A4 G-Note 7100 Tablets with cordless mouse and two stylus pen (KYE systems, Corp, China), and then imported into a specialized software program (Photoshop C4me) to calculate WSA. The percentage of reduction in WSA was determined from the following equation [30]:

$$\% \downarrow WSA = \frac{[\text{initial WSA(cm}^2\text{)} - \text{WSA(cm}^2\text{)} \times \text{at x weeks}]}{\text{Initial WSA(cm}^2\text{)} \times 100$$

The percentage of WSA reduction for wounds that had completely healed was detected at each measurement time. The wounds were labeled completely healed only if they clinically closed (100% re-epithelization) without drainage or dressing requirement.

The time to complete healing was recorded as the number of days from the beginning of the treatment on the date in which the wound achieved complete healing. If healing did not occur within the 20 weeks, the patient was considered to be nonhealing and no time was recorded.

2.4. Wound bed preparation, scores

The wound bed preparation, scores and the percentage of granulation and necrotic tissues and the presence of the exudates have been determined. The presence of exudates
was determined as: none, minimal, moderate and heavy, based on wound bed preparation, scores developed by Falanga et al. [31,32].

2.5 Interventions

All patients received standardized wound care consisting of debridement, blood-glucose control agents, and footwear modification for pressure reduction. Wound dressing was changed once a day by the patient, or home-health care providers, depending on the patient’s individual capabilities and resources.

ESWT-group: Therapist cleaned the ulcer with saline and removed necrotic tissues and then dried the ulcer before application of SWT. The ulcer was covered with a sterilized transparent plastic thin film that allows 100% transmission of waves through it and to avoid cross-contamination. Ultrasound gel was applied directly over the plastic sheet to be in contact with the shockwave probe. The probe was held vertically against each ulcer by direct contact with slight pressure to minimize power loss due to beam divergence. Each ulcer was received ESWT at a frequency of 100 pulse/cm², and energy flux density of 0.11 ml/cm² [28,33]. The ESWT was applied twice a week, with one-week interval, and for a total of eight sessions.

After each session, the therapist inspected the area surrounding an ulcer for adverse events such as dermatitis, erythema, infection, excessive granulation and necrotic tissue.

2.6 Statistical analysis

Continuous variables were presented as mean and standard deviation while categorical variables were described by frequency and percentage. Because most of the measured data were not normally distributed, nonparametric tests had been used for analyses. The Wilcoxon test was used to test the differences in outcome measures within group. The Mann–Whitney U test was used for comparison between the groups. Significant differences were assumed at p < 0.05. Statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) version 21.0.

3. Results

Fig. 1 shows the flow chart of patient enrollment. Among the total of 44 patients who met the inclusion/exclusion criteria, three patients (one in the ESWT-group and two in the control-group) did not complete their treatment. The other three patients were excluded because of the development of infection (one in the ESWT-group and two in the control-group). Therefore, 38 patients with 45 ulcers (19 patients with 24 ulcers in the ESWT-group, and 19 patients with 21 ulcers in the control-group) completed the study procedures and were included in the final analysis.

Table 1 represents the demographic and clinical characteristics of patients. Both groups were comparable in respect to age (p = 0.81), duration of diabetes (p = 0.35), and duration of ulcer (p = 0.59), smoking history (p = 0.79), and associated diabetic complications (p = 0.89), which varied markedly between patients. The patients were predominantly males (71%). Ulcers were located mostly on the plantar surface of the foot (64.4%). The age and duration of ulcer were not significantly correlated with the improvement ratio in both groups (p > 0.05). No adverse effects were observed secondary to the application of ESWT.

Table 2 represents ulcer size and percentage of WSA reduction. The initial ulcer sizes were comparable in both groups. The average WSA was (7.89 ± 2.97 cm² and 8.62 ± 3.47 cm²) in the ESWT and control groups respectively. Significant declines in the WSA were observed in the ESWT-group (p < 0.05) at each evaluation time, while the considerable reduction was observed only at time of follow-up in the control group. The mean percentage of reductions in WSA were significantly higher in the ESWT-group in comparison to the control-group after the intervention (W8) (60.08 ± 28.07 vs 36.19 ± 22.95, p < 0.05), and at follow-up (W20), (83.32 ± 20.68 vs 63.31 ± 24.87, p < 0.05).

At baseline, the wound bed preparation scores had no significant differences between both groups (p > 0.05). The percentage of granulation tissues was varying from 30% to 70% of the raw WSR, with mean values of 50.47% and 46.67% for ESWT and control groups respectively. The amount of exudates was recorded as: none in six ulcers (3 in each group), minimal in 14 ulcers (8 in the ESWT-group and 6 in the control-group), moderate in 15 ulcers (8 in the ESWT-group and 7 in the control group) and heavy in 10 ulcers (5 in each group).

After eight weeks (W8), the rate of ulcers that reported complete healing was (33.3% and 14.28%) in the ESWT and control groups respectively. At twenty-week follow-up (W20), both groups maintained significantly higher rates of healing. Where there were 13 ulcers (54%) in ESWT-group and 6 ulcers (28.5%) in the control-group healed completely. For the ulcers that healed within 20-week, the average healing time...
was significantly lower in ESWT-group (64.5 ± 8.06 days) compared to the control group (81.17 ± 4.35 days).

There were significant differences (p < 0.05) among non-healed ulcers in both groups. Where >50% reduction of WSA reported in 33.5%, and 19% unchanged ulcers were 12.5%, and 52.5%, in the ESWT and the control group respectively. In addition, the granulation tissue was significantly increased to 69.68% (33.4%–75%), and 51.9% (25%–66.6%) in the ESWT compared to the control group respectively. During the 20-week of follow-up, recurrent ulcers developed in one patient (5.26%), had 2 ulcers (8.34%) in the ESWT group, while recurrent ulcers developed in 3 patient (15.79%) with four ulcers (19%) in the control group.

4. Discussion

Poor wound healing is a life-threatening complication with an associated increased rate of morbidity and mortality [1,2]. In this study, we assessed the efficacy of ESWT on the chronic diabetic foot ulcers by examining the wound surface area, healing time and wound bed preparation. The ESWT treatment significantly reduced wound surface area, healing time and improved wound bed preparation. Furthermore, these effects were observable in nonhealed foot ulcer compared to the control group.

The results from this study are supported by reports from several studies used ESWT for wound healing [18–20,28]. Our results are in agreement with recent work of Wang et al., who found a similar rate of complete healing (57% vs 54%), improved healing (32% vs 33.5%), unchanged (11% vs 12.5%) following application ESWT [34]. Moreover, our results regard to the rate and time of healing was comparable with the findings of Moretti et al. [20]. After 20 weeks of treatment, the ESWT-treated patients had completed (53.33% vs 54%) wound closure compared with (33.33% vs 28.5%) of the control patients. The healing times were being (60.8 days vs 61.5 days) and (82.2 days vs 84.5 days) respectively. In addition,
Saggini et al. [19] concluded that 50% of chronic wounds were healed completely with no reported adverse events following ESWT. However, the rate of healing was obtained from heterogeneous ulcers; posttraumatic ulcers (69%), venous ulcers (36%), and diabetic ulcers (25%).

Early work of Wang et al. [28] showed a lower rate of complete healing (31%) and high rate of improvement (58%) than obtained from the current study. Contrast to this finding Schaden et al. [38] reported a higher healing rate of 75% in the mean follow-up period of 44 days. These discrepancies might be attributed to the heterogeneity of wounds. As one-third of the wounds in the study of Schaden et al. were acute, with two-thirds of them due to surgical failure and trauma. Nearly 80% of patients had persistence wounds one month or less after initial diagnosis. While reporting wounds of the current study was chronic with persistence of more than three months. However, there was a similarity between the two studies in respect to the initial wound size and parameters of ESWT (100 pulses/cm², and energy density 0.1 mJ/mm²).

Preclinical studies by Kuo et al. demonstrated that ESWT (800 pulse, 0.09 mJ/cm²) significantly reduced the wound size in diabetic rats, with greater reduction seen with more treatments [35]. Recently, a study on Sprague-Dawley rats with incisional diabetic wound reported that focused ESWT (100 pulse, 0.11 mJ/mm²) increased collagen content, enhanced wound breaking strength and improve the healing of incisional wound [33]. However, a recent study conducted by Zins et al. on db/db mice with full-thickness dorsal skin defects found that unfocused ESWT (200 pulses, 0.1 mJ/mm²) had no effect on wound closure in both diabetic and control mice. Moreover, multiple treatments caused delayed wound healing after initially increasing the size of the wound [36].

The exact mechanism of ESWT remains poorly understood. Some studies demonstrated that ESWT acts as mechanotransduction that induces shearing forces within tissues. This will initiate a biological response at a cellular level, producing angiogenesis-related growth and proliferation factors, such as nitric oxide synthesis (eNOS), vessels endothelial growth factors (VEGF) and proliferative cell nuclear antigen (PCNA) leading to increase blood supply and tissue regeneration [37–40]. In addition, ESWT activates cells that are sensitive to mechanical stimulation (e.g. Macrophages) results in increased motility and attraction of immune cells, increased phagocytosis and release of nonspecific cytokines, interleukins and nitric oxide [41–43].

The classic process of wound healing consists of three phases: inflammatory phase, proliferative phase, and remodeling phase. Fibroblasts are the main cells involved in the last two phases. The migration and proliferation of fibroblasts are essential for collagen synthesis and extracellular matrix secretion [44]. However, the function of fibroblasts becomes impaired in diabetic wounds [45]. Yang et al. found that the number of fibroblasts that migrate to the diabetic wound site increased after ESWT application. This result is consistent with the finding of Berta et al. [46], who reported that application of ESWT enhances human dermal fibroblast proliferation in vitro. In addition, results of study conducted by Kue et al. [35] indicated that appropriate dosage of ESWT could modulate fibroblast recruitment, and thus, promote tissue remodeling. Moreover, application of the ESWT significantly improved topical blood flow perfusion rate, increased cell proliferation and decreased cell apoptosis [34]. Overall, these findings strongly suggested that application of ESWT results in enhancement of tissue regeneration.

In this study, the control-group had a rate of healing of 28.5%, at 20-week follow-up, which is nearly similar to that reported in the meta-analysis study conducted by Margolis et al. [6], who found that 31% of wounds healed after 20 weeks of commencing good wound care. While, ESWT group had a rate of healing (54%) higher than that reported from the control group and meta-analysis study [6].

Several factors significantly influenced the results from these studies. As, there are discrepancies in the initial wound size, stages and types of wound involved, optimal energy level, number of ESWT sessions, interval time between sessions and types of ESWT (focused vs unfocused). It is still unclear how frequently ESWT needs to be provided. In this study two sessions of the ESWT/week, with one-week interval was provided with a minimum of six and a maximum of eight sessions. The same energy was used for every wound. This was done to reduce the confounding variables during assessment of the results. It is possible that one session of therapy was sufficient, or perhaps the treatment would have been more effective if more frequent sessions were provided. However, in the literature, good results of angiogenesis were reported using different protocols in which the interval between sessions of shock waves varies from 48 hours to two weeks [19,47]. Nevertheless, the regime used here was effective for this group of patients.

Several limitations were identified in this study included a small sample size and grade of ulcers (1A and 2A) according to the University of Texas Diabetic Wound Classification System. So making generalization of this treatment regimen to ulcer with different classification might be difficult. However, the patient selections were randomized and blinded. The length of follow-up is relatively short, and the long-term results are not available, so the recurrence rate was not determined. So, further experimental and clinical studies are still required to standardize a protocol for the management of diabetic foot ulcers.

5. Conclusion

This study confirms that ESWT has a potential benefit in the management of chronic diabetic ulcers when used with appropriate off-loading and local wound care. ESWT-treated ulcers had a significant reduction in wound size and median time required for ulcer healing, with no adverse reactions. So, the ESWT is advocated as an adjunctive therapy in chronic diabetic wound.

Conflict of interest statement

The authors report no conflicts of interest, financial or otherwise.
REFERENCES


