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Treatment of diabetic foot ulcers: A comparative study of extracorporeal shockwave therapy and hyperbaric oxygen therapy (TR / Diyabetik ayak ülserinin tedavisi: ESWT ile Hiperbarik Oksijen Tedavisi arasında karşılaştırmalı bir çalışma)

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ABSTRACT

AMAÇ: Bu çalışma, ayakta kronik diyabetik ülserin tedavisinde ESWT ile Hiperbarik Oksijen Tedavisi(HBOT) ni etkinlik yönünden kıyaslamaktadır.

Hasta ve Metodlar: ESWT grubuna (39 hasta/44 ayak) haftada iki kez olmak üzere toplamda altı seans şok dalga tedavisi uygulandı. HBOT grubu (38 hasta/40 ayak) HBO tedavisini günlük olarak aldılar ve toplamda 40 seans uygulandı. Değerlendirmeler arasında kan akımı (perfüzyonu) taramaları ve histopatolojik muayeneler yer almaktadır.

Özet: Tüm klinik sonuçlar gösterdiki; ESWT hastalarının %57'sinde ülser tamamen iyileşti, bu oran HBO grubunda ise %25'dir. Ülserin yarısından(>%50) fazlasının iyileştiği vaka dağılımı ESWT için %32 ve HBO için %15. Ülserde herhangi bir değişikliğin ve gelişmenin olmadığı vaka oranları ESWT için %11, HBOT için %60. Tedaviden önce iki grubun da kan akımı perfüzyon oranları benzerdi (P=.002) ancak tedaviden sonra ESWT grubu lehine büyük farklar gözlemlenmiştir. Histopatolojik muayeneler ortaya çıkardı ki; hücre proliferasyonunda artış ve hücre apoptozisinde ki azalma, HBOT ile kıyaslandığında ESWT grubunda oldukça fazlaydı.

Sonuç: Kronik diyabetik ayak ülserinin tedavisinde ESWT, HBOT ile kıyaslandığında daya etkilidir. ESWT ile tedavi edilen ülserler HBOT ile tedavi edilenlere göre (daha iyi tedaviye sebebiyet veren) kan akım perfüzyonu oranında ve hücre aktivisitesinde kayda değer gelişmeler göstermiştirlerdir.

1. Introduction

A chronic diabetic foot ulcer is defined as a foot ulcer that fails to heal in 3 months with standard treatment [1,2]. The etiology of diabetic foot ulcer is multi-factorial including ischemic, neuropathic, or combined neuro-ischemic [3–8]. Ischemic ulcers are caused by angiopathy with small vessel occlusion, whereas neuropathic ulcers are due to peripheral neuropathy and secondary infection or trauma [6,7]. Managements of chronic diabetic foot ulcers require multi-disciplinary approaches including control of patient's diabetes, appropriate orthotic shoe wear, off loading device~~s~~, wound care and surgery in selected cases [4,6,7]. Frequent debridement is often crucial to ulcer healing, but the results of both surgical and non-surgical treatments are unsatisfactory [6,7,9]. Therefore, many adjunctive therapies are designed for the care of chronic diabetic foot ulcers including hyperbaric oxygen therapy (HBOT), negative pressure wound therapy (NPWT), ultrasound, recombinant

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human platelet-derived growth factor-BB (rPDGF-BB) and acellular matrix products [10–17]. Among them, HBOT is the most commonly utilized adjunctive therapy. Many studies have reported beneficial effect of HBOT, but none showed universal success [12,14–17]. Therefore, a need exists for a new and effective method of treatment in diabetic foot ulcers.

In clinical application, the positive effects of extracorporeal shockwave therapy (ESWT) in orthopedic disorders were supported by many papers published in the literature [18–24]. In animal experiments, ESWT was shown to induce neovascularization and up-regulation of angiogenic growth factors including eNOS, VEGF and PCNA [25,26]. Recently, ESWT was reported effective in the initiation and acceleration of wound healing in burns, traumatic wounds, reconstructive skin flaps, and diabetic ulcers [27–30]. We hypothesized that ESWT may be more effective than HBOT in the treatment of diabetic foot ulcers. This study was designed to compare the effectiveness of ESWT and HBOT in chronic diabetic foot ulcers.

2. Patients and methods

The Institutional Review Board approved this study protocol and patients gave their written informed consent prior to participation in the study. The clinical trial registration code of this study is NCT01219127. The inclusion criteria included patients with chronic non-healing diabetic foot ulcers for more than 3 months duration. Exclusion criteria included patients with cardiac arrhythmia or a pacemaker, pregnancy, skeletal immaturity, patients with malignancy, and patients lacking complete follow-up data.

This is a prospective open-label, randomized, but not blinded study. Eighty-eight diabetic patients with 95 chronic non-healing ulcers in the foot area were enrolled in this study. Patients were randomly divided into two groups according to the computer generated block labels. Forty-three patients with 48 feet with odd numbers were assigned to the ESWT group. Forty-five patients with 47 feet with even numbers were assigned to the HBOT group. During the course of treatment, 11 patients were excluded including 4 in the ESWT group (2 unrelated deaths and 2 poor compliance) and seven in the HBO group (7 incomplete follow-up data). Therefore, 77 patients with 84 feet (39 patients with 44 feet in the ESWT group, and 38 patients with 40 feet in HBOT group) were included in the final analysis. Five patients in the ESWT group and 2 in the HBOT group had bilateral foot ulcers, and each foot was counted individually. The flow chart of patient recruitment is shown in Table 1. The patient demographic characteristics are summarized in Table 2. Ten patients (4 in the ESWT group and 6 in the HBOT group) underwent surgical debridement for deep wound sepsis or necrosis, and were enrolled in the study after the ulcers became stable without further signs of sepsis or necrosis.

Pre-treatment evaluations included a complete history and physical examination, chemistry and coagulation profiles including HBA1c data for blood sugar control, and the details

Table 1 – The flow chart of patient recruitment.

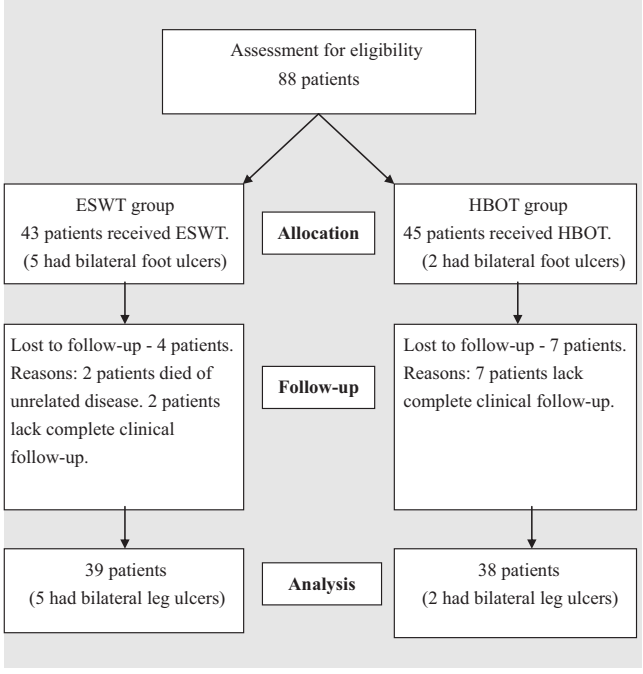

Table 2 – Patient demographic characteristics.

	ESWT group	HBOT group	P-Value
Numbers of patients/numbers of foot	39/44	38/40	0.826
Average age (years) (range)	60.51 ± 13.97 (20–81)	62.45 ± 13.95 (23–88)	0.795
Average size (cm^2)			
Median (range)	4 (1.5–9)	7 (2–12)	0.059
Average duration (months)			
Median (range)	6 (3–16)	6 (6–10)	0.060
Right/left	17/27	24/16	0.257
Bilateral feet	5	2	
Location of ulcer			
Dorsal	13	11	0.836
Plantar	31	29	
Ave. HBA1c (range)	8.76 ± 2.23 (5.6–12.4)	8.09 ± 1.76 (5.4–12.1)	0.327
Ave. ABI[a] (range)	1.07 ± 0.10 (0.83–1.25)	0.91 ± 0.27 (0.36–1.25)	0.060
Average follow-up (months) (range)	13.50 ± 4.31 (3–18)	11.1 ± 5.19 (3–18)	0.079

[a] Ankle brachial pressure index.

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of past surgical and medical treatments. The circulatory status of the affected limb was evaluated with ankle-brachial pressure index (ABI) using Doppler scan. Skin sensitivity was evaluated with a monofilament pinprick test. The size, depth, and appearance of the ulcer were quantitatively assessed with physical examination and photo-documentation. The blood flow perfusion scan and biopsy from the edge of the ulcer including intact skin were performed prior to the initiation of the treatment protocol and at the end of the treatment protocol. The biopsy specimens were subjected to histopathological examination. The histopathological examinations including cell proliferation, cell concentration, cell activity and cell apoptosis were performed microscopically with hematoxylin-eosin (H-E) stain.

2.1. Shockwave application

The source of shockwave was from a dermaPACE device (Sanuwave, Alpharetta, GA, USA). The treatment was performed as an outpatient care procedure with no anesthesia. The ulcer was covered with a sterile cellulose barrier. Ultrasound gel was applied to the area of skin in contact with the shockwave applicator. The treatment dosage was ulcer size dependent with the numbers of impulses equal to the treatment area in $cm^2 \times 8$, with a minimum of 500 impulses at energy setting E2 (equivalent to 0.23 mJ/mm^2 energy flux density) at a rate of 4 shocks per second. The treatment area was calculated by extending the actual perimeter of the ulcer for 1.0 cm in all directions. The treatments were conducted two times per week for 3 weeks for a total of 6 treatments. After ESWT, patients resumed their initial wound care protocol including off loading on the affected foot, wound cleansing with sterile normal saline solution and application of silver sulfadiazine cream. The administration of additional antibiotic was at the discretion of the treating physician.

2.2. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) was performed with patients in a sealed multi-place chamber at a pressure of 2.5 atmospheres absolute (ATA). Air pressure was gradually increased from 1 ATA to 2.5 ATA over a 15 min interval. Oxygen of 100% medical grade was inhaled through a plastic facemask for 25 min followed by a 5 min break for a total of 90 min per treatment. Air pressure was then decompressed from 2.5 ATA down 1.0 ATA within 15 min to complete the treatment. HBO was performed daily, five times a week, for a total of 40 treatments. Patients in the HBOT group received the same standard wound care protocol after treatment as the ESWT group.

2.3. Blood flow perfusion scan

Tissue viability was evaluated by local blood flow perfusion scan. Local blood flow perfusion was measured using the Peri-Scan PIM II Laser Doppler Perfusion Imager (Perimed AB, Stockholm, Sweden). To perform this analysis, the object was placed on a light absorbing background material such as a black or a dark green cloth. The distance between the scanner head and the object was 15 cm. The minimum and maximum values were set at 0 and 5 V respectively. The perfusion scan image color scale displayed the lowest value in dark blue and the highest value in dark red. LDPIwin software in Window 95/98/2000 was used for data analysis including the minimal value, the maximal value and the mean and standard deviation.

2.4. Histopathological examination

The biopsy specimens were subjected to histopathological examination. The specimens were fixed in 4% PBS-buffered formaldehyde at 4 °C and embedded in paraffin wax. The specimens were then dissected into 5 μm-thick sections with a microtome and stained with hematoxylin-eosin stain. The cell morphology was examined microscopically under 40× magnification to determine cell proliferation, cell concentration, cell activity and cell apoptosis. Two pathologist blinded to the group assignment performed the examinations.

The follow-up examinations were scheduled at 3 and 6 weeks, then once every 3 months. Clinical assessment of the ulcer status was performed by physical examination including visual observation and photo-documentation. Blood flow perfusion scan and histopathological examination were performed prior to the initiation of the treatment protocol and as part of the last examination.

Table 3 – The overall clinical results.

Ulcer status	ESWT	HBOT	P-Value
After one course of treatment	(N = 44)	(N = 40)	
Completely healed ulcers	57% (24 of 44)	25% (10 of 40)	0.003
≥50% improved ulcers	32% (14 of 44)	15% (6 of 40)	0.071
Unchanged ulcers	11% (5 of 44)	60% (24 of 40)	<0.001
Worsened ulcers	0	0	
After second course of treatment	(N = 14)	(N = 17)	
Completely healed ulcers	50% (7 of 14)	6% (1 of 17)	0.005
≥50% improved ulcers	43% (6 of 14)	47% (8 of 17)	0.815
Unchanged ulcers	7% (1 of 14)	47% (8 of 17)	0.015
Worsened ulcers	0	0	

N: Numbers of foot.
P-Values: comparison between the ESWT group and the HBOT group.

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Table 4 – The results of blood flow perfusion scan before and after treatment.

	Before treatment	After treatment	P-Value-1
ESWT (N = 44) (range)	0.48 (0.32–0.64)	0.61 (0.40–0.79)	<0.001
HBOT (N = 40) (range)	0.59 (0.50–0.63)	0.50 (0.11–0.53)	0.916
P-Value-2	0.245	0.002	

N: numbers of foot.
P-Value-1: comparison of the data before and after treatment within the same group.
P-Value-2: comparison of the data between ESWT and HBOT groups.

2.5. *Statistical analysis*

A power analysis revealed that a sample size of 40 in each group would be required to establish the statistical significance with $\alpha = 0.05$ and power = 0.80 based on the estimated outcomes of 85% and 50% for ESWT and HBOT respectively in chronic diabetic foot ulcers. We anticipate a 10–15% dropout rate during the study period. The data before and after treatment within the same group were compared statistically using a paired *t*-test. The data between the ESWT group and the HBOT group were compared statistically using Mann–Whitney *U*-test. The statistical significance was set at $P < 0.05$.

3. Results

The overall clinical results are shown in Table 3. The clinical results after one treatment course showed completely healed ulcers in 57% and 25% ($P = 0.003$); ≥50% improved ulcers in 32% and 15% ($P = 0.071$); unchanged ulcers in 11% and 60% ($P < 0.001$) and none worsened for the ESWT group and the HBOT group respectively. Twenty-seven patients (12 patients with 14 feet in the ESWT group and 15 patients with 17 feet in the HBOT group) also received a second course of treatment due to improved but incomplete healing of the ulcers 4–6 weeks from the first treatment. The decision for a second treatment was at the discretion of the treating physician upon patient consent. The results after a second course of treatment showed completely healed ulcers in 50% and 6% ($P = 0.005$); ≥50% improved ulcers in 43% and 47% ($P = 0.815$); unchanged ulcers in 7% and 47% ($P = 0.015$) and none worse for the ESWT group and the HBOT group respectively.

The results of blood flow perfusion scan are shown in Table 4. The blood flow perfusion scans are shown in Fig. 1. The blood flow perfusion rates were significantly increased after ESWT ($P < 0.001$), whereas, the changes after HBOT were statistically not significant ($P = 0.916$). Prior to the initiation of treatment, the blood flow perfusion rates were comparable between the two groups ($P = 0.245$). Following the treatment

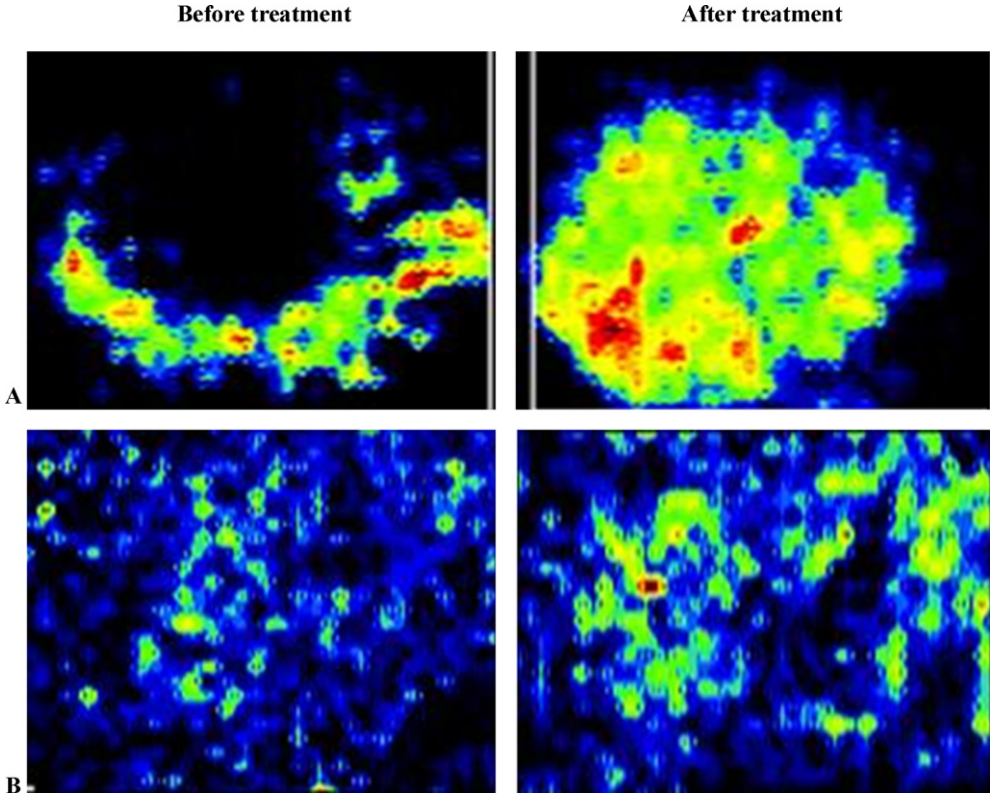

Fig. 1 – Blood flow perfusion scan of the lower limb before and after treatment: (A) poor blood perfusion before ESWT, and significant increase in blood perfusion rate after ESWT; (B) poor blood perfusion before HBOT, and unchanged blood flow perfusion rate after HBOT.

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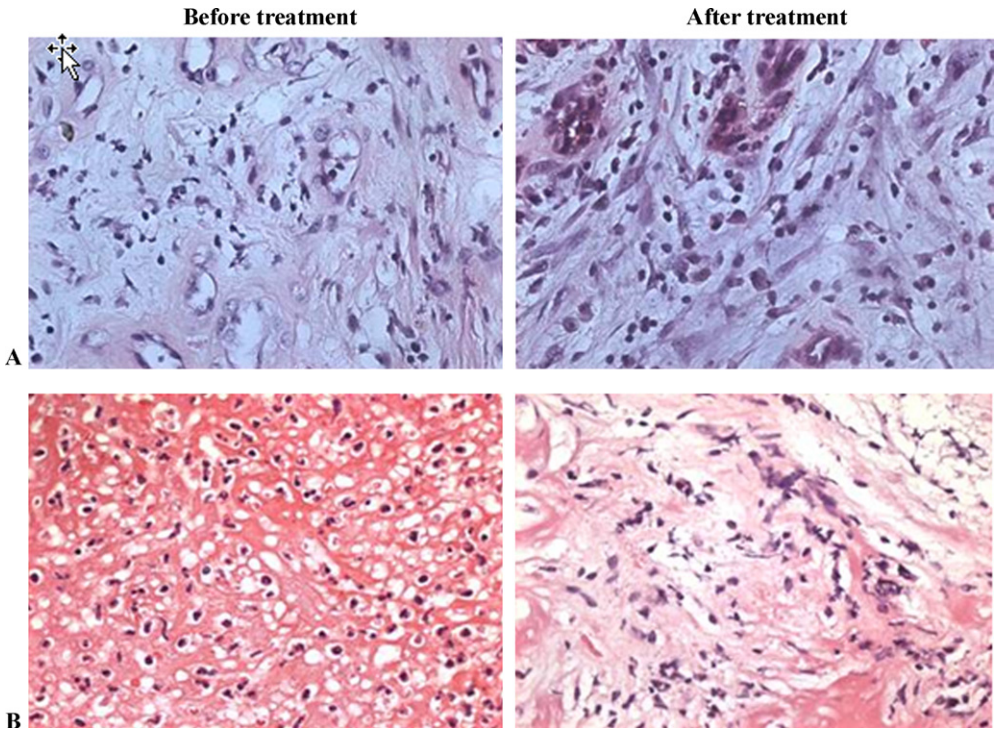

Fig. 2 – Microscopic feathers of the histopathological examination before and after treatment: (A) considerably higher cell proliferation, cell concentration and cell activity, and lower cell apoptosis after ESWT (40×); (B) lower cell proliferation, cell concentration and cell activity, and higher cell apoptosis after HBOT (40×).

protocol, the difference in blood flow perfusion rate between the two groups became statistically significant favoring the ESWT group ($P = 0.002$).

In histopathological examination, the ESWT group showed considerable increases in cell proliferation, cell concentration and cell activity, and a decrease in cell apoptosis as compared to the HBOT group (Fig. 2).

3.1. *Complications*

Four patients in the HBOT group developed complications of the middle ear barotraumas and sinus pain. The symptoms resolved spontaneously upon the release of the chamber air pressure. In the ESWT group, there was no systemic or local complication. None of the ulcers worsened after treatment. There was no neurovascular complication or device related problems.

4. Discussion

The results of the current study showed that ESWT is more effective than HBOT in the treatment of chronic diabetic foot ulcers. Application of ESWT significantly improved topical blood flow perfusion rate, increased cell proliferation and cell activity and decreased cell apoptosis. The results of the current study are supported by a report when a different shockwave device was utilized [30]. Furthermore, ESWT was shown to enhance wound healing via increasing topical blood perfusion and tissue regeneration in a rat model of STZ-induced diabetes [31]. It appears that dermaPACE shockwave device has the ability to improve wound healing by increasing perfusion in the wound environment and normalizing the rates of cell apoptosis and tissue regeneration in chronic diabetic foot ulcers.

The stages of wound healing include inflammation, proliferation, epithelization, and remodeling. Non-healing wounds occur when this process is interrupted or out of sequence, often the case in diabetes, peripheral vascular disease (PVD) and infection, etc. [1,2,4,6,32]. ESWT has been shown to cause shear forces within tissues that initiate a biological response at a cellular level producing angiogenic growth factors, including eNOS, VEGF, and PCNA [25,26], which are known to be present during normal wound healing. Increased perfusion has a direct effect on ischemic wound conditions that are causative or a contributing co-morbidity in chronic diabetic wounds. The increased perfusion response is an immediate inflammatory reaction to acoustic waves that put shear stress and mechanical forces on the microcirculatory system [1,2,6]. By elevating perfusion in the wound area, the ischemic component of the chronic wound disease state is decreased immediately within a wound healing environment. A decrease in cell apoptosis and an increase in cell activity on the wound bed and the adjacent tissues were observed following the shockwave treatment.

The exact mechanism of HBOT remains poorly understood. Some studies have reported that HBOT has important effects on the biology of cytokines and other mediators of inflammation [33,34]. HBOT causes cytokine down-regulation and growth factor up-regulation. HBOT transiently suppresses stimulus-induced pro-inflammatory cytokine production and affects the

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liberation of TNF-α (tumor necrosis factor alpha) and endothelins [12,33]. VEGF levels are significantly increased with HBOT, whereas the values of PGE2 (prostaglandin E2), COX-2 (cyclooxygenase 2) and mRNA expression are markedly reduced. Therefore, cytokines, prostaglandins (PGs), and nitric oxide (NO) may play a major role in the mechanism of action of HBOT [13].

Several limitations to this study should be noted. This study is limited by virtue of a small patient population that may create a low power of statistical analysis. The patient selections were randomized but not blinded. As a result, patients were randomized in a predictable way, and both patients and healthcare providers were not blinded to the treatment group. Patients enrolled in this study were mixtures of Wagner 2, 3 and 4 ulcers with predominant grade 3 and 4 where infection is a component of the problem. However, the effects of HBOT in this study showed different results from previous studies [32]. The length of follow-up is relatively short, and the long-term results are not available in this study. Lastly, only one type of shockwave device was used in this study. It was not the authors' intention to compare the effectiveness of different shockwave devices in this study.

In conclusion, the results of the current study demonstrated that ESWT is more effective than HBOT in chronic diabetic foot ulcers. ESWT-treated ulcers showed better blood flow perfusion rate and cell activity and decreased cell apoptosis relative to HBOT in chronic diabetic foot ulcers.

Authors' contributions

Ching-Jen Wang, M.D. participated in the study with the primary responsibility of the conception and design drafting, overview of the entire study, data collection and analysis, literature review, reference search, drafting and critically revised the manuscript and read proof the final paper submitted.

Re-Wen Wu, M.D. participated in the study with primary responsibility of conducting HBO treatment, data collection and analysis and proof read the final manuscript.

Ya-Ju Yang, BS participated in the study with primary responsibility in ESWT application, and assistance in HBOT, performing blood flow perfusion scan, and photo documentation on follow-up examinations, case review and proof read the final manuscript.

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Conflict of interest

The authors declared that they did not receive any honoraria or consultancy fees for writing this manuscript. One author (CJW) has served as a member of the scientific advisory board of Sanuwave until November 2010. The remaining authors declared no conflict of interest.

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