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● *Clinical Note*

DEFOCUSED SHOCK WAVE THERAPY FOR CHRONIC SOFT TISSUE WOUNDS IN THE LOWER LIMBS: A PILOT STUDY

Manuela Porso,* Simona Loreti,* Sveva Maria Nusca,* Sara Luziatelli,* Donatella Caccia,* Giulia Taborri,* Donatella Trischitta,* Maurizio Taurino,† Luca Padua,‡§ Vincenzo Maria Saraceni,* Maria Chiara Vulpiani,* and Mario Vetrano*

*Physical Medicine and Rehabilitation Unit, Sant'Andrea Hospital, University of Rome "La Sapienza," Rome, Italy; †Department of Vascular Surgery, Sant'Andrea Hospital, University of Rome "La Sapienza," Rome, Italy; ‡Department of Geriatrics, Neurosciences and Orthopaedics, Catholic University of the Sacred Heart, Rome, Italy; and §Don Carlo Gnocchi Onlus Foundation, Milan, Italy

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Abstract—Chronic soft tissue wounds of the lower limbs are debilitating, painful and often unresponsive to advanced dressing treatments. Extracorporeal shock wave therapy (ESWT) could represent an alternative treatment. Ten patients with chronic soft tissue wounds of the legs, unresponsive to advanced dressing treatments for more than 3 mo, underwent three defocused ESWT sessions at 72-h intervals. In every session, the sum of 300 standard pulses + 100 pulses per square centimeter was applied at 0.15 mJ/mm^2 and 4 Hz over the edge of the wound. The wound size in square centimeters, Bates-Jensen Wound Assessment Tool and visual analogue scale were used as outcome measures. A significant reduction in wound size and Bates-Jensen Wound Assessment Tool and visual analogue scale values from pre-treatment to 90 d was observed. Seven of ten ulcers healed completely and nine of ten patients reported complete pain relief. Defocused ESWT represents a non-invasive, feasible strategy for difficult-to-treat soft tissue wounds of the lower limbs. (E-mail: mariovetrano@gmail.com) © 2016 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Defocused extracorporeal shock wave therapy, Chronic soft tissue wound, Advanced dressing treatment, Wound size, Bates-Jensen Wound Assessment Tool, Visual analogue scale.**

INTRODUCTION

Chronic, soft tissue wounds in the lower limbs, defined as ulcers persisting longer than 3 mo and demanding specialized care (Werdin et al. 2008), have a prevalence of 1% in the adult population, including 3.6% in people older than 65 y, in developed countries (London and Donnelly 2000).

The most common etiology is multifactorial and includes local (*e.g.,* venous or arterial insufficiency, infection and local pressure) and systemic (*e.g.,* diabetes and nutritional status) factors; another common cause is represented by traumatic injuries or surgery (Ferriera et al. 2006). The primary goal in the treatment of chronic soft tissue wounds is to obtain wound closure. Their management includes medical and nutritional optimization, mechanical or surgical debridement, compression, treatment of ischemia, treatment of infection, appropriate wound bed preparation and topical therapies ranging from conservative to advanced (Frykberg and Banks 2015). When chronic wounds do not respond sufficiently to standard care, new wound care therapies are encouraged (Snyder et al. 2010). Among these, the most known are negative pressure wound therapy (Armstrong et al. 2004), hyperbaric oxygen therapy (Zamboni et al. 2003), biological and bio-engineered therapies (Frykberg et al. 2010), biophysical therapies such as electrical stimulation (Baker et al. 1997), pulsed radio frequency energy (Frykberg et al. 2011) and extracorporeal shock wave therapy (ESWT) (Schaden et al. 2007). However, for most of these treatments there is neither a high level of evidence, nor randomized prospective studies assessing their efficacy.

The use of ESWT for clinical applications was introduced more than three decades ago for the treatment of urolithiasis (Demling et al. 1982). ESWT was then used

Address correspondence to: Mario Vetrano, Physical Medicine and Rehabilitation Unit, Sant'Andrea Hospital, Via di Grottarossa 1035-1039, Rome, 00189, Italy. E-mail: mariovetrano@gmail.com

to treat several musculoskeletal conditions (Seil et al. 2006). Schaden et al. (2001) observed that the application of ESWT resulted in bony consolidation and soft tissue healing in patients with non-unions and delayed bone fracture healing. Starting from these observations, different studies (Haupt and Chvapil 1990; Kuo et al. 2009a) have reported that ESWT acts to accelerate wound healing through the recruitment of skin fibroblasts and release of endogenous angiogenic factors from endothelial cells and fibroblasts. Other studies have found that ESWT is also responsible for reducing pain in the short term after exposure to ESWT by an as yet incompletely clarified mechanism (Abed et al. 2007; Mariotto et al. 2005, 2009; Ochiai et al. 2007; Ohtori et al. 2001; Takahashi et al. 2003).

Focused ESWT is defined as a sequence of sonic pulses characterized by high peak pressure >100 MPa, rapid pressure rise and short life cycle (Wang 2003). Defocused ESWT is characterized by lower energy values delivered into the soft tissues with a superficial and quite large (3–5 cm^2) zone of impact (Mittermayr et al. 2012). Consequently, defocused is more useful than focused ESWT to treat superficial, wide wounds such as ulcers. However, both focused ESWT (Moretti et al. 2009; Omar et al. 2014; Saggini et al. 2008; Wang et al. 2009) and defocused ESWT (Larking et al. 2010; Schaden et al. 2007; Wang et al. 2011; Wolff et al. 2011) have recently been reported to be effective in the treatment of chronic wounds.

The present pilot study examines the effects of defocused ESWT on healing and pain in chronic soft tissue wounds of the lower limbs that were unresponsive to conservative and advanced dressing longer than 3 mo. Two quantitative measures of chronic soft tissue wound healing and a quantitative measure of pain were used to assess treatment progress, which has been explored together for the first time, to obtain a comprehensive overview of the healing journey of chronic wounds. To minimize observer bias, changes in size were evaluated using dedicated software (Woundsoft), changes in other parameters (signs of ulcer healing) were evaluated using the Bates-Jensen Wound Assessment Tool (BJWAT) and changes in pain were assessed using the visual analogue scale (VAS) at each follow-up.

METHODS

Patient recruitment

Ten consecutive patients (ten ulcers) from the Vascular Surgery Department of Sant'Andrea Hospital, University of Rome "La Sapienza," were enrolled from February 2014 through March 2015 and treated as outpatients at the Physical Medicine and Rehabilitation Unit. Patients of both sexes older than 18 y were included if chronic soft tissue wounds in the lower limbs were unresponsive to conservative (wound cleansing with sterile normal saline solution and sharp debridement) and advanced medical care (application of hydrocolloid dressing–Askina gel 15 g, Braun, Milan, Italy) longer than 3 mo. Other inclusion criteria were wound surface larger than 0.5 cm^2 and wound diameter between 0.5 and 5 cm. Ulcers of various etiologies were included (post-traumatic, venous, arterial, diabetic or mixed ulcers). Patients with pressure ulcers were excluded from the study, as these patients often require hospitalization because of their general clinical conditions. Other exclusion criteria included deep chronic soft tissue wounds penetrating through subcutaneous tissue and involving muscle and bone, ankle brachial pressure index (ABPI) < 0.8 (moderate arterial disease sign) (Cole 2001), absence of dorsalis pedis or posterior tibial artery pulse, presence of pacemaker, coagulation disorders, use of anticoagulant drugs, history of neoplasia, pregnancy, soft tissue wound infections and osteomyelitis.

The study protocol (Trial Registration No. http://www.clinicaltrials.gov NCT02410447) was approved by the Ethics and Experimental Research Committee of our Hospital, (RS:3053/2014) and was carried out in accordance with National Health Council Resolution No. 196/96. All patients were voluntarily enrolled after written informed consent was obtained.

Administration of shock waves

An electromagnetic generator (DUOLITH SD1, Storz Medical, Tägerwilen, Switzerland) delivering defocused ESWT was used in this study. The protocol consisted of a course of three sessions at 72-h intervals, using an energy flux density of 0.15 mJ/mm^2 and frequency of 4 Hz. In every ESWT session, the total dose was calculated by adding up to 300 standard pulses, 100 $pulses/cm^2$ (according to wound surface area). The average time for each session was 5–10 min. Before each session, after careful, sharp wound debridement and cleansing with sterile normal saline solution, a digital image of the ulcer was taken with perpendicular orientation to the skin to evaluate wound area. Sterile ultrasound gel (sterile Aquasonic 100, Parker Laboratories, Fairfield, NJ, USA) was applied to the wound surface, and then a protective film was placed over the wound (Protect Film, Farmac-Zabban, Bologna, Italy), thus reducing the formation of air bubbles. Finally, ultrasound gel was applied to the protective film, and the defocused lens shock wave applicator was placed on the wound. Shock waves were delivered to the wound edges, as the probe was slowly moved around the wound perimeter for the entire treatment duration. The treatment was administered in an outpatient setting, without anesthesia or topical drugs. At the end of each treatment, the ultrasound gel was removed and pre-ESWT wound dressing therapy remained unchanged. During follow-up, wound dressing therapy was applied twice a week in an outpatient setting at the Department of Vascular Surgery.

Outcome assessments

Wound healing and pain were assessed before treatment and at the 15-, 30- and 90-d follow-ups.

Size of the wound in square centimeters and the Bates-Jensen Wound Assessment Tool (BJWAT) were used as measures of chronic soft tissue wound healing. Wound size was defined with computerized digital photo documentation using dedicated software (Woundsoft Version 1.3 Coloplast, Bologna, Italy). This software provided an objective method of accurate surface measurements of the wound through calibrated digital images. A picture of the ulcer next to a measuring tape was realized with a perpendicular orientation to the skin and without a flash. The characteristics of each wound were assessed by providing a score from 1 to 5 for 13 items (BJWAT score): size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin color surrounding wound, peripheral tissue edema and induration, granulation tissue and epithelialization. The final BJWAT score ranges between 13 and 65. The higher the score, the more severe is the wound status; a total score of 13 indicates complete wound closure (Harris et al. 2010). This tool is adapted from the valid, reliable, Pressure Sore Status Tool (Bates-Jensen et al. 1992, Bates-Jensen and McNees, 1995) for use on all types of wounds (Bolton et al. 2004; Romanelli et al. 2007).

The visual analogue scale (VAS) for self-assessment of pain measurement was administered to the patient to quantify the painful sensation before treatment and during follow-up. The scale consists of a 10-cm horizontal axis, where 0 is "no pain" and 10 is "the worst pain possible" (Price et al. 1994).

The same clinical investigator assessed wound size (as previously described), BJWAT and VAS for all patients before treatment and at the 15-, 30- and 90-d follow-ups, thus monitoring the efficacy and tolerability of treatment.

Statistical analysis

Continuous variables are expressed as the median and range, whereas categorical variables are described as the frequency and percentage. Friedman/Wilcoxon non-parametric tests were used for pairwise comparison of size, BJWAT and VAS at all follow-up points (within analysis). Significant differences were assumed at $p < 0.05$. All analyses were performed with the software STATA/SE 12.1 (Stata, College Station, TX, USA).

RESULTS

The patients' demographic and clinical data are summarized in Table 1. There were four men and six women. Median patient age was 65 (range: 35–81). Median body mass index was 35 (range: 24.9–36.4). Comorbidities were diabetes mellitus type 2 and arterial hypertension in three patients, arterial hypertension (alone) in five patients, venous insufficiency in seven patients and arterial insufficiency in one patient. Four patients were smokers. Wound etiology was mixed (diabetic plus venous in two patients, post-surgical dehiscence plus venous in two patients), venous (three patients) and post-surgical dehiscence, diabetic and arterial (one patient each).

The outcome measures at each follow-up are summarized in Table 2. Eight of ten patients completed the study; two patients dropped out before the third follow-up at 90 d. One patient required a further surgical intervention for a bone fracture, and one patient did not attend the last follow-up appointment. Therefore, last observation carried forward (LOCF) was applied. This method takes the last observation measured in a longitudinal study and uses it to impute future missing observation. By use of this method, all missing data are filled in, and analyses are then performed as if there are no missing data (Ambrosius 2007).

At the 15-d follow up, one wound (10%) exhibited complete epithelialization. At the 30-d follow up, another

Table 1. Patient demographic and clinical data (10 patients/10 ulcers)

Characteristics	Patient data
Age, y*	65.11 (35–81)
Gender, M/F†	4 (40)/6 (60)
Body mass index*	35 (24.9–36.4)
Diabetes mellitus, no/yes†	7 (70)/3 (30)
Arterial hypertension, no/yes†	2 (20)/8 (80)
Smoke, no/yes†	6 (60)/4 (40)
Venous stasis, no/yes†	3 (30)/7 (70)
Arterial insufficiency, no/yes†	9 (90)/1 (10)
Ulcer type†	
Arterial	1 (10)
Diabetic	1 (10)
Mixed	4 (40)
Post-traumatic	1 (10)
Venous	3 (30)
Site†	
Internal malleolar region	3 (30)
External malleolar region	2 (20)
Calcaneal region	1 (10)
Foot stump	1 (10)
Anterior aspect lower leg	1 (10)
Posterior distal lower leg	1 (10)
Achilles tendon	1 (10)
Side, left/right†	6 (60)/4 (40)
Duration of symptoms, mo*	10 (3–52)

* Median (range).
† Number (%).

Table 2. Outcome measures at each follow-up for each patient

	Outcome											
	Baseline			15-d follow-up			30-d follow-up			90-d follow-up		
Patient	Size (cm^2)	BJWAT	VAS (cm)	Size (cm^2)	BJWAT	VAS (cm)	Size (cm^2)	BJWAT	VAS (cm)	Size (cm^2)	BJWAT	VAS (cm)
1	1.5	31	8	1.1	25	3	0.5	20	0	0	13	0
2	5.1	22	6	1.7	19	2	0	13	0	0	13	0
3	3.8	32	4	0	13	0	0	13	0	0	13	0
4	5.5	40	4	4.3	40	1	5	40	1	5	40	1
5	4.2	23	4	1.5	20	0	0	13	0	0	13	0
6	8.8	45	4	5.4	43	0	5.9	41	0	5.9	38	0
7	1.6	30	5	0.8	18	0	0	13	0	0	13	0
8	2.8	38	7	6.7	38	3	2.6	36	0	2.6	36	0
9	8.4	32	0	4.4	25	0	4.2	20	0	0	13	0
10	0.5	22	2	0.1	18	0	0	13	0	0	13	0

BJWAT = Bates-Jensen Wound Assessment Tool; VAS = visual analogue scale.

four wounds (40%) were healed. At the 90-d follow up, an additional two wounds (20%) were healed. At the end of the study, seven wounds (70%) were completely healed (100% epithelialization) and one wound (10%) was improved (33% epithelialization). The last two wounds (20%) remained unchanged. Nonetheless, these two patients with absence of wound improvement at last follow-up (90-d follow-up) experienced a significant improvement in pain symptoms. The distribution of healed, improved and unchanged ulcers is outlined in Table 3.

Mean time to complete healing (100% epithelialization), defined as the number of days from the start of treatment to the date on which each patient achieved complete wound healing, was 45 d (range: 15–90). At the 90-d follow up, size had a median value of 0 (range: 0.0–5.9) and BJWAT had a median value of 13 (range: 13–40), which means completely healed. The VAS had a median value of 0 (range: 0–3) at the 15-d follow-up and a median value of 0 (range: 0–1) at the 90-d follow-up, with cessation of pain in nine of ten patients.

The distribution of the data points for each measurement outcome (size, BJWAT and VAS scores at baseline and 15-, 30- and 90-d follow-ups) is illustrated in Figures 1–3. Pairwise comparisons of size, BJWAT and VAS at all follow-up points (within analysis) are outlined in Table 4.

Table 3. Frequency and percentage of completely healed, improved and unchanged ulcers at the 90-d follow-up (size)

Ulcer*	Number (%)
Completely healed	7 (70)
Improved	1 (10)
Unchanged	2 (20)

* Completely healed indicates 100% epithelialization, and improved indicates 33% epithelialization.

Side effects

Patients reported no pain during the treatment. We did not observe bleeding, petechiae, hematomas or seromas. During the whole study period, there were no treatment-related toxic effects, infections or wound deterioration.

DISCUSSION

This pilot study revealed positive effects of defocused ESWT on healing and pain in a small cohort of patients with chronic soft tissue wounds of the lower limbs that were unresponsive to conservative and advanced dressing. Our study reported a significant reduction in

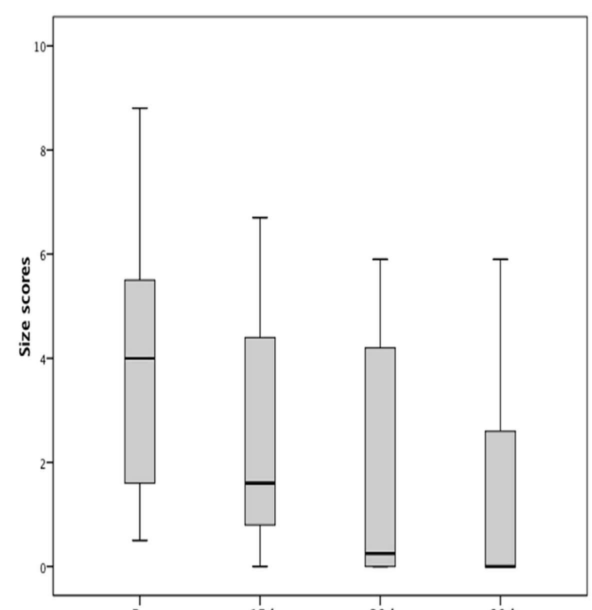

Fig. 1. Distribution of the data points for size scores at baseline and the 15-, 30- and 90-d follow-ups.

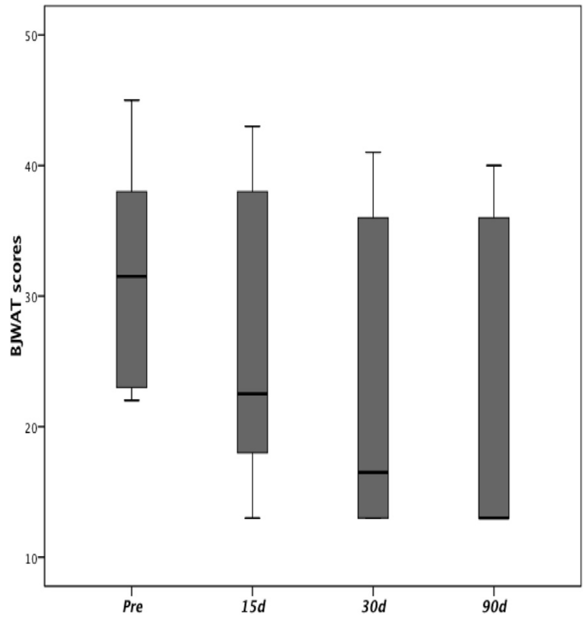

Fig. 2. Distribution of the data points for Bates-Jensen Wound Assessment Tool (BJWAT) scores at baseline and the 15-, 30- and 90-d follow-ups.

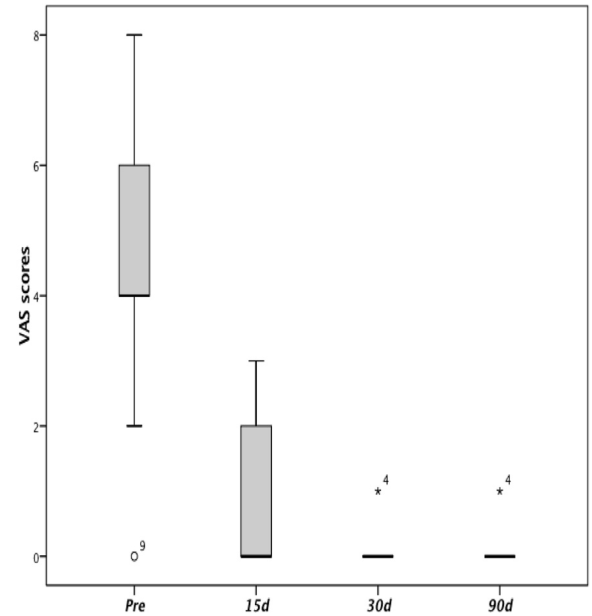

Fig. 3. Distribution of the data points for visual analog scale (VAS) scores at baseline and the 15-, 30- and 90-d follow-ups. *Extreme outliers.

size from pre-treatment to follow-up (at 15 and 90 d), with complete healing of seven of ten ulcers (70% of patients) and wound improvement (33% epithelialization) in one of ten ulcers (10% of patients) at the 90-d follow up. A significant reduction in the BJWAT score from pre-treatment to follow-up (at 15, 30 and 90 d) was observed. In addition, ESWT was responsible for a significant reduction in VAS for pain evaluation by the 15-d follow up, with cessation of pain in nearly all patients. Pain reduction also occurred in the two patients with unchanged ulcer size.

The rationale for the use of ESWT in chronic soft tissue wounds of the lower extremities is stimulation of tissue healing, especially with respect to angiogenesis, anti-inflammatory responses and the tissue regeneration process, as reported in animal models (Kuo et al. 2009b; Mittermayr et al. 2011) and clinical studies (Arnó et al. 2010; Larking et al. 2010; Saggini et al. 2008; Wang et al. 2009, 2011). Other authors have highlighted the analgesic effect of ESWT by an unknown mechanism. Some studies hypothesized a reduction in calcitonin gene-related peptide (CGRP) expression in dorsal root ganglion (DRG) neurons after shock wave application (Abed et al. 2007; Ochiai et al. 2007; Takahashi et al. 2003). Others reported a degeneration of epidermal nerve fibers (Ohtori et al. 2001) or a reduction of pro-inflammatory activities (Mariotto et al. 2005, 2009).

Some clinical studies (Larking et al. 2010; Schaden et al. 2007; Wang et al. 2011; Wolff et al. 2011) regarding chronic wounds of the lower limbs of different etiology have reported promising results using defocused ESWT, as in our pilot study. Defocused ESWT is employed because of its lower energy peak, lower depth of action and wider range of action compared with focused ESWT (Mittermayr et al. 2012).

The first case series study on wound healing with defocused ESWT was performed by Schaden et al. (2007). Two hundred eight patients with complicated, non-healing, acute and chronic soft tissue wounds of different etiology at different locations were prospectively enrolled to receive defocused ESWT *via* an electrohydraulic generator (100–1000 shocks/cm^2 at 0.1 mJ/mm^2, according to wound size, initially weekly, then biweekly over mean three treatments, range: 1–10). The results indicated 100% wound epithelialization in 75% (156/208) of patients during a 3- to 12-wk period of monitoring. In 2010, Larking et al. performed a double-blind, randomized crossover study. Nine chronic decubitus ulcers were randomly selected to receive either defocused ESWT generated by an electrohydraulic source (in every session, the sum of 200 standard impulses plus 100 impulses/cm^2 at 0.1 mJ/mm^2 at the rate of 5/s was applied; four sessions at weekly intervals) or the placebo for a 4-wk period, followed by a 2-wk "washout" period and then a 4-wk period of the crossover treatment/placebo. Results indicated improved healing in all ulcers without any significant differences between groups, but the ESWT seemed to heal wounds more rapidly. In a randomized controlled trial, Wang et al. (2011) randomly assigned 77 patients with chronic diabetic foot ulcers to hyperbaric oxygen therapy treatment (HBOT) (n = 38)

Table 4. Pairwise comparisons of size and BJWAT and VAS scores at all follow-up points (within analysis)

	Follow-up					
Outcome	Baseline to 15 d	Baseline to 30 d	Baseline to 90 d	15–30 d	15–90 d	30–90 d
Size	0.059*	0.005†	0.005†	0.086	0.038†	0.180
BJWAT	0.012†	0.008†	0.008†	0.011†	0.011†	0.102
VAS	0.007†	0.007†	0.007†	0.102	0.102	1.000

BJWT = Bates-Jensen Wound Assessment Tool; VAS = visual analogue scale.
* Values are p values resulting from a pairwise comparison test.
† Significant difference ($p < 0.05$).

or ESWT (n = 39) with a defocused electromagnetic applicator. ESWT sessions (at 0.23 mJ/mm^2 with a minimum of 500 pulses/cm^2 of wound, frequency = 4 Hz) were performed twice per wk for a total of six treatments over 3 wk. After 3 wk, 57% and 32% of wounds in the ESWT and 25% and 15% of wounds in the HBOT group completely healed and improved, respectively. In 2011, Wolff et al. enrolled 258 patients with chronic soft tissue wounds at different locations and with different wound etiologies in a single group assignment study (one-armed, open, prospective). The protocol started with two defocused ESWT treatments with a defocused electrohydraulic device at 1-wk intervals. After the second ESWT, the interval was extended to 2 wk, and a maximum of 10 sessions, at 0.1 mJ/mm^2 and a frequency of 5 Hz. Median follow-up was 31.8 mo. Wound closure occurred in 191 patients (74.03%) in a median of two treatment sessions, without significant comorbidities and wound etiologies.

These studies concluded that defocused ESWT is an effective treatment modality in the management of chronic wounds of different etiology at different locations and with different treatment protocols. Other studies obtained promising results with focused ESWT (Moretti et al. 2009; Omar et al. 2014; Saggini et al. 2008; Wang et al. 2009). However, all of the aforementioned studies are not homogenous with respect to the number of samples, presence of a control group, wound etiology, location, treatment protocol and outcome assessments.

At present, to the best of our knowledge, there is no specific guideline on indications, type of ESWT used (focused or defocused), number of sessions (range: 2–10), intervals of treatment (range: 72 h to 2 wk), frequency, number of pulses and intensity of shock wave treatment for ulcers (range: 0.037–0.15 mJ/mm^2).

The threshold of energy flux density we used has previously been defined for biological response of treated tissue in laboratory animal models (Leone et al. 2012, 2016). The same energy was also used by Arnó et al. (2010) for acute burns. The number of pulses per square centimeter was decided on the basis of the previous study by Wang et al. (2009) on chronic diabetic foot ulcer; the number and interval of sessions correspond with those of the previous study by Moretti et al. (2009).

This pilot study was the first to provide together two quantitative measures of chronic soft tissue wound healing. To minimize observer bias, changes in size were evaluated using dedicated software (Woundsoft), and changes in other parameters (signs of ulcer healing) were evaluated with the BJWAT at each follow-up. The VAS provided a quantitative measure of chronic soft tissue wound pain. This approach was used to obtain an overview of the chronic soft tissue wound healing journey with respect to wound changes and changes in pain perception.

In the study by Wang et al. (2009), the dimension, depth and appearance of the skin ulcer were assessed clinically only with photo documentation. In the studies of Schaden et al. (2007), Moretti et al. (2009) and Larking et al. (2010), computerized systems were used to define the size of the wound, but other quantitative measures of chronic soft tissue wound healing were not used. In the study by Wolff et al. (2011), only a quantifiable description of wound characteristics was provided through the Wound Bed Preparation (WBP) score. In fact, the WBP, similar to the BJWAT, was used to apply a uniform and reproducible scoring system for chronic soft tissue wounds (Falanga et al. 2006). As did our study, only one other used both a specialized software program (Photoshop C4 me) for ulcer size and a quantitative measure of wound healing (WBP) for chronic diabetic ulcers treated with focused ESWT (Omar et al. 2014). In addition, Saggini et al. (2008) assessed three outcome measures: pain self-assessment numeric box scale, ulcer size without computer systems and ulcer parameter features, such as the percentage of granulation tissue, percentage of fibrin tissue or necrotic tissue, presence of exudates and bacterial colonization (positive culture swabs or tissue scrapings), without an assessment scale of wound healing.

This study has several limitations: the small number of patients, the heterogeneity of the population and the lack of a control group. However, because it is a pilot study, it only describes our data and results, which confirm that defocused ESWT produces a wide variety of positive results, including complete wound closure with re-epithelialization and cessation of pain in the majority of patients. Subsequent studies should be useful and, in particular, well-designed randomized controlled trials with larger patient populations, a control group and long-term follow-up to support this wound treatment modality, to define the most important parameters and to evaluate the tolerability and efficacy of ESWT used as an adjunct to standard therapy for complex wounds.

CONCLUSIONS

The preliminary findings of this single-arm pilot study suggest that defocused ESWT (three defocused ESWT sessions at 72-h intervals, starting with the sum of 300 standard pulses + 100 pulses/cm^2 at 0.15 mJ/mm^2 and a frequency of 4 Hz) is a non-invasive, feasible, simple, effective, complication-free tool for a variety of difficult-to-treat chronic soft tissue wounds of the lower limbs. However, we need further consideration before suggesting the clinical use of ESWT on chronic soft tissue wound ulcers. Our specified application parameters could be useful for a future well-designed, randomized clinical trial in a broader population.

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