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Shock Wave Therapy for Acute and Chronic Soft Tissue Wounds: A Feasibility Study[1]

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Background. **Nonhealing wounds are a major, functionally-limiting medical problem impairing quality of life for millions of people each year. Various studies report complete wound epithelialization of 48 to 56% over 30 to 65 d with different treatment modalities including ultrasound, topical rPDGF-BB, and composite acellular matrix. This is in contrast to comparison control patients treated with standard wound care, demonstrating complete epithelialization rates of 25 to 39%. Extracorporeal shock wave therapy (ESWT) may accelerate and improve wound repair. This study assesses the feasibility and safety of ESWT for acute and chronic soft-tissue wounds.**

Study design. **Two hundred and eight patients with complicated, nonhealing, acute and chronic soft-tissue wounds were prospectively enrolled onto this trial between August 2004 and June 2006. Treatment consisted of debridement, outpatient ESWT [100 to 1000 shocks/cm^2 at 0.1 mJ/mm^2, according to wound size, every 1 to 2 wk over mean three treatments], and moist dressings.**

Results. **Thirty-two (15.4%) patients dropped out of the study following first ESWT and were analyzed on an intent-to-treat basis as incomplete healing. Of 208 patients enrolled, 156 (75%) had 100% wound epithelialization. During mean follow-up period of 44 d, there was no treatment-related toxicity, infection, or deterioration of any ESWT-treated wound. Intent-to-treat multivariate analysis identified age ($P = 0.01$), wound size ≤10 cm^2 ($P = 0.01$; OR = 0.36; 95% CI, 0.16 to 0.80), and duration ≤1 mo ($P < 0.001$; OR = 0.25; 95% CI, 0.11 to 0.55) as independent predictors of complete healing.**

Conclusions. **The ESWT strategy is feasible and well tolerated by patients with acute and chronic soft tissue wounds. Shock wave therapy is being evaluated in a Phase III trial for acute traumatic wounds.**

Key Words: **extracorporeal shock wave therapy; soft tissue wounds.**

INTRODUCTION

The serendipitous finding of iliac bone thickening in patients undergoing extracorporeal shock wave lithotripsy ushered into the realm of clinical medicine an entirely new means of treating various degenerative and inflammatory soft tissue disorders as well as osseous delayed union and nonunion fractures [1, 2]. The primary intent of shock wave therapy for kidney stones is disintegration of the bothersome calculus. Quite the opposite, the fundamental therapeutic objective of orthopedic shock wave application is not to destroy tissue, but rather to stimulate vascular in-growth and osteogenesis [3, 4]. Although the exact mechanism of shock wave biology remains to be defined, recent ani-

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mal data point to dose-dependent neovascularization and cell proliferation and possible stem cell differentiation through multiple inter-related pathways stimulating tissue regeneration and healing [3, 5, 6].

Notwithstanding the mechanistic conundrum, orthopedic shock wave therapy devices have been used over the past 15 y to treat chronic nonunion long bone fractures with suggestive but unproven efficacy [7–11]. The analgesic effect of shock wave therapy along with its ability to disintegrate calcific deposits and favorably alter osseous and tendinous biology, coupled with demonstrated safety and noninvasiveness, made it uniquely suited to the treatment of ubiquitous orthopedic disorders in the out-patient setting. Controlled clinical trials have supported the safety and efficacy of shock wave therapy in the treatment of common lifestyle-limiting musculoskeletal conditions such as plantar fasciitis, lateral epicondylitis of the elbow, and calcific tendonitis of the shoulder [12–20]. Despite lacking standardized, disease-specific treatment protocols including shockwave generation, dose intensity and number of treatments, maximal energy, and depth of penetration, shockwave therapy has become an attractive alternative to the treatment of these musculoskeletal conditions, and represents a standard of practice in many countries, particularly when these conditions prove refractory to conventional nonoperative and operative intervention.

Little work has been done with shock waves for nonhealing soft tissue wounds. However, one more unanticipated finding of positive soft tissue wound response to shock waves led us to expand the application of shock wave therapy in the setting of a clinical trial. In the course of an on-going prospective appraisal of shock wave therapy for orthopedic nonunion and delayed union fractures, we identified cases complicated by osteocutaneous fistulae and/or overlying soft tissue defects (open fractures) that would consolidate the disrupted bone as well as the soft tissue wound in response to treatment, the latter with noteworthy rapidity. Prior animal studies indicated positive responses of shockwave therapy for soft tissue indications and suggested a possible, heretofore unproven, antibacterial effect in addition to enhanced neovascularization and possible tissue regeneration [21–23]. Encouraged by these findings, we have undertaken this feasibility trial evaluating shock wave therapy for soft tissue wounds. Modifications in the core technology were necessary to tailor shock wave therapy to this specific indication. A multiwave device was developed that contains a parabolic rather than ellipsoid reflector in the shock wave therapy head, which allows delivery of defocused waves of acoustic energy over a broad target soft tissue wound surface area with reduced depth of penetration. This clinical trial assesses the feasibility and safety of unfocused shock wave therapy for the treatment of acute and chronic soft tissue wounds.

METHODS

Eligibility

Study subjects had either acute or chronic complicated, nonhealing, soft tissue wounds of various etiologies including trauma, failure of primary closure following operation, venous or arterial insufficiency, pressure necrosis, or burn in the absence of extension to underlying bone or associated bone disruption (Table 1). We included patients who volunteered to participate in the study or refused standard therapy to avoid hospitalization. Pregnant patients were not enrolled. Patients with Stage I (intact skin with impending ulceration) and Stage IV (full-thickness loss of soft tissue and extension into muscle, bone, tendon, or joint capsule) decubitus ulcers, and superficial first- and second-degree or circumferential burns requiring escharotomy, compartment syndrome, necrotizing fasciitis, or lymphedema were excluded. Patients with current participation in another clinical investigation of a medical device or a drug the requirements of which precluded involvement in the current study and those with active or previous (within 60 d prior to the study screening visit) systemic chemotherapy and/or radiation to the affected area to be treated by investigational shock wave therapy were excluded. Patients with physical or mental disability or geographical concerns that would hamper compliance with required study visits were also excluded. The study was approved by the Institutional Review Board of each of two participating medical centers and written informed consent provided by each study participant.

Shock Wave Treatment

As soft tissue wounds typically cover a larger surface area as opposed to fractures or nephrolithiasis, the reflector contained within the DermaGold (Tissue Regeneration Technologies, LLC, Woodstock, GA) applicator is comprised of a parabolic reflector. The generalized parabolic reflector used in the DermaGold™ allows the plane waves to be unfocused, nearly parallel, and the energy density realized by this reflector configuration higher than with an exact parabolic reflector; hence, a large target treatment area is stimulated by the acoustical field. On account of our previous experience treating soft tissue pathologies (tendonopathies) we decided to use the average energy flux density (0.1 mJ/mm^2) typically applied for

TABLE 1

Baseline Characteristics in 208 Patients

Characteristic	No. of patients	%
Gender		
Male	109	54.4
Female	99	47.6
Age		
Mean	61	
Median (range)	62 (18–95)	
Wound site		
Distal extremity	187	89.9
Proximal extremity	12	5.8
Trunk	7	3.4
Head	2	0.9
Wound etiology		
Disturbed healing	82	39.4
Post traumatic necrosis	67	32.2
Venous stasis ulcer	25	12.0
Decubitus ulcer	14	6.7
Plaster cast pressure ulcer	7	3.4
Arterial insufficiency ulcer	6	2.9
Burn wound	7	3.4

these indications in the range of 0.03 to 0.15 mJ/mm^2. By using this energy flux density, the threshold for biological response of the treated tissue could be attained, which was defined in laboratory animal models. Our dose response experiments in laboratory rats indicated 100 pulses per cm^2 as the optimal dose for the proposed indication. The protocol regimen was modified from weekly to every other week shock wave therapy following preliminary data demonstrating similar treatment responses between treatment schedules. Shock wave therapy was the primary wound therapy delivered to study in conjunction with adjunctive wound debridement and dressing.

Prior to shock wave therapy, thorough debridement of the soft tissue wound was performed to remove necrotic tissue. Sterile ultrasound gel was applied to the wound surface. To allow good coupling conditions, a plastic drape was placed over the wound. Ultrasound gel was then applied onto the drape as a coupling media. The DermaGold device was calibrated prior to each treatment: energy level, 0.1 mJ/mm^2; frequency, 5 pulses/s. The unfocused lens shock wave head was placed onto the wound. One hundred to 1000 pulses were applied according to wound size (100 pulses/cm^2) initially weekly, then biweekly. The ultrasound gel was removed at the conclusion of shockwave therapy and a wound dressing applied. Pre-ESWT wound dressing therapy was not modified and continued after ESWT. Clean wounds/ulcers were treated with wet-to-wet dressings using Tender-wet (Hartmann, Heidenheim, Germany), wounds with heavy secretions with Seasorb (Smith & Nephew, Aukland, New Zealand) or Comfeel (Coloplast, Humlebaek, Denmark), those having necrotic tissue with Aquacel (ConvaTec, A Bristol-Myers Squibb Company, Princeton, NJ).

Data

Patient, wound, and treatment-related factors were correlated with complete wound healing (100% epithelialization). Patient variables analyzed included age at presentation (continuous variable) and gender. Anatomical sites were classified as soft tissue wound of the distal extremity, proximal extremity, trunk, or head. Wound-specific variables included etiology (disturbed healing, posttraumatic necrosis, venous stasis ulcer, decubitus ulcer, plaster cast pressure ulcer, arterial insufficiency ulcer, or burn), size ($\leq$5 or $>$5 cm^2; $\leq$10 or $>$10 cm^2; and continuous variable, cm^2), depth (superficial or deep), cavitation (none, $\leq$1 cm, or $>$1 cm), and duration ($\leq$1 mo, $>$1 mo to $<$12 mo, or 1+ y; and continuous variable, d). Treatment-related factors analyzed were number of shock wave treatments (continuous variable) and shock wave impulses delivered (continuous variable).

Definitions

Wounds of the head were those located at or above the skull base or involving the face. Wounds at the groin, at the knee, or between the groin and the knee and those at or between the shoulder and the elbow were defined as proximal extremity wounds. Wounds at or distal to the knee and elbow were categorized as distal extremity. Wounds of the superficial trunk including the gluteal and sacral regions were defined as truncal. Disturbed healing was defined as partial or complete failure to heal after primary closure of a surgical wound. Skin grafts or flaps were not performed in this study. Soft tissue wounds resulting from direct penetrating or blunt trauma associated with necrosis of epithelial and nonepithelial extraskeletal structures (e.g., fibrous and adipose tissue, skeletal muscle, vasculature, etc.) were categorized as posttraumatic. Venous stasis ulcers were nonhealing sores or wounds (shallow, exuding ulcer with diffuse edges, brown pigmentation, surrounding skin scaling) of the lower leg near the medial malleolus in patients with known incompetence of the perforating draining veins of the leg (with generalized affected limb edema) apparent by duplex ultrasound. Decubitus ulcers were defined as sores resulting from pressure exerted on the skin, soft tissue, muscle, and bone by the weight of the patient against a surface beneath them. For the purpose of this trial, decubitus ulcers demonstrating partial-thickness loss of skin involving epidermis and dermis, or full-thickness loss of skin with extension into subcutaneous tissue, but not through the underlying fascia were included. Pressure sores in this study characterized by partial thickness loss of skin involving epidermis, dermis, and/or subcutaneous tissue, but not superficial investing muscular fascia, resulting from skin necrosis attributable to localized pressure from the inner aspect of a plaster cast over a bony prominence were defined as plaster cast pressure ulcers. An arterial insufficiency ulcer (deep with localized edema and shiny, hairless surrounding skin) was defined by chronic, nonhealing, distal limb ulceration in patients with known atherosclerotic peripheral vascular disease unable to receive revascularization due to medical comorbidity or lack of suitable outflow artery in the affected extremity with ankle/brachial indices $<$0.80 or toe pressure $<$50 mmHg. Burn wounds in this study were defined as noncircumferential deep second or third degree burns typically characterized by presence of blisters, mottled/patchy appearance, and diminished or no sensation.

Computerized digital management planimetry was used to define the size of the wound (two dimensional planar surface area in cm^2) based on maximum horizontal width and length measurements. This software provides an objective method for accurate surface measurements of the wound through calibrated digital images. It provides

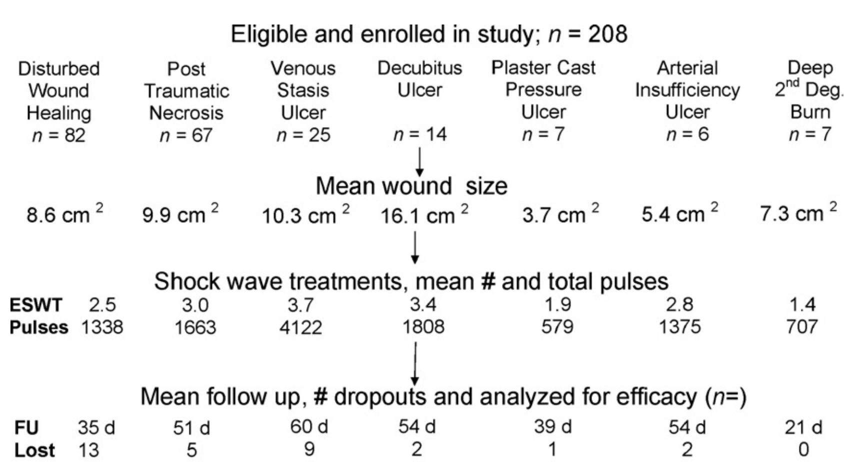

FIG. 1. Distribution of the study subjects according to eligibility and enrollment, wound etiology and size, shock wave therapy characteristics, and follow-up.

automatically the length, width, surface area, circumference, depth, and estimated volume of the wound. Such an approach was used to minimize observer bias.

Wound depth was defined relative to the dermis. Soft tissue wounds extending beyond the dermis into the underlying subcutaneous tissue were defined as deep. Wounds confined to the epidermis and dermis were regarded as superficial. Wound cavity or soft tissue defect was defined as absent, ≤1 cm, or >1 cm relative to the epidermis. Wound duration was defined from the date of diagnosis of the soft tissue wound under study to the date of first shock wave application. No patient received antibiotic therapy during shock wave treatment.

Statistics

The primary endpoints of this study were feasibility and safety of shock wave therapy. Summary statistics were obtained using established methods. Associations between categorical variables were studied with Fisher's exact test or χ^2 test, as appropriate. Differences in observed sample means for single measurements were evaluated using analysis of covariance to adjust for potentially important clinical factors. Study dropouts were considered as partial responders (treatment failures, i.e., incomplete wound healing) in the wound healing analyses (intent-to-treat). To assess the independent predictive effect of a covariate for a nominal response (complete wound healing, i.e., 100% epithelialization) a logistic regression model was constructed and parameters estimated using maximum likelihood. Only those factors identified to be potentially significant ($P < 0.05$) on categorical contingency analysis were entered into the multivariate model to determine the independent prognostic effect of these variables. The Wald-test statistic was computed for each effect in the model. Confidence limits and odds ratios were calculated for the maximum likelihood parameter estimates. Statistical analysis was performed using JMP and SAS software (JMP and SAS, version 5, release 5.1; Cary, NC). A P value <0.05 was considered significant.

RESULTS

Study Summary

Between August 2004 and June 2006, 208 patients with complicated acute (33.2%) and chronic (66.8%) soft tissue wounds underwent treatment with unfocused shock wave therapy in this prospective single-arm study. Patients received a mean of 2.8 (range 1 to 10) shock wave treatments each lasting an average of 3.0 min. Study subjects were observed for a mean of 44 d following initial shock wave treatment (median 31 d). No patient had to be removed from the study due to wound progression or deterioration.

Thirty-two (15.4%) patients dropped out of the study and were considered in the incomplete healing group in statistical analyses. Reasons for drop out included: death ($n = 1$), perceived bias toward treatment failure ($n = 1$), noncompliant alcoholic ($n = 1$), demented patient whose family elected not to transport to clinic for scheduled follow-up ($n = 1$), improved soft tissue healing over a healed open fracture but lost to follow-up ($n = 1$), required vascular operation to improve extremity inflow that interrupted shock wave therapy ($n = 2$), and failure to return for wound assessment ($n = 25$). Of these 25 subjects, 17 showed improved wound healing after 1 to 5 treatments and

TABLE 2

Baseline Characteristics in 208 Patients

Characteristic	Disturbed wound healing (N = 82)		Posttraumatic necrosis (N = 67)		Venous stasis ulcer (N = 25)		Decubitus ulcer (N = 14)		Plaster cast pressure ulcer (N = 7)		Arterial insufficiency ulcer (N = 6)		Burn wound (N = 7)		Total patients	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Wound Location																
Distal extremity	70	85.4	65	97.0	25	100	7	50.0	7	100	6	100	7	100	187	89.9
Proximal extremity	9	11.0	2	3.0	0	0	1	7.1	0	0	0	0	0	0	12	5.8
Trunk	2	2.4	0	0	0	0	5	35.7	0	0	0	0	0	0	7	3.4
Head	1	1.2	0	0	0	0	1	7.1	0	0	0	0	0	0	2	0.9
Wound size ≤ 10 cm^2	63	76.8	44	65.7	19	76.0	10	71.4	6	85.7	5	83.3	6	85.7	153	73.6
Wound size > 10 cm^2	19	23.7	21	31.3	6	24.0	3	21.4	1	14.3	0	0	1	14.3	51	24.5
Wound, superficial	44	53.7	53	79.1	19	76.0	8	57.1	4	57.1	4	66.7	7	100	139	66.8
Wound, deep	37	44.1	12	17.9	6	24.0	6	42.9	3	42.9	1	16.6	0	0	65	31.3
No wound cavitation	57	69.5	58	86.6	20	80.0	9	64.3	7	100	5	83.3	7	100	163	78.4
Wound cavitation ≤ 1 cm	17	20.7	8	11.9	5	20.0	3	21.4	0	0	0	0.0	0	0	33	15.9
Wound cavitation > 1 cm	8	9.8	1	1.5	0	0	2	14.3	0	0	1	16.7	0	0	12	5.7
Mean no. ESWT treatments	2.5		3.0		3.7		3.4		1.9		2.8		1.4		2.8	
Mean no. ESWT pulses	1338		1663		4122		1808		579		1375		707		1764	
Mean time to complete healing, d	35.3 ± 6.2		50.7 ± 6.4		60.4 ± 16.3		53.9 ± 24.4		38.5 ± 19.9		53.5 ± 24.4		19.3 ± 18.5		43.5 ± 3.9	

% refers to percent of column total.

five demonstrated no response after 2 to 3 treatments; three patients with deep soft tissue wounds had one shock wave treatment, were lost to follow-up, and could not be assessed.

Distribution of the study subjects according to eligibility and enrollment, wound etiology and size, shock wave therapy characteristics, and follow-up is shown in Fig. 1. The most common soft tissue wounds treated in this cohort were those complicated by partial or complete failure to heal after primary surgical closure (39.4%) and those resulting from direct penetrating or blunt trauma associated with necrosis of epithelial and nonepithelial extraskeletal structures (32.2%). Mean wound surface area was 9.4 cm^2 (median = 5 cm^2). A mean number of 1764 impulses (median = 900) were delivered over three shock wave treatment sessions (median = 2). For the 208 patients who completed the study, mean follow-up period was 6.3 wk (median = 4.2 wk).

Patients

Patient, wound, and treatment-related factors are summarized in Tables 1 and 2. Mean patient age was 61 y and most common soft tissue wound location the distal extremity. One hundred fifty-three (75.0%) patients had wound surface area $\leq$10 cm^2. Most of the treated wounds were superficial and without apparent cavity. Nearly 80% of patients presented with persistent wounds 1 mo or less after initial diagnosis of the localized soft tissue abnormality. Mean time to complete healing (100% epithelialization) varied between groups with most rapid healing in burns (19.3 $\pm$ 18.5 d), disturbed postoperative healing (35.3 $\pm$ 6.2 d), and plaster cast pressure ulcer (38.5 $\pm$ 19.9 d) and delayed healing in arterial insufficiency (53.5 $\pm$ 24.4 d), decubitus (53.9 $\pm$ 19.9 d), and venous stasis ulcers (60.4 $\pm$ 16.3 d).

Treatment Response

Of 208 patients enrolled in the trial, 156 (75%) had 100% wound epithelialization. One hundred seventy-six patients completed the study; of these, 156 (88.6%) showed complete healing. Complete epithelialization of the open wound was significantly associated with wound size (81.0% *versus* 61.8% for wounds $\leq$10 *versus* $>$10 cm^2 surface area; P = 0.005) and duration (83.0% *versus* 57.1% for wound $\leq$1 mo- *versus* $>$1-mo-old; $P <$ 0.001). Similar significant difference in wound outcome

FIG. 2. (A) Postoperative site of a 43-y-old male patient 10 d following left clavicular fracture plating with wound dehiscence and exposed hardware, and immediately prior to first shockwave treatment (900 pulses over 3 min). (B) The same patient is shown 12 d later after first shockwave treatment (22 d postop), and immediately before the second treatment (500 pulses over 1 min 40 s). (C) The wound had completely epithelialized 3 wk after the first treatment, 31 d after initial operation. Total shockwave treatments, 2; impulses, 1400; treatment time, 4 min 40 s. This photograph shows the same patient 4 mo later prior to planned removal of the clavicular plate.

FIG. 3. (A) Left lateral foot pressure ulcer of a 50-y-old paraplegic male prior to shockwave treatment (1000 pulses over 3 min 20 s). (B) The same patient 2 wk after single shockwave treatment.

was apparent when acute and chronic wounds were compared (81.0% *versus* 56.3%, acute *versus* chronic; $P = 0.001$).

Clinical images obtained over the course of therapy in shockwave treated patients are shown in Figs. 2, 3, 4, and 5 according to wound etiology, treatment number and dose intensity, and clinical course. Soft tissue wound healing was significantly better in younger than older patients ($P < 0.001$, Table 3). There was a trend to increased prevalence of co-morbidity (diabetes, peripheral vascular disease) that correlated with age ($P = 0.08$). Venous stasis ulcers demonstrated the worst overall healing rates (36.0% *versus* >66.0% for all others, $P = 0.001$). Treatment response did not correlate significantly with wound location, depth, or cavitation (Table 3). Complete wound healing was not significantly different for patients with (12/14, 85.7%) or without (144/194, 74.2%) underlying diabetes.

Overall shock wave treatment intensity (mean dose density) was significantly higher in the partial responders, consistent with efforts to achieve complete wound healing in study subjects with incomplete treatment response (Table 3). None of the wounds deteriorated with shock wave therapy.

Statistical Analysis of Variables Correlating with Treatment Response

Patient age, wound etiology, wound size and duration, and shock wave treatment intensity were significantly associated with complete healing of the soft tissue wound. On multivariate logistic regression analysis, patient age, wound size (surface area), and duration emerged as independent predictors of complete wound healing (Table 4). Wound size >10 cm^2 and wounds persisting in excess of 1 mo carried a nearly three-times (OR = 0.36 for size ≤10 cm^2) and four-times (OR = 0.25 for duration ≤1 month) increased risk, respectively, of incomplete healing after shock wave therapy (Table 4).

On that basis, post hoc analysis was performed comparing healing response between groups stratified according to wound size and duration (≤10 cm^2 and ≤1 mo *versus* ≤10 cm^2 and >1 mo *versus* >10 cm^2 and ≤1 mo *versus* >10 cm^2 and >1 mo). Significant differences were detected between groups according to etiology of wound and intensity and duration of shock wave treatments (Table 5). There was no statistically significant difference in complete wound healing time between the following three groups: ≤10 cm^2 and ≤1 mo *versus* ≤10 cm^2 and >1 mo *versus* >10 cm^2 and ≤1 mo ($P = 0.49$). Complete healing was significantly less likely and healing time prolonged in patients with large (>10 cm^2) chronic (>1 mo) wounds, (Table 5, $P < 0.005$).

Toxicities

There were no reported cardiac, neurological, dermal, thermal, or allergic reactions or adverse events. No anesthesia was necessary in any of the patients studied, as the delivered shock wave was defocused and applied over a broad treatment front. For the few patients who reported pain during unfocused shock wave treatment, appropriate reduction in energy flux density (0.06 to 0.08 mJ/mm^2) and frequency (2 to 3 pulses per s) for the first 50 to 100 impulses with subsequent gradual escalation to target parameters was well tolerated. All ESWT was administered on an outpatient basis (excluding those patients hospitalized for various medical reasons such as femoral neck fractures, polytrauma, etc.). No clinically evident wound infection developed in soft tissue defects treated with shock waves, and no patient in this study experienced any deterioration of the treated wound.

FIG. 4. (A) The pretibial posttraumatic wound of an 86-y-old female 20 d after having missed a step mounting a bus immediately prior to first shockwave treatment (800 pulses over 2 min 40 s). (B) The same patient 2 wk later just prior to second treatment (400 pulses over 1 min 20 s). (C) The same patient 4 wk and (D) 21 mo after first shockwave treatment. Total shockwave treatments, 2; impulses, 1200; treatment time, 4 min. The traumatic wound healed completely.

DISCUSSION

Unfocused shock wave therapy in this nonrandomized study was assessed for efficacy and safety in treating acute and chronic soft-tissue wounds of various etiologies, many known to represent formidable treatment challenges. Complete response was defined as bringing the open wound to complete closure. Overall treatment response (100% wound epithelialization) was 75%. During mean follow-up period of 44 d, there was no treatment-related toxicity, infection, or deterioration of any ESWT-treated wound.

Despite significant advances over the past decade, definitive closure of complex wounds remains a challenge. Wound size, location, etiology, and comorbidities all impact the clinical management of such complex and difficult to heal wounds. A current standard of care has evolved centered on topical negative pressure or vacuum assisted wound closure (VAWC) augmented by newer dressings with selective use of hyperbaric therapy [24]. While the widespread adoption of VAWC has contributed to a decrease in the size of complex wounds, definitive closure still typically requires skin grafting or flap coverage. Additionally, complex wounds frequently require multiple operative debridements to achieve satisfactory results. Therefore, the ability to treat these wounds in an outpatient setting and achieve definitive closure in a timely and cost-effective fashion is highly desirable.

We have demonstrated that unfocused ESWT with the specified application parameters used in this study (100 to 1000 shocks/cm^2; 0.1 mJ/mm^2, according to wound surface area) appears to be associated with definitive closure of the majority of a diverse group of wounds while using a simple series of outpatient treatments without a requirement for anesthesia. The exact mechanism of action of ESWT is undefined and its true

FIG. 5. (A) The lower leg of a 57-y-old male patient with chronic (>1 y duration) arterial ulcer prior to the first shock wave treatment (800 pulses over 2 min 40 s); despite attempts to treat the lesion with various forms of topical therapy and dressings, successful healing was unattainable. (B) The lesion of the same patient 2 wk later just before the second shockwave treatment (400 pulses over 1 min 20 s). (C) The soft tissue wound of the same patient 2 wk later after the dressing was changed. No further ESWT was necessary at that stage. (D) Complete healing of the wound 6 wk after starting shockwave therapy. Total shockwave treatments, 2; impulses, 1200; treatment time, 4 min. Gross appearance of the healed ulcer indicates better skin quality than the surrounding tissues.

impact on the natural history of soft tissue wound healing remains to be determined in the setting of a blinded, randomized trial. However, the preliminary findings of this study suggest that unfocused low energy shock wave therapy is a feasible modality for a variety of difficult-to-treat soft tissue wounds, particularly post-traumatic and postoperative wounds, decubitus ulcers, and burns. With the exception of venous stasis ulcers and arterial insufficiency ulcers, wound etiology did not influence treatment success with all other categories of wound healing completely over 70% of the time (Table 3). The etiologies of poor wound healing in this study were multifactorial. We expected that wound healing would proceed differently in patients with and without underlying diabetes mellitus; however, wound healing did not significantly differ according to presence or absence of diabetes. However, subset sample size was relatively small, thereby precluding definitive commentary on the basis of the current analysis.

Average time to healing in this study was 43.5 d after a mean of three unfocused shock wave therapy sessions. The recommended shock wave dose was empirical based on our preliminary clinical experience. Presently, there is no specific guideline on the indication, frequency or intensity of shock wave treatment. Studies are under way to define these parameters.

The healing behaviors of wounds at different locations may vary. In this study, the most common wounds were those complicated by partial or complete failure to heal after surgical closure and those wounds resulting from direct trauma associated with necrosis of the epidermis. Most chronic skin ulcers are located in the lower extremity, including those in diabetics and nondiabetics. Site-specific differences in healing were not observed in this study, as most wounds in all etiologic categories were located on the distal extremity (100% of arterial and venous ulcers, burns, and plaster cast necrosis; 97% of traumatic and 85% of postsurgical wounds; 50% of decubitus ulcers). Although we anticipated anatomical site, etiology, and wound severity (large, deep, cavitary) and chronicity to be important determinants of healing, only patient age, wound size, and duration were independently associated with complete wound epithelialization on multivariate analysis.

TABLE 3

Treatment Response in 208 Patients

	Less than complete epithelialization (n = 52)		Complete epithelialization (n = 156)			Total patients (n = 208)	
Characteristic	No.	%	No.	%	P value	No.	%
Patient age, y					0.0003		
Mean	69.1 ± 2.6		57.7 ± 1.5				
Etiology of wound					0.001		
Disturbed healing	20	24.4	62	75.6		82	39.4
Post traumatic	9	13.4	58	86.6		67	32.2
Venous stasis ulcer	16	64.0	9	36.0		25	12.0
Decubitus ulcer	4	28.6	10	71.4		14	6.7
Plaster cast pressure sore	1	14.3	6	85.7		7	3.4
Arterial insufficiency ulcer	2	33.3	4	66.7		6	2.9
Burn	0	0	7	100		7	3.4
Underlying diabetes					0.31		
Yes	2	14.3	12	85.7		14	6.7
Location of wound					0.10		
Head	0	0	2	100		2	0.9
Extremity	48	24.1	151	75.9		199	95.7
Trunk	4	57.1	3	42.9		7	3.4
Size of wound category					0.005		
$\leq$10 cm^2	29	19.0	124	81.0		153	75.0
$>$10 cm^2	20	39.2	31	61.8		51	25.0
Size of wound, cm^2, continuous					0.003		
Mean	14.4 ± 1.9		7.9 ± 1.1				
Depth of wound					0.12		
Superficial	29	20.9	110	79.1		139	66.8
Deep	21	32.3	44	67.7		65	31.3
Cavitation of wound					0.95		
None	40	24.5	123	75.5		163	78.4
$\leq$1 cm	9	27.3	24	72.7		33	15.9
$>$1 cm	3	25.0	9	75.0		12	5.7
Wound duration category					$<$0.001		
$\leq$1 mo	27	17.0	132	83.0		159	79.0
$>$1 mo to $<$12 mo	4	19.0	17	81.0		21	10.5
1 y or more	14	66.7	7	33.3		21	10.5
ESWT treatments, continuous					0.13		
Mean	3.2 ± 0.3		2.7 ± 0.2				
ESWT impulses, continuous					0.003		
Mean	3107 ± 502		1342 ± 282				

% refers to percent of row total.

Acute wounds may heal with less intensive methods of therapy including dressing changes. As healing characteristics of acute and chronic soft tissue wounds may be different, healing was assessed according to chronicity. Acute wounds treated in this study were significantly more likely to heal completely than

TABLE 4

Multivariate Nominal Logistic Regression Analysis of Factors Predicting Complete Healing Response (100% Epithelialization) to Shock Wave Therapy in 208 Patients

Characteristic	P value (chi square)	Odds ratio	95% Wald confidence interval
Etiology of wound	0.06		
Total # ESWT impulses (continuous variable)	0.16		
Age (continuous variable)	0.01		
Size of wound (continuous variable)	0.02		
Size of wound $\leq$ 10 cm^2 *versus* $>$ 10 cm^2	0.01	0.36	0.16–0.80
Duration of wound $\leq$ 1 mo *versus* $>$ 1 mo	$<$0.001	0.25	0.11–0.55

TABLE 5

Outcomes According to Wound Size and Duration

Characteristic	≤10 cm^2 and ≤1 mo n = 116		≤10 cm^2 and >1 mo n = 35		>10 cm^2 and ≤1 mo n = 41		>10 cm^2 and >1 mo n = 7		P
	No.	%	No.	%	No.	%	No.	%	
Patient age, y									0.03
Mean	56.8 ± 1.8		64.3 ± 3.2		63.5 ± 3.0		72.1 ± 7.6		
Etiology of wound									<0.001
Disturbed healing	49	62.0	12	15.2	17	21.5	1	1.3	
Post traumatic	41	64.0	3	4.7	20	31.3	0	0	
Venous stasis ulcer	4	16.0	15	60.0	1	4.0	5	20.0	
Decubitus ulcer	8	66.7	2	16.7	1	8.3	1	8.3	
Plaster cast pressure sore	6	85.7	0	0	1	14.3	0	0	
Arterial insufficiency ulcer	2	40.0	3	60.0	0	0	0	0	
Burn	6	85.7	0	0	1	14.3	0	0	
Size of wound, cm^2, continuous									<0.001
Mean	3.8 ± 0.9		4.1 ± 1.6		26.7 ± 1.5		26.1 ± 3.6		
ESWT treatments, continuous									<0.001
Mean	2.3 ± 0.2		3.6 ± 0.3		3.4 ± 0.3		5.6 ± 0.7		
ESWT impulses, continuous									<0.001
Mean	872 ± 289		1609 ± 526		2974 ± 487		10829 ± 1178		
Healing									<0.001
<Complete epithelialization	14	12.1	13	37.1	12	29.3	5	71.4	
Complete epithelialization	102	87.9	22	62.9	29	70.7	2	28.6	
Complete healing time, d	39.4 ± 4.7		42.5 ± 10.1		51.4 ± 8.8		164.5 ± 33.4		0.003

% refers to percent of row total, except in Healing category; statistically significant comparisons presented only; $P > 0.05$ for all other comparisons according to wound location, depth, cavitation, etc.

chronic wounds. When stratified based on wound-specific variables of size (≤10 cm^2) of skin defect and duration (≤1 mo), not unexpectedly, small wounds of short duration healed uniformly. In addition, large wounds of a short duration and small wounds of long duration also demonstrated a high and timely complete response rate (Table 5). Only those wounds of large size and long duration, the majority of which were venous stasis ulcers, demonstrated suboptimal healing response. Additionally, a progressive decline in treatment response was temporally associated with treatment delay (Table 2).

Overall, these preliminary results surpass those reported with other currently used wound treatment strategies. Prospective trials evaluating VAWC therapy have demonstrated accelerated, albeit incomplete, treatment response, given significant wound size reduction without complete epithelialization [25, 26]. The use of ultrasound to accelerate healing in diabetic wounds has resulted in the ability to close 40.7% of small wounds in approximately 2 mo time [27]. Topical application of rPDGF-BB or human skin equivalent acellular matrix (placed as a graft) was shown to diminish the size of large wounds but without demonstrated complete epithelialization [28, 29]. While hyperbaric oxygen therapy has shown significant promise with success rates similar to those presented herein, this has been limited to specific patient sub-groups and has not been universally reproducible [30, 31]. The biological response to shock wave therapy administered for osseous and soft tissue indications remains an area of active research. While up-regulation of VEGF and flt-1, key genes involved in angiogenesis, has been demonstrated in animal models of ESWT, the mechanisms involved in human soft tissue effects have yet to be defined [6]. The ability of local or circulating precursor cells to effect healing has been demonstrated in several animal models and may play a role in the biology of healing in response to low energy, unfocused shock waves [32–34]. Our group and others are actively perusing this hypothesis.

The strength of this study is the introduction of a new shockwave device for the treatment of soft tissue wounds with a high rate of success. However, our study has several limitations, especially when compared with previous clinical trials. The lack of a control group is related to the design of this feasibility trial in which wounds considered pre-shock wave treatment failures were enrolled. The follow-up duration in this study was relatively short. As chronic soft tissue wounds in the lower extremity (e.g., arterial and venous ulcers) may recur despite initial favorable clinical response to therapy, evaluation of chronic distal extremity wounds of greater number and follow-up time will be necessary before definitive conclusions can be made regarding treatment efficacy. The cohort of patients included all kinds of acute and chronic wounds of the body including postsurgical dehiscence. The heterogeneity of the population may have introduced bias; for this reason, patient-, wound-, disease-, and treatment-related factors were included in the multivariate logistic regression analysis. It should also be noted that the close attention and intensive treatment these patients received in the context of a clinical study—including regular debridement and better wound care likely exceeding standard of care—may have introduced bias such that any perceived increased wound healing seen in this uncontrolled study may be at least partly due to concomitant wound care delivered. While those wounds in the smaller size and short duration (prior to initiation of therapy) category may be expected to heal with standard dressing changes in an ideal patient population, the ability to achieve complete epithelialization in the majority of wounds that were large (>10 cm^2) is compelling.

In summary, the use of unfocused, low energy ESWT on a large population of patients with acute and chronic soft tissue wounds was associated with complete closure of the majority of wounds. This study indicates that shock wave therapy can be applied safely over a short period of time in an outpatient environment, without the requirement for anesthesia. Moreover, shock wave technology meets the characteristics required of novel, therapeutic approaches to managing chronic wounds—seemingly comparable effectiveness to current therapies, improved side-effect profile, straightforward treatment application, and minimal drug interactions [24]. This study suggests promising contribution of this technology to accelerated tissue healing with a highly favorable risk/benefit profile for treating soft tissue wounds. While the precise mechanisms underlying these intriguing results remain unclear, this is yet another example of physical energy exerting a biological effect, and represents a potential novel series of wound healing pathways to investigate. The ability to effectively achieve wound closure and implement shock wave technology as either an adjunct to standard therapy or as a stand-alone treatment for complex wounds needs to be evaluated in controlled trials that are currently underway. We are cautiously optimistic that this technology may advance wound care in a similar fashion as the introduction of vacuum assisted wound closure did a decade ago.

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