EXTRACORPOREAL SHOCKWAVE THERAPY (ESWT) IMPROVES HEALING OF CHRONIC ULCERS AND PATIENTS’ QUALITY OF LIFE

STUDY UNIVERSITY HOSPITAL BRUSSELS
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DR. GAËLLE LEEMANS

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1 ABSTRACT

1.1 Background and Objectives
The management of chronic ulcers is complex, due to poor healing and despite the availability of multiple wound care products. Recent studies suggest that extracorporeal shock wave therapy (ESWT) may be beneficial. This prospective open study evaluated the efficacy and safety of ESWT on wound healing in patients with chronic ulcers, and assessed patients’ quality of life (QoL).

1.2 Patients and Methods
Ten patients with chronic, therapy-resistant ulcers were enrolled. Treatment consisted of regular wound care (best medical care) complemented by four sessions of ESWT.

1.3 Results
A mean decrease in wound surface and wound depth of 71% and 60% respectively were observed six weeks after the first treatment session. QoL improved significantly after treatment (60%) and pain scores decreased significantly (62%). Three patients had mild side effects (mild pain, edema, superficial hematoma), all disappearing spontaneously within 24 hours.

1.4 Conclusions
Additional ESWT seems to be effective and safe in the treatment of chronic ulcers, and improves patients’ QoL.

2 INTRODUCTION

Chronic ulcers are soft tissue defects, which reach the deeper layers of the skin, and fail to pass all phases of wound healing within the time interval of three months (1). Frequent causes are: chronic venous insufficiency (45-60%), diabetes mellitus (15-25%), peripheral artery disease (10-20%), or a combination of these (10-15%) (2). Because of general ageing of the population and an increase in patients with chronic diseases, chronic ulcers have become a major healthcare problem with important medical, social, and financial consequences (3). The prevalence of chronic lower leg ulcers in Western countries is estimated at 0.3% (lifetime prevalence 1%) of the general adult population, up to 2% (lifetime prevalence 3-5%) of people aged 65 and above (2,4). Treatment options include cleaning and debriding of ulcers, selecting appropriate dressings, compression therapy, skin grafting, and vascular surgery. However, these modalities are time-consuming and often not successful (5,6). Therefore, the need for adjuvant therapies rises. Extracorporeal Shock Wave Therapy (ESWT) was introduced in Urology as lithotripsy in 1980 (7), and is currently also being used to treat musculoskeletal diseases (non-union bones, plantar fasciitis, epicondylitis lateralis, and tendinitis of the shoulder) (8-10). Shock waves are single longitudinal acoustic waves with a high peak-pressure (500 bar), rapidly followed by a negative phase. They have a short duration (10 milliseconds), short wave length, and a broad frequency spectrum (10-20 MHz) (11). Beneficial effects of ESWT have been described in ischemic skin flaps (12,13), burn wounds (14,15), and ulcers, in particular diabetic ulcers (1,16-19). There is an increasing use of ESWT in chronic ulcers and most research is being focused on the underlying therapeutic mechanisms, which are not yet fully understood. This study however was undertaken to evaluate the efficacy of ESWT on wound healing in patients with different chronic ulcers, to assess their quality of life (QoL), and to explore the safety of ESWT.
Patients with chronic ulcers and unsuccessful regular treatment for at least four months were enrolled in a prospective, single-arm clinical trial between December 2014 and March 2015. Patients with a pacemaker or cardiac arrhythmia, malignancy, coagulopathy, local acute inflammation, pregnancy/breastfeeding, or possible poor compliance were excluded. This study was approved by the medical ethics review board of the University Hospital Brussels and conducted according to the Declaration of Helsinki principles. All patients signed an informed consent upon participation.

Besides regular wound care (‘best medical care’) consisting of ulcer cleaning and debridement, selection of the appropriate wound dressing, and compression therapy when necessary, all participants received ESWT (Sanuwave, Ortho Medico) without local anesthetics. Sterile ultrasound gel was applied on the ulcer and the head of the device was covered with a sterile sleeve. Depending on the ulcer size and in accordance with previously established protocols, 500 to 1000 impulses/cm² at 0.11 mJ/mm² energy flux density were applied during four sessions twice weekly (for diabetic ulcers) or once weekly (for all other ulcers) (2,20). The head was gently glided over the ulcer surface and one centimeter around. Patient characteristics (gender, date of birth, tobacco or alcohol use, and medication) and wound characteristics (etiology, duration, and treatment) were obtained at baseline. Evaluation at each visit included measurements of the ulcer, description of the base and border, assessment of wound exudate and infection, and questions regarding side effects. To assess QoL, patients were asked to complete a Dermatology Life Quality Index (DLQI) questionnaire at baseline and after the last treatment session to evaluate the impact on daily life (21). Pain was assessed with a Visual Analogue Scale (VAS) and was completed during each visit (22). Final evaluation at six weeks after start of treatment consisted of a re-evaluation of patients’ wound characteristics (Figure 1).

Statistical analyses were performed with the Statistical Package for Social Sciences (SPSS) software version 21.0. Results are presented as descriptive statistics (percentages, mean ± SD, median and percentiles) and are visualized with boxplots and error bars. Changes at each visit were compared to baseline with the Wilcoxon signed-rank test (for non-parametric data) with Bonferroni correction to adjust for multiple testing. Therefore, a sophisticated longitudinal statistical model was not necessary (there was no loss to follow-up).
4 RESULTS

4.1 Patient population

Thirty-five patients with ulcers were screened, of which ten were eligible: four men and six women. Their median age was 76.5 year (25th percentile 67.5 – 75th percentile 82.5). Tobacco and alcohol use were present in 30 and 40% of patients and 30% was previously diagnosed with diabetes type 2.

4.2 Wound characteristics

All subjects had one ulcer; these were venous (50%), related to diabetes (30%), because of peripheral artery disease (10%), or post-traumatic (10%). All ulcers were localized on the lower extremities: 60% in the malleolar region, 30% on the feet, and 10% on the lower legs. Median ulcers' age was 11 months (25th percentile 5 – 75th percentile 57).
At baseline, median ulcers' size was 3.6 cm² (25th percentile 2.4 – 75th percentile 15.7) and median depth was 4.5 mm (25th percentile 3.0 – 75th percentile 6.3). Ulcers had a median epithelialization rate of 10% (25th percentile 10 – 75th percentile 20) and 70% were exudative.

Six weeks after start of treatment, median ulcers' size was 1.2 cm² (25th percentile 0.6 – 75th percentile 6.0) and median depth was 2.0 mm (25th percentile 1.0 – 75th percentile 3.0). Ulcers had a median epithelialization rate of 45% (25th percentile 38 – 75th percentile 80) and 40% were exudative.
No device-related side effects were declared. Mild pain, mild edema, and superficial hematoma were each seen in 10% of subjects and resolved spontaneously within 24 hours.

### 4.3 Photographs documentation

During each patient contact the ulcerations were documented by means of photographs.

<table>
<thead>
<tr>
<th>Patient 1:</th>
<th>A. Status before shockwave therapy</th>
<th>B. Status after 2 treatments</th>
<th>C. Status after 4 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous ulcer</td>
<td>Left malleolus medialis</td>
<td>Present since 15 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 2:</th>
<th>A. Status before shockwave therapy</th>
<th>B. Status after 2 treatments</th>
<th>C. Status after 4 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traumatic ulcer</td>
<td>Right malleolus medialis</td>
<td>Present since 144 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 3:</th>
<th>A. Status before shockwave therapy</th>
<th>B. Status after 2 treatments</th>
<th>C. Status after 4 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous ulcer</td>
<td>Right malleolus medialis</td>
<td>Present since 36 months</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Patient 4:</th>
<th>A. Status before shockwave therapy</th>
<th>B. Status after 2 treatments</th>
<th>C. Status after 4 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic ulcer</td>
<td>Foot sole</td>
<td>Present since 7 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 5:</th>
<th>A. Status before shockwave therapy</th>
<th>B. Status after 2 treatments</th>
<th>C. Status after 4 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic ulcer</td>
<td>Right lateral foot</td>
<td>Present since 4 months</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient 6:</th>
<th>A. Status before shockwave therapy</th>
<th>B. Status after 2 treatments</th>
<th>C. Status after 4 treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial ulcer</td>
<td>Medial side lower extremity</td>
<td>Present since 12 months</td>
<td></td>
</tr>
</tbody>
</table>
Patient 7:
Venous ulcer
Left malleolus medialis
Present since 10 months

Patient 8:
Arterial ulcer
Medial side lower extremity
Present since 120 months

Patient 9:
Neuropathic ulcer
Medial side right foot
Present since 5 months

Patient 10:
Venous ulcer
Left Medial side lower extremity
Present since 12 months

4.4 Quality of Life

Before the start of the treatment the mean DLQI score was 8.4 (SD 2.9) and mean VAS score was 2.1 (SD 2.2).

6 weeks after the first treatment the mean DLQI score was 3.4 (SD 1.8) and mean VAS score was 0.8 (SD 1.1). All changes were statistically significant compared to baseline. Changes in ulcer measurements, QoL, and pain scores at different time points are shown in Figure 2 and Table 2 (online-only supporting information).
This study demonstrated improvement in 10 out of 10 investigated ulcers in all measured parameters (wound-surface, depth, and re-epithelialization; DLQI and VAS) after ESWT. Moreover, a positive evolution of QoL was accompanied by a decrease of ulcer-associated pain, while no severe side effects were noted. Median ulcer size decreased from 3.6 cm² at baseline to 1.2 cm² after six weeks, median ulcer depth decreased from 4.5 to 2.0 mm, and median percentage of epithelialization increased from 10 to 45%. Furthermore, mean DLQI and VAS scores decreased from 8.4 to 3.4 and 2.1 to 0.8, respectively.

Important causes of delayed wound healing are increasing age and co-morbidities such as diabetes, peripheral vessel disease, tobacco use, and malnutrition (23). Our population also had a high median age (76.5 years). Hyperglycemia (50% of all patients), chronic venous insufficiency (60%), smoking (30%), and hypoalbuminemia (40%) were indeed frequently present, but the sample size precludes definitive statements.

Moretti et al (19) found complete re-epithelialization of 53% of ulcers in their ESWT group compared to 33% in the control group and Wang et al (16) described better healing of diabetic ulcers after ESWT compared to oxygen therapy. In a subsequent study of Wang et al (1) 37.5% of all ulcers were healed after ESWT, 18.1% were improved >50%, and 44.4% were unchanged or worse. After five years, a decrease in these percentages was observed, probably because of the underlying disease. The mean decrease of 71% in wound surface and 60% in wound depth are even higher in our study, confirming the positive effects of ESWT on chronic ulcers. No ulcers were unchanged or worse. Saggini et al (3) found a larger decrease of wound exudate after ESWT (47.4%) compared to conservative treatment (11.1%). In our study, there was a 43% decrease in the number of patients with exudative wounds. This decrease might fit with the reduction in ulcer size or with the bactericidal effects of shock waves on wound contamination described earlier (24,25).

Chronic ulcers and pain have a significant impact on patients’ QoL. Wang et al (1) found an improved QoL after ESWT compared to hyperbaric oxygen therapy. In our study, a mean decrease in DLQI scores (i.e. an increase in QoL) of 60% was observed. Because of a significant improvement in all patients and despite the small study population, ESWT probably had positive effects on patients’ QoL. Pain is one of the major causes of the poor QoL in patients with chronic ulcers. In our study, we observed a significant mean decrease of 62% in VAS scores (i.e. a decrease in the amount of pain) after ESWT. This decrease is in accordance with the results of Ohtori et al (26) and Takahashi et al (27), who demonstrated a degeneration of epidermal nerve fibers after ESWT. They noted re-innervation after 21 days, implying a re-increase in VAS scores, which was not observed in our study.

The most common reported side effects of ESWT are pain, swelling, and superficial hematoma, which were all mildly present in 10% of our subjects (28). Saggini et al (3) noted an increase in pain in 27% of patients during ESWT. In our study only one patient had pain induced by ESWT, however, every other manipulation of the ulcer was painful too. Therefore, ESWT can be considered as a safe and well-tolerated treatment method, pending confirmation in larger trials.

Limitations of this study include the small sample size, which precludes definitive statements. Also, this is a single-arm trial without comparison group, but in our academic center each patient with therapy-resistant ulcers already received optimal medical care in a specialized wound clinic prior to initiation of the study and served thereby as his/her own control. Therefore, healing after ESWT implies an effect of this treatment modality. ESWT was administered according to a standardized protocol.
In comparison with other additional treatment options such as negative-pressure wound therapy or hyperbaric oxygen, ESWT is a non-time-consuming method and does not have systemic side effects such as pneumothorax or barotrauma (29,30). A vacuum pump is visible but ESWT is invisible for others. Not many extra materials are needed and ESWT does not have extensive financial consequences in contrast to e.g. the use of local growth factors or fibroblast cultures (6). ESWT is a non-invasive, straightforward adjuvant method. Its use can be recommended in addition to standard therapy, whereas negative-pressure wound therapy or hyperbaric oxygen must be used in a third-line setting.

We conclude that additional ESWT on best care is safe and can lead to an improvement of chronic ulcers after six weeks. Furthermore, it improves patients’ QoL. The results of this study highlight the need for larger and randomized studies to confirm the effects of ESWT, to investigate side effects more thoroughly, and to create standardized treatment protocols.
STUDY:

EXTRACORPOREAL SHOCKWAVE THERAPY (ESWT)

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