Benefits of extracorporeal shockwave in the treatment of skin ulcers: a literature review

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ABSTRACT
Extracorporeal shockwave therapy (ESWT) has analgesic and anti-inflammatory effects. With the evolution and comprehension of its biological and physical mechanisms, the application of ESWT on other pathologies has also been studied, especially in musculoskeletal diseases. Recently, studies on animal models have shown its angiogenic capacity and a higher rate of local re-epithelization. These small studies led to few trials using low-energy, radial ESWT to treat problematic chronic skin ulcers. Skin ulcers have diverse etiologies, ranging from pressure ulcers, burns, venous or arterial ulcers, and even diabetic ulcers. Their treatment is usually a challenge, due to the long-term treatment and high costs. **Objective:** To review the literature and evaluate the efficacy of ESWT in caring for skin ulcers of various etiologies: diabetic ulcers, pressure ulcers, burns, post-traumatic ulcers, venous and arterial ulcers. **Method:** A literature review was made, with only human trials included. **Results:** 9 articles were selected that fulfilled the eligibility criteria. The studies included evaluations of 788 patients. The manuscripts demonstrated a large variability regarding the interventions made. There was heterogeneity regarding intervention time, number of pulses, frequency of sessions, and also the number of sessions, energy density used, and the type of shock wave used in therapies. Some of the included trials found a higher rate of complete wound healing and faster epithelization in patients with chronic lesions, unresponsive to the traditional measures. However, there were few studies in the literature with proper methodological quality. **Conclusion:** ESWT is a promising alternative for the treatment of patients unresponsive to conventional measures. The results are promising, although the evidence regarding wound healing and acceleration of wound healing is still limited. The studies selected did not report any significant side effects. 

**Keywords:** High-Energy Shock Waves, Treatment Outcome, Therapeutics
INTRODUCTION

Extracorporeal shock wave therapy (ESWT) was originally used for lithotripsy of kidney stones. In recent years, however, with the evolution and understanding of its physical and biological mechanisms, its application was studied in various other diseases, mainly in bone, muscle, and tendon affections such as pseudoarthrosis, plantar fasciitis, and lateral epicondylitis.

In ESWT, mechanical acoustic waves are transmitted through liquid and gaseous means, with their biological effect coming from the mechanical action of these ultrasonic vibrations on the tissues. This technique has an analgesic and anti-inflammatory action, it induces neovascularization, and its mechanical stimulation results in the proliferation of various cells such as the osteoblasts. Other studies have demonstrated its angiogenic capacity and improvement of microcirculation in animal models, resulting in an accelerated angiogenesis and higher rate of local re-epithelization. According to Takahashi, it also presents an antibacterial effect against Staphylococcus aureus.

These studies led to the beginning of using radial low energy ESWT in the treatment and management of various problematic skin lesions. Cutaneous ulcers have different etiologies, ranging from pressure ulcers, burns, arterial and venous ulcers, and even diabetic ulcers. These injuries are still an important cause of morbidity and mortality, presenting an impact on the quality of life of patients due to complications such as pain, infections, and amputations, as well as on their relatives, resulting not only in a health problem, but also in a social and economic one.

Their treatment is challenging due to its prolonged duration (resulting in difficulties regarding the clinical follow-up) and also high costs. The conservative treatment generally consists of a multidisciplinary team, involving mainly a medical and a nursing team to perform the cleaning, hydration, debridement, and dressing of the lesions.

OBJECTIVE

To evaluate the efficacy of ESWT in the healing of ulcers of various etiologies: diabetic, pressure, burns, post-traumatic, venous and arterial vascular, through a literature review.

Secondary objectives

- To compare ESWT with other established therapies.
- To evaluate the different prescriptions of ESWT in relation to the quantity of pulses, frequency, number of sessions, and energy density used.

METHODS

Search methods

A literature review was conducted using the following scientific databases: Medline/ Pubmed, SciELO, LILACS, Cochrane, and PEDro. The following keywords were used in English: shock waves AND skin ulcers, shock waves AND diabetic foot, shock waves AND leg ulcer, shock waves AND foot ulcer, shock waves AND ulcer, shock waves AND wound healing, and their respective terms in Portuguese. Two authors made the selection and evaluation of articles independently. With the selected articles, the authors gathered to discuss the inclusion and exclusion of articles in the review. In case there was disagreement between the reviewers, a third reviewer would be requested to analyze the differences. However, this was not necessary.

Types of studies

Only clinical studies on humans were included in this review. Articles in Portuguese and English were included. The search was limited to articles published between 2000 and 2014. Articles repeated in the databases were excluded as well as studies of experimentation on animals and case reports.

The methodological quality and the risk of bias of the studies were evaluated by two authors using the Jadad and the Van Tulder scales. Due to the small number of clinical studies on humans, low methodological quality and few randomized and controlled studies, these were also included in this review.

Types of participants in the studies

Adults (over 18 years of age), with acute or chronic ulcers of various causes, such as ulcers on diabetic feet, vascular ulcers, venous and arterial ulcers, pressure ulcers, ulcers caused by burns, and post-traumatic ulcers.

Types of interventions

This review included studies with patients receiving only shock wave therapies, and also comparative studies with patients in other groups receiving other treatments, such as the standard cleaning treatment for injuries and dressings, and also therapy in the hyperbaric chamber.

Types of outcome measurements

Studies included presented at least one of these primary outcomes:

- Size of lesion
- Closure of the lesion
- Healing time
- Pain

RESULTS

Description of the studies

Through electronic search, 24 articles were found with 9 articles meeting the inclusion criteria (Chart 1 and Chart 2). Duplicate articles were manually removed. The studies included comprised 788 patients.

Included were 3 articles from Austria (590 patients), 2 from Italy (70 patients), 1 from Taiwan (77 patients), 1 from Germany (28 patients), 1 from Spain (15 patients) and 1 from England (8 patients). All the articles were published in the English language.

Description of individual studies

Moretti et al. assessed 30 patients with ulcers on diabetic feet. The patients were randomly divided into 2 groups, with the first group (B) receiving standard treatment with debridement and wound dressing, and the second group (A) receiving ESWT. The ESWT group received 3 applications of shock waves, every 72 hours, with duration of 1 to 2 minutes. They used 100 pulses per cm² of lesion with density in the flow of 0.03 ml/mm², with radial focus. The size of ulcers was evaluated through photos and calculation of the areas through computer software. The results were tabulated in terms of days needed for the closing of the ulcers. The proportion of patients (in %) that presented closing of the lesions and the rate of re-epithelization between the two groups were also compared. Group A showed closing of 53.33% of lesions by the end of the study, compared to 33.33% from group B. As for ulcers healed during the 20 weeks, the mean time was 60.8 ± 4.7 days in group A and 82.2 ± 4.7 days in group B (p < 0.001). There was also a statistically significant difference in the rate of re-epithelization between the 2 groups, with 2.97 ± 0.34 mm²/die in group A and 1.30 ± 0.26 in group B (p < 0.001). Thus,
both the improvement rate and the healing time were better in the ESWT group, with a statistically significant difference.

Larking et al.\textsuperscript{14} evaluated 8 hospitalized patients, with 9 pressure ulcers. The patients were randomly allocated into two groups, the first (A) with ESWT treatment, and the second, (B) with an ESWT placebo. The ESWT was performed with 200 impulses, a frequency of 5 per second, and 100 pulses per cm\textsuperscript{2} with energy of 0.1 J/cm\textsuperscript{2}. The patients included were initially observed for a period of 3 weeks, being then submitted to treatment with ESWT or a placebo, with 4 weekly sessions. After a 2-week washout period, there was an intersection of the groups. The lesion area was examined after the therapy sessions for 12 weeks. In the group that received the ESWT treatment, there was a statistically significant improvement 6 weeks after the beginning of treatment (difference in lesion size of -0.83, < 0.05, 8 weeks after the ESWT). However, in the group that received the placebo treatment, there was a statistically significant improvement 14 weeks after the beginning of the study (or 8 weeks after the beginning of the ESWT), with a difference in lesion size of -1.15, p < 0.05 after 8 weeks of ESWT.

Schaden et al.\textsuperscript{13} assessed 208 patients with cutaneous lesions of various etiologies, including trauma, arterial or venous insufficiency, pressure ulcers, and also burns. The patients were combined into a single group treated with ESWT. Radial and superficial ESWT were applied, with a median of 2.8 sessions of ESWT, with an average duration of 3 minutes. Of the 208 patients included in the article, 176 completed the treatment, with 156 of these (88.6%) presenting complete closure of their lesions. Complete closure of the lesion was associated with its size, where 81% of patients with lesions < 10 cm\textsuperscript{2} had complete closure compared to 61.8% of those with lesions > 10 cm\textsuperscript{2} (p = 0.005). The duration of the lesion also influenced the healing, with 83% closure for lesions with < 1 month compared to 57.1% for lesions with > 1 month (p < 0.001). Younger patients presented more healing improvement than the elderly (p < 0.001). Complete closure showed no statistically significant difference for patients with diabetes (12/14, 85.7%) or without it (144/194, 74.2%).

Wang et al.\textsuperscript{16} evaluated 72 patients with ulcers on diabetic feet. These were randomly divided into 2 groups: group A received ESWT, and group B received hyperbaric oxygen therapy (HOT). The ESWT group received treatment with at least 500 impulses at 4 Hz with power of 0.23 mJ/cm\textsuperscript{2}, every 2 weeks for 6 weeks. Group B received hyperbaric oxygen therapy daily, with a total of 20 sessions. There was complete closure in 57% and 25%, respectively (p = 0.003), improvement of ≥ 50% in 32 compared to 15% (p = 0.071), no changes in 11% and 60% (p < 0.001), and no patient showed worsening of their lesions in either the ESWT or HOT groups. In the histological analysis, greater concentration, proliferation, and cellular activity was found in patients after ESWT than after HOT. There was also a significant increase in intravenous nitric oxide, VEGF, and expression of PCNA after ESWT. A significant improvement of local blood perfusion was also present after ESWT (p < 0.04), and not after HOT (p = 0.140).
Wolff et al.\textsuperscript{17} evaluated 282 patients from September 2003 to February 2007. The patients included presented cutaneous ulcers of various etiologies (excluding 2nd or 3rd degree burns) with duration of more than 30 days. Thirty days after the last ESWT session, the primary outcome was death while secondary outcomes were the closure rate of lesions, and the number of ESWT sessions needed, the rate of lesions that did not heal and the number of sessions until the abandonment of treatment. The first 2 ESWT sessions were weekly, with the interval increased to 2 weeks after the second session. An average of 167 pulses/cm\(^2\) were used, with a frequency of 5 Hz and energy of 0.1 mJ/mm\(^2\). The \textit{Wound Bed Score} (WBS) was applied before each application; this is a scale that offers a predictive factor as to the success of the healing, incorporating the following parameters in its score: edges, presence of pressure ulcers, greater depth of lesion, amount of exudate, edema, perilesional dermatitis, perilesional fibrosis, and local hyperemia. Twenty-four (8.51\%) of the patients were lost in the follow-up. No patient died within 30 days of the last ESWT session. 191 patients (74.03\%) had their injuries healed, with an average of 2 sessions needed. Lesions aged 4 to 12 weeks showed a success rate of 82.23\%. Lesions aged 4 to 12 months presented complete healing in 63.64\%, while in lesions with duration greater than 1 year the rate was 28.57\%.

Arnó et al.\textsuperscript{18} conducted a prospective pilot study on 15 patients with burns on less than 5\% of the body surface, and applied 2 ESWT sessions to them, on the 3rd and 5th days after the lesions occurred. The shock waves were applied with 100 impulses/cm\(^2\) and energy of 0.15 mJ/mm\(^2\). Before each session, laser Doppler was used to evaluate the depth of the lesion and perfusion alterations. After that, the patients were evaluated weekly for one month, and then monthly. If there was no re-epithelization of the lesion in up to 2.5 weeks after ESWT, surgical debridement was performed on the lesion. One patient was lost, and 12 other patients presented complete closure of their lesions. Thus, 2 patients who did not report improvement underwent surgical debridement and skin graft.

Saggini et al.\textsuperscript{19} evaluated 40 patients with chronic ulcers of the lower limbs, of various etiologies, such as diabetic ulcers, vascular, and post traumatic, who had no response to conservative treatment. The mean age of the lesions was 5.3 months and the mean age of the patients of 60.4 years. Thirty patients received ESWT (32 ulcers), and 10 received conservative measures and served as a control group. In the ESWT group, the average area of ulcers was initially 5.29 cm\(^2\), with dimensions ranging from 1.2 x 2 to 5.4 x 2.8 cm. Between the 4th and 6th ESWT session, there was complete closure of the lesions in 16 of the patients in the ESWT group (50\%) with \(p < 0.01\). All the lesions showed a decrease of exudate, and an increase in the percentage of granulation tissue in relation to the necrotic tissue/fibrin (\(p < 0.01\)) as well. There was also a reduction in pain after the ESWT (\(p < 0.001\)).

Ottoman et al.\textsuperscript{20} evaluated the rate of re-epithelization in the skin grafts of 28 patients. The patients were divided into 2 groups, the first (A) with a radial ESWT session and standard treatment, and the second (B) with only standard treatment. The average time of treatment was 13 minutes, using 100 impulses/cm\(^2\), with energy to 0.1 mJ/mm\(^2\). The average time for full closure for patients in group A was 13.9 ± 2.0 days, and 16.7 ± 2.0 days for group B, with \(p = 0.0001\).

Dumfarth et al.\textsuperscript{21} conducted a study with prophylactic ESWT in cutaneous lesions of patients who would undergo coronary revascularization surgery. It evaluated 100 patients, with 50 in an ESWT group and 50 in a control group. The ESWT was applied at the site of the vein harvesting for the bypass, with 25 impulses/cm\(^2\), at 5 Hz and energy of 0.1 mJ/mm\(^2\). The post-operative lesions were evaluated by the ASEPSIS scale that evaluates additional treatments, erythema, purulent exude, isolation of bacteria, presence of serous secretion, separation of deep tissue, and duration of hospitalization. Lower ASEPSIS scores were found in the ESWT group (4.4 ± 5.3) in comparison with the control group (11.6 ± 8.3, \(p = 0.0001\)). There was also a smaller rate of lesions that became infected in the ESWT group (4\%, \(p = 0.015\)) in comparison with the control group (22\%).

### ESWT v. conservative therapy

Moretti et al.\textsuperscript{21} and Ottoman et al.\textsuperscript{20} compared ESWT with conservative therapy with local debridement and dressings, and found a statistically significant decrease in the average time of closure for the lesions. Moretti et al.\textsuperscript{23} also found a statistically significant difference in the rate of closure of the lesions of the patients submitted to ESWT. Dumfarth et al.\textsuperscript{21} found a lower ASEPSIS score in patients of the ESWT group when compared with the conservative group, and also a lower rate of subsequent infections.

### ESWT v. other treatments

Wang\textsuperscript{24} compared ESWT with hyperbaric oxygen therapy in patients with ulcers on diabetic feet. The ESWT group presented higher rates of complete closure (57\% vs. 25\%, \(p = 0.003\)), improvement of ≥ 50\% (32\% vs. 15\%, \(p = 0.071\)) and lower rates of lesions without change (11\% vs. 60\%, \(p < 0.001\)). Wang\textsuperscript{24} also performed a histological analysis between the groups. In the ESWT group, there was a significant increase of intravenous nitric oxide, VEGF, expression of PCNA, and also of local blood perfusion after ESWT (\(p < 0.04\)).
Side effects
The ESWT side effects reported in the literature include local bleeding, petechiae, hematoma, seroma, and worsening of pain, and also potentially more serious effects such as syncope and headaches. 12,19
The selected articles have not reported significant adverse effects such as cardiac, neurological, dermatological, or allergic effects. The adverse effects found were local erythema and mild local pain with VAS < 314 not requiring interruption of the therapy.

Possible Bias
Some of the studies were performed with authors and/or co-authors with possible conflicts of interest, such as being partners of manufacturers of ESWT devices. 15,17,20,21

DISCUSSION
The use of extracorporeal shock waves in renal lithotripsy, aiming to dissolve kidney stones, started in the 80s. After that, in the 90s, shock wave therapy was being used in Europe, mainly in Germany and Austria, initially for orthopedic pathologies such as Achilles tendinitis and plantar fasciitis, after experimental studies indicated a potential effect of neovascularization, peristomal stimulus and also an analgesic and anti-inflammatory action. 1,2 Its exact mechanism of action is unknown.
In ESWT, the acoustic mechanical waves used can be of low or high energy, depending on the pathology to be treated, causing microbubbles in the tissues affected. The mechanical impact of these waves generates this eruption, resulting in a series of local physiological changes.
The tissue repair of a lesion involves regeneration and fibrous healing. These processes involve a complexity of vascular, cellular, and biochemical factors. Initially, there is a local inflammatory reaction, with the action of inflammatory cells such as neutrophils, lymphocytes, macrophages, and also vascular endothelial cells. The inflammatory cells are induced by various chemical mediators in the target tissue, such as histamine, prostaglandin (PGE2), nitric oxide (NO), and interleukins IL1 and IL6, stimulating the inflammatory response with reabsorption of cell debris and blood extravasation by phagocytic cells. 25 After the resolution of inflammation with the removal of the exudate, there is the formation of granulation tissue due to endothelial and fibroblast proliferation. There is an increase in the quantity of collagen, replacement of collagen type I with type III, differentiation of fibroblasts into myofibroblasts, and the formation of new vessels. 24

Basic research and animal models indicate a potential action on the stimulation of endothelial NO, 16 increased expression of vascular endothelial growth factor (VGEF), increased modulation of oxygen radicals, decreased infiltration of leukocytes, reduced apoptosis of tissues, the recruitment of fibroblasts, 24 and an increase in insulin-like growth factor type 1 (IGF-I), 25 therefore resulting in a suppression of local inflammation and an increase in neovascularization with increased local peripheral tissue perfusion, with direct and/or indirect effects to the endothelial stimulation, with an increased rate of epithelization and local connective tissue. 25
According to Schaden et al. 15 The ESWT in both acute and chronic lesions is well tolerated, with no need to use anesthetics for its application. In one study, patients reported an increase of local pain during the application of therapy, although this increase was mild and tolerated. 20 In the literature, the adverse effects most commonly found are pain, local hyperemia, and the appearance of petechiae and small hematomas. Other more unusual adverse effects include migraines and vasovagal synapses. 22
There are few studies in the literature evaluating its biological effects on the healing of skin ulcers, with the oldest article being from 2007. Only 9 studies were found, with only one study being prospective, double-blind, and randomized. 14 Most of the studies had low methodological quality, with no control group, lacking in blinding, in data standardization, and in sample loss, with failures in the randomization, and poorly defined inclusion and exclusion criteria-all of which hampered the decision-making based on the literature and the comparison between research findings (Chart 3 and Chart 4).
As the research on the effects of shock waves on the healing of skin ulcers has begun recently, the present study also included those studies with low methodological quality, such as the case series by Arnó et al. 18 and Schaden et al. 15 for the description and discussion of their results. Only Wang et al. performed sampling calculation. Some of the studies included did not describe their losses. 19,21 The randomization details of the study by Moretti et al. 13 were not described. In view of that, the present analysis saw no homogeneity regarding the number of participants.
Only one study was double blind. The ESWT equipment offers the possibility of using a placebo applicator, with the same physical characteristics as the original applicator, however without the emission of waves. Only Larking et al. 14 used a comparison between a real ESWT and a sham ESWT. The other studies included compared ESWT with hyperbaric oxygen therapy, 16 with a standard treatment, 15,19,20,21 or were case series with ESWT. 15,17,18
The studies showed a variety of different intervention standards. There was heterogeneity in the intervention time, number of pulses, and in the frequency of sessions, as well as in the number of sessions, the energy density applied, and also in the type of shock waves used in the therapies. The parameters employed varied from 25 up to 1000 pulses per cm2. The frequency used, when described, was 4 to 5 Hz. The number of sessions also varied from a single session to 10 weekly sessions, and the energy used varied from 0.03 mJ/mm2 to 0.1 J/mm2. There was also no consensus as to the interval necessary between sessions, with some studies performing the therapy every 2 days, but mostly varying between one and two weeks (Chart 2).
The intensity and dose of therapies varied even for patients of the same study. In the studies by Want et al. 16 and Schaden et al. 15 the number of sessions and energy was dependent on the size of the ulcer. Other studies by Saggini et al. 19 and Wolff et al. 17 showed that the number of sessions varied from 4 to 10 and from 1 to 10, respectively. Thus, it is not possible to accurately assess the establishment of a standard treatment dose. No direct comparison between the use of focal or radial waves was found in the literature. Most of the studies used radial shock waves, with only two studies using focal waves, whereas the article by Larking et al. 14 did not describe the type of stimulus used.
As to the results, Moretti et al. 13 found a higher rate in the healing of the lesions in patients undergoing ESWT in relation to the conservative treatment (53.33% vs. 33.33%), and also a statistically significant decrease in healing time (60.8 ± 4.7 and 82.2 ± 4.7 days). Larking et al. 14 conducted a study with placebo ESWT, and also found a statistically significant reduction in lesion size after the initiation of treatment. Arnó et al. 18 conducted a study with a single group with no control, and found a complete closure of lesions in 80% of the patients. Saggini 19 also found a significant closure rate, and also a reduced exudate, an increased percentage of granulation tissue, and also reduced pain after ESWT sessions.
Cutaneous ulcers are lesions with a prolonged and challenging treatment, and may involve high costs. The conservative standard treatment consists of cleaning, debridement, and dressings. In
general, the patients also present other complications and systemic diseases, such as diabetes mellitus, vascular diseases such as venous insufficiency, making the treatment and healing of the lesions more difficult. These lesions, when chronic, present a high incidence of local and systemic infections, resulting in an increase in the morbidity and mortality of these patients, and also in a significant worsening of their quality of life.\textsuperscript{11,12}

\textbf{CONCLUSION}

\textbf{Clinical perspectives}

ESWT appears to be a promising alternative for patients who do not respond well to conservative therapies, and possibly also as a primary treatment, showing promising results but with limited evidence regarding the decrease of healing time and acceleration in the closure of the lesions. The studies selected have reported no significant side effects, indicating it is a safe therapy.

\textbf{Research Prospects}

There are few studies in the literature with appropriate methodological quality. ESWT is a new therapy, with few studies in the orthopedic area and even fewer in relation to cutaneous lesions. Several basic studies and animal models have demonstrated some of its biological effects. There is a need for more rigorous prospective and randomized studies to analyze its effects and biological mechanisms, and also for the standardization of the number of pulses, frequency, power, and the number and interval of sessions to be performed for an effective treatment.

\textbf{REFERENCES}


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