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Extracorporeal Shock Waves Therapy for the Treatment of Acute and Chronic Wounds—A Prospective, Monocentric Clinical Trial to Examine the Effect of Shock Waves on Wound Healing

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Keywords: acute wounds | chronic wounds | extracorporeal shock waves | split skin graft | wound healing

ABSTRACT

Introduction: The aim of our prospective blinded clinical study was to examine a possible improvement and acceleration of epithelialization by treatment with low-energy extracorporeal shock waves on skin graft donor and recipient sites in patients with chronic wounds. In addition, several secondary parameters were investigated to evaluate the compatibility of the therapeutic method, its influence on infection occurrence and bacterial colonization.

Materials and Methods: A total of 35 patients were included in the study. Of these, 25 participants were assigned to the verum-placebo group and 10 to the sham treatment group. The study of the sham control group was done to exclude a possible "remote effect" of the placebo area. Depending on the group, the wound areas were treated with low-frequency shock waves, placebo, or sham. The examinations were performed immediately on Day 0 after surgical treatment and on Days 5, 7, 9, and 12 after surgery. To record long-term results, an additional evaluation of the wound situation was performed on Day 90.

Results: Epithelialization was statistically significantly accelerated by shock wave application at both skin graft recipient sites and donor sites (0.86 vs. 0.92, $p < 0.05$). Furthermore, the risk of wound infection was significantly reduced by using extracorporeal shock waves. Serious side effects were not reported.

Conclusion: A repeated application of ESWT followed by standardized wound care was shown to significantly accelerate the time to re-epithelialization at the skin graft donor and recipient site compared with re-epithelialization time in patients of the sham/placebo group.

Summary

We see ESWT as a promising approach to treating acute and chronic wounds. Based on the significant results and clinical observations from our clinical trial, we assume that ESWT could complement conventional surgical and conservative wound therapy to achieve faster wound healing.

1 | Introduction

Despite multimodal treatment options, chronic wounds are often prolonged and resistant to therapy. The associated impairment of the patient's quality of life, in combination with the enormous costs for the health care system, make this chronic disease a burning issue of current research.

In the last years, the use of extracorporeal shock wave therapy (ESWT) as a therapeutic option for chronic wounds moved into scientific focus [1–3]. Extracorporeal shock waves are acoustic waves produced outside the body and characterized by a high peak pressure (500 bar), a short lifetime (10 μs), a rapid pressure rise (< 10 ns) as well as a broad frequency spectrum (16 Hz–20 MHz) [4, 5]. According to the administered energy flux density, shock wave therapy is classified into high, medium, or low energy. A commonly used grouping defines an energy density < 0.08 mJ/mm^2 as low energy, 0.08–0.28 mJ/mm^2 as medium energy, and 0.28 mJ/mm^2 as high energy. The selected energy flux density is then applied in pulses to the affected area [6, 7].

The main mechanism is based on mechanotransduction: it is a chemical reaction of the cell to mechanical stimuli like shear and pressure forces. The response seems to be a biological reaction at the cellular level [2, 8, 9]. Recent wound healing studies have shown that the physical qualities of shock waves stimulate complex biomolecular processes that are significantly involved in improving tissue perfusion and angiogenesis [10–14]. The suppression of pro-inflammatory processes and a presumed antimicrobial effect by shock wave application have an additional positive influence on the wound healing cascade [10]. Another interesting approach was taken by Modena and colleagues in their study published in 2024. They investigated how ESWT affects the mitochondrial and cellular functions of superficial adipose tissue. The study found that ESWT can improve mitochondrial activity, increase cellular energy production, and improve the overall functionality of adipose tissue cells. These effects suggest that ESWT may have therapeutic potential in improving tissue health and treating conditions associated with impaired adipose tissue function [15].

Taken together, these are promising properties that could accelerate wound healing and shorten the course of disease in patients with chronic wounds. A paper by Dymarek et al. [16] goes so far as to state that a single session of ESWT may be clinically effective and beneficial in the management of chronic wounds.

The split skin graft has been used for decades to cover wound defects when the skin's own ability to regenerate is insufficient to produce a qualitative replacement tissue. The mesh graft comprises the epidermis with shares of the stratum germinativum and parts of the dermis, with a thickness in our cases of about 0.2 mm [17]. As a rule, the graft donor site typically re-epithelializes within 10–14 days [17]. The healing and the survival of the skin graft in the recipient wound bed depends, in particular, on angiogenesis [18]. The healing process in both localizations is usually associated with pain and a reduction in quality of life [18]. This explains why treatments that can accelerate keratinocyte proliferation and angiogenesis at the donor site and effectively relieve pain and discomfort are urgently needed.

A well-established approach to promote neovascularization, the granulation of the wound ground, and epithelial cell proliferation is the vacuum-assisted wound therapy [19]. Although the efficacy of vacuum therapy in the treatment of chronic wounds has been well studied, it is an invasive therapeutic procedure that usually requires surgical intervention [20]. For adequate wound conditioning, a regular surgical change of wound dressings is also necessary. An innovative and noninvasive procedure that has been shown to support wound healing is the extracorporeal shock wave therapy (ESWT) [21, 22]. Stojadinovic et al. [11] were able to show in an animal study that shock waves applied immediately after skin transplantation stimulate proangiogenic gene expression and suppress local inflammatory response. In a study on split-thickness skin grafts, Ottomann et al. [18] were able to demonstrate that ESWT can significantly accelerate donor site epithelialization.

Although there is preliminary data on the efficacy of shock waves in the treatment of chronic wounds, the evidence is weak due to the small number of studies and participants, different applications, and short observation periods. No treatment regimens exist regarding optimal dose, interval number, focus, and frequency of shock wave therapy in the treatment of chronic wounds. It is therefore necessary to gain new insights into this treatment method. Our study aimed to investigate the effects of ESWT on wound healing in people who received split skin graft.

The primary aim of our blinded prospective within-person clinical study was to examine a possible improvement and acceleration of epithelialization by treatment with low-energy extracorporeal shock waves on skin graft donor and recipient sites in patients with chronic wounds.

2 | Materials and Methods

2.1 | Ethical Considerations

This prospective randomized clinical trial was approved by the Ethics Committee (Ärztekammer Berlin), under authorization number Eth-13/16. All participants provided written informed consent.

2.2 | Study Population

In the period from May 2016 to July 2020, 35 participants with chronic wounds and a medical ground for split-thickness skin transplantation were included in the study. The inclusion criteria were an age range of 18–80 years and an expected transplanted wound area of > 50 cm^2.

Exclusion criteria include severe illness and/or systemic medication (< 30 days before study entry) that may affect wound healing. These include, for example, chemotherapy, corticosteroids, or immunosuppressants.

Participants requiring dialysis or intubation were also excluded, as were participants with HIV/hepatitis infection, tumor disease in the treatment area, those with alcohol and drug abuse, and pregnant participants.

Infections in the surrounding area of the wound or at the split-skin donor site also led to exclusion. Participation in other interventional trials was also considered an exclusion criterion.

2.3 | Study Groups and Randomization

Twenty-five people were randomized intraindividually, with the areas of the split-thickness skin graft and the donor site randomly divided into A and B. One of the two halves was treated with shock waves (verum, Area A), the other with placebo (Area B).

The intraindividual comparisons were used to reduce the number of cases and to homogenize the wound areas.

A further 10 patients (Group 2) were also intraindividually randomized, with the areas of the split-thickness skin graft and the donor site randomized as A and B. The split-thickness skin graft and the donor site were then treated with a sham using a shock wave-absorbing transducer. This additional placebo group was used to detect possible systemic effects of local shock wave treatment that could affect both Areas A and B.

Randomization was performed randomly by drawing lots to assign participants to groups. The randomization procedure was performed manually without the use of any special randomization software.

Randomization and allocation to the groups was carried out by an investigator who was not involved in the evaluation of the data, so the investigator was blinded during data analysis.

At randomization, patients were assigned a numeric patient ID. The ID did not allow any conclusions to be drawn about group allocation.

The study participants were also blinded throughout the study and had no knowledge of whether they were receiving a real, placebo, or sham treatment.

The allocation to wound Area A and wound Area B took place in alternation. If the upper wound area was treated in the participant with ID 01, then the lower area was treated in the participant with ID 02, and so on.

2.4 | Primary Objective

The re-epithelialization level was evaluated as a parameter for wound healing. In addition to a clinical assessment of the wounds, photo documentation and computer-assisted planimetric evaluation of the wound surfaces were done. The primary outcome was the intraindividual difference in epithelialized area between ESWT and placebo/sham ESWT-treated skin graft donor and recipient sites.

2.5 | Secondary Objectives

A total of five secondary parameters were examined. These included wound infection, wound moisture, wound pain, and wound microbial colonization. The dropout from the study was also considered as a secondary outcome parameter.

2.6 | Surgical Procedure

All participants underwent a wound debridement and a split-thickness skin grafting at Day 0. The operation was performed under general anesthesia by a plastic surgeon from our department. The split skin was removed using a standardized procedure with an electric dermatome and a thickness of 0.2 mm (Figure 1). The right/left thigh or the back served as the donor site.

The skin graft was meshed at a ratio of 1:1.5 and then transplanted to the recipient region (Figure 2).

The resulting wound areas were each randomly divided into an Area A/B, and the wound size at Day 0 was set as 100% and the re-epithelialization rate as 0%.

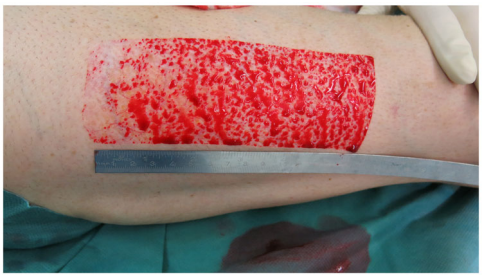

FIGURE 1 | Donor site on D0: the split skin was removed using a standardized procedure with an electric dermatome and a thickness of 0.2 mm.

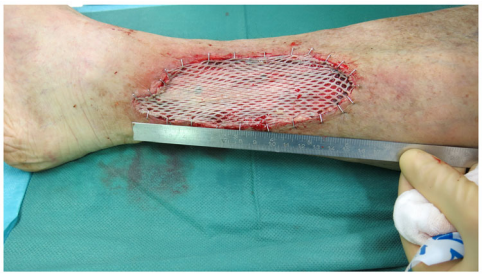

FIGURE 2 | Recipient site on D0: the skin graft was meshed at a rate of 1:1.5 and then transplanted to the recipient region.

2.6.1 | Standard Therapy

Regardless of the group, after surgery, the donor site was supplied with a transparent occlusive foil (V.A.C. drape, 3M + KCI). The recipient site was dressed in a single-layered fat gauze (Lomatuell H, Lohmann & Rauscher) and a foam overlayer (V.A.C. GranuFoamTM, KCI Licensing Inc), which was fixed over the skin graft with staple sutures. The dressings were left on the wounds without change until Day 5 postsurgery.

2.7 | ESWT Procedure—Shock Wave Administration

The shock waves were delivered to the skin graft donor (acute wound) and recipient site (chronic wound) as a repeated treatment. For the application of shock waves, a sterile foil was first applied to the wound (Figure 3a). The ultrasonic gel was used as a coupling medium (Figure 3b). Focused shock waves were then applied to the wound bed using the Duolith SD1 Tower Ultra (STORZ Medical AG, Tägerwilen, Switzerland), which is a CE-marked medical device in Europe (Figures 3c and 4). There are two different handpieces for the Duolith SD1. In this study, the C-Actor handpiece was used. The handpiece can be used either without a stand-off or with two different stand-offs (short/long) to adjust the focal zone penetration depth (0–65 mm). In our case, we used the stand-off device I with a focus depth of 15 mm and a penetration depth of 0–50 mm.

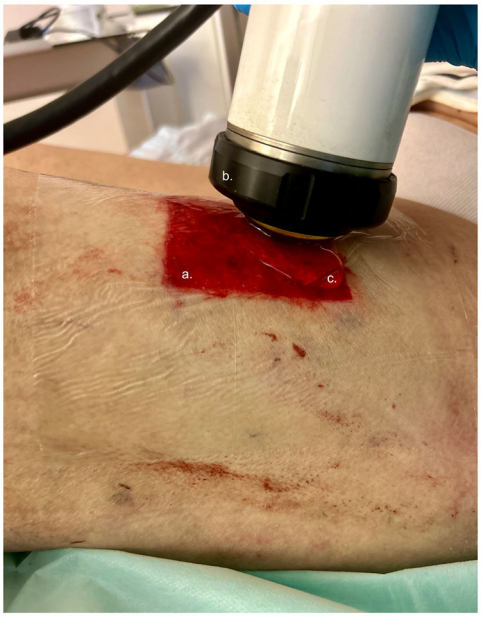

FIGURE 3 | Experimental design on the example of the donor site wound. (a) Wound surface with the sterile foil. (b) Ultrasonic gel as a coupling medium. (c) Duolith SD1 Tower Ultra probe (STORZ Medical AG, Tägerwilen, Switzerland).

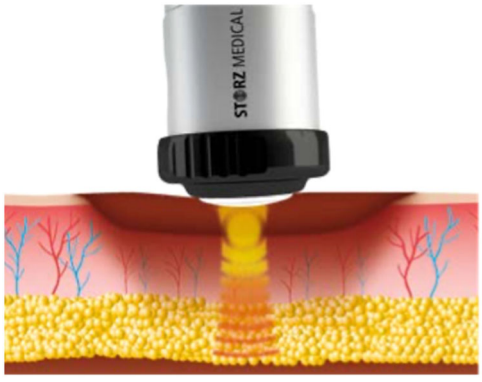

FIGURE 4 | Graphical scheme of an ESWT treatment (with kind permission from STORZ Medical AG).

One hundred pulses per square centimeter of wound area were applied per treatment, using a low-energy flux density of 0.25 mJ/mm^2 and a frequency of 4 Hz.

Measured by a wound area of a minimum of 50 cm^2, at least 5000 impulses were set to the wound and the surrounding area. ESWT was applied on Days 5, 7, and 9 after surgery.

After each application the skin graft donor site was supplied with a transparent occlusive foil (V.A.C. drape, 3M + KCI). The recipient site was covered with a single-layered fat gauze (Lomatuell H, Lohmann & Rauscher), sterile compresses as well as an elastic compression bandage.

2.7.1 | Sham–ESWT

Participants in the sham treatment group were also randomly divided into A and B for both the donor site and the transplanted region. Both areas were then treated with a shock wave-absorbing transducer. The procedure was similar to Group 1. The probe was placed directly over the wound surface. Protected by a sterile foil, the relevant wound area was treated with the shock wave probe (including the shock wave-absorbing transducer). In Group 2A, the device was switched on, and in Group 2B, the device was left switched off. This additional placebo group was used to detect possible systemic effects of the local shock wave treatment.

2.8 | Evaluation Tools and Timelines

Photo documentation, a clinical assessment of the wound as well as a wound swab for a microbiological testing were performed on Days 0.5, 7, 9, 12, and Day 90 after surgery. The photos were taken in a standardized manner using a reflex camera (Canon PowerShot G15) on a fixed tripod. To maintain an exact distance from the wound, an electro-optical measurement was taken with a laser. The distance to the wound surface of the donor and recipient sites was 30 cm in each case.

Microbial colonization was assessed in the laboratory using wound swabs. Swabs were taken on Days D0/D5/D7/D9/D12. Both qualitative (exact microbial specification) and quantitative (microbial count) analysis was performed.

On examination Day 5/7/9/12, the study participants' wound pain in the area of the split skin donor site was recorded. Pain was recorded using the Visual Analogue Scale (VAS), in which the study participants assigned a number from 0 (no pain) to

10 (worst pain imaginable) to describe the pain they subjectively felt.

The clinical assessment of the wounds (donor and recipient) was based on a clinical score, which included six general wound healing criteria (moist, dry, sensitive to pain, infected, reddening, and other). The clinical parameters such as visual impression with clinical signs for a wound infection, pain (visual analogue scale, 0 [no pain] to 10 [worst pain]) or paresthesia were recorded and documented on the current examination day with a wound assessment sheet.

Complications of the treatment were also recorded. These involved wound infections, skin loss (at the recipient site), dropout of treatment, anxiety, and newly occurring comorbidities.

For the analysis of the collected image data, we used Adobe Photoshop CS6 and ImageJ. The wound surface (nonepithelialized areas) was captured planimetrically by its color, where differentiation between wound and epithelialization is feasible.

2.9 | Statistical Analysis

Means and standard deviation were calculated for all outcomes. For the primary parameter (epithelialization), the following evaluations were performed: Calculating the average epithelialization of the wound surfaces of all patients at each measurement time and the proportion of patients with complete wound closure per measurement day, calculating the variance and standard deviation, and testing the data for normal distribution.

The normal distribution of data was tested by the Shapiro–Wilk test for equal variances.

2.9.1 | Primary Outcome Parameter

For the primary outcome parameter (re-epithelialization level), the mean degree of wound surface closure was determined for all patients at each time point.

A two-way repeated measures ANOVA was used to compare the mean differences between the groups. A Bonferroni post hoc test was added in case of significant ANOVA interaction.

2.9.2 | Secondary Outcome Parameters

For the secondary parameters, mean value calculations were made for each measurement time point.

For paired data, that is comparisons within a group (1A vs. 1B), McNemar's test was used.

Unpaired data sets, that is, comparisons between 1A/2A or 1B/2B, were analyzed with the χ^2 test.

Post hoc testing was performed using the Bonferroni multiple comparison test. Values of $p < 0.05$ were considered statistically significant.

3 | Results

Group 1A = verum shock wave therapy (split skin donor and split skin recipient site)

Group 1B = placebo therapy (device off, split skin donor and split skin recipient site)

Group 2A = Sham therapy (device on, shock waves were absorbed, split skin donor and split skin recipient site)

Group 2B = Sham therapy (device off, but placing the transducer over the wound bed as in 2A; split skin donor and split skin recipient site).

3.1 | Demographic Data of the Participants

The table below presents data from the 35 participants, with a majority being male (60%) and an average age of 68.6 years, ranging from 49 to 92 years (Table 1). The patients were treated

TABLE 1 | Tabular overview with the demographic data of the study participants.

Parameter	Overall ($n = 35$)
Gender, *n* (%)	
Male	21 (60%)
Female	14 (40%)
Age, years	68.6 (92/49 years)
Wound type, *n* (%)	
Decollement injury	2 (5.7%)
Ulcus cruris	9 (25.7%)
Wound healing disorders after osteosynthesis	4 (11.4%)
Soft tissue defect after necrotizing fasciitis	3 (8.6%)
Diabetic foot syndrome	9 (25.7%)
Wound healing disorders of various types	8 (22.9%)
Wound localization (recipient region)	
Lower right leg	8 (22.9%)
Lower left leg	10 (28.6%)
Right foot	9 (25.7%)
Left foot	7 (20%)
Right arm	1 (2.8%)
Wound localization (donor region)	
Right thigh	15 (42.9%)
Left thigh	14 (20%)
Back	6 (17.1%)
Patients completed the treatment (till D90)	31 (88.6%)
Patients who did not show up for the follow-up on D90	4 (11.4%)

for various wound types, with the most common being Ulcus cruris and diabetic foot syndrome, each affecting 25.7% of the patients. Other wound types included wound healing disorders after osteosynthesis (11.4%), soft tissue defects following necrotizing fasciitis (8.6%), decollement injuries (5.7%), and other wound healing disorders (22.9%).

The wounds were primarily located in the lower extremities, with the lower left leg (28.6%) and right foot (25.7%) being the most common recipient regions. Other affected areas included the lower right leg (22.9%), left foot (20%), and right arm (2.8%).

For the skin graft, the donor regions were predominantly the right thigh (42.9%), followed by the left thigh (20%) and the back (17.1%). A significant majority of patients (88.6%) completed their treatment by Day 90, while 11.4% did not attend the follow-up (Table 1).

3.2 | Donor Site Re-Epithelialization

3.2.1 | Group 1

Starting from a wound area measured as 100% at the donor site on Day 0, (re-epithelialization rate 0%), the wound area decreased by 31% (group 1A) and 32% (group 1B) within the first 5 days.

Comparing the two groups in the further course of the study, there was a significant difference regarding the re-epithelialization rate at day 7 (Group 1 A 0.68% vs. Group 1B 0.6%; $p < 0.01$), Day 9 (1 A 0.82% vs. 1B 0.71%; $p < 0.01$) and Day 12 (0.92 vs. 0.82 $p < 0.05$) (Figure 5).

After three shock wave treatments (d12), the residual wound area in group 1A was 8%.

In the placebo-treated group, 14% wound area remained nonepithelialized (Figure 5). This confirms our hypothesis that shock wave treatment has an accelerating effect on wound healing (Figure 6a–e). No significant difference was seen 90 days postoperatively.

3.3 | Recipient Site Re-Epithelialization

3.3.1 | Group 1

A positive effect of the shock wave treatment could also be shown in connection with the split skin recipient site (Figure 7a–e). Regarding the re-epithelialization of the transplanted split skin area, there were significant differences depending on the group. At Day 7 ($p < 0.001$), 9 ($p < 0.001$), and 12 ($p = 0.008$), a significantly smaller residual wound area was measured in the verum-treated group than in the placebo-treated group (Figure 8).

3.3.2 | Group 2

To exclude a possible remote effect of the shock waves, a sham-therapy group with a total of 10 participants was also examined. Afterward, the results of Group 1 were compared with those of the sham-treated Group 2. In detail, Groups 1A and 2A, as well as 1B and 2B, were opposed.

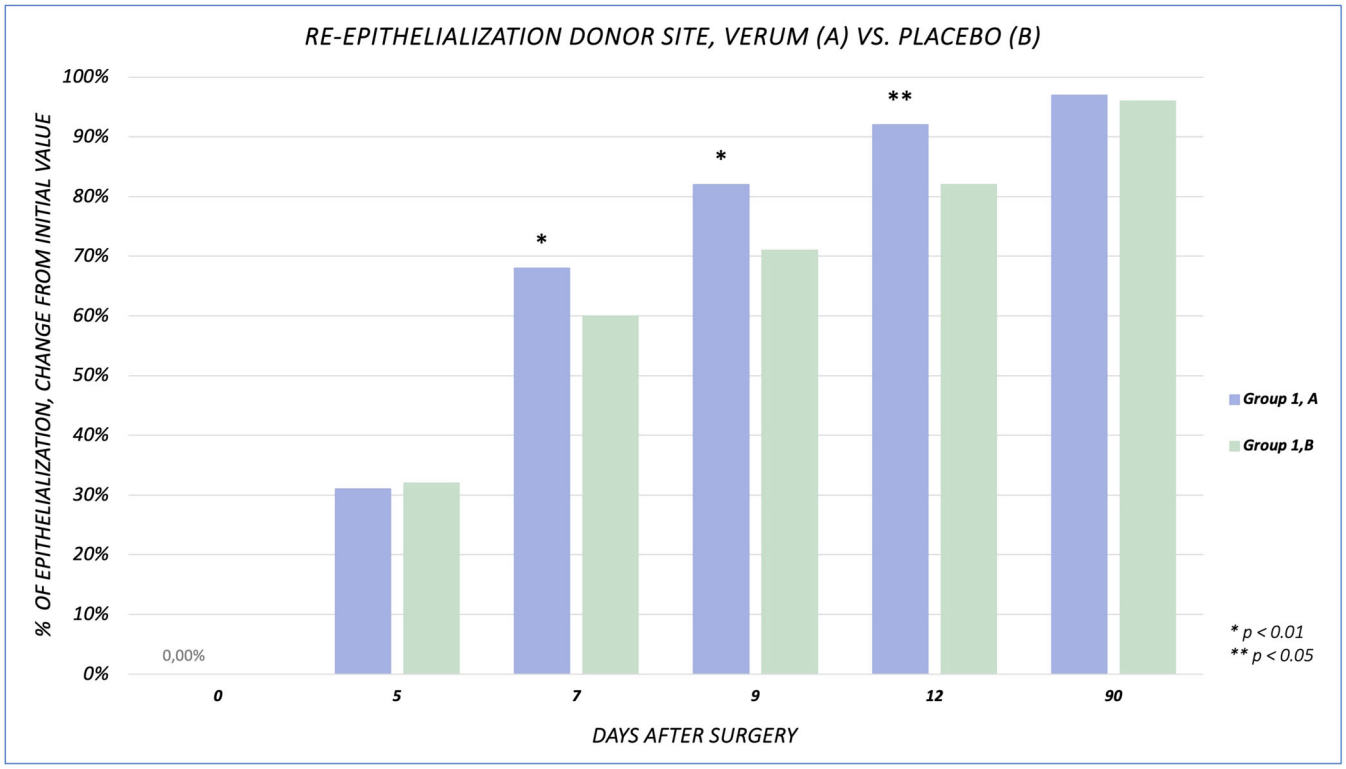

FIGURE 5 | Re-epithelialization of the donor site, 1A versus 1B.

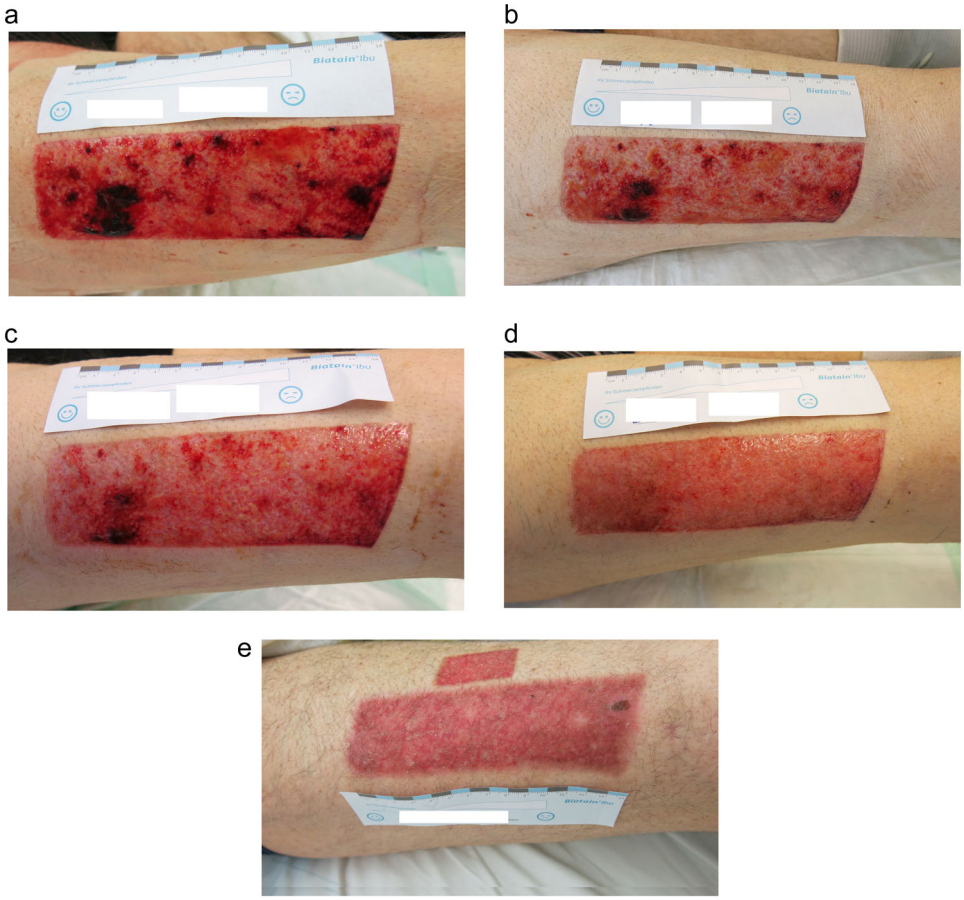

FIGURE 6 | Example of the wound healing process over time at the donor site on: (a) Day 5. (b) Day 7. (c) Day 9. (d) Day 12. (e) Day 90.

Contrary to expectations, no significance at the 0.05 level was detected between the verum and the sham group (neither for donor nor for recipient site) (Figure 9).

3.4 | Wound Infection

Both at the donor and the recipient site, in Group 1 there was a lower clinical infection rate in the verum-treated half of the wound compared with the placebo-treated half. Significantly lower infection rates were recorded on Days 7, 9, and 12 (Figure 10).

There were no significant differences between Group 1 (Verum–Placebo) and Group 2 (Sham).

3.5 | Wound Moisture

The shock wave-treated recipient site showed a faster drying of the wound after three treatment cycles compared with the placebo-treated area of the same wound.

The split graft donor site of the verum-treated group was also less moist after three treatments compared with the placebo site.

Nevertheless, group differences were statistically not significant.

3.6 | Side Effects

No side effects were reported (including allergic reactions or adverse skin reactions like swelling, bleeding, or redness) developed at the shock wave treated areas.

Only two of the participants reported pain during treatment, but there was no statistically significant difference between the treatment groups at any time point of the study. (This was observed by asking the patients about the presence of pain during the treatment. The pain was further analyzed through the 10-point pain scale).

4 | Discussion

The split-thickness skin graft is a well-established treatment for covering wounds that cannot be closed primarily [17]. The first-place healing of skin grafts is dependent on angiogenesis [18]. This process provides revascularization and supply of oxygen and nutrients to the tissue, which are crucial for the healing process [4, 23]. Despite the widespread use of the skin graft method, there are just few studies on additional noninvasive methods that show significant improvement in re-epithelialization of split skin donor and recipient sites after application.

Currently, there are just a few study data describing the effects of ESWT on skin grafts. Stojadinovic et al. [11] and Antonic

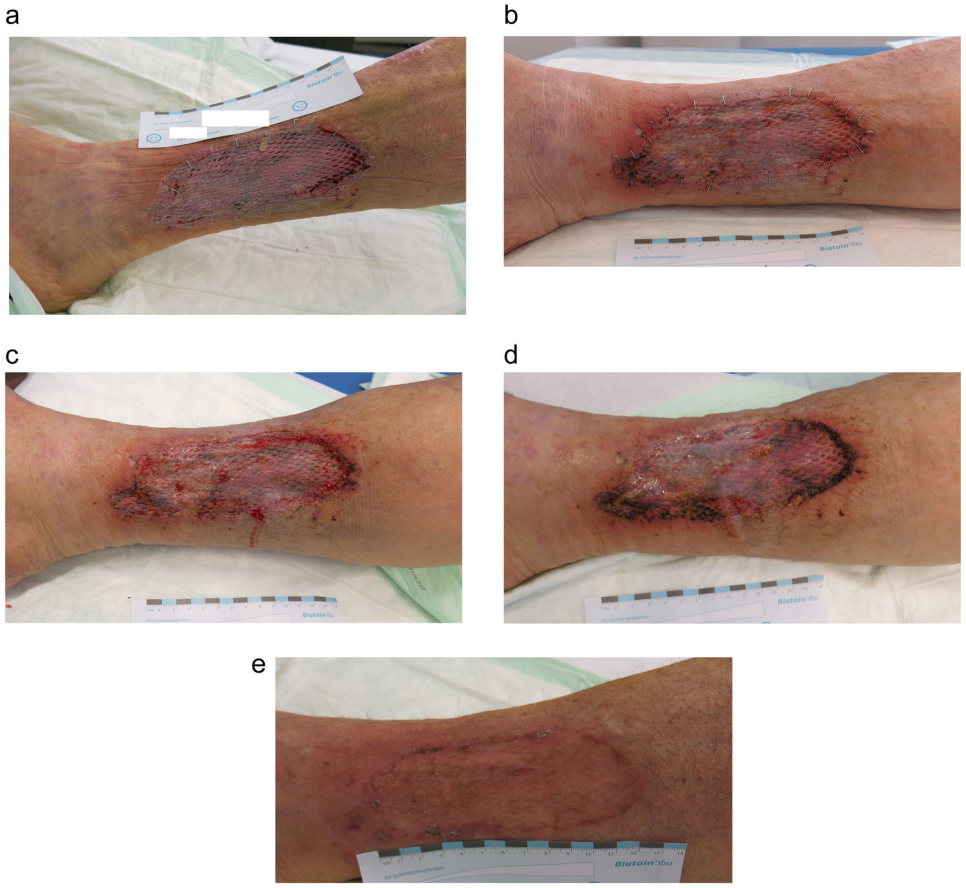

FIGURE 7 | Example of the wound healing process overtime at the recipient site on: (a) Day 5; (b) Day 7; (c) Day 9; (d) Day 12; (e) Day 90.

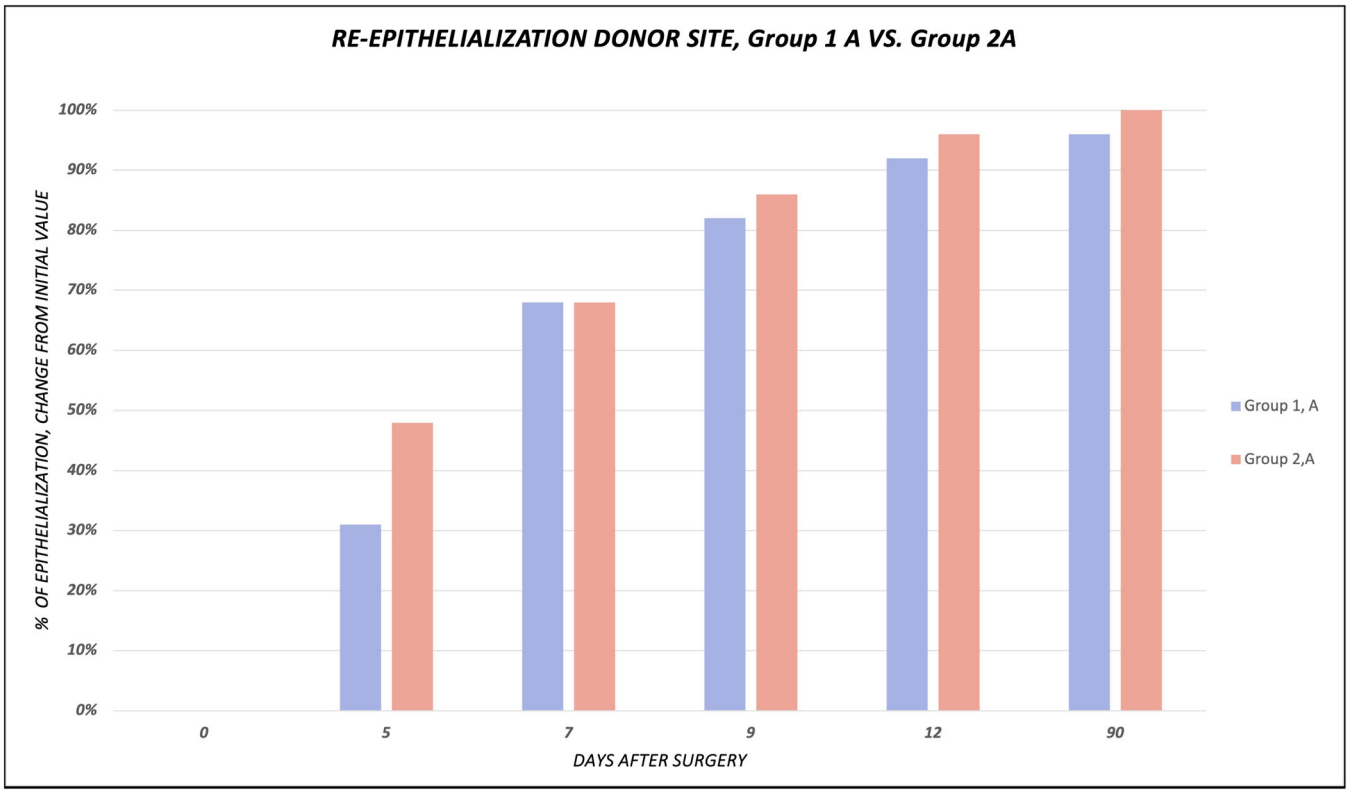

FIGURE 8 | Re-epithelialization of the recipient site, 1A versus 1B.

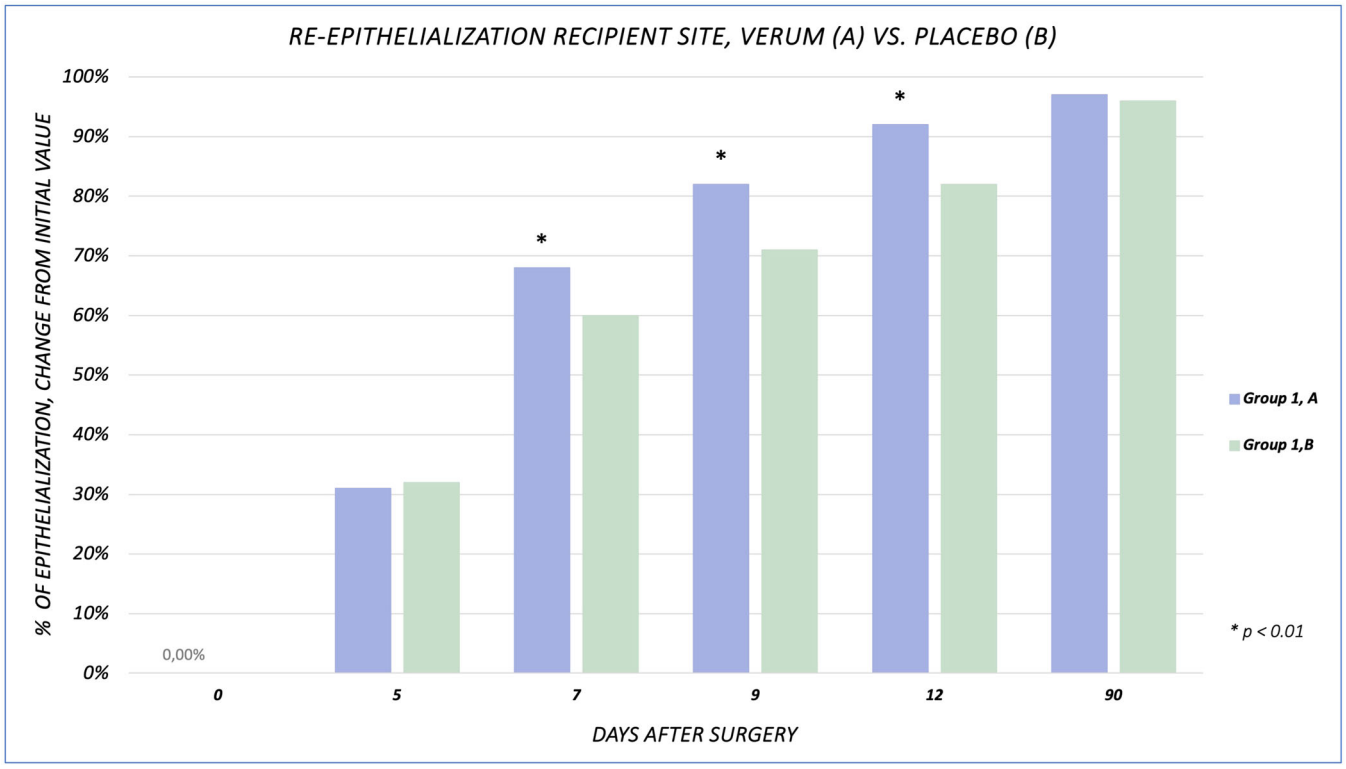

FIGURE 9 | Re-epithelialization of the donor site 1A versus 2A.

FIGURE 10 | Rate of wound infections, 1A versus 1B.

et al. [4] have previously demonstrated that ESWT has an accelerating effect on epithelialization in skin grafts using an animal wound model.

Our prospective randomized trial examined a possible improvement and acceleration of epithelialization by repeated treatment with low-energy extracorporeal shock waves on skin graft donor and recipient sites in patients with acute (donor site) and chronic wounds (recipient site).

Our results show that the application of shock waves has a positive and accelerating effect on wound healing at the donor and at the recipient site.

Patients receiving shock wave therapy (100 impulses/cm^2 at 0.1 mJ/mm^2) on Day 5/7/9 after surgery showed a significantly higher proportion of epithelialization of the wound at both locations compared to the placebo group.

The ESWT/sham treatment was supplemented by standardized wound care. Therefore we used a transparent occlusive foil (V.A.C. drape, 3 M+KCI) at the donor site and a single-layered fat gauze covering at the recipient site. For the first 5 days postoperatively, the recipient site was supplied with a foam overlayer, which was fixed over the skin graft, and a layer of gauze with staple sutures. Diverse wound care strategies are used in the treatment of skin graft donor and recipient areas [18]. Regarding the skin graft donor site, Rennekampff et al. [24] examined different commonly used dressings, including fat gauze, a biosynthetic wound dressing (Biobrane, Smith&Nephew) or an occlusive film dressing (Foil e, Baxter). The median healing time ranged from 14 to 19 days, whereby the Barrier flex film (adhesive transparent foil) treated areas showed an 18% (or 3 days) faster rate of re-epithelialization than the mean of all groups [24].

Despite extensive research, no standardized algorithm for wound treatment of split-thickness skin areas has been shown to be decisively superior.

ESWT is a technology that has been tried and tested for decades and has been used in particular for the treatment of nephrolithiasis and orthopedic diseases [18, 25, 26]. Study results from recent years show that ESWT also has great potential for wound treatment. ESWT has been used for a variety of traditional problematic soft tissue wounds, including burns, diabetic foot ulcers, and chronic wounds [10, 27–30]. In 2005, Schaden and colleagues first reported on the use of ESWT in the treatment of skin lesions. Complete healing was achieved in 74% [2]. In a further study of chronic wounds, the authors reported complete healing in 74.5% of cases [10]. Ottoman et al. [31] examined the use of ESWT in burn wounds. They observed that patients in the ESWT group showed a faster re-epithelization rate (9.6 ± 1.7 days vs. 12.5 ± 2.2 days, $p < 0.00$). Wang et al. [32] also looked at the effect of ESWT on burn wounds in their review published in 2024. The studies cited suggest that ESWT can improve wound healing results by reducing wound size, speeding healing time, and reducing scar formation.

To date, the underlying mechanisms of the effects of ESWT in acute and chronic wounds are not completely understood. It is commonly assumed that the physical qualities of the ESWT cause a biological response in the treated tissues [21, 33]. The application of ESWT increases tissue density and favors the development of radical formation, which in turn can cause cell proliferation and tissue regeneration in the therapeutic target tissue [21]. Wang et al. [10] have done extensive studies trying to find out what triggers the improvement of wound healing. They found that ESWT can increase proliferation and cell density as well as activate angiogenesis-related growth factors, (e.g., eNOS, VEGF, and PCNA) in chronic wounds [10, 34, 35]. Using Doppler imaging and a TcPo2 measurement, these authors also proved that the local blood flow perfusion and TcPO2 were significantly increased after shock wave therapy compared with conservative wound care [10, 36].

Ottomann et al. [18] carried out the first study of extracorporeal shock wave treatment in split skin grafts, choosing a single postsurgery application. They also hypothesize that the faster re-epithelialization of EWST-treated sites is attributed to the anti-inflammatory and proangiogenic properties of the shock waves, in combination with the ESWT-increased release of growth factors and recruitment of fibroblasts [18, 31, 37]. Like Ottoman and colleagues, in our study, we did not analyze inflammatory markers in blood serum or wound fluid to assess the local or systemic response of cytokines or chemokines, but this approach would certainly be interesting for follow-up studies.

It is not entirely clear why, contrary to expectations, no significant differences were detected between the ESWT and sham groups. A possible explanation for the nonsignificant results between Groups 1 and 2 may be low statistical power due to the small number of cases in Group 2. However, since no significant differences between the sham groups were demonstrated, a systemic effect of the shock waves does not seem likely.

Besides an improvement in the re-epithelialization rate we observed a positive effect of ESWT on the occurrence of infections. In our research the shock wave-treated group also showed fewer clinical infections than the sham group. In both, the donor and recipient sites, fewer pathogens were detected in the wound swabs.

A bactericidal effect of extracorporeal shock waves was already described by von Eiff et al. [38] in a study published in 2000. Also, Gerdesmeyer et al. [39] suggested the antibacterial effects of shock waves. From their results, it appears that the antibacterial effect is dependent on energy and impulse number. An exponential bactericidal effect was only observed with over 1000 impulses per treatment [39]. In our research, 5000 pulses per treatment were distributed to the wound, so that the required level was safely surpassed. A possible explanation for the antibacterial effect is based on the impairment of the membrane systems by ESWT, leading to an increased permeability of membranes and cell walls. Thin cell layers of bacteria and intracellular structures get severely injured, and leakage occurs, so that the cells perish [39, 40].

Low-frequency shock wave therapy is a noninvasive procedure with a favorable side effect profile. As is already evident from many other clinical studies examining shock waves, we did not identify any side effects like a local skin reaction or persistent pain [18, 22, 31]. Altogether, we can confirm good tolerability of

shock waves. None of the more than 100 applications had to be discontinued due to side effects. Also, no objectifiable pain was caused by the shock wave treatment, which massively increases the acceptance of the treatment by the patients. Wang et al. [10] discovered that the decreased sensation of pain in the wound area is significantly alleviated by the regulation substance P-positive sensory nerve fibers and calcitonin gene-related peptides by ESWT.

5 | Limitations of the Study

Despite the demonstrated benefits of the ESWT, like faster epithelialization or reduced bacterial colonization at the donor and recipient sites, our study has limitations.

The limited sample size of our study, with only 35 patients, does not allow us to set a standardized treatment protocol for patients with chronic wounds. It would be helpful to investigate in further studies whether and how the frequency of application, the number of pulses delivered, and the timing of therapy influence the wound healing process.

In the treatment of the chronic wounds, we have also ignored comorbidities and wound aetiologies. In further studies, we could evaluate if these factors have an influence on the effects of ESWT and seek to identify certain wounds that are most likely to benefit from ESWT.

6 | Conclusion

A repeated application of ESWT followed by standardized wound care was shown to significantly accelerate the time to re-epithelialization at the skin graft donor and recipient site compared with re-epithelialization time in patients of the sham/placebo group.

In view of the anti-inflammatory and proangiogenic qualities of shock waves, the potential applications in the context of chronic wounds are numerous. Chronic, nonhealing ulcers with exhausted angioplasty vascular improvement or wound healing disorders with disturbed microcirculation (diabetes mellitus, diabetic foot syndrome) are only two possible indications for the use of shock wave therapy.

Author Contributions

Kristina Landscheidt: data curation, validation, writing—original draft, writing—review and editing. **Ahmed Alabdulmohsen:** data curation, formal analysis, investigation, project administration, software, visualization. **Markus Hübscher:** formal analysis, writing—review and editing. **Benjamin Geber:** data curation. **Jochen-Frederick Hernekamp:** supervision. **Ole Goertz:** conceptualization, funding acquisition, methodology, project administration, supervision, validation. All authors have read and approved the final version of the manuscript.

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Conflicts of Interest

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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