Die extrakorporale Stoßwellentherapie in der Behandlung chronischer Wunden in der Wundsprechstunde – Ein Erfahrungsbericht

Treatment of chronic wounds with extracorporeal shockwave therapy – an experience report

C. Moosmann, C. Grabosch, B. Jänigen

ZUSAMMENFASSUNG

Die extrakorporale Stoßwellentherapie (Abkürzung: ESWT) wird seit Beginn der 80er Jahre in der Urologie zur Nierensteinzertrümmerung eingesetzt und hat sich auch in der Orthopädie zur Behandlung von Pseudarthrosen und Sehnenansatzverkalkungen etabliert. In den letzten Jahren wird die ESWT vermehrt in der Behandlung chronischer Wunden eingesetzt. Mit Stoßwellen kann nicht-invasiv Energie in Wunde und Wundumgebung appliziert werden, um eine wundheilungsfördernde Wirkung auszulösen. In der Literatur sind Gefäßneubildungen, lokale Durchblutungsförderung, Ausschüttung von Wachstumsfaktoren, Fibroblastenstimulation, antibakterielle Effekte und die Unterdrückung von pro-inflammatorischen Prozessen beschrieben. In der Praxis werden die radial unfokussierte- und die linear fokussierte ESWT zur Behandlung chronischer Wunden eingesetzt. Eine erste randomisierte Studie von Moretti et al. 2009 gibt Hinweise, dass die Wundheilung durch ESWT beim diabetischen Fußsyndrom positiv beeinflusst werden kann, allerdings ist das Evidenz-level gegenwärtig noch niedrig. In der Wundsprechstunde der Klinik für Allgemein- und Viszeralchirurgie der Uniklinik Freiburg wurden seit 2010 chronische Wunden bei über 600 Patienten mit ESWT behandelt. Dieser Artikel soll die Erfahrungswerte aus dem praktischen Alltag mit der radial unfokussierten- und der linear fokussierten ESWT in der Behandlung chronischer Wunden wiedergeben.

SCHLÜSSELWÖRTER

ESWT, extrakorporale Stoßwellentherapie, radiale umfokussierte ESWT, rESWT, lineare fokussierte Stoßwellentherapie, Stimulation von chronischen Wunden

ABSTRACT

Extracorporeal shockwave therapy has been used for lithotripsy procedures in urology since the 1980s and has also established itself as a method to treat osseous non-union and tendon calcifications. In recent years, ESWT has also begun to be used to treat chronic wounds. The noninvasive energy of shockwaves is applied to the wound and wound environment to trigger healing processes. Angiogenesis, improved local blood circulation, release of growth factors, fibroblast stimulation, antibacterial effects and suppression of pro-inflammatory processes have all been reported following ESWT. In clinical practice, radial unfocused and linear focused extracorporeal shockwaves can both be used to treat chronic wounds. A first randomized trial by Moretti et al. in 2009 provided evidence that ESWT can positively affect wound healing in diabetic foot syndrome; however, the level of evidence was low. More than 600 patients with chronic wounds have been treated with ESWT in the Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital since 2010. This article describes our experience with radial unfocused and linear focused shockwaves to treat chronic wounds.

KEYWORDS

ESWT, extracorporeal shockwave therapy, radial unfocused ESWT, rESWT, linear focused shockwave therapy, stimulation of chronic wounds

Introduction

Shockwaves are a special form of acoustic waves which can be used to apply physical energy to a body, e.g. the human body. When the energy is generated, there is a very steep short increase in pressure which occurs in the space of just a few nanoseconds followed by a gradual, slower drop in pressure. As the shockwave dies away, a brief negative pressure (suction effect) is created, the so-called “pulling phase” (s. Fig. 1). Depending on the intensity, the entire shockwave takes between a few microseconds and a maximum of a few milliseconds. After approximately 1 second, the ambient pressure in the treated tissue will have returned to normal again [1].

Shockwaves are a well-known physical phenomena which occur in nature (e.g. following a lightning strike), where they are often experienced by human ears as a loud bang. The energy which shockwaves can generate is visible in the bursting of windows following the detonation of explosives or the descent of an avalanche after an explosion in the mountains.

The idea of using shockwaves for medical treatment was first proposed in the 1950s.

Christian Moosmann
Wundfachkraft, BBA
Christine Grabosch
Dr. med. Bernd Jänigen
Universitätsklinikum Freiburg,
Klinik für Allgemein- & Viszeralchirurgie,
Hugstetterstr. 55, 79106 Freiburg
E-Mail: christian.moosmann@uniklinik-freiburg.de

In 1951 Frank Rieber applied for a patent in the USA for an electrohydraulic shockwave unit to treat brain tumors. In 1966 Dornier (a company domiciled in Friedrichshafen, Germany) accidently discovered during experiments with high-speed projectiles that shockwaves can pass through the human body without causing direct damage [2]. Since that time, research has been carried out into shockwaves and their applications. The first disintegration of kidney stones using ESWT was performed in 1980. The discovery that shockwaves can be used not just to destroy certain types of tissue such as renal calculi and gallstones but can also trigger other biological effects if the intensity of the shockwave is adjusted appropriately, has continually expanded the range of applications for ESWT. In addition to the treatment of kidney stones [3] and sialoliths [4] shockwaves are also used in orthopedics to treat non-union [5], calcific tendonitis [6], and pain arising from enthesitis such as calcaneal spurs or tennis elbow [7]. Other clinical areas of application include disorders of cardiac circulation [8], erectile dysfunction [9] and cellulite [10]. The treatment of chronic wounds is a relatively new application area for ESWT [11].

The Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital has continually used ESWT since 2010. Our experience with the use of ESWT to treat chronic wounds is described below.

Types of extracorporeal shockwave therapy

When treating wounds, the shockwave is generated outside the body and the treatment is therefore referred to as extracorporeal shockwave therapy (abbreviated to ESWT). The shockwave can be generated by an underwater spark discharge, by electromagnetic, electro-pneumatic, electrohydraulic, ballistic, piezo-electric, pulsed laser and by micro-explosions. Ballistic and piezo-electric ESWT units are mainly used to treat wounds. The classification of the energy flux density of shockwaves as defined by Rompe et al. [12] is as follows:

- low energy: up to 0.08 mJ/mm²
- medium energy: up to 0.28 mJ/mm²
- high energy: more than 0.28 mJ/mm²

Low to medium energy flux densities are used to treat chronic wounds.

Radial unfocused shockwave therapy

Radial unfocused shockwaves (rESWT) are generated by a pneumatically driven projectile inside a cylinder which hits a metal die at high speed in the unit's applicator. The metal die which transfers the shockwave to the skin. The energy is unfocused (s. Fig. 2) when it is released into the tissue, which is why these pressure waves are referred to as unfocused shockwaves. The highest energy with rESWT always occurs at the point of contact of the skin with the applicator, after which the pressure wave is then absorbed by the skin. Because of the scattering of the shockwave, rESWT is particularly suited to treat superficial structures, e.g. the skin. By definition, because the wave is not very steep, it is not a shockwave in the true sense of the word but a pressure wave [13]. The Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital used a rESWT Swiss Dolorclast unit from EMS for a period of 6 months. It has an ESWT power+ handpiece with 36 mm head; and an energy flux density of 0.07 mJ/mm², so the generated pressure waves are low energy. The unit has been approved to treat wounds since 2010 (EMS manufacturer's data).

rESWT is generated ballistically, which affects the noise levels when the unit is operated. Talking to patients during procedures is only possible using a very loud voice. Because of the pneumatic-ballistic generation of the pressure wave, the handpiece has to be serviced after it has been triggered 500,000 times. In practice, this corresponds to an average of around 600 treatments. Because of the short, hard thrust of the applicator, the authors are of the opinion that rESWT should not be applied directly to bone as it is conceivable that direct contact between metal and bone could result in injury to the bone.

Linear focused extracorporeal shockwave therapy

Linear focused extracorporeal shockwaves are generated piezo-electrically in a concave handpiece (s. Fig. 3). Each individual piezo crystal generates a pressure wave at the same time, all of which meet up at a focal point to create the shockwave. The spherical concave shape creates a point-focused shockwave in the focus, which is suitable to treat small areas. Wider, flatter, laterally concave shapes create a linear focus, which is suitable to treat larger areas, for example the skin or wounds. In contrast to rESWT, the area where the shockwave is generated (focus) lies outside the handpiece, allowing

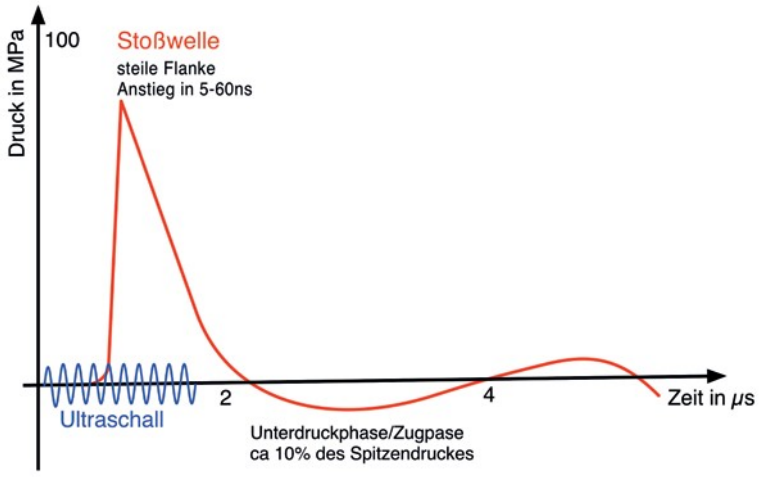

Figure 1
Schematic representation of a shockwave (red) compared to ultrasound (blue).

the depth where the shockwave develops to be varied. The depth is determined using spacers (gel pads) of different heights which are placed in the applicator. As the gel pads are interchangeable, it is not necessary to exchange the applicator. Since 2012, the Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital has used a linear extracorporeal piezo-wave shockwave unit (Richard Wolf) and a linear FBL10 x 5G2 handpiece which has an energy flux density of 0.018–0.16 mJ/mm^2, i.e., a medium to low energy flux density. According to the manufacturer, the focal zone of the handpiece is 46 mm long and 4 mm wide, allowing the piezo-electrically generated shockwaves to be applied over larger surfaces in a shorter period of time. When treating wounds, the Outpatient Wound Clinic uses the 0 gel pad. This results in the application of an energy flux density of 0.16 mJ/mm^2 at skin level. The level of noise during applications is 65 dB (A) (manufacturer's data from ELvation), which is much quieter than the noise levels generated with rESWT; medical staff can talk to patients during procedures without difficulty. The applicator needs to be serviced after 5 million shockwave pulses, which corresponds to an average of 6000 treatments.

Mode of action and evidence

Shockwave energy is transformed through direct or indirect effects into mechanical, thermal or chemical energy [14].

The understanding of how shockwaves work has largely been obtained from animal and in vitro testing. The clinical relevance of these findings in terms of their efficacy when treating people with chronic wounds has not yet been adequately proven.

The effects of shockwave therapy described in the literature include:

- Neovascularization and improvement of local blood flow [15]
- Growth factor expression [16]
- Fibroblast stimulation [17]
- Antibacterial effects [18]
- Suppression of pro-inflammatory processes [19]

In the S3-guideline on the local therapy of chronic wounds in high-risk patients with chronic venous insufficiency (CVI), peripheral arterial occlusive disease (PAOD) or diabetes mellitus, the evidence level on the use of ESWT to treat chronic wounds was classified as low [20]. Double-blinded, randomized, controlled studies on the use of ESWT to treat chronic wounds are currently not available. There is one randomized (but not double-blinded) controlled study of 30 patients by Moretti et al. on neuropathic wounds in patients with diabetic foot syndrome. The study reported that wound healing was faster in the ESWT group (ESWT group: 2.97 mm^2/day; control group: 1.30 mm^2/day) [21].

Practical experience in the Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital

Indications to use ESWT to treat wounds (manufacturer's data):

- Chronic wounds caused by diabetic foot syndrome, neuropathic ulcerations, venous ulcers, pressure ulcers, etc.

Contraindications to treat wounds with ESWT (manufacturer's data)

- Pregnancy
- Untreated infection in or around the wound
- Necrosis
- Malignant tumor at the wound site
- Clotting disorders
- Oncologic disease with thrombocytopenia
- Pacemaker implant
- Applications in the vicinity of the lungs or thorax.

There is still no data available on the interaction between shockwaves and metal implants. For this reason, the above-listed contraindications were expanded in-house in the Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital to avoid potential complications such as hemorrhage or bone defects as follows:

Figure 2
Radial unfocused, extracorporeal shockwave (rESWT): scattered (radial) radiation.

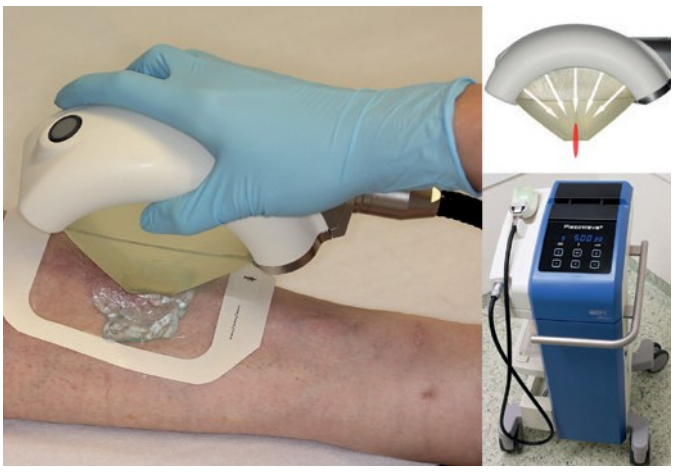

Figure 3
Linear focused, extracorporeal shockwave: piezo-electrically generated energy.

- Freshly implanted vascular stent in the vicinity of the wound (ESWT treatment only after clearance by an angiologist).
- Metal implant (e.g. arthrodesis) in the vicinity of the wound (ESWT treatment only after clearance by the treating orthopedist)
- Only applies to radial unfocused ESWT: projecting exposed bone (e.g. in a large deep wound at the calcaneus) where the pressure applicator could come into direct contact with bone
- Cause of wound is unknown/has not yet been diagnosed and/or wound treatment has not yet commenced.

Possible side effects of ESWT described in the literature include hematoma, swelling and pain during treatment, and redness due to irritation of the skin.

More than 600 patients with chronic wounds have been treated with ESWT in the Outpatient Wound Clinic of the General and Visceral Surgery Department since 2010. Up to now, no cases of internal bleeding, swelling or skin irritations have been reported in these patients. Some skin redness in the vicinity of the wound has been reported in the context of hyperemia (s. Fig. 4) which developed after ESWT. In cases where this effect occurred, patients reported that the area around the wound felt warmer and that they experienced a tingling sensation in the area treated with ESWT. We recommend keeping the intensity low at the start of treatment when treating pain-sensitive wounds and only gradually increasing the intensity over the course of treatment.

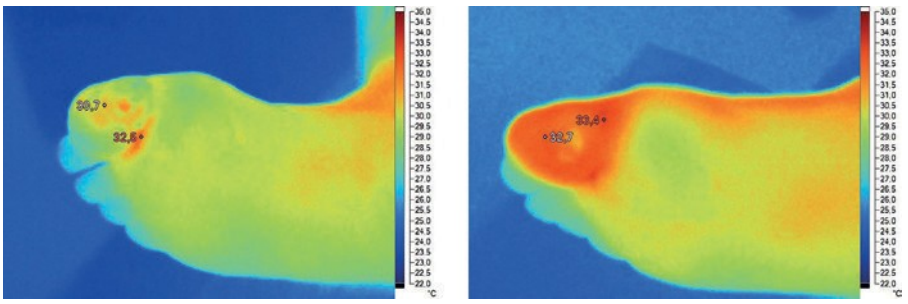

Figure 4
Temperature increase (hyperemia) in tissue 5 min. after shockwave application; energy = 0.16 mJ/mm², 1000 pulses, 8 Hz, focused linear ESWT in a patient with diabetic foot syndrome and an ABI of 0.9.

ESWT procedures

The physician is responsible for the diagnostic evaluation, for obtaining the patient's informed consent, performing the first application, deciding on the intensity of treatment (frequency, pulse intensity, number of pulses) and the area to be treated. The area at and around the wound is then prepared for treatment.

The following items are additionally required to carry out an ESWT application:

- Unsterile items: ultrasound gel, wipes for cleaning, surface disinfectants to clean the shockwave applicator
- Sterile items: gauze compresses to clean the wound, hydrogel (bubble-free) to fill the wound, foil to cover the wound and the edge of the wound

The individual steps of the procedure are shown in Figure 5. Special positioning of the patient is not required. ESWT can be applied when the patient is sitting or lying down; however, it is important to avoid muscle tension around the wound. The area requiring treatment must be clearly visible, easily reached by the shockwave applicator and should not put any strain on the therapist's back. The wound must be clean with no necrosis: it may therefore be necessary to carry out debridement before starting treatment (1). The wound is then filled with (bubble-free) hydrogel up to the level of the skin (2) and covered with sterile foil. It is important to ensure there are no

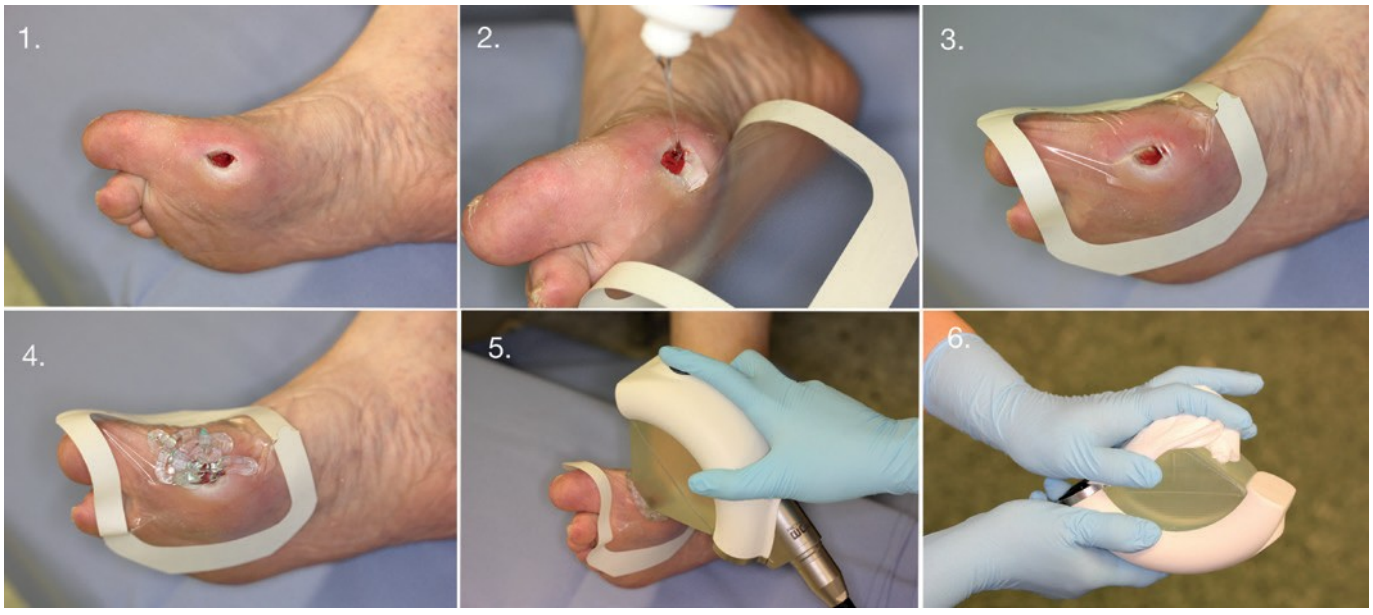

Figure 5
ESWT procedure. The individual steps 1–6 are explained in the text.

bubbles between the gel and the foil (3). To prevent contamination/direct contact between the applicator head and the skin of the patient, the foil should completely cover the area requiring treatment direct contact. Ultrasound gel is used to ensure that coupling between the shockwave applicator is free from bubbles (4). The applicator is placed on the site and the pre-set number of pulses at the required frequency and pulse intensity are applied (5). The applicator is slowly moved across the wound and the edges of the wound during treatment. The application is stopped after the planned number of pulses has been applied, the head of the applicator is then cleaned (6) and the various aids (ultrasound gel, foil, hydrogel) are removed. The wound is cleaned again and the wound is dressed.

The average time required for preparation, application and final wound cleaning is 5 minutes. This means that ESWT can be used to treat large numbers of patients in a short time, even when the available space (rooms) is limited.

The use of ESWT to treat chronic wounds is currently not included in the list of services covered by statutory health insurance in Germany. Whether or not private health insurance companies cover this form of treatment varies and decisions are made on a case-by-case basis in each individual case. Focused shockwave treatments are covered by the statutory scale of fees for physicians in Germany (GOÄ) no. 1800 and radial unfocused shockwave treatments by GOÄ no. 302.

Initial retrospective analysis for the Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital

To obtain an initial assessment on the use of ESWT in the Outpatient Wound Clinic, the wound healing of patients treated over a period of 6 months (August 2010–January 2011) was retrospectively evaluated. A total of 89 patients with chronic wounds were treated with rESWT in this period. 49 patients were excluded from the final evaluation as they received other additional treatments to improve healing, for example revascularization, or their treatment was discontinued (the patient was transferred to a different hospital or the patient died). A total of 40 patients with different chronic wounds (healing of an abdominal wound by intention [n=2], pilonidal sinus [n=2], sacral pressure ulcers [n=2], venous ulcers [n=12], diabetic foot syndrome [n=22]) were included in the analysis. The wounds of all patients had persisted for least 8 weeks, the cause of the wound was known, and the wound had been treated for at least 4 weeks. Wound diameters ranged from 0.4 cm^2 to 86 cm^2.

During the observation period of 4 weeks, no changes were made to local therapy or treatment of the cause of the wound. In two sessions per week, an average of 1000 pulses/10 Hz were administered to the wound and the area around the wound with a rESWT unit. Changes to the wound were recorded prior to, during and after treatment using software-based documentation, changes were measured by planimetric photography, and pain was assessed using the VAS scale.

None of the patients required any analgesia for rESWT. The maximum change to the VAS score during treatment was two points. Patients reported that they experienced the noise of the unit during operation as more unpleasant than any pain.

29 patients showed no change in the speed of wound healing (decrease in wound area) compared to treatment received prior to ESWT. In 23 patients of this cohort who did not respond to rESWT, the therapy used to treat the cause of the wound was found to be insufficient. Treatment of these patients was changed after the end of the observation period (surgical intervention [n=8], optimization of decongestive therapy [n=8], additional pressure relief for the foot [n=5], revascularization therapy [n=2]).

In 11 patients (diabetic foot syndrome [n=8], pressure ulcers [n=3]), wound healing accelerated following rESWT; the wounds of 4 patients (wound area <0.5 cm^2, all with diabetic foot syndrome) healed spontaneously after 2 rESWT applications (no healing prior to rESWT). The formation of granulation tissue over exposed tendons was particularly noteworthy (n=3; one example is shown in Fig. 6 a–d).

The most significant positive effects (i.e., accelerated decrease of the area and depth of the wound) were observed in patients with diabetic foot syndrome compared to patients with other underlying disease, (one example is shown in Fig. 7 a–c).

Randomized controlled studies will be necessary to obtain reliable data about the impact of ESWT on wound healing.

Figure 6
a: Mixed venous ulcer in patient s/p trauma of the heel 3 weeks previously and CVI + POAD stage II (ABI 0.7). Treatment consisted of moist wound treatment appropriate to the stage of wound healing, class 2 padded compresses, special shoes and surgical debridement b: In the 23rd week of therapy: surgical debridement and ESWT started. c: In the 26th week of therapy: 6th session of ESWT, tendon now almost covered with granulation tissue. d: In the 28th week of treatment: wound status after 11 sessions of ESWT.

Figure 7
Patient aged 86 years old, diabetic foot syndrome, ulcer caused by too tight shoes. a: Wound at initial presentation showed no tendency to improve since 4 weeks. Joint was initially exposed and the bone affected. Oral antibiosis was initiated with moxifloxacin 400 mg/day for 4 weeks, moist wound treatment was applied as appropriate to the stage of wound healing, b: Start of granulation and retraction at the edges of the wound in the third week of treatment after 2 sessions of ESWT. c: Healing after 3 sessions of shockwave therapy over a period of 12 weeks.

Conclusions for clinical practice

The use of ESWT to treat chronic wounds is a relatively new therapeutic field. It is now an established additional therapeutic option of the Outpatient Wound Clinic of the General and Visceral Surgery Department of Freiburg University Hospital, where it is used to promote wound healing of chronic wounds, particularly in patients with diabetic foot syndrome. Because of the low cost, the short amount of time required, and the uncomplicated application, ESWT can be easily integrated into the clinical routine of an outpatient wound clinic. The next step in the scientific evaluation of ESWT to treat chronic wounds must consist of randomized studies to determine the effects and the selection of patients more precisely.

Conflict of Interest

The authors state that they had no conflict of interest as defined by the guidelines of the International Committee of Medical Journal Editors (ICMJE).

References

1. Ueberle F: Der Einsatz von Stoßwellen in der Medizin, R. Kramme: Medizintechnik: 533–564. Springer-Verlag 2011.
2. Hepp: Überblick über die Entwicklung der Stoßwellenlithotripsie, September 1984. Dornier Medizintechnik 1984, Friedrichshafen.
3. Chaussy: Berührungsfreie Nierensteinzertrümmerung durch extrakorporal erzeugte, fokussierte Stoßwellen. S. Karger Verlag 1980, Basel.
4. Iro H, Nitsche N, Schneider HT, Ell C: Extracorporeal shockwave lithotripsy of salivary gland stones. Lancet 1989; 2: 115.
5. Valchanou VD, Michailov P: High energy shock waves in the treatment of delayed and nonunion of fractures. Int Orthop 1991; 15: 181–184.
6. Loew M, Jurgowski W: [Initial experiences with extracorporeal shockwave lithotripsy (ESWL) in treatment of tendinosis calcarea of the shoulder]. Z Orthop Ihre Grenzgeb 1993; 131: 470–473.
7. Heller KD, Niethard FU: 1998. [Using extracorporeal shockwave therapy in orthopedics – a meta-analysis]. Z Orthop Ihre Grenzgeb 1998; 136: 390–401.
8. Nishida T, Shimokawa H, Oi K., Tatewaki H, Uwatoku T, Abe K, Matsomoto Y., Kajihara N, Et M, Matsuda T, Yasui H, Takeshita A, Sunagawa K: Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. Circulation 2004; 110: 3055–3061.
9. Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I: Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. Eur Urol 2010; 58: 243–248.
10. Knobloch K, Joest B, Krämer R, Vogt PM: Cellulite and focused extracorporeal shockwave therapy for non-invasive body contouring: a randomized trial. Dermatol Ther (Heidelb) 2013; 3: 143–155.
11. Schaden W, Thiele R, Kölpl C, Pusch M, Nissan A, Attinger CE, Maniscalco-Theberge ME, Peoples GE, Elster EA, Stojadinovic A: Shock wave therapy for acute and chronic soft tissue wounds: a feasibility study. J Surg Res 2007; 143: 1–12.
12. Rompe JD, Kirkpatrick CJ, Küllmer K, Schwitalle M, Krischek O: Dose-related effects of shock waves on rabbit tendo Achillis. A sonographic and histological study. J Bone Joint Surg Br 1998; 80: 546–552.
13. Auersperg: Physik und Technik der ESWT. Leitlinie der Deutschsprachigen Internationalen Gesellschaft für Extracorporale Stoßwellentherapie 2012. S.14–15. http://www.digest-ev.de/leitlinien/ accessed 01.02.2016.
14. Gerdesmeyer L, Maier M, Haake M, Schmitz C: Physical-technical principles of extracorporeal shockwave therapy (ESWT). Orthopade 2002; 31: 610–617.
15. Yan X, Zeng B, Chai Y, Luo C, Li X: Improvement of blood flow, expression of nitric oxide, and vascular endothelial growth factor by low-energy shockwave therapy in random-pattern skin flap model. Ann Plast Surg 2008; 61: 646–653.
16. Link KA, Koenig JB, Silveira A, Plattner BL, Lillie BN: Effect of unfocused extra-corporeal shock wave therapy on growth factor gene expression in wounds and intact skin of horses. Am J Vet Res 2013; 74: 324–332.
17. Berta L, Fazzari A, Ficco AM, Enrica PM, Catalano MG, Frairia R: Extracorporeal shock waves enhance normal fibroblast proliferation in vitro and activate mRNA expression for TGF-beta1 and for collagen types I and III. Acta Orthop 2009; 80: 612–617.
18. Gerdesmeyer L, Von Eiff C, Horn C, Henne M, Roessner M, Diehl P, Gollwitzer H: Anti-bacterial effects of extracorporeal shock waves. Ultrasound Med Biol 2005; 31: 115–119.
19. Sukubo NG, Tibalt E, Respizzi S, Locati M, D'Agostino MC: Effect of shock waves on macrophages: A possible role in tissue regeneration and remodeling. Int J Surg 2015; 24: 124–130.
20. Wolff R, Gregor S: Stoßwellentherapie. AWMF S3-Leitlinie 091-001 Lokaltherapie chronischer Wunden bei den Risiken CVI, PAVK und Diabetes mellitus. 2012; S215. http://www.awmf.org/leitlinien/detail/ll/091-001.html accessed 01.02.2016.
21. Moretti B, Notarnicola A, Maggio G et al.: The management of neuropathic ulcers of the foot in diabetes by shock wave therapy. BMC Musculoskeletal Disorders (2009) 10: 54–61.