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REVIEW ARTICLE

Efficacy and Theoretical Basis of Low-Intensity Shock Wave Therapy in the Management of Different Forms of Wound Healing: Own Experiences and a Review of the Literature

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ABSTRACT

Objectives: Wound healing is a complex process that involves inflammation, proliferation, and tissue remodeling to restore damaged tissue integrity. Chronic wounds and ulcers, with incomplete healing and a high risk of recurrence, pose significant challenges to conventional treatments. Extracorporeal Shock Wave Therapy (ESWT) has emerged as a promising wound healing therapy.

Material and Methods: In this review, we summarize the current state of ESWT for wound management based on personal experiences and a comprehensive literature review. Among 184 data sources from 1990 to 2022, 19 relevant publications were identified, including systematic reviews, meta-analyses, and clinical studies applying focused and radial ESWT for various wound types.

Results: ESWT's mechanism of action involves generating focused or radial shock waves, stimulating tissue repair through angiogenesis, fibroblast proliferation, and collagen expression. Data extracted from systematic reviews showed positive outcomes for wound healing, healing rate, and wound area reduction for chronic wounds such as diabetic foot ulcers, pressure ulcers, and venous ulcers. Studies on radial ESWT revealed similar positive effects in pain reduction and wound healing, with no serious adverse events reported. ESWT exhibited a well-tolerated safety profile, with minor and transient side effects such as reddening, swelling, and mild pain at the treatment site. Comparatively, Hyperbaric Oxygenation Therapy (HBO), an alternative treatment option, showed unique adverse events not observed with ESWT. Our evaluation confirms ESWT as a safe and effective treatment for wound management, offering hope for patients with chronic wounds or ulcers.

Conclusions: ESWT presents a compelling non-invasive and safe treatment option for various wound healing challenges, improving outcomes for patients with chronic wounds and ulcers. This review highlights the potential of ESWT as an advanced wound healing therapy, complementing conventional approaches. Further studies should explore potential differences between focal and radial ESWT for wound healing.

Keywords: Extracorporeal shock wave therapy, radial shock waves, focused shock waves, Wound healing, Diabetic foot ulcers, venous leg ulcers, pressure ulcers, Fournier Gangrene, Stem cell activation

Introduction

Wound healing is a complex process involving inflammation, proliferation, and tissue remodeling, which ultimately restores the integrity of damaged tissue. While most wounds close within weeks, disruption of the healing process can lead to chronic wounds or ulcers, characterized by incomplete or prolonged healing with a high risk of recurrence. Various factors, including local causes like infection and tissue hypoxia, systemic diseases like diabetes mellitus, and certain medications, contribute to the development of chronic wounds such as diabetic ulcers, venous leg ulcers, or pressure ulcers (1-3).

Managing chronic wounds requires addressing the primary cause, such as controlling blood sugar levels in diabetics or vascular surgery for patients with venous or ischemic vascular disease. Additionally, treatments involve removing necrotic or infected tissue, maintaining a moist wound environment, wound cleansing, and proper diet. Compression therapy is particularly relevant for venous leg ulcers as it improves venous return. Despite these measures, many chronic wounds fail to heal or recur, prompting the search for new effective treatment options (4).

Among the strategies for chronic wound treatment, extracorporeal shock wave therapy (ESWT) has shown promise. Initially used for treating renal and ureteral calculi (5,6), ESWT's success in urology prompted exploration in other areas, including wound healing (7-9). Its primary mechanism of action is believed to be improving tissue circulation by stimulating the production of energy-rich nitric oxide (NO), leading to reduced muscle rigidity and improved biomechanical functioning, enhancing mobility and self-perception. ESWT can also activate key factors involved in connective tissue repair, such as fibroblasts that increase proliferation and expression of essential factors like TGF-beta-1 and collagen types I and III (10-14).

Recent trials using ESWT for wound healing after Fournier's gangrene suggest its potential to stimulate local stem cells (15). As researchers focused on harnessing ESWT's capabilities, we aim to summarize the current state of art in ESWT for wound management based on personal experience and a review of the literature.

By understanding ESWT's efficacy and theoretical basis, we hope to shed light on its potential as an advanced wound healing therapy. This article provides valuable insights into how ESWT can complement existing wound management approaches, offering new hope for patients with chronic wounds or ulcers.

Material and Methods

Literature search, selection of relevant publication, data extraction, assessment of methodological quality and appraisal has been performed according to the search strategy and predefined criteria according to International Organization for Standardization and Biological evaluation of medical devices (16). After screening and appraisal of 184 new data sources identified in the literature search for the update period (1990-2022), 14 new primary clinical data studies and 5 state-of-the-art data publications were included as relevant, and thus 165 studies excluded. The 19 relevant publications comprised 1 guidance document, 4 systematic reviews/meta-analyses, 11 clinical studies applying focused ESWT, as well as 3 publications reporting on the use radial ESWT. The latter three publications represent off-label use and were included for assessment of related implication. At our four centers, we had different personal experiences using focused ESWT for different types of wound healing problems, such as diabetic and venous ulcers, and Fournier`s gangrene (9,11,15). This allowed us to illustrate the results of the literature review with relevant images.

Results

TECHNICAL BACKGROUND

FOCUSED SHOCK WAVES

Shock waves are mechanical, acoustic waves that are characterized by high pressure amplitudes and a steep increase in pressure. Unlike usual ultrasound that consists of periodic oscillations with limited bandwidth, shock waves are represented by a single, mainly positive pressure pulse that is followed by comparatively small tensile wave components. The duration of the positive pressure pulse is only about 0.3-0.5 µs, the duration of the total pulse is about 3x the amount, thus about 1-2 µs. Such a pulse contains frequencies ranging from a few kHz to over 10 MHz (16).

Focused shock waves can be generated by means of electrohydraulic, piezoelectric or electromagnetic shock wave generators. The method of electromagnetic shock wave generation is based on the physical principle of electromagnetic induction. Electromagnetic devices may use a cylindrical coil, focusing the shock waves by means of a rotation paraboloid.

The method of electrohydraulic shock wave generation is based on a spark that is initiated due to high voltage applied between two electrode tips placed at the focal point of a parabolic reflector. The spark generates a spherical shock wave by rapid vaporization of the water between the tips.

Due to the comparatively large aperture of the shock wave sources relative to the focus size, the shock wave energy can be introduced into the body over a large coupling area. Most of the shock wave energy is only released in the relatively small focal zone inside the body.

RADIAL SHOCK WAVES

The method of action of a ballistic pressure wave system is based exactly on the linear impulse-momentum principle deduced from Newton's law. Pressure waves have wavelengths of between 0.15 and 1.5 m. First of all, a projectile is accelerated with compressed air (similarly to an air gun), to a speed of several meters per second (approx. 5 to 25 m/s, far below the sound velocity in water of about 1500 m/s) and then abruptly slowed down by hitting an impact body (transmitter). When the projectile strikes the impact body, some of its kinetic energy is transmitted to the impact body. The impact body then performs a translational movement over a short distance (typically < 1 mm) at slower speed (typically < 1 m/s) until the coupled tissue or the handpiece decelerates the impact body movement. The motion of the impact body is transmitted to the tissue at the point of contact, from where it propagates divergently in the form of a "radial" pressure wave. Typical peak pressures of radial pressure waves are about 0.1 to 1 MPa (17).

MECHANISM OF ACTION OF ESWT

Based on early studies of Haupt et al. in 1992 (8), several animal studies have been performed to evaluate the potential of ESWT for the treatment of wounds. In mouse and rat burn wound models, ESWT was found to induce angiogenesis and to enhance the percentage of wound closure, the re-epithelialization rates, blood flow, and the number of rolling and sticking leukocytes, suggesting improved metabolism (18). It was further reported that repeated ESWT application accelerates angiogenesis in burn wounds significantly more than a single application (19). The angiogenic effects of ESWT were confirmed in a murine skin graft model, also showing increased expression of VEGF-A and other cytokines involved in angiogenesis (20). In diabetic wound models, it could be demonstrated that ESWT reduces wound size and inflammatory reaction, while increasing the wound breaking strength and the number of fibroblasts and collagen fibers at the wound site (21,22). Finally, ESWT has been found to have potential in the rescue of ischemic skin flaps, as it reduced the necrotic area and the number of apoptotic cells in a rat skin flap model. ESWT also substantially increased the modulation of oxygen radicals, attenuation of leukocyte infiltration, decrease in tissue apoptosis, and recruitment of skin fibroblasts (23). Recent trials using ESWT for improvement of wound healing after Fournier`s gangrene indicate also a stimulation of local stem cells (15).

Performance data identified from systematic review literature

TREATMENT PARAMETERS

The reviews reported on the use of ESWT in the treatment of the indications of acute and chronic wounds, including burns, post-burn scars, venous ulcers, pressure ulcers, decubitus ulcers, diabetic foot ulcers, and gangrene, primarily affecting the limbs and extremities. most treatments with ESWT involved multiple treatment sessions and there was a range of values applied for the technical parameters of the ESWT devices (Table 1).

Table 1: Parameter ranges for Extracorporeal Shock Wave Therapy of wounds identified from the reviewed literature

Indication	Energy flux density [mJ/mm²]	Frequency [Hz]	Impulses [*pulses*/cm²]	Sessions
Burns / burn scars [27]	*0.05-0.23*	4	*100*	1-6
Burn scars [22]	*0.03-0.25*	NR	*100 -600*	1-10
Chronic wounds (CWLE) [25]	*0.03-0.25*	NR	*100-600*	1-10
Diabetic foot ulcer [20,21,28]	*0.03-0.23*	4-5	*100-500*	3-20
Mixed Ulcers (PU/VU/DFU) [23,24]	*0.03-0.27*	4-5	*25-500*	1-10
Overall range for all indications	*0.03-0.27*	*4-5*	*25-2000*	*1-30*

Abbreviations: CWLE: Chronic Wounds of the Lower Extremity; DFU: Diabetic Foot Ulcer; NR: Not reported; PBS: Post Burn Scars; PU: Pressure Ulcers; VU: Venous Ulcer

CLINICAL OUTCOME

Performance data reported in all eleven systematic reviews supported an additional positive clinical effect of the ESWT intervention when used in conjunction with standard wound care (Table 2). Outcomes were assessed for healing of wounds, proportion of completely healed wounds, healing time, healing rate, reduction wound area/healed wound area, as well as number of unresponsive wounds, recurring wounds and infection rates. Outcomes for the treatment of burn scars included assessment of specific performance, such as pain, pruritis, scare appearance score (VSS), scar thickness, scar elasticity and trans-epidermal water loss (24,25).

Table 1: Overview of relevant systematic reviews and meta-analyses of Extracorporeal Shock Wave Therapy for wound healing

a) Burns

Reference	Aim	Study details population / indications	Intervention(s)	Outcomes	Authors conclusions
Aguilera-Sáez J, et al. 2020[27]	To review the literature for published evidence on the use of ESWT for the treatment of acute burn patients and its sequelae	• 14 studies (5 RCTs) Indications: • Acute burns • Post burn scars • Post-burn heterotopic ossification	• ESWT + Standard Care (14 studies) • Standard Care (10 studies) *ESWT protocols:* *100 pulses/cm², 0.05-0.23mJ/mm², 4Hz, 1-6 sessions*	• VSS • TTE • Scar thickness • Pain • Pruritus Follow-up: NR	ESWT seems to be a promising tool in this field and therefore more high-quality trials should be conducted.
Yang Y, et al. 2022[22]	To quantitatively evaluate the efficacy and safety of ESWT combined with rehabilitation therapy on post-burn pathological scars compared to rehabili-tation therapy alone.	• 9 studies (n=422) Indications: • Post burn scars	• ESWT + Standard Care (9 studies) • Standard Care (9 studies) *ESWT protocols:* *100-600 pulses/cm², 0.03-0.25mJ/mm², 1-10 sessions*	• Pain • Thickness • Pruritus • Adverse events Follow-up: NR	This review demonstrated mild to moderate evidence to support the use of ESWT as an adjuvant therapy with a standardized wound care program.
Abbreviations: ESWT = Extracorporeal shock wave therapy; TTE = Time to epithelialization; VSS = Vancouver Scar Scale; NR = not reported					

b) Diabetic foot ulcers

Reference	Aim	Study details population / indications	Intervention(s)	Outcomes	Authors conclusions
Hitchman LH, et al. 2019[20]	To assess the currently available evidence examining the efficacy of ESWT on healing of Diabetic foot ulcers	• 5 studies (n=255) Indications: • Diabetic foot ulcers	• ESWT + Standard Care (5 studies) • Standard Care ± sham (3 studies) • HBO + Standard Care (2 studies) *ESWT protocols:* *100-500 pulses/cm², 0.03-0.2mJ/mm², 4-5Hz, 3-16 sessions*	• Healing/RE (%, time) • QoL • Adverse events (incl. infection) Follow-up: NR	ESWT has the potential to improve healing in Diabetic foot ulcers, although there is, as yet, insufficient evidence to justify its use in routine clinical practice.
Huang Q, et al. 2020[21]	To assess the efficacy and safety of ESWT on the healing of Diabetic foot ulcers	• 8 studies (n=339) Indications: • Diabetic foot ulcers	• ESWT + Standard Care (8 studies) • Standard Care ± sham (6 studies) • HBO + Standard Care (2 studies) *ESWT protocols:* *100-500 pulses/cm², 0.03-0.23mJ/mm², 3-8 sessions*	• Healing/RE (%, time) • SA/closure • Adverse events Follow-up: NR	ESWT is a feasible adjuvant treatment for Diabetic foot ulcers. It can effectively improve the complete cure rate, shorten the healing period and significantly enhance treatment efficacy.

Reference	Aim	Study details population / indications	Intervention(s)	Outcomes	Authors conclusions
Hitchman LH., et al. 2023[28]	To appraise the evidence on role of ESWT in Diabetic foot ulcer healing and impact of different ESWT doses.	•6 studies (n=471) Indications: • Diabetic foot ulcers	•ESWT + S Standard Care (6 studies) •Standard Care ± sham (6 studies) *ESWT protocols: 100-500 pulses/cm², 0.03-0.23mJ/mm², 3-20 sessions*	•Healing/RE (%, time) •SA/closure •QoL •Adverse events Follow-up: 20 weeks	Patients treated with ESWT were more likely to heal at 20 weeks post-ESWT compared with those treated with standard ulcer care alone.
Abbreviations: ESWT = Extracorporeal shock wave therapy; HBO = hyperbaric oxygenation; NR = not reported;QoL = Quality of Life; RE = Re-epithelialization; SA = Surface Area					

c) Different types of wounds

Reference	Aim	Study details population / indications	Intervention(s)	Outcomes	Authors conclusions
Dymarek R, et al. 2014[23]	To evaluate available evidence of ESWT effectiveness in humans.	•13 studies (n=919) Indications: • Wounds • Post-surgical wounds • Diabetic foot ulcers • Pressure ulcers	•ESWT + Standard Care (13 studies) •Standard Care ± sham (7 studies) •HBO + Standard Care (2 studies) *ESWT protocols: 25-500 pulses/cm², 0.03-0.23mJ/mm², 4-5Hz, 1-6 sessions*	•Healing/RE (%, time) •Severity •SA/closure •Adverse events Follow-up: NR	In the controlled clinical studies statistically significant differences in rates of wound closure compared to a variety of standard topical treatment modalities, sham ESWT treatment, and HBO
Butterworth PA, et al. 2015[24]	To investigate the effectiveness of ESWT for the treatment of lower limb ulceration.	5 studies (n=249) Indications: • Ulcers of lower limb, • Venous ulcers • Diabetic foot ulcers	•ESWT + Standard Care (n=149, 5 studies) •Standard Care (n=25; 1 study) •HBO + Standard Care (n=75; 2 studies) *ESWT protocols: 100 pulses/cm², 0.03-0.27mJ/mm², 4Hz, 1-10 sessions*	•Healing/RE (%, time) •Severity •SA/closure •Adverse events Follow-up: NR	Considering the limited evidence identified, further research is needed to support the use of extracorporeal shock wave therapy in the treatment of lower limb ulceration.
Omar MT, et al. 2017[25]	To provide an up-to-date review for the accurate estimation of the efficacy of ESWT on the healing of chronic wounds on the lower extremity.	•11 studies (n=925) Indications: • Chronic wounds of lower extremity	•ESWT + Standard Care (11 studies) •Standard Care ± sham (4 studies) •HBO + Standard Care (2 studies) *ESWT protocols: 100-600 pulses/cm², 0.03-0.25mJ/mm², 1-10 sessions*	•Healing/RE (%, time) •SA/closure •Adverse events Follow-up: 5-60 months (3 studies)	This review demonstrated mild to moderate evidence to support the use of ESWT as an adjuvant therapy with a standardized wound care program.
Dolibog P, et al. 2018[26]	To present the current state of knowledge on the use of shockwave therapy in the treatment of soft tissue wounds,	•14 studies Indications: • Burns • Diabetic foot ulcers • Venous ulcers • Pressure ulcers • Gangrene	•ESWT + Standard Care (14 studies) •Standard Care ± sham (8 studies) •HBO (1 studies) *ESWT protocols: 100-2000 pulses/cm², 0.03-0.25mJ/mm², 4-5Hz, 1-30 sessions*	•Healing/RE (%) •Severity •SA/closure •Adverse events Follow-up: NR	Evidence from the articles analyzed in this study suggests a beneficial effect of ESWT to treat diabetic foot ulcers, venous leg ulcers, pressure ulcers and burns.

Reference	Aim	Study details population / indications	Intervention(s)	Outcomes	Authors conclusions
Zhang L, et al. 2017[18]	To assess the effectiveness of ESWT compared with that of the standard care treatment for the healing of chronic wounds	•7 studies (n=301) Indications: • Chronic Wounds • Diabetic foot ulcers • Decubitus ulcers	•ESWT + Standard Care (7 studies) •Standard Care (5 studies) •Standard Care +HBO (2 studies) *ESWT protocols: 100-500 pulses/cm², 0.03-0.23mJ/mm², 3-8 sessions*	•Healing/RE (%, time) •SA/closure •Adverse events (incl. infection, pain) Follow-up: 7-72 weeks	ESWT as an adjunct to wound treatment, could more significantly improve the healing process of chronic wounds than the standard care treatment alone.
Zhang L, et al. 2018[19]	To evaluate and compare the effects of ESWT and conventional wound therapy for acute and chronic soft tissue wounds.	•10 studies (n=473) Indications: • Wounds (acute / chronic) • Burns • Diabetic foot ulcers	•ESWT + Standard Care (10 studies) •Standard Care (8 studies) •Standard Care +HBO (2 studies) *ESWT protocols: 25-500 pulses/cm², 0.03-0.23mJ/mm², 1-8 sessions*	•Healing/RE (%, time) •SA/closure •Adverse events (incl. infection) Follow-up: 1-72 weeks	ESWT showed better therapeutic effects on acute and chronic soft tissue wounds compared with classical wound therapy alone.

Abbreviations: ESWT = Extracorporeal shock wave therapy; HBO = hyperbaric oxygenation; NR = not reported; RE = Re-epithelialization; SA = Surface Area.

DETAILED EFFECTS OF ESWT ON WOUND HEALING

Based on these criteria, positive clinical performance was reported for diabetic foot ulcers (Fig.1), pressure ulcers, venous ulcers, decubitus ulcers, chronic wounds, acute burn wounds, post-burn scars and post-burn heterotopic ossification. A summary of identified key clinical performance outcomes identified from the systematic reviews is provided for treatment of post-burn scars (Table 3a), mixed wound studies (Table 3b), mixed ulcer studies and diabetic ulcers (Table 3c).

Fig. 1: 82-year old female with diabetic foot syndrome. Complete healing after three treatments with Low-intensity extracorporeal shock wave therapy (Li-ESWT) using an electrohydraulic focal shock wave generator (2300 impulses at 4Hz).

a) Initial finding with a large ulcus resistant to classical wound dressing.
b) Good healing of the wound 7 weeks after the first ESWT-treatment
c) Complete healing of the wound with minimal scar formation

For a number of studies these sub-groups indications were not specifically assessed and data for acute burn wound treatment and post-burn heterotopic ossification were limited to a small number of studies or lower quality data assessing re-epithelialization, pain and heterotopic ossification. The systematic reviews only reported on one alternative treatment options, Hyperbaric oxygenation therapy (HBO), used specifically in the treatment of diabetic foot ulcers (27,28,33). ESWT demonstrated mostly better performance than HBO in the assessed performance outcomes; complete healing, unresponsive wounds and healing rate (Table 3d). Moreover, a recent study on the use of ESWT in postoperative wound management of Fournier`s gangrene (15) showed complete restoration of the filling skin defect with adequate local skin tissue (ie. penile vs. scrotal) without any side-effects for the patients (Fig. 2,3).

Table 3: Performance data of Extracorporeal Shock Wave Therapy from identified from systematic reviews

a) Post burn wounds

Parameter	Studies	ESWT	Comparator	ESWT vs control	Reference
Pain of scar (VAS-score)	5 (ESWT=122, Control=126)	•-1.17 to -1.57	• -0.52 to -1.37	Reduction	Yang Y, et al. 2022[22]
		•SMD=-0.47 [95%CI:-0.61 to -0.32], p<0.00001			
Pruritus of scar (score)	3 (ESWT=60, Control=62)	•-1.7 to -4.1	•-0.8 to -3.0	Reduction	Yang Y, et al. 2022[22]
		•SMD=-0.94 [95%CI:-1.25 to -0.63], p= 0.004)			
Appearance of scar (VSS-score)	4 ESWT=76, Control=80)	•-0.35 to -4.76	•+0.32 to -4.0	Improvement	Yang Y, et al. 2022[22]
		•SMD=-1.78 [95%CI:-3.37 to -0.19], p=0.03			
Thickness of scar (cm)	4 (ESWT=88, Control=88)	•-2.86 to +0.01	•-0.95 to +0.07	Decrease	Yang Y, et al. 2022[22]
		•SMD= 0.13 [95%CI:-0.25 to 0.01], p=0.04			
Transepider-mal water loss of scar	2 (ESWT=45, Control=43)	•-6.57 to -1.31	•-3.58 to 0	Decreased	Yang Y, et al. 2022[22]
		•SMD=-2.86 [95%CI:3.96 to -1.76], p<0.00001			
Elasticity of scar	2 (ESWT=45, Control=43)	•0.03 to 0.31	•-0.13 to 0.06	Increased	Yang Y, et al. 2022[22]
		•SMD=0.25 [95%CI:0.21 to 0.29], p<0.00001			

b) **mixed wounds**

Parameter	Studies	ESWT	Comparator	ESWT vs control	Reference
Healing time (days)	4 (ESWT=74, Control=73)	•9.6-64.5	•12.5-82.2	Improvement	Zhang L, et al. 2018[19]
		•SMD=-10.72 [95%CI: -17.68 to -3.77], p=0.003			
Healing rate (complete)	6 (ESWT=173, Control=167)	•50%-88.9%	•0%-72.2%	Improvement	Zhang L, et al. 2018[19]
Infection rate (%)	6 (ESWT=146, Control=149)	•0%-23.1%	•0%-36.1%	Improvement	Zhang L, et al. 2018[19]
		•OR=0.47 [95%CI: 0.24 to 0.92], p=0.03			
Area (cm^2)	5 (ESWT=66, Control=62)	•34.5-83.32	•5.6-63.31	Improvement	Zhang L, et al. 2018[19]
		•SMD=30.45 [95%CI: 23.79 to 37.12], p<0.00001			

c) **Diabetic foot ulcers**

Parameter	Studies	ESWT	Comparator	ESWT vs control	Reference
Healed ulcer (%)	4 (ESWT=211, Control=100)	•35.4%-55.5%	•26.2%-33.3%	Improvement	Hitchman L, et al. 2023[28]
Healed ulcer (%) (complete)	2 (ESWT=39, Control=36)	•53.3%-54.2%	•28.6%-33.3%	Improvement, 2.6-fold	Hitchman L, et al. 2019[20]
		•OR=2.66 [95%CI: 1.07 to 5.61], p=0.04			
Healing time		•60.8-64.5	•81.17-82.2	Improvement	

Parameter	Studies	ESWT	Comparator	ESWT vs control	Reference
(days)	2 (ESWT=39, Control=36)	•SMD=-19.11 [95%CI: -23.74 to -14.47], p<0.00001			Zhang L, et al. 2017[18]
Healing rate complete (days) -	5 (ESWT=43, Standard wound care=41)	•50%-88.9%	•0%-33.3%	Improvement 3-fold	Zhang L, et al. 2017[18]
		•OR=3.00 [95%CI:1.22 to 7.41], p=0.02			
Area reduction (%)	3 (ESWT=101, Control =89)	•78%-83%	•44%-67%	Improvement	Omar MT, et al. 2017[25]
Area healed (cm^2)	5 (ESWT=66, Control =62)	•34.5-83.32	•11.1-63.31	Improvement	Zhang L, et al. 2017[18]

d) **Diabetic foot ulcers treated with ESWT compared to hyperbaric oxygen therapy (HBO)**

Parameter	Studies	ESWT	HBO	ESWT vs HBO	Reference
Healed ulcers (complete)	4 (n=156)	•RR=1.83; 95%CI, 1.14 to 2.94; p=0.012 (vs HBO)		Improvement, 1.8-fold	Huang Q, et al. 2020[21]
Healed ulcers (complete)	2 (ESWT=80, HBO=76)	•30.6%-54.5%	•22.2%-25.0%	Improvement, 2.4-fold	Hitchman L, et al. 2019[20]
		•OR=2.45 [95%CI: 1.03 to 6.87], p=0.03			
Unresponsive ulcers	4 (n=156)	•RR=0.25; 95%CI, 0.13 to 0.48; p<0.001		Improvement, 4-fold	Huang Q, et al. 2020[21]
Healing rate of ulcers	5 (ESWT=80, HBO=76)	•50%-88.9%	•0%-72.2%	Improvement 2.7-fold	Zhang L, et al. 2017[18]
		•OR=2.77 [95%CI: 1.34 to 4.71], p=0.006			
		•OR=2.77 [95%CI: 1.34 to 4.71], p=0.006			

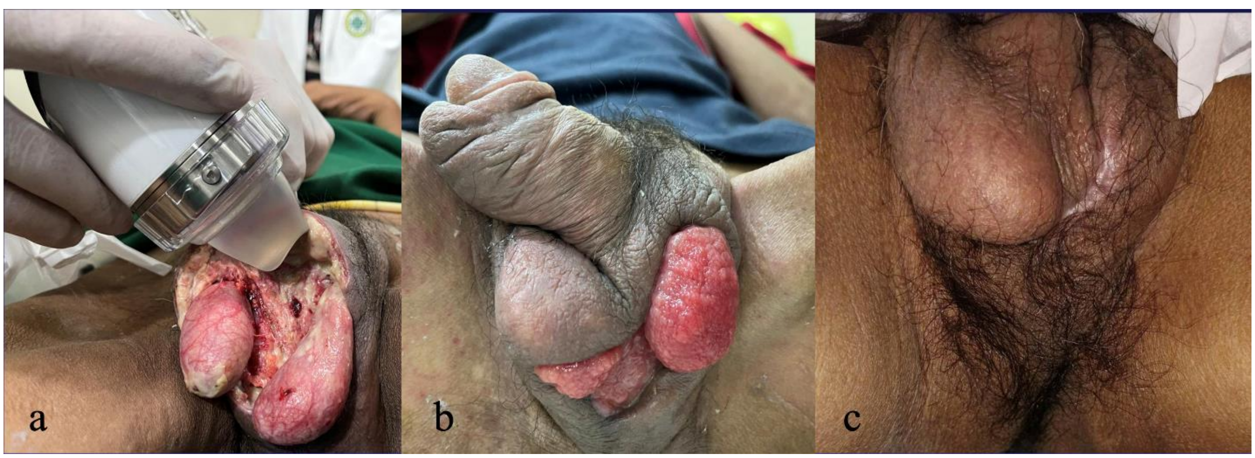

Fig. 2: Technique of LI-ESWT for postoperative wound healing after radical excision in patient with Fournier´s gangrene

a. Application of 3000 Shock Waves on the rim of the wound using the Handpiece of the electromagnetic device Duolith SD (Storz-Medical, Taegerwilen, Switzerland) with 0.25 mJ/mm^2 at 3 Hz.

b. Significant improvement of the wound healing after three weeks following 4 treatments of ESWT.

c. Complete healing of the scrotal wound after 6 treatments with Li-ESWT following 6 months after the first treatment. Basically, no scar formation. No surgery required.

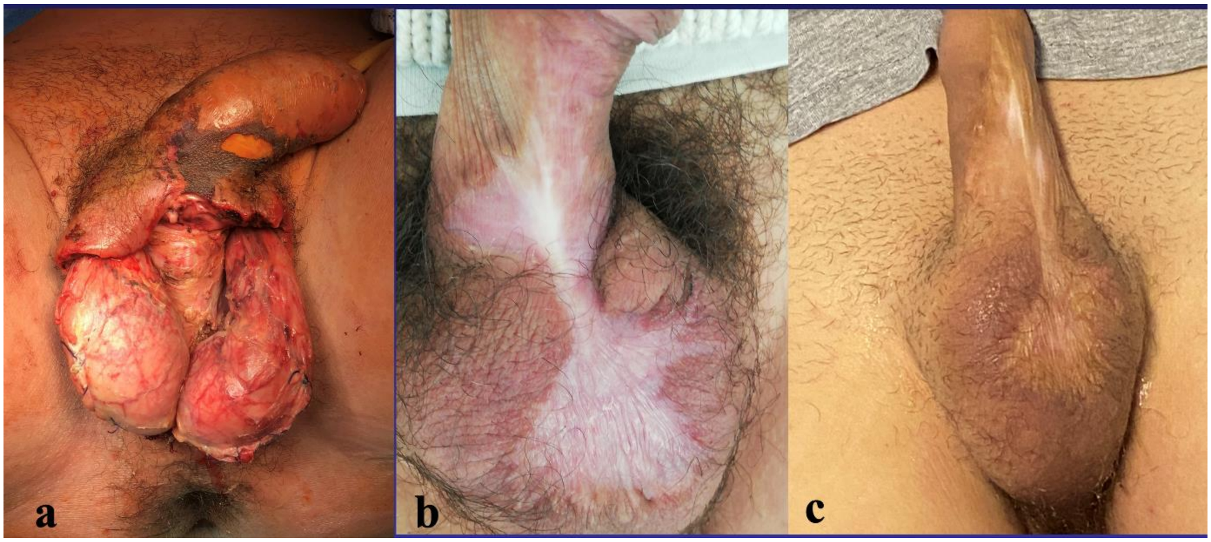

Fig. 3: Low-intensity extracorporeal shock wave therapy (Li-ESWT) using an electromagnetic device as single management of wound healing following radical excision of infected tissue after Fournier`s gangrene.

a) Radical excision of the involved tissue
b) Complete restoration of the wound by scrotal and penile tissue after 12 weeks. No surgery required at all.
c) Final cosmetic result after 3 months with minimal scar formation.

EXPERIENCE WITH RADIAL SHOCK WAVE THERAPY

We identified four studies were identified that reported on the use of radial ESWT for the treatment of wounds (35-38). Treatment of burns was performed with radial ESWT and water-filtered infrared-A irradiation and compared to water-filtered infrared-A irradiation alone (36). Statistically significant improvement in the group receiving treatment with radial ESWT was reported for pain measured by VAS, and healing, specifically wound healing rate, time (including related duration of hospital stay), scar scores, and blood perfusion. No report of pruritis or assessment of pruritis was performed. No adverse events were reported. However, water-filtered infrared-A irradiation does not represent a standardized approach in wound-healing. Therefore, it cannot really be taken as a control group to radial ESWT.

Treatment of a variety of chronic wounds (> 3months) diagnosed as ulcers full thickness or subcutaneous damage with necrosis were treated with radial ESWT and standard wounds care and compared to treatment with standard wound care alone. Pain and pruritis were not reported or subject to specifically assessed. Extensive assessment of wound healing and related wound characteristics was performed and statistically significant improvements in the rESWT group was seen for change in wound area (and related length and width), wound bed score, and Bates-Jensen wound assessment tool score length. However, they did report that there were two unusual adverse events observed in the wound area; local bleeding episodes (vascular background) and uncontrolled hyper-granulation tissue (inflammatory background). Neither were indicated to be serious nor prevented ongoing treatment (37).

Overall, the clinical data detailing off-label use of radial ESWT in the treatment of wounds demonstrated some positive outcomes. Nevertheless, based on these early and incomplete data, the DIGEST-guidelines recommend radial extracorporeal shock wave therapy only treatment of scars following burns and not for open wounds (39).

Side effects of ESWT

The most serious adverse events were infection and amputation. Infection was reported to occur in up to 36.8% of patients being treated for ulcers and up to 9% of patients being treated with ESWT for burns. In all studies reporting infection, the incidence in the ESWT was similar of less than the comparator standard care alone group. Similarly for amputation that was reported in one study, the incidence in the ESWT ground was lower than in the control group. The most common reported safety events were transient and mild events such as reddening, bruising, swelling, small hematomas, petechiae, and oedema of the skin, as well as mild pain or discomfort at the treatment site during treatment (Table 4).

Table 4: Overview the Guidelines of DIGEST (German Speaking Society of Shock Wave Therapy) – also applied by the International Society of Medical Shock Wave Therapy (ISMST)

Reference	Scope/Aim	Populations / Indications	Relevance for clinical evaluation
DIGEST Guidelines for Extracorporeal Shock Wave Therapy, 2019[37]	Guidance providing evidence-based background on clinical use of EWST and indication recommendations.	Populations: • Any patient affected by burn injuries (including skin and internal injury, from thermal, chemical, electrical toxic/inhalation) in any patient) Indications • Wounds ➢ Burn injuries ➢ Burn scars	ESWT recommended for use with: • Wounds, including burn injuries and burn scars, in conjunction with conservative treatment for 1st-2nd degree (class a) burns, or after initial surgical wound treatment for 2nd(class b)-4th degree burns. Significant improvements reported for split skin removal site healing and 2a° burns as well as burn scars, consistent with pre-clinical study reports. • Burn scars: Healing speed (rESWT) and perfusion (ESWT), pain (fESWT: 0.05-0.15 mJ/mm2, 2000 impulses, three sessions, 4 Hz), pruritis (fESWT: 0.05-0.2 mJ/mm2, 2000 pulses), hand function/VSS (rESWT)

Table 5: Identified safety events reported in systematic reviews of Extracorporeal Shock Wave Therapy for wound healing

Systematic review	Safety event
Hitchman L, et al. 2023[28]	• Safety events in 4 of 6 included studies of Diabetic foot ulcers • Infection: ESWT: 28%-36.8%, control: 25.3%-35.8% • Amputation: ESWT: 2.3%, control: 3.0%
Yang Y, et al. 2022[22]	• Safety events in 3 of 9 included studies • Transitory reddening and oedema of the skin, • Mild-to-moderate pain • No serious adverse events
Aguilera-Sáez J, et al. 2020[27]	• No reported safety events in 9 included studies
Huang Q, et al. 2020[21]	• Safety events in 5 of 8 included studies • Transitory reddening of the skin • Slight pain • Small hematomas
Hitchman L, et al. 2019[20]	• No reported safety events in 7 included studies
Zhang L, et al. 2018[19]	• Safety events in 6 of 12 included studies • Transitory reddening of the skin • Slight pain • Small hematomas
Dolibog P, et al. 2018[26]	• Safety events in 9 of 11 included studies during treatment • Safety events in 2 of 11 included studies after treatment was completed; (Arno et al: pain which was also reported before and during treatment; Jankovic et al: inflammatory reaction) Ulcers • Infection : ESWT: 28%-36.8%, control: 25.3%-35.8%) • Increase in pressure ulcer size during treatment: n=3 • Mild pain during application (Ulcers): 2/6 studies (n=8/30 (27%) Burns • Infection: ESWT: 9%, Control: 14% • Microtrauma, swelling, bruising, petechiae, as well as pain (before, during and after treatment)
Zhang L, et al. 2017[18]	• No serious adverse events in 7 included studies
Omar MT, et al. 2017[25]	• Safety events in 10 of 11 included studies • Pain • Itching • Skin irritation / pigmentation • Local infection (n=1 in ESWT and Control groups; Moretti et al) • (HBO: middle ear barotraumas and sinus pain)
Butterworth PA, et al. 2015[24]	• Safety events in 3 of 5 included studies • No serious adverse events in 5 included studies
Dymarek R, et al. 2014[23]	• Safety events in 3 of 7 included studies • Local signs of infection (n=1)) • Wound infection rates: 9% ESWT vs 14% with standard wound care • Enlarged ulcers with ischemic edges (n=3)

The systematic reviews only reported on one alternative treatment option, which was HBO. While the localized safety events reported for ESWT treatment were not reported with HBO, this treatment option was associated with unique adverse events, including middle ear barotraumas and sinus pain. Overall. the systematic reviews reported that ESWT was well-tolerated, and did not display a causal association with any serious adverse events.

RECOMMENDATION OF ESWT IN GUIDELINES

A single relevant guideline was identified from screening of expert associations and their repositories. This was a DIGEST guideline (39) supporting the use of ESWT (both fESWT and rESWT) for wounds, principally for treatment of burn wounds and scars (Table 5).

Discussion

After positive effects on still existing wounds were repeatedly observed in the treatment of pseudarthroses, especially on the lower leg, 208 patients with a wide variety of wound healing disorders were treated with shock waves in a pilot trial (9). The essential aspect of this anecdotal case collection was to demonstrate that the patients obviously benefited from ESWT and that it could be applied with practically no side effects. Now the challenge was to prove the effect of shockwaves on wound healing in a clean clinical trial.

The main problem was to treat standardized wounds in order to assess the influence of ESWT. For this purpose, the harvest sites for skin grafts (Mehscraft plasty) on the thigh were chosen. These "standardized" wounds could be brought to complete epithelialization significantly faster with ESWT compared to the placebo group (40).

Extensive assessment post-market experience data for the devices, and data extracted from identified relevant literature in this clinical evaluation, have shown only single minor safety events, with the majority of potential risks identified (24-34). This provides a validation of the effectiveness of the implemented risk control measures; both during development and in the technical design of the different devices, as well as through the adequate communication of risk information and appropriate safe use instructions in the accompanying device materials. This underlines, that ESWT is a very safe treatment option for the patients

Off-label use of radial ESWT in the treatment of wounds, was identified and assessed in this clinical evaluation. These few studies demonstrated some positive outcomes, with statistically significant improvements in pain, and wound healing for a number of wound types. No serious adverse events were reported (35-37). Thus, Off-label use might be justified by the treating physician based on their assessment of the positive benefit that an 41off-label intervention will provide in the treatment of their patients` specific condition (38). However, it has to be emphasized, that at the moment there are only sparse data available (39). This might be an issue for further studies (i.e. comparing the efficacy of radial versus focal ESWT).

Even, if still only based on case studies, the healing effect of ESWT following extensive tissue resection due to Fournier`s gangrene shows a complete restoration of the pre-existing local skin, such as perineal, penile or scrotal (Fig. 2,3). The underlying mechanism for this should be related to a stimulation of stem cells, which has been already shown experimentally in animal models of trauma of the pelvic floor or of erectile dysfunction (41,42). The skin offers the unique opportunity to watch the progress of healing and tissue restauration as a model for regenerative medicine.

In conclusion, ESWT offers a safe and non-invasive treatment option for a variety of wound healing problems, from improving the healing of ulcers to complete restauration of the skin after extensive surgery in the management of Fournier`s gangrene.

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