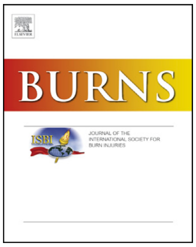
BURNS XXX (2019) XXX–XXX

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/burns



Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review

Jorge Aguilera-Sáez [*], *Pablo Muñoz, Jordi Serracanta, Alejandra Monte, Juan P. Barret*

Department of Plastic Surgery and Burn Center, Vall d'Hebron University Hospital, Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain

ARTICLE INFO

Article history:
Accepted 12 July 2019
Available online xxx

Keywords:
Extracorporeal shock wave therapy
Shock waves
Acoustic energy
Burn scar
Wound healing

ABSTRACT

Introduction: Extracorporeal shock wave therapy (ESWT), first described in the eighties for the treatment of urolithiasis, has also been applied in other fields such as orthopaedics and chronic wound care. Recently it has also been used in the treatment of burns and its sequelae since several studies suggest it could be an important tool in the conservative management of these conditions. The aim of this article is to review the literature for published evidence on the use of ESWT for the treatment of acute burn patients and its sequelae and to elaborate a brief report on the current state of the matter.

Material and methods: We carried on a search on PUBMED database and Cochrane database with the following terms: ('burns' [title/abstract] OR 'burn' [title/abstract]) AND "shock wave" ([title/abstract]). For an optimal reporting of the studies found we followed the PRISMA statement.

Results: This search found 34 articles from which only 15 were actually related to the use of ESWT in burn patients. From these 15 articles, 7 involved the use of ESWT in the treatment of acute burns, 6 related to its application in post-burn scars, 1 in the treatment of heterotopic ossification and 1 was about the use of ESWT in skin-graft donor site. Except for the latter, all of them were carefully reviewed.

Conclusion: Scientific evidence on the use of ESWT for the treatment of burn patients is weak due to the paucity of studies and their low quality. However, ESWT seems to be a promising tool in this field and therefore more high-quality trials should be conducted.

Contents

---

[*] *Corresponding author at*: Department of Plastic Surgery and Burn Center, Vall d'Hebron University Hospital, c/Passeig de la Vall d'Hebron 119-129, 08035 Barcelona, Spain.
E-mail address: joaguile@vhebron.net (J. Aguilera-Sáez).

https://doi.org/10.1016/j.burns.2019.07.023
0305-4179/© 2019 Elsevier Ltd and ISBI. All rights reserved.

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

1. Introduction

Wound healing is a complex and dynamic process which does not end until the complete maturation of the scar. This process is usually divided into three phases: inflammation, proliferation and maturation.

In deep wounds during the inflammation stage a fibrin clot is formed, serving as a scaffold over where the rest of the process is built. Different cytokines and chemokines (PDGF, TGF-β, EGF . . .) recruit mast cells, fibroblasts, macrophages and other cells to restore the cutaneous barrier. Around two or three days after the injury the inflammatory response evolves into a proliferative phase that can last up to six weeks. During this period fibroblasts from deep dermis slowly proliferate producing inflammatory cytokines (including TGF-β) and synthesizing hyaluronic acid, proteoglycans, elastin and procollagen to create granulation tissue. In this granulation tissue new vessels are formed. Fibrocytes migrate from the bone marrow to the wound differentiating into fibroblasts and increasing the production of TGF-β which stimulates the turning of fibroblasts into myofibroblasts. These myofibroblasts are responsible for wound contraction. From here on, the scar enters a phase of maturation which can last for up to two years defined by the remodeling of the extracellular matrix and the substitution of collagen type III for collagen type I [1–3].

In superficial wounds the epidermis is regenerated through the migration and proliferation of keratinocytes coming from the basal layer of epidermis, hair follicles and sebaceous glands. It is known that pluripotential cells from the "protuberance", a structure located in the hair follicle below the sebaceous gland, proliferate and differentiate into keratinocytes [4].

Despite the importance of the inflammatory response in the process of wound-healing, the excessive production of pro-inflammatory mediators or the lack of early suppression of this response can cause additional harm to the wound, impairing the healing process or even producing and over-regeneration of connective tissue followed by an abnormal remodeling of the extracellular matrix which contributes to pathological scar formation.

Shockwaves are acoustic waves of great amplitude characterized for a fast alternation between positive and negative pressures. These waves are defined by several physical parameters. For a complete description of the therapy some of them should be recorded, e.g. maximum peak pressure, energy flux density (EFD), number of pulses, frequency of repetition of these pulses and the number of sessions and the interval between them. Unfortunately, most of the publications lack of this information which hinders the comparison of results [5]. Extracorporeal Shock Wave Therapy (ESWT) have been divided in high energy ESWT ($> 0.12\,\mathrm{mJ/mm^2}$) and low energy ESWT ($<0.12\,\mathrm{mJ/mm^2}$) depending on the amount of energy applied for pulse in a certain point during a treatment session, which is known as 'energy flux density' [6].

ESWT uses two main types of generators: focused and non-focused or radial. They differ in terms of propagation of the shockwaves and the physical characteristics of its energy. In the case of radial ESWT, waves are produced by pneumatic devices placed inside the generator creating a lineal pressure with low energy levels. This energy is absorbed by the skin and reaches a maximum depth of around 3 cm but covers a greater surface area due to a wider beam. On the other hand, focused ESWT come from either electromagnetic, electrohydraulic or piezoelectric sources. In this case the pulse pressure increases rapidly in a range from 10 to 100 MPa, focusing its acoustic energy in a reduced area with a penetration depth of around 12 cm [6].

Although the first clinical application of this therapy was the treatment of urolithiasis [7], its use has expanded to other fields such as orthopaedics in cases of tendinopathies, fasciitis or pseudoarthrosis [8–11] showing also promising results in the treatment of complex or chronic wounds [12–15]. For its use in soft tissues radial ESWT are preferred. As explained before this type of ESWT covers a greater surface area allowing to reduce the number of pulses and the duration of the session thus making it more bearable for the patient. Recently it has also been used in the treatment of burns and its sequelae since several studies suggest it could be an interesting tool in the conservative management of these conditions.

The aim of this current work is to review the evidence available concerning the use of ESWT in the treatment of burn patients, both acute injuries and eventual sequelae.

2. Material and methods

To elaborate this systematic review, we have used the PRISMA [16] statement, an evidence-based set of 27 items for reporting in systematic reviews and meta-analysis (http://prisma-statement.org/prismastatement/Checklist.aspx). On February 15th we carried on a search on PUBMED database and Cochrane database with the following terms: ('burns' [title/abstract] OR 'burn' [title/abstract]) AND "shock wave" ([title/abstract]). No additional inclusion or exclusion criteria related

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

to the characteristics of the studies (e.g. language, year of publication, etc.) were determined.

3. Results

This search found 34 articles and all of their abstracts were read thoroughly.

Only 15 papers were actually related to the use of ESWT specifically in the treatment of burn patients. From these 15 articles, 7 involved the use of ESWT in the treatment of acute burns, 6 related to its application in post-burn scars, 1 in the treatment of post-burn heterotopic ossification and 1 was about the use of ESWT in skin-graft donor site [17]. Of these, full text was carefully reviewed, emphasizing the type of study, number of participants, the characteristics of the ESWT, number of sessions and the results obtained. The article on skin-graft donor sites in burn patients was excluded since these are considered to be simple wounds not burns or direct burn-sequelae. The rest of the studies were selected. Fig. 1 shows a flowchart made for this review and Table 1 summarizes the articles.

4. Use in acute burn injuries

The proposed mechanism responsible for the helping role of ESWT in wound healing involves a biological effect consisting of an optimization of the wound environment at both cellular and molecular levels, provoked by the mechanical stimulus of the waves.

It has been speculated that mechanical energy from ESWT alters the cell membrane potential affecting the intracellular signaling processes [18]. These processes involve chemical mediators such as IL-1a, IL-1β, eNOS, VEGF, TGF-β1, Erk1/2, laminin-332, ki67 and would regulate cell proliferation, fibroblast and keratinocyte migration and new blood vessel formation thus stimulating wound healing [19–24]. This concept is known as mechanotransduction [25]. It is well known that burn injuries show a persistent proinflammatory environment due to eschar formation, colonization from bacteria and leukocyte infiltration and that is why ESWT are believed to be useful in the treatment of burn patients.

First evidence of the use of ESWT in burns comes from a case report published in 2005 which described the application of this therapy in a deep partial thickness burn of the dorsum of the hand and forearm in a patient refusing surgery. The burnt area was treated at days 3 and 7 after the injury with ESWT (1500 impulses of 0.11 mJ/mm^2). This burn healed in 15 days and no pathological scar was found after 6 months of follow-up [26].

4.1. *Preclinical evidence*

Our literature search yielded 4 preclinical controlled studies related to acute deep burns, 3 were performed in mice full-thickness burns [27–29] and 1 in rat deep-dermal burns [30]. Initially Davis et al. [27] conducted a controlled experiment in which the ESWT treatment consisted of a single application of 200 impulses of 0.1 mJ/mm^2 with a frequency of 5 Hz, 1-h postburn. The rate of macroscopic wound closure did not significantly differ between both groups at 1, 7, 14, 21 and 28 days after the injury. However, they described an anti-inflammatory effect characterized by a decrease in both the level of neutrophil (60–68%, $P < 0.05$) and macrophage (55–66%, $P < 0.05$) cell infiltration within the wound bed at 24 h after injury and gene expression of chemokines, proinflammatory cytokines and matrix metalloproteinases at 4 h and at 24 h post burn injury ($P < 0.05$ in both). On the other hand posterior studies by Goertz et al. [28,29] found a shock waves pro-inflammatory effect consisting of an increase in the number of rolling leukocytes in the ESWT treated animals (mice without burn and exposed to ESWT 0.04 mJ/mm^2 on days 1, 3 and 7 postburn: 210.8% vs mice without burns and with no ESWT:

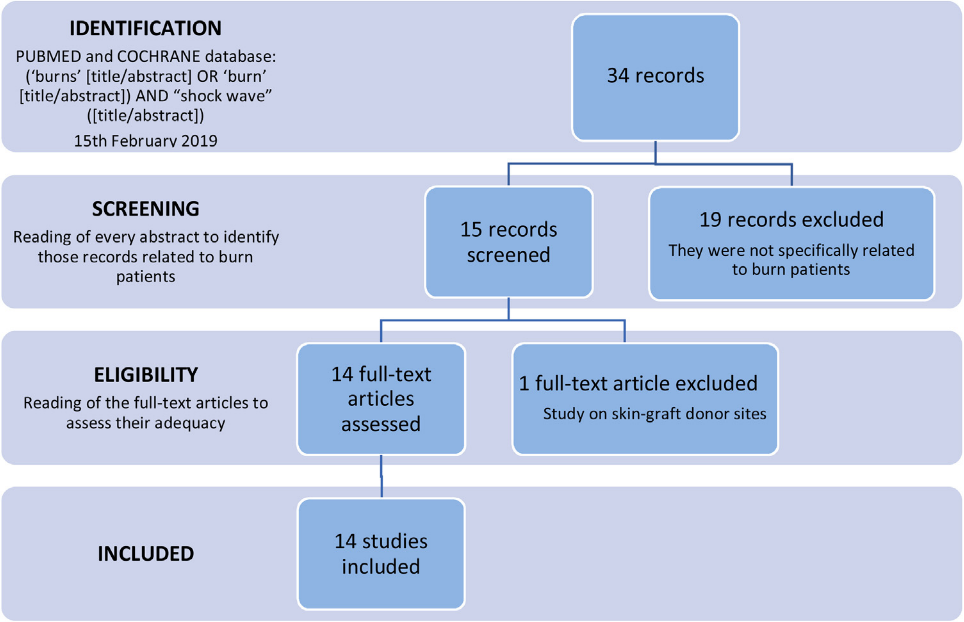


Fig. 1 – Information flowchart through the different phases of the systematic review.

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

Table 1 – Summary of studies on extracorporeal shock wave therapy in burns patients. ESWT: extracorporeal shock wave therapy; QE: quasi-experimental; CT: clinical trial; LDI: laser doppler imaging; TGF: transforming growth factor.

Authors	Study	Year	Object/injury	Control group	Parameters	Results
Merier et al. [26]	Case report	2005	Deep partial-thickness burn	No	1500 pulses, 0.11 mJ/mm^2, 2 sessions	Re-epithelialization in 15 days. No scar contractures after 6 months.
Davis et al. [27]	Animal study (mice)	2009	Full-thickness dorsal burn	Yes	200 pulses, 0.1 mJ/mm^2, 5 Hz, 1 session	Decrease of inflammatory cells, proinflammatory cytokines and proteases in the wound.
Goertz et al. [28]	Animal study (mice)	2012	Full-thickness ear burns	Yes	0.04 ml/mm^2 or 0,015 mJ/mm^2 or none, 3 sessions	Improved blood flow. Increased number of rolling leukocytes.
Goertz et al. [29]	Animal study (mice)	2014	Full-thickness ear burns	Yes	500 pulses, 0.03 mJ/mm2, 1 Hz, 1, 2 or 3 sessions.	Significantly accelerated angiogenesis which increases with a higher number of sessions. Produced vasodilation and increased leukocytes migration to the wound.
Djedovic et al. [30]	Animal study (rats)	2014	Deep partial-thickness burn	Yes	500 pulses, E = 0.11 mJ/mm2, 1 session	Enhanced percentage of wound closure in ESWT group. Increased vascularization on day 5 valued with LDI Improved reepithelialization rate on day 15.
Arnó et al. [31]	QE study in humans	2009	Deep partial/full thickness burns	No	500 pulses, E = 0.15 mJ/mm^2, 2 sessions	Increased vascularization valued with LDI. 80% of burns healed uneventfully prior to 3 weeks; 15% required grafting and 5% developed hypertrophic scarring.
Ottomann et al. [32]	Randomized CT in humans	2012	Acute second-degree burns	Yes	100 pulses/cm^2, E = 0,1 mJ/mm2, 1 session	Mean time to complete epithelialization 9.6 ± 1.7 (ESWT) vs. 12.5 ± 2.2 days (No ESWT) ($P < 0.0005$).
Fioramonti et al. [35]	QE study in humans	2012	Postburn scars contractures, hypertrophic scars	No	100 pulses, 0.037 mJ/mm^2, 4 Hz, 12 sessions	More acceptable appearance (more pliable, less evident color-mismatch).
Cui et al. [36]	In vitro study	2018	Primary dermal human fibroblasts	Yes	1000 pulses/cm2, E = 0.03 or 0.1 or 0.3 mJ/mm^2, 1 session.	Decreased fibroblast migration. Decreased the expression of related molecules with postburn hypertrophic scars: TGF- β1, α-SMA, vimentin, collagen I, fibronectin and N-cadherin
Zaghoul et al. [39]	Randomized CT in humans	2016	Hypertrophic scars	Yes	2500 to 3000 pulses, 12 sessions	Decreased scar thickness. Improved Vancouver Scar Scale score.
Cho et al. [40]	Randomized CT in humans	2016	Burn scars	Yes	100 pulses/cm^2, 0,05–0.12 mJ/mm^2, 4 Hz, 3 sessions	Reduced burn-associated pain.
Joo et al. [41]	Randomized CT in humans	2018	Burn scars	Yes	100 pulses/cm^2, 0,05–0.12 mJ/mm^2, 4 Hz, 3 sessions	Reduced burn-associated pruritus.
Taheri et al. [42]	QE study in humans	2018	Burns scars	No	100 pulses/cm^2, 0.1 mJ/mm2, 4 Hz, 6 sessions	Reduced burn-associated pain and itching and improved Vancouver Scar Scale score.
Mowafy et al. [43]	Randomized CT in humans	2016	Postburn heterotopic ossification	Yes	100 pulses/cm^2, from 0.13 to 0.23 mJ/mm^2, 3 sessions	Reduced pain and size of heterotopic ossification.

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

83.3%, $p = 0.017$ on day 7; and 172.3 vs 90.9%, $p = 0.01$ on day 12) [28] and also a greater number of adherent leukocytes (3 applications ESWT 0.03 mJ/mm^2 on days 1, 3 and 7 post burn: 115 ± 22.6% vs 2 applications ESWT 0.03 mJ/mm^2 on days 1 and 3: 106.2 ± 12.1% vs 1 application ESWT 0.03 mJ/mm^2 on day 1: 94.0 ± 13.5% vs control group: 82.8 ± 12.4%, these differences were not significant) [29]. These studies showed accelerated angiogenesis in shock-wave treated groups compared to the control group (non-perfused area on day 12 after 1 session of 0.04 mJ/mm^2: 5.3% vs 1 session of 0.015 mJ/mm^2: 9.1% and control group: 12.6%, $p = 0.005$) [28] which kept improving after several sessions of ESWT (non-perfused area on day 12 after 1 application: 2.7 ± 0.4% ($p = 0.001$), after 2 applications: 1.4 ± 0.5% ($p < 0.001$), after 3 applications: 1.0 ± 0.3% ($p < 0.001$) vs control group: 6.1 ± 0.9%) [29]. Djedovic et al. [30] also identified an increase in the vascularization of the burn wound measured by laser doppler imaging after a single application of ESWT (500 shocks, EFD = 0.11 mJ/mm^2, 4 Hz). This effect was only significant when evaluated on day 5 after treatment (ESW-treated group: 145.2 ± 22.7% vs control group: 92.7 ± 32.6%, $P < 0.01$) but not on subsequent evaluations on days 10 and 15. However clinical evaluations (percentage of remained wound area: 0.1 ± 0.1% vs 3.8 ± 5.5%, $P = 0.028$) and histological analysis (histologic healing score: 14.3 ± 0.5 vs 11.6 ± 1.5, $P < 0.01$) of the wounds in the ESWT group were better compared to those in the control group on day 15.

4.2. *Clinical evidence*

Current evidence in humans is limited to two studies conducted in burns of different characteristics. Arnó et al. [31] carried on two sessions of ESWT (3rd and 5th day after injury, 500 impulses of 0.15 mJ/mm^2) in a series of 15 patients with deep dermal or full thickness burns. All these burns were evaluated using Laser Doppler Imaging and considered to be deep enough to require surgical treatment. They observed an increase in wound perfusion objectivated by LDI before the second ESWT session. Only 2 out of the 15 patients required surgical debridement and grafting.

Ottoman et al. [32] applied a single session of ESWT (0.1 mJ/mm^2) to 50 patients within the first 24 h after suffering superficial dermal burns and compared the results with a control group. 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, $p < 0.005$).

5. Use in post-burn scars

The prevalence of hypertrophic scarring after a burn injury has been described in up to 60% of the cases [33] and the prevalence of contracture of this scar varies between 38 and 54% of the cases [32]. The underlying mechanism remains poorly understood. It is known though that an excessive production of connective tissue occurs, followed by an abnormal remodeling of collagen in the extracellular matrix. It has been observed an overproduction of type I collagen, fibronectin and hyaluronic acid and a reduction in the formation of type III collagen, decorin and elastin [2,3].

Compression garments, massage, silicone gels and dressings, laser therapy, and corticoid infiltration are the most common conservative treatments for hypertrophic scarring [3,34]. ESWT has also been used for this purpose [35–39].

Initially it was thought that shockwaves could break the collagen fibers in the scar promoting their remodeling but more recent studies showed that a mechanotransduction mechanism is also implied, affecting the migration of fibroblasts into the scar and regulating the production of molecules such as TGF-β1, Smad, fibronectin or type I and III collagen [36–38].

5.1. *Preclinical evidence*

A controlled in-vitro study conducted on fibroblasts obtained from hypertrophic post-burn scars [36] showed that one application of ESWT (1000 impulses/cm^2 of 0.03, 0.1 and 0.3 mJ/mm^2 EFD and frequency of 4 Hz) decreases the expression of molecules related to post-burn hypertrophic scars, such as TGF- β1, α-SMA, vimentin, collagen I, fibronectin or N-cadherin ($p < 0.05$); also reducing the migration of fibroblasts ($p < 0.05$).

5.2. *Clinical evidence*

Fioramonti et al. [35] performed two ESWT (100 impulses of 0.037 mJ/mm^2/cm^2 with a frequency of 4 Hz) weekly sessions during 6 weeks in 16 patients with hypertrophic scars or scar contractures. Patients themselves evaluated the appearance of the scar at the beginning and two months after finishing the treatment by means of a visual analogue scale. Scoring improved in 3, 2 and 1 points in 18.75%, 50% and 12.5% of the cases respectively and did not change in 18.75% of the patients. Based on these results, a randomized clinical trial [39] was carried out on 40 patients with hypertrophic postburn scars. The study group received ESWT (2500–3000 impulses during 10–15 min, twice a week for 6 weeks) and traditional physical therapy, while the control group only received traditional physical therapy. This study showed a significant greater decrease of scar thickness measured by ultrasonography in the ESWT group than in the control group (42.55% vs 12.15%, $p = 0.0001$) and a significant improvement of Vancouver Scar Scale (VSS) (48.57% vs 14.04%, $p = 0.0001$).

The Hangang Sacred Heart Hospital of Seoul (South Korea) has recently conducted two prospective single-blind placebo controlled randomized trials. In both studies patients in the ESWT group underwent a weekly session for a total of three weeks (EFD of 0.05 to 0.15 mJ/mm^2 depending on the patient's pain tolerance, frequency of 4 Hz and 2000 pulses). In the first study, patients with a pain score of 5 or more out of 10 were included. In this case patients in the ESWT group showed a significant decrease in their pain score after the three-week treatment (from 7.80 ± 1.54 to 3.00 ± 2.35 vs from 7.30 ± 1.30 to 5.55 ± 1.50, $p < 0.001$) [40]. In the second study, patients with a pruritus score of 5 or more out of 10 were included and equally showed a decrease in the score after third session of ESWT (from 6.30 ± 1.29 to 3.57 ± 2.09 vs from 6.87 ± 1.32 to 5.35 ± 2.31, $p = 0.009$) [41].

The most recent publication on this matter is a prospective quasi-experimental study carried on in 17 patients with

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

burn scars in their limbs. These patients were treated with ESWT weakly (EFD of 0.1 mJ/mm^2, 100 impulses/cm^2 and a frequency of 4 Hz) for a period of six weeks. Visual Analogue Scale (VAS) to measure patient's pain and itching and VSS to evaluate scar appearance were both employed at different times (pretreatment, right after treatment, at 1 month and 3 months follow-up). Mean VAS for pain and inching and VSS score decreased significantly ($P = 0.009$, $P < 0.001$ and $P < 0.001$ respectively) [42].

6. Use in post-burn heterotopic ossification

ESWT has been used in the treatment of tendinopathies, fasciitis, delayed union and nonunion [8–11]. The exact mechanism by which ESWT may act on bone healing remains unknown.

A randomized clinical trial was carried out on 30 patients with post-burn heterotopic ossification [43]. 15 patients received ESWT (0.13– 0.23 mJ/mm^2, 100 shocks per cm^2, every 2 weeks, 3 sessions in total) and 15 patients received traditional medical treatment only. The group with ESWT showed a decrease of pain measured by means of the Visual Analog Scale (from 8.633 ± 0.166 to 2.200 ± 0.221, $P < 0.0001$ vs from 8.630 ± 0.162 to 8.628 ± 0.158, $P = 0.973$) and a decrease in the size of heterotopic ossification measured by computed tomography (from 1.98 cm ± 0.34 to 0.88 ± 0.19, $P < 0.0001$ vs from 1.99 ± 0.36 to 1.96 ± 0.34, $P = 0.816$).

7. Precautions and undesirable effects

ESWT device manufacturers and the International Society for Medical Shockwave Treatment contraindicate the use of this therapy in cases of suspected malignancy in the area to be treated, when this area is close to any of these structures: head, spine, lungs, bowels, gonads, fetus in pregnant women or electronic implants, or in the presence of severe coagulopathy [44]. The undesirable effects described in the literature are pain during or as a consequence of the treatment, redness of the skin, petechiae, migraine, nausea or even syncope [6,44]. In studies performed in burn patients however, only pain (30%) [31,35].

8. Limitations

The main limitation has to do with animal experimentation [27–30] since it has been stated that the extrapolation to humans of the results found after animal research are not reliable [45]. Besides, the most promising findings from animal studies often fail in human trials and are rarely adopted into clinical practice [46].

Other limitation is the lack of a control-group in some of the quasi-experimental studies [31,35,42] which does not allow to prove a significant correlation between ESWT and the measured outcomes.

The controlled studies were either no-blind [32,39,43] or single-blind [40,41] and therefore can be influenced by placebo effect or observer bias.

The paucity of studies and their discrepancy in terms of type of study, ESWT parameters, measuring tools and timing make it very difficult to combine the results in order to obtain solid evidence.

9. Conclusions

Scientific evidence on the use of ESWT in burn injuries and post-burn scars is scarce and weak given the small number of published studies and their low quality. This review analyzed 14 studies about the use of ESWT in acute burn injuries and its sequelae, published between 2005 and 2018. Only nine of the studies were carried on in humans and only five of these included a control group. The physical parameters of the shock waves employed, the measuring tools and the timing were different in most studies and therefore no definitive findings can be drawn. Many questions regarding its use, indications and biological effects have not been answered yet.

However, current literature suggests that ESWT could be a useful tool in this field. ESWT could improve the healing of acute burns and the appearance, itching and pain of burn scars.

Our present knowledge on ESWT though does not allow to elaborate a standardized protocol for its application in burn patients. More quality studies should be conducted to get a better understanding of ESWT applied to burn injuries in order to establish an optimal dosage (energy flux density and number of shocks) at each moment of the burn healing process and to decide for how long ESWT sessions should be held and with what frequency. Besides, further study on how mechanical energy affects each step of the burn healing process would be helpful.

Conflict of interest

None of the authors has any financial interest whatsoever in any techniques or instruments mentioned in this article.

REFERENCES

[1] Broughton G, Janis JE. Wound healing: an overview. Plast Reconstr Surg 2006;117(7 Suppl):1e-S-32e-S.
[2] Wolfram D, Tzankov A, Pülzl P, Piza-katzer H. Hypertrophic scars and keloids—a review of their pathophysiology, risk factors, and therapeutic management. Dermatol Surg 2009;35 (2):171–81.
[3] Finnerty CC, Jeschke MG, Branski LK, Barret JP, Dziewulski P, Herndon DN. Hypertrophic scarring: the greatest unmet challenge after burn injury. Lancet 2016;388(10052):1427–36.
[4] Cotsarelis G. Epithelial stem cells: a folliculocentric view. J Invest Dermatol 2006;126:1459–68.
[5] Mittermayr R, Antonic V, Hartinger J, Kaufmann H, Redl H, Téot L, et al. Extracorporeal shock wave therapy (ESWT) for wound healing: technology, mechanisms, and clinical efficacy. Wound Repair Regen 2012;20(4):456–65.
[6] Dymarek R, Halski T, Ptaszkowski K, Slupska L, Rosinczuk J, Taradaj J. Extracorporeal shock wave therapy as an adjunct wound treatment: a systematic review of the literature. Ostomy Wound Manage 2014;60(7):26–39.

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

[7] Chaussy C, Brendel W, Schmiedt E. Extracorporeally induced destruction of kidney stones by shock waves. Lancet 1980;2 (8207):1265–8.

[8] Chen YJ, Wang CJ, Yang KD, Kuo YR, Huang HC, Sun YC, et al. Extracorporeal shock waves promote healing of collagenase-induced Achilles tendinitis and increase TGF-beta1 and IGF-I expression. J Orthop Res 2004;22(4):854–61.

[9] Xu ZH, Jiang Q, Chen DY, Xiong J, Shi DQ, Yuan T, et al. Extracorporeal shock wave treatment in nonunions of long bone fractures. Int Orthop 2008;33(3):789–93.

[10] Elster E, Stojadinovic A, Forsberg J, Shawen S, Andersen R, Schaden W. Extracorporeal shock wave therapy for nonunion of the tibia. J Orthop Trauma 2010;24(3):133–41.

[11] Sun J, Gao F, Wan Y, Sun W, Jiang B, Li Z. Extracorporeal shock wave therapy is effective in treating chronic plantar fasciitis: a meta-analysis of RCTs Roever L. ed. Medicine 2017;96(15):e6621.

[12] Ennis WJ, Foremann P, Mozen N, Massey J, Conner-Kerr T, Meneses P. Ultrasound therapy for recalcitrant diabetic foot ulcers: results of a randomized, double-blind, controlled, multicenter study. Ostomy Wound Manage 2005;51:24–39.

[13] Schaden W, Thiele R, Kolpl C, Pusch M, Nissan A, Attinger CE, et al. Shock wave therapy for acute and chronic soft tissue wounds: a feasibility study. J Surg Res 2007;143:1–12.

[14] Saggini R, Figus A, Troccola A, Cocco V, Saggini A, Scuderi N. Extracorporeal shock wave therapy for the management of chronic ulcers in the lower extremities. Ultrasound Med Biol 2008;34(8):1261–71.

[15] Jeppesen SM, Yderstraede KB, Rasmussen BS, Hanna M, Lund L. Extracorporeal shockwave therapy in the treatment of chronic diabetic foot ulcers: a prospective randomized trial. J Wound Care 2016;25(11):641–9.

[16] Moher D, Liberti A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6(7): e1000097.

[17] Ottomann C, Hartmann B, Tyler J, Maier H, Thiele R, Schaden W, et al. Prospective randomized trial of accelerated re-epithelization of skin graft donor sites using extracorporeal shock wave therapy. J Am Coll Surg 2010;211:361–7.

[18] Wang FS, Yang KD, Wang CJ, Huang HC, Chio CC, Hsu TY, et al. Shockwave stimulates oxygen radical-mediated osteogenesis of the mesenchymal cells from human umbilical cord blood. J Bone Miner Res 2004;19:973–82.

[19] Hayashi D, Kawakami K, Ito K, Ishii K, Tanno H, Imai Y, et al. Low-energy extracorporeal shock wave therapy enhances skin wound healing in diabetic mice: a critical role of endothelial nitric oxide synthase. Wound Repair Regen 2012;20(6):887–95.

[20] Link KA, Loenig JB, Silveira A, Plattner BL, Lillie BN. Effect of unfocused extracorporeal shock wave therapy on growth factor gene expression in wounds and intact skin of horses. Am J Vet Res 2013;74(2):324–32.

[21] Suhr F, Delhasse Y, Bungartz G, Schmidt A, Pfannkeche K, Bloch W. Cell biological effects of mechanical stimulations generated by focused extracorporeal shock wave applications on cultured human bone marrow stromal cells. Stem Cell Res 2013;11(2):951–64.

[22] Weihs AM, Fuchs C, Teuschl AH, Hartinger J, Slezak P, Mittermayr R, et al. Shock wave treatment enhances cell proliferation and improves wound healing by ATP realease-coupled extracellular signal-regulated kinase (ERK) activation. J Biol Chem 2014;289(39):27090–104.

[23] Aschermann I, Noor S, Venturelli S, Sinnberg T, Mnich CD, Busch C. Extracorporeal shock waves activate migration, proliferation and inflammatory pathways in fibroblasts and keratinocytes, and improve wound healing in an open-label, single-arm study in patients with therapy-refractory chronic leg ulcers. Cell Physiol Biochem 2017;41(3):890–906.

[24] Birgin E, Gebhardt C, Hetjens S, Fischer S, Rückert F, Reichenberger MA. Extracorporeal shock wave therapy enhances receptor for advanced glycated end-product-dependent flap survival and angiogénesis. Ann Plast Surg 2018;80(4):424–31.

[25] Ingber DE. Cellular mechanotransduction: putting all the pieces together again. FASEB J 2006;20(7):811–27.

[26] Merier R, Kamelger FS, Piza-Katzer H. Shock wave therapy: an innovative treatment method for partial thickness burns. Burns 2005;31(7):921–2.

[27] Davis TA, Stojadinovic A, Anam K, Amare M, Naik S, Peoples GE, et al. Extracorporeal shock wave therapy suppresses the early proinflammatory immune response to a severe cutaneous burn injury. Int Wound J 2009;6(1):11–21.

[28] Goertz O, Lauer H, Hirsch T, Ring A, Lenhardt M, Langer S, et al. Extracorporeal shock waves improve angiogénesis after full thickness burn. Burns 2012;38(7):1010–8.

[29] Goertz O, von der Lohe L, Lauer H, Khosrawipour T, Ring A, Diageler A, et al. Repetitive extracorporeal shock wave applications are superior in inducing angiogénesis after full thickness burn compared to single application. Burns 2014;40 (7):1365–74.

[30] Djedovic G, Kamelger FS, Jeschke J, Piza-Katzer H. Effect of extracorporeal shock wave treatment on deep partial-thickness burn injury in rats: a pilot study. Plast Surg Int 2014;2014:495967.

[31] Arnó A, García O, Hernán I, Sancho J, Acosta A, Barret JP. Extracorporeal shock waves, a new non-surgical method to treat severe burns. Burns 2010;36(6):844–9.

[32] Ottoman C, Stojadinovic A, Lavin PT, Gannon FH, Heggeness MH, Thiele R, et al. Prospective randomized phase II trial of accelerated reepithelization of superficial second-degree burn wounds using extracorporeal shock wave therapy. Ann Surg 2012;255(1):23–9.

[33] Bombaro KM, Engrav LH, Carrougher GJ, Wiechman SA, Faucher L, Costa BA, et al. What is the prevalence of hypertrophic scarring following burns? Burns 2003;29(4):299–302.

[34] Stekelenburg CM, Marck RE, Tuinebreijer WE, de Vet HC, Ogawa R, van Zuijlen PP. A systematic review on burn scar contracture treatment: searching for evidence. J Burn Care Res 2015;36(3):e153–61.

[35] Fioramonti P, Cigna E, Onesti MG, Fino P, Fallico N, Scuderi N. Extracorporeal shock wave therapy for the management of burn scars. Dermatol Surg 2012;28(5):778–82.

[36] Cui HS, Hong AR, Kim JB, Yu JH, Cho YS, Joo SY, et al. Extracorporeal shock wave therapy alters the expression of fibrosis-related molecules in fibroblast derived from human hypertrophic scar. Int J Mol Sci 2018;19(1):124.

[37] Zhao JC, Zhang BR, Shi K, Wang J, Yu JA. Lower energy radial shock wave therapy improves characteristics of hypertrophic scar in a rabbit ear model. Exp Ther Med 2018;15(1):933–9.

[38] Saggini R, Saggini A, Spagnoli AM, Dodaj I, Cigna E, Maruccia M, et al. Extracorporeal shock wave therapy: an emerging treatment modality for retracting scars of the hands. Ultrasound Med Biol 2016;42(1):185–95.

[39] Zaghloul MS, Khalaf WN, Thabet WN, Asham HN. Effect of extracorporeal shock wave therapy on Post Burn Scars. Int J PharmTech Res 2016;9(3):78–85.

[40] Cho YS, Joo SY, Cui H, Cho SR, Yim H, Seo CH. Effect of extracorporeal schock wave therapy on scar pain in burn patients: a prospective, randomized, single-blind, placebo-controlled study. Medicine (Batimore) 2016;95(32):e4575.

[41] Joo SY, Cho YS, Seo CH. The clinical utility of extracorporeal shock wave therapy for burn pruritus: a prospective, randomized, single-blind study. Burns 2018;44(3):612–9.

[42] Taheri P, Khosrawi S, Mazaheri M, Parsa MA, Mokhtarian A. Effect of extracorporeal shock wave therapy on improving burn scar in patients with burnt extremities in Infahan, Iran. J Res Med Sci 2018;23:81.

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023

[43] Mowafy ZME, Monem MA, Khowailed KA-E, Shawky OM. Efficacy of extracorporeal shock wave in the treatment of heterotopic ossification in burned patients. Int J PharmaTech Res 2016;9(5):46–52.

[44] International Society for Medical Shockwave Treatment. Consensus statement on extracorporeal shockwave technology indications and contraindications. October. . http://www.ismst.com.

[45] Greek R, Pippus A, Hansen LA. The Nuremberg Code subverts human health and safety by requiring animal modeling. BMC Med Ethics 2012;13:16.

[46] Pound P, Bracken MB. Is animal research sufficiently evidence based to be a cornerstone of biomedical research? BMJ 201430: g3387.

Please cite this article in press as: J. Aguilera-Sáez, et al., Extracorporeal shock wave therapy role in the treatment of burn patients. A systematic literature review, Burns (2019), https://doi.org/10.1016/j.burns.2019.07.023