Horizon Scanning in Surgery: Application to Surgical Education and Practice

Extracorporeal Shock Wave Therapy for Wound Healing

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Disclaimer

This report is not a comprehensive systematic review. Rather, it is an assessment of an emerging surgical procedure or technology in which the methodology has been limited in one or more areas to shorten the timeline for its completion.

Therefore, this report is a limited evidence-based assessment that is based on a search of studies published in the peer-reviewed literature. This report is based on information available at the time of research and cannot be expected to cover any developments arising from subsequent improvements in health technologies. This report is based on a limited literature search and is not a definitive statement on the safety, effectiveness or cost-effectiveness of the health technology covered.

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Objective

This horizon scanning assessment provides short, rapidly completed, “state of play” documents. These provide current information on technologies to alert clinicians, planners and policy makers of the advent and potential impact of a new or emerging procedure or device. This information can then assist clinicians, planners and policy makers to control and monitor the introduction of new health technologies as well as assist in the prioritization and allocation of resources to promote efficient utilization of available resources.

This report is a preliminary summary of the safety and effectiveness of extracorporeal shock wave therapy for the facilitation of reepithelialization and closure of chronic and non-healing wounds.

Acronyms

ESWT	Extracorporeal shock wave therapy
FDA	Food and Drug Administration
HBOT	Hyperbaric oxygen therapy
NGC	National Guideline Clearinghouse
NICE	National Institute for Health and Care Excellence
RCT	Randomized control trial
TBSA	Total body surface area

Introduction

Background

Chronic soft tissue wounds are an extraordinary burden to patients' quality of life, as well as to health systems. Chronic wounds are defined as wounds that have not undergone orderly and timely tissue repair to reconstitute anatomic and functional integrity after several months (Mittermayr et al. 2012). The etiology of chronic wounds is varied. Common chronic wounds are mostly superficial and dermatological wounds including skin ulcers, burn wounds and skin graft wounds.

Extracorporeal shock wave therapy (ESWT), which is commonly used to treat urolithiasis, has emerged as a new technology to treat chronic wounds. Although the action of mechanisms of ESWT is not yet elucidated, it has been proven in many clinical trials to be safe and effective in facilitating wound closure and reepithelialization. Compared with standard wound care, ESWT provides benefits of non-invasiveness, low complications and adverse event rates.

Burden of disease

In the United States, chronic wounds affect around 6.5 million people. This number is rapidly growing due to the aging population and the sharp rise in incidence of diabetes and obesity. The latest data from the National Center for Health Statistics showed that approximately 71.5 million patients were treated with surgical procedures in either in-patient or out-patient settings in the United States in 2000. The need for post-surgical wound care is sharply on the rise (Sen et al. 2009). Without proper wound care procedures, the immense economic and social impact on patients due to delayed or non-healing wounds could be overwhelming.

In particular, burn injuries are one of the greatest contributions to the burden of wounds. Burn injuries rank in the top 15 leading causes of burden of disease around the world according to the World Health Organization (WHO 2012). Burns are more common in children and the elderly as well as among populations with poorer socioeconomic status. The majority of burn injuries are unintentional. The American Burn Association has estimated that 450,000 people are treated for burns every year, and a large proportion of these patients (40,000) require hospitalization. The mean age of patients presenting with burns injuries is 32 years, and nearly 70% of burn patients are men. Burn injuries are most prevalent among white Americans (59%). The majority (72%) of reported burns covers less than 10% of the total body surface area (TBSA), and the mortality rate as a result of burns is approximately 0.06%. Burn injuries most commonly occur at home (ABA 2012).

Technology

ESWT has been used in the treatment of kidney stones for several decades (Qureshi et al. 2011). In recent years, ESWT has emerged as a new approach to treat various other conditions including bone fracture (Elster et al. 2010), pain due to musculoskeletal disorders such as tendonitis (Gruenwald et al. 2013) and epicondylitis (Maffulli et al. 2010), burn wounds (Fioramonti et al. 2012), and ulcers (Dinh, Elder & Veves 2011).

The shock waves for ESWT are generated using an electrohydraulic, electromagnetic, or piezoelectric generator. For chronic wounds, ESWT is applied within 24 hours of wound debridement. Sterile ultrasound conducting gel is often applied to the wound surface, and a sterile plastic protective film is placed directly on the wound surface (Ottomann et al. 2012). Unfocused shock waves are then applied through the gel and the protective film to wounds. The density and duration of the shock waves vary according to the characteristics of the wound. The applied energy density ranges from 0.03 mJ/mm^2 to 0.1 mJ/mm^2, and the number of pulses varies from 25 to 800 (Qureshi et al. 2011).

Action of Mechanism

The biological mechanism by which ESWT promotes wound healing is not yet understood. It has been shown that superficial tissue perfusion can be significantly enhanced by the application of shock waves (Arno et al. 2010; Wang, Wu & Yang 2011). However, it is also theorized that the increased levels of nitric oxide produced by shock wave administration assists neovascularization and reepithelialization (Ito, Fukumoto & Shimokawa 2011; Jargin 2010; Mittermayr et al. 2012; Sansone et al. 2012). Shock wave therapy may also lessen local inflammatory reactions (Tinazzi et al. 2011).

Stage of Development

There have been three generations of shock wave generators developed: the electrohydraulic mode was the first generation and is the most widely used method. In the mid-nineties, electromagnetic shock wave generators (second generation) emerged with the improvement of producing less noise. The third, and the most recent, generation of ESWT generators uses crystal or ceramic material to produce shock waves referred to as the piezoelectric generator. This generator creates more stable shock waves with minimal noise but with much higher price.

Regulatory Approval

Fifty extracorporeal shock wave devices have been identified as having approval by the United States Food and Drug Administration (US FDA). However, none of these devices have been approved for wound healing purposes. Indications of conditions approved by FDA include lithotripsies and pain relief.

The following ESWT devices were used in the studies included in this report:

- DermaPACE® by SANUWAVE Health, Inc. (Alpharetta, GA, USA) (Wang, Wu & Yang 2011)
- DermaGold® by MTS Europe GmbH (Konstanz, Germany; TÜV Rheinland CE 1275) (Ottomann et al. 2010; Ottomann et al. 2012)
- Minilith SL1® by Storz Medical (Tagerwilen, Switzerland) (Moretti et al. 2009)

The Australian authority (Australian Therapeutic Goods Administration; TGA) has approved the Dermatological Extracorporeal Shock Wave Therapy System, manufactured by Aurura BioScience Pty Ltd (Baulkhan Hills, NSW Australia). This device is specifically approved for the indication of soft tissue injury and subcutaneous wounds. Examples of subcutaneous wounds, given by the TGA, include arterial, venous, diabetic or pressure ulcers; burns; and postoperative or traumatic wounds.

Current Clinical Trials

A search of Clinicaltrial.gov identified seven clinical trials that are directly focused on the use of ESWT for wound healing (Table 1).

Table 1: Current clinical trials involving extracorporeal shock wave therapy for the treatment of wounds

Study Name/ID/Location	Study Design	Clinical Interventions	Study Size and Wound Type	Study Status/End Date
Extracorporeal Shockwave Treatment for Chronic Soft Tissue Wounds NCT00545896 Austria	Non-randomized, single group assignment, interventional, safety/efficacy study	Application of extracorporeal shock waves on the surface of chronic wounds which have not been successfully treated	N=282 General chronic wounds caused by injuries, ulcers and surgeries	Completed/June 2010
Healing of Burns and the Effect of Shockwave Therapy on the Recovery of Skin Grafts NCT01242423 Berlin, Germany	Randomized, parallel assignment, non-blinded safety/efficacy study	Patients with skin graft donor site wounds • receiving standard wound care (n=50) versus • receiving ESWT (n=50) Additional patients (n=50) with superficial second degree burn wounds also receiving ESWT	N=150 Skin graft wounds	Completed/October 2010
Study to Determine if Shock Wave Therapy Applied to Traumatic Wounds of the Extremity Improves Healing Time (CWI) NCT00486733 District of Columbia, United States	Randomized, parallel assignment, double blinded safety/efficacy study	Standard wound care versus standard wound care plus ESWT for soft tissue wounds	N=213 (estimated) Traumatic wounds	Ongoing and recruiting/ December 2014
Safety & Efficacy Study for the Use of Extracorporeal Shockwaves in the Treatment of Diabetic Foot Ulcers NCT00366132 Multi-state, USA	Randomized, controlled, non-blinded efficacy/safety study	Standard wound care versus standard wound care plus ESWT for soft tissue wounds	N=200 Plantar foot ulcers	Not reported/ Not reported
Comparing the Expected Benefit of Extra-corporeal-shockwave Therapy (ESWT) Treatment to Standard Care in Treating Diabetic Foot Ulcers NCT01499472 Israel	Randomized, double-blinded control trial for efficacy	Standard wound care versus standard wound care plus ESWT for soft tissue wounds	N=300 (estimated) Diabetic ulcer	Not yet recruiting/ Not reported

Current treatment and alternatives

Many standard cares and therapeutic approaches have been utilized to treat chronic superficial wounds. Conventional clinical standards of practice include adequate wound bed preparations with surgical and nonsurgical debridement, specialized wound dressing to provide the wound with a moist environment and interventions to attain adequate vascular inflow and outflow to avoid pressure necrosis.

Current management of wounds starts with wound assessment. A number of wound assessment tools exist, allowing determination of wound progress. After assessing the wound, wound bed preparation is normally performed. Wound bed preparation requires debridement, moisture balance and bacterial balance. It has been defined as the general management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures (Schultz et al. 2004). The debridement of wounds is a key aspect of wound healing. Frequent maintenance of debridement is required to remove debris which is no longer responsive to cellular growth factors and may impair healing (Stephen-Haynes & Thompson 2007). A moist environment is beneficial for wound healing. Direct methods of dealing with wound exudate are well known as compression bandaging, highly absorbent dressings or mechanical systems (Harding, Morris & Patel 2002). However, excessive exudate is a manifestation of heavy colonization of bacteria, indicating a constant pro-inflammatory stimulus in the wound (Chen & Li 2013). Therefore, antiseptics and antibiotics are used to deal with infections.

Additionally, many adjunctive therapies have been used to facilitate the healing. Examples include negative pressure wound therapy, hyperbaric oxygen therapy (HBOT) and ultrasound. Other experimental treatments, including gene therapy and bioengineered skin and stem cell therapy, are on the horizon to be evaluated and further improved (Cha & Falanga 2007; Eming, Krieg & Davidson 2007).

However, treatment of chronic wounds is often insufficient and prolonged (Mittermayr et al 2012). Due to the variety in etiology of wounds, the wound management process, especially for chronic wounds, is a complex system (ABA 2012). Evidence-based guidelines and clinical algorithms can be found in clinical practice to deal with traumatic wounds. However, the process can be very time and resource demanding. Therefore, extracorporeal shockwave therapy has been innovated over time to facilitate the wound healing process, as well as to reduce the patients' suffering and the tremendous costs to the health system.

Literature Review

Search criteria

Keywords/MeSH terms utilized:

Search Strategy for PubMed

#1 extracorpor*[tw]
#2 shockwave*[tw]
#3 shock wave*[tw]
#4 #2 OR #3
#5 #1 AND #4
#6 "wound healing"[mesh]
#7 "wound healing*"[tw]
#8 "wound recover*"[tw]
#9 "wound regenerat*[tw]
#10 "wound repair*"[tw]
#11 #6 OR #7 OR #8 OR #9 OR #10
#12 #5 AND #11

Search Strategy for Ovid EMBASE

#1 extracorpor*
#2 'shock wave'/syn OR shockwave* OR (shock AND wave*)
#3 #2 AND #3
#4 'wound healing'/syn
#5 ('wound'/de OR wound) AND ('healing'/de OR healing)
#6 wound AND (regenerat* OR repair* OR recover*)
#7 wound AND (vasculari* OR angiogenes*)
#8 'stem cell'/syn OR (stem AND cell*)
#9 'nitrous oxide'/syn OR 'nitrous oxide'
#10 #4 OR #5 OR #6 OR #7 OR #8 #9
#11 #3 AND #10

Databases utilized:

PubMed, Ovid EMBASE, the Cochrane Database of Systematic Reviews, the York CRD databases, National Guideline Clearinghouse, NICE, Guideline International Network.

Inclusion criteria

Inclusion criteria used to determine study eligibility are listed in Table 2.

Table 2: Inclusion criteria for identification of relevant studies

Characteristics	Criteria
Publication type	Randomized controlled trials only
Publication date	2000 onwards
Patients	Patients with superficial epidermal wounds including burn wounds, skin graft wounds and ulcers
Intervention	Extracorporeal shock wave therapy
Comparator	Standard wound care or hyperbaric oxygen therapy
Outcome	Wound healing time, neo-vascularization and reepithelialization, adverse events
Language	English only

Studies identified in the literature search which were excluded from this assessment are listed in Appendix C.

Included studies

A total of ten clinical trials were identified from the literature search as eligible for inclusion. Four of these were randomized control trials (RCTs) and hence selected for inclusion in this report. Two relevant systematic reviews were also identified. Since the two systematic reviews include some studies which would be formally discussed in this report in detail, these two identified systematic reviews will not be closely examined again. However, the two systematic reviews consistently acknowledge the effectiveness of ESWT in general and suggest further and more robust clinical trials be performed to test its efficacy in wound healing.

Each of the included studies was designated a level of evidence according to the National Health and Medical Research Council (NHMRC) hierarchy of evidence (Appendix A). Further study details are provided in Appendix B, with excluded studies and reasons for exclusion provided in Appendix C. The characteristics of the included studies are outlined in Table 3. Two of the included studies focused on diabetic foot ulcers (Moretti et al 2009; Wang, Wu & Yang 2011), one on second degree burns (Ottomann et al 2012), and the last focused on epidermis wounds associated with skin graft donor sites (Ottomann et al 2010). Three of the four included studies used the conservative treatment for wounds as the comparator and Wang Wu and Yang (2011) used HBOT as the comparator.

Although the four included studies focus on different types of dermatological or skin wounds, the way in which they heal is similar (i.e. inflammation, proliferation, epithelialization etc.), therefore, it was deemed appropriate to group them based on measuring the therapeutic effect of extracorporeal shock wave therapy.

Table 3: Included studies characteristics

Study/Location/Wound type	Level of evidence/Blinding/ Control	Number of patients	Follow-up
Moretti et al. (2009) Italy Diabetic foot ulcer	Level II No blinding Conservative treatment	ESWT group n=15 Control group n=15	Duration: 20 weeks Loss of follow-up=NR
Ottoman et al. (2010) Germany Skin graft donor site	Level II Double blinded Conservative treatment	ESWT group n=13 Control group n=15	Duration: not reported Loss of follow-up=NR
Ottoman et al. (2012) Germany Burn	Level II Single-blind Conservative treatment	ESWT group n=22 Control group n=22	Duration: 13 days Loss of follow-up=6
Wang, Wu & Yang (2011) Taiwan Diabetic foot ulcer	Level II No blinding HBOT	ESWT group n=44 Control group n=40	Duration: 18 months Loss of follow-up=NR

NR = not reported; HBOT = hyperbaric oxygen therapy; ESWT = extracorporeal shockwave therapy

Moretti et al. (2009)

Moretti et al. (2009) evaluated the effectiveness of ESWT in the management of chronic diabetic foot ulcers. In this randomized, prospective, controlled study, researchers recruited 30 patients (aged from 30 to 70 years) who had a wound area of greater than 1 cm^2 that had not healed in six months. Half of the patients were treated with standard care plus shock wave therapy, while the other 15 patients were treated with standard care only. Standard care included debridement, adequate pressure relief and treatment of infection. There were no statistically significant differences between the two treatment groups at baseline with respect to patients' demographic data such as age and gender. The ulcer healing was evaluated over a 20-week follow-up period by measuring the rate of reepithelialization.

Ottomann et al. (2010)

This RCT investigated the effectiveness of ESWT in of the repair of soft tissue wounds. Twenty-eight patients with acute traumatic wounds and burns requiring skin grafting were randomly assigned in a 1:1 fashion to receive standard topical therapy (non-adherent silicone mesh) to their graft donor sites, with (n=13) or without (n=15) defocused ESWT (100 impulses/cm^2 at 0.1 mJ/mm^2). ESWT was applied once to the donor site, immediately after skin harvest. The age of the included patients ranged from 18 to 30 years; there were no statistically significant differences between the treatment groups with respect to patients' age and gender. The primary endpoint was time to complete donor site epithelialization, which was determined by an independent observer who was blinded to treatment allocation.

Ottomann et al. (2012)

This study focused on how shock wave therapy affects burn wounds. A predefined cohort of 50 patients with acute second-degree burns were selected from a larger study of 100 patients and randomly assigned to receive standard therapy with (n=22) or without (n=22) defocused ESWT

between December 2006 and December 2007. Standard therapy consisted of burn wound debridement and topical antiseptic therapy, and ESWT was applied once to the burn after debridement (100 impulses/cm at 0.1 mJ/mm). The primary endpoint, time to complete burn wound epithelialization, was determined by an independent, blinded-observer. A worst case scenario was applied to those lost to follow-up to rule out the impact of withdrawal bias. There were six patients with incomplete data or lost to follow-up. Patient characteristics across the two study groups were balanced ($p > 0.05$) with respect to patients' demographic information except that the patients in the ESWT group were older than those in the standard care group (53 years versus 38 years, $p = 0.002$).

Wang, Wu and Yang (2011)

This study compared the effectiveness of ESWT with HBOT in healing chronic diabetic foot ulcers. The trial included 88 diabetic patients (93 wounds) with chronic foot ulcers. All patients were randomized after pre-treatment evaluation and there were no statistically significant differences between the treatment groups with respect to patients' demographic parameters. The ESWT group (39 patients/44 feet) received shock wave therapy twice per week for a total of six treatments. The comparator group (38 patients/40 feet) received HBOT daily for a total of 20 treatments. Evaluations included clinical assessment, blood flow perfusion scans and histopathological examination.

Critical Appraisal

All of the included studies stated a clearly defined research question.

Randomization method was reported in two of the four included studies (Ottoman et al. 2010; Ottoman et al. 2012). These same studies undertook blinding of their patients and assessors in order to ensure allocation concealment. The reported method of allocation concealment is appropriate in both included studies.

There were no significant differences in patient demographics between the treatment groups in any of the four included studies. The number of patients enrolled in each study ranged from 28 to 30, which is acceptable. Patient selection criteria were reported in all of the included studies. The rate of losses to follow-up is notable in two of the included studies: 12 per cent (6/50) of patients were lost to follow-up and excluded from analysis in Ottomann et al. (2012) and 10 per cent (9/86) of patients were lost to follow-up in Wang, Wu and Yang (2011).

Although the outcomes reported across the four included studies all focused on wound healing and reepithelialization time, the way in which they were quantified varied. The common approach used to determine wound closure included observation and/or photographic documentation. The observation of wound closure and/or over 95% reepithelialization was defined as the clinical endpoint by all studies during the follow-up and assessment period. Additional clinical assessment methodologies were also used. Blood flow perfusion scans and histopathological examinations were performed before and after the intervention in the study by Wang, Wu and Yang (2011). Reepithelialization index, which was quantified as mm^2 per die, was used in one of the studies (Moretti et al. 2011). However, a clear definition of the reepithelialization index was not identified; therefore, it may be problematic to compare results across the included studies. Using objective measures of wound healing to allow for less biased inter-group and inter-study comparisons is necessary.

No statistical power information is reported in the included studies. Confounding factors were identified. For example, in the burn wound study conducted by Ottomann et al. (2010), there was a significant difference in the age of participants between the treatment groups. Missing values, possibly caused by losses to follow-up, were influential in this study as well. However, no imputation methods were used to minimize the bias.

Safety and Efficacy

Safety

Mortality

None of the four included studies reported deaths after the application of shockwave therapy on all wounds. Due to the non-invasive, extracorporeal nature of the intervention, no ESWT-associated deaths were expected.

Complications

Potential complications due to the therapeutic effect of ESWT were considered in all of the included studies.

Extracorporeal Shockwave Therapy versus Standard Care

Three of the included RCTs that compared ESWT to standard wound care reported the incidence of complications. In Ottoman et al. (2012), approximately 9% (2/22) and 14% (3/22) of patients with burn wounds developed infections in the treatment and control groups, respectively. However, this difference was not statistically significant (p=0.99). No cardiac, neurologic, dermal, thermal or allergic adverse events occurred in either treatment group (Ottomann et al. 2010; Ottomann et al. 2012). Moretti et al. (2009) reported local signs of infection during the treatment course. The infection presented in one patient from each of the treatment groups and required the administration of oral antibiotics (Moretti et al. 2009). Both of the patients were free of symptoms within seven days of receiving medication and they both remained in the trial.

The aforementioned studies all acknowledged the limitations of their investigations around adverse events. As well as this, patient perceptions, including pain and symptom distress, were not addressed in those studies (Ottoman et al. 2010; Ottoman et al. 2012, Moretti et al. 2009). It was suggested that structured adverse event assessments should be conducted in the future.

Extracorporeal Shockwave Therapy versus Hyperbaric Oxygen Therapy

In the one study comparing ESWT to HBOT, there were no adverse events reported in the treatment group. However, the comparator group reported that participants developed complications including middle ear barotraumas and sinus pain. This potentially demonstrates the superiority of ESWT compared with HBOT; however, additional studies are required to support this. In all cases, adverse events resolved after the release of the chamber pressure.

Efficacy

The common efficacy endpoint reported across the included studies was time to wound closure and/or re-epithelialization. Additional clinical assessments included Doppler blood perfusion scans (Mittermayr et al. 2012; Wang, Wu & Yang 2011) and histopathological tissue examinations (Wang, Wu and Yang 2011), which will not be discussed here.

In all four studies, re-epithelialization and time to wound closure were significantly lower in the ESWT groups, compared with standard therapy or HBOT (Table 4).

Table 4: Efficacy of ESWT in the included studies

Study/ Wound size	Mean time of re-epithelialization (days)			Proportion of completion of wound closure (%)†	
	ESWT	Comparator	p-value	ESWT	Comparator
Moretti et al. 2009 Wound size: mean 300 mm^2 (SD 130)	60.8 [SD 4.7]	82.2 [SD 4.7]	<0.001	53.33% over 20 weeks	33.33% over 20 weeks
Ottoman et al. 2010 Wound size: 1% to 36% of TBSA	13.9 [SD 2.0]	16.7 [SD 2.0]	<0.001	100%‡	NR
Ottoman et al. 2012 Wound size: 1% to 30% of TBSA	9.6 [SD 1.7]	12.5 [SD 2.2]	<0.001	100% over 13 days	68% over 13 days
Wang, Wu & Yang 2009 Wound size: 1.5 cm^2 to 12 cm^2	NR	NR	NR	57% up to 18 months	25% up to 18 months

SD = standard deviation; TBSA = Total body surface area; NR = not reported
† the p-value for proportion of completion of wound closure was not reported except in Wang, Wu & Yang(2009) (p=0.003). The proportion is in respect to the wound not the patients. ‡ The time of completion of wound closure was not reported in this study.

Re-epithelialization process

Three of the four included studies assessed re-epithelialization (Moretti et al. 2009; Ottoman et al. 2010; Ottoman et al. 2012). This outcome was evaluated by subjective assessment in most cases. Moretti et al. (2009) also used a re-epithelialization index as a quantifiable measurement; however, the index was not clearly described.

A precise definition of re-epithelialization was not provided in any of the studies. The two studies by Ottoman et al. (2010 & 2012) defined the completion of reepithelialization as at least 95% of wounds being covered with full-thickness epidermis (Ottomann et al. 2012). The most remarkable acceleration of wound reepithelialization was reported as being up to 20 days faster than standard wound care over 20 weeks (Moretti et al. 2009).

Complete wound closure proportion across populations

The proportion of patients with complete wound closure between the treatment and control groups was significantly different during the treatment course in the four included studies. A noticeably larger proportion of patients undergoing ESWT had complete wound closure compared with standard care. Due to the different size and nature of wounds, the overall time required to achieve complete wound closure was different across the four included studies. The longest treatment duration and follow-up was up to 18 months. On average, approximately 30 per cent more patients had their wounds healed after ESWT compared with standard wound care.

Cost Impact

None of the included studies have considered the cost-effectiveness of ESWT and there does not appear to be any cost-effectiveness analyses available in the published literature. It has been pointed out, however, that ESWT is cost-effective in comparison with the traditional treatment course of chronic wounds, which is disproportionally prolonged and often insufficient (Mittermayr et al 2012). The studies included in this report show a significant reduction in time for wound closure when ESWT was administered, potentially reducing the need for prolonged wound dressing and care. The price of ESWT devices is not publicly available.

Clinical guidelines and consensus statements

No clinical guidelines or consensus statements for the use of ESWT in wound healing were identified in the published literature. However, guidelines for the use of extracorporeal shock wave therapy for treatment of other indications, such as plantar fasciitis, epicondylitis, and bone fracture have been found. Overall, these guidelines reported no safety concerns for ESWT. However, it was suggested that ESWT should only be used with special arrangements for clinical governance, consent and audit and research due to lack of consistent clinical conclusions.

Summary

From the data reported in the included trials, all patients experienced a noticeable reduction in healing time when treated with ESWT, compared with standard wound care and hyperbaric oxygen therapy. The primary clinical end point to wound healing, which was 95 per cent or more re-epithelialization, was determined by observations. The way in which these end points were defined was not clearly quantified or reported. Therefore, it is possible that what was considered 95 per cent re-epithelialization in one study was not consistent with the criteria of this outcome in others. No severe complications and adverse events were observed in the four included studies. ESWT has demonstrated superiority in regards to effectiveness when compared with other wound care approaches; however, this was obtained from preliminary data. More rigorous clinical studies are still needed to provide more solid evidence in this regard. Furthermore, the cost-effectiveness of the ESWT is still to be evaluated.

Recommendation

Due to the limitations of the evidence presented in this report, it is not possible to draw firm conclusions as to the efficacy of ESWT for the treatment of chronic superficial wounds.

The lack of explicit definitions of what is considered complete re-epithelialization or wound closure led to inconsistency in the primary clinical end point reported, both intra- and inter-study. Therefore, more robust and high-quality clinical trials are required in the future. Future research should also consider the mechanisms of ESWT and wound healing.

In addition, adverse events and complications of ESWT are not reported across the included studies and it is important these, along with patients' perceptions (including their experience with pain and quality of life), be addressed. Furthermore, cost-effectiveness information is needed to assess the applicability of ESWT in wound healing from the health economic perspective.

In summary, ESWT is a new way to treat chronic superficial wounds, especially for patients who have ulcers or burn wounds. However, it is too early to precisely assess the efficacy and cost-effectiveness of this new technology.

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Appendix A

NHMRC Evidence Hierarchy: designation of 'levels of evidence' according to type of research question

Level	Intervention [1]	Diagnostic accuracy [2]	Prognosis	Etiology [3]	Screening Intervention
I [4]	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies	A systematic review of level II studies
II	A randomized controlled trial	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among consecutive persons with a defined clinical presentation[6]	A prospective cohort study[7]	A prospective cohort study	A randomized controlled trial
III-1	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)	A study of test accuracy with: an independent, blinded comparison with a valid reference standard,[5] among non-consecutive persons with a defined clinical presentation[6]	All or none[8]	All or none[8]	A pseudorandomized controlled trial (i.e. alternate allocation or some other method)
III-2	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial[9] ▪ Cohort study ▪ Case-control study ▪ Interrupted time series with a control group	A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence	Analysis of prognostic factors amongst persons in a single arm of a randomized controlled trial	A retrospective cohort study	A comparative study with concurrent controls: ▪ Non-randomized, experimental trial ▪ Cohort study ▪ Case-control study
III-3	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm studies[10] ▪ Interrupted time series without a parallel control group	Diagnostic case-control study[6]	A retrospective cohort study	A case-control study	A comparative study without concurrent controls: ▪ Historical control study ▪ Two or more single arm study
IV	Case series with either post-test or pre-test/post-test outcomes	Study of diagnostic yield (no reference standard)[11]	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series	Case series

Explanatory notes

1 Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

2 The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes (Medical Services Advisory Committee 2005, Sackett and Haynes 2002).

3 If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilized. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Etiology' hierarchy of evidence should be utilized.

4 A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence. Systematic reviews of level II evidence provide more data than the individual studies and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review *quality* should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome/result as different studies (and study designs) might contribute to each different outcome.

5 The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study (Whiting et al 2003).

6 Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfill the requirements for a valid assembly of patients. However, in some cases, the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies, a selected sample of patients already known to have the disease is compared with a separate group of normal/healthy people known to be free of the disease. In this situation, patients with borderline or mild expressions of the disease, and conditions mimicking the disease, are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias or spectrum effect because the spectrum of study participants will not be representative of patients seen in practice (Mulherin and Miller 2002).

7 At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomized controlled trial with persons either non-diseased or at the same stage of the disease in *both* arms of the trial would also meet the criterion for this level of evidence.

8 All or none of the people with the risk factor(s) experience the outcome, and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus, and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

9 This also includes controlled before-and-after (pre-test/post-test) studies, as well as adjusted indirect comparisons (i.e. utilize A vs. B and B vs. C to determine A vs. C, with statistical adjustment for B).

10 Comparing single arm studies (i.e. case series from two studies). This would also include unadjusted indirect comparisons (i.e. utilize A vs. B and B vs. C to determine A vs. C but where there is no statistical adjustment for B).

11 Studies of diagnostic yield provide the yield of diagnosed patients, as determined by an index test, without confirmation of the accuracy of this diagnosis by a reference standard. These may be the only alternative when there is no reliable reference standard.

Note A: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomized controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note B: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence, level IV diagnostic evidence, or level III-2 prognostic evidence.

Source: Hierarchies adapted and modified from: NHMRC 1999; Bandolier 1999; Lijmer et al. 1999; Phillips et al. 2001.

Appendix B

Profile of the included studies

Study	Ottoman et al. 2012	Ottoman et al. 2010	Moretti et al. 2009	Wang, Wu & Yang 2009
Number of Patients	44	28	30	84
Age	18–80	18–80	30–70	20–81
Number of Wounds	n/a	28	30	36
Nature of Wounds	Non-healing burn wound	Skin graft donor site	Diabetic ulcer	Diabetic ulcer
Size of Wound	Second-degree burn wound from 1% to 30% of the TBSA	Wound from 1% to 36% of the TBSA	300 [SD 130mm^2]	From 1.5 cm^2 to 12 cm^2
Comparator	Standard wound dressing	Standard wound dressing	Standard wound dressing	Hyperbaric Oxygen Therapy
ESWT Specification	0.1 mJ/mm^2 for 100 pulses/cm^2	0.1 mJ/mm^2 for 100 pulses/cm^2 over 500 pulses	0.03 mJ/mm^2 for 100 pulses/cm^2 pulse number not provided	0.11 mJ/mm^2 for 100 pulses/cm^2 over 300 pulses
Shock wave generator	Electrohydraulic generator	Electrohydraulic generator	Electromagnetic generator	Electrohydraulic generator

TBSA = total body surface area

Appendix C

Excluded Studies

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