ORIGINAL ARTICLE

Extracorporeal shockwave therapy for the treatment of chronic wound of lower extremity: current perspective and systematic review

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Abstract

The purpose of this study was to provide an up-to-date review for the accurate estimation of the efficacy of extracorporeal shock wave therapy (ESWT) on the healing of chronic wounds on the lower extremity (CWLE). A systematic review of 10 databases for clinical trials about ESWT in the management of CWLE published between 2000 and 2016 was performed. A total of 11 studies with 925 patients were found. Expert therapists assessed the methodological qualities of the selected studies using the Physiotherapy Evidence Database (PEDro) scale and categorised each study according to Sackett's levels of evidence. Eight studies were categorised as level II; two studies were categorised as level III and one study was categorised as level V. In conclusion, this review demonstrated mild to moderate evidence to support the use of ESWT as an adjuvant therapy with a standardised wound care programme. However, it is difficult to draw firm conclusions about the efficacy of ESWT. So, future researches with high methodological quality are required to assess the efficacy and cost-effectiveness of this relatively new physical therapy application.

Introduction

Chronic wounds are defined as wounds that are unresponsive to initial therapy or the failure of proper care to produce anatomic and functional integrity over a period of 3 months (1,2). Chronic wounds of the lower extremities (CWLEs) have a significant effect on the amount of resources spent every year to treat, prevent or slow down the progress of the disease (1,3,4). CWLEs cause limitations in daily living activities, impaired mobility and decreased work capacity, restricted social activities and negative body image, loss of productivity and reduced quality of life (5,6).

The most common types of CWLEs are described by their aetiology. These include venous, arterial, neurotrophic, lymphatic, malignant, infectious and inflammatory (7,8). Currently, 15% of diabetic patients will develop CWLEs, and about 25% of those will have to undergo amputation (9,10). However,

Key Messages

- chronic wounds of the lower extremities (CWLEs) cause limitations in daily living activities, impaired mobility and decreased work capacity, restricted social activities and negative body image, loss of productivity and reduced quality of life
- extracorporeal shock wave therapy (ESWT) is considered feasible for healing of chronic wounds in humans and may play an important role in wound care once evidence-based practice guidelines are developed
- the evidence demonstrated mild to moderate support for the use of ESWT as an adjuvant therapy with a standardised wound care programme

the most common cause of chronic ulceration of the lower extremities is venous insufficiency. Although the risk of amputation associated with venous ulceration is lower than diabetic ulceration, the prognosis for healing is only 40%, and the rate of recurrence averages 75% (11).

Treatment of chronic wounds involves various approaches to protect and promote healing. These include hyperbaric oxygen therapy (HBOT) (12), vacuum-assisted wound closure (13), low-level laser therapy (14) and electrical stimulation (15). However, results from these studies are inconsistent and reported limited success with no conclusive remark on its effect (12–17).

A relatively new physical therapy application for chronic wounds is represented by extracorporeal shock wave therapy (ESWT). ESWs are biphasic acoustic waves, characterised by a high-peak pressure (up to 100 MPa), short-time duration (<1000 ns) and rapid rise in pressure (< 10 ns) (18–21). For the past 20 years, ESWT has been used for the treatment of musculoskeletal disorders (22–25).

In traditional ESW devices, an electromagnetic, electrohydraulic or piezoelectric source generates shock waves that concentrate ('focus') the acoustic energy beam on the target by means of a parabolic lens, with a penetration depth of approximately 12 cm (19–21). To treat larger surfaces of tissue loss (as in ulcers, chronic or complicated wounds), some ESW generators are designed and marketed to generate unfocused ESWs: the same biphasic wave assumes the form of a planar or defocused wave during application. Obviously, for these devices, the depth of penetration is lower so that their therapeutic indication is limited to the more superficial lesions, like cutaneous ulcers and related disorders (21). Pneumatic sources generate ball-shaped waves, which propagate in a spherical way, thus driving the descriptive term of 'radial waves,' spreading across a wider target area with a penetration depth of approximately 3 cm. Compared to the conventional shock waves, radial waves differ for the centring of the focus (placed on the tip of the applicator instead of on the target site) and the shape of the waves themselves (showing a lower peak pressure and a very long rise).

ESWT is considered feasible for healing of the chronic wound in humans (26–37). However, the findings of studies conducted so far are still inconclusive, and the clinical use for wound healing is under investigation. Despite the increasing use of ESWT, substantial uncertainty continues to exist because of insufficient and inconsistent supporting evidence. The limited scientific information available has been obtained from animal studies (38–40), case series studies (26,31,36,37), single case reports (41,42) and a few clinical trials (27–30,32,33).

In the last 5 years, five systematic reviews (22,25,43–45) provided limited evidence to support the use of ESWT for the treatment of lower limb ulceration. However, ESWT may play an important role in wound care once evidence-based practice guidelines are developed. For these reasons, the authors recognised the need for an up-to-date systematic review to detect a more accurate estimation of the efficacy of ESWT and their impact on the healing of chronic lower limb ulcers.

Materials and methods

Search strategy

As a first step in this review process, we framed our review questions using the PICOT (population, intervention/exposure, comparative, outcome, time frame) framework as in Table 1. The authors conducted a comprehensive search using the following electronic databases: OVID, MEDLINE, CINAHL, EMBASE, PubMed, Physiotherapy Evidence Database (PEDro), Scopus, Web of knowledge, the Cochrane Central Register of Controlled Trials (CENTRAL) and Clinical trial register. Only articles published in English since the 2000s were included.

Keywords and Medical Subject Headings (MeSH) used included 'foot ulcer', 'diabetic or neuropathic foot ulcer', 'diabetic wound', 'chronic wound', 'ulcer',' traumatic wound', 'venous or arterial leg ulcers', 'Shock wave therapy (SWT)' and 'ESWT'. Upon completing the electronic search, one reviewer (MO) examined reference lists of all relevant articles to capture additional articles that met inclusion criteria and may not be indexed in the database.

Criteria for considering studies for this review

Type of studies

All randomised controlled trials (RCTs), quasi-experimental, control before-and-after design and crossover design were eligible for inclusion in this review because of a limited number of studies.

Data extraction

Two reviewers independently screened all identified studies based on the titles and abstracts to detect possible eligibility. We retrieved the full reports of all related trials for further assessment of eligibility based on the inclusion criteria. Two reviewers (MO and RG) independently retrieved data from the included studies using a standardised form of data extraction: (i) characteristics of the trial (setting, location of care, country, level of evidence); (ii) participants (number of subjects, age, gender, type and size of the wound, duration of the wound, length of follow-up); (iii) intervention, including ESWT protocol (type of generator, energy flux density, frequency, number of pulses per square centimetre, number of treatment sessions, time interval between each session); (iv) comparison intervention and (v) results of all relevant outcomes. The reviewers were not blind of studies authorship. In case of any disagreement, the third reviewer (AS) was involved, and an agreement was achieved to reach consensus.

Level of evidence

The studies were categorised according to Sackett's rules of evidence. Sackett's rules of evidence ranges from high certainty to decreasing certainty, from level I to V, respectively. Level I is a large, RCT (included 100 or more participants) with low false-positive or false-negative errors. Level II is a small RCT with high false-positive or low false-negative errors. Level III is a non-randomised, concurrent cohort comparison between

Table 1 The PICOT format

Population	Male and/or females adult >18 years or older with chronic wounds of the lower extremities (CWLEs) including diabetic foot ulcer (DFU), traumatic wound (TW), venous and/or arterial leg ulcer (VLU, ALU), surgical wound (SW), burn wound (BW) and pressure ulcers (PU).
Intervention/exposure	Extracorporeal shock wave therapy (ESWT, focused/unfocused).
Comparative	Any standard wound care, sham and other physical modalities and different ESWT protocols.
Outcome	Wound healing, measured objectively:

- Time to complete healing (days)
- Percentage of reduction in wound surface area (WSA)
- Proportion of wounds completely healed at a specified time point
- Blood perfusion measurements
- Adverse effects (e.g. neurovascular complications, infection, dermatitis, erythema, excessive granulation and necrotic tissue).

Time frame	If more than one follow-up set of data presented within the same category of timing of an outcome measure, only one set was considered (e.g. short-term follow-up refers to outcomes measured closest to 4 weeks after randomisation; intermediate follow-up refers to measures taken at least 6 months after treatment, and long-term follow-up refers to measurement taken close to 2 years after treatment) (38).

subjects who did and did not receive the intervention. Level IV is a non-randomised, historical cohort comparison between current subjects who received the intervention and former subjects who did not receive the intervention. Level V is a case series without controls (46).

Assessment of methodological quality

Assessment of methodological quality was performed using the PEDro scale. This tool is reliable (47) and valid (48) for rating the quality of RCTs. Each of the 11 items of the PEDro scale was scored as 'yes' where quality met the specified criteria and 'no' where criteria were unclear. Two reviewers (MO and AS) independently assessed and scored each of the articles and presented their findings to the entire group. In case of any disagreement, the third reviewer (RG) was involved, and an agreement was achieved to reach consensus. Studies scoring 9–10 on the PEDro scale were considered methodologically to be of 'excellent' quality; scores ranging from 6 to 8 were considered to be of 'good' quality, studies scoring 4 or 5 of 'fair' quality, and studies scoring less than 4 were of 'poor' quality (47–49).

Results

Search results

Figure 1 illustrates the flow chart of the study selection for systematic review. A total of 594 studies were found in the databases. After reviewing the title and abstract using the inclusion and exclusion criteria, 583 studies were rejected, while the remaining 11 studies met the inclusion criteria for this review. Overall, five studies were conducted in Europe (30,31,35–37), five studies in Asia (26–28,32,34) and one study in Africa (29). These studies included seven RCTs (27–30,32,34,35), one clinical controlled trial (CCT) (36) and three case series studies (CSS) (26,31,37). The studies were critically evaluated. Eight studies were categorised as level II (27–30,32,34–36), two studies as level III (31,37) and one study as level V (26).
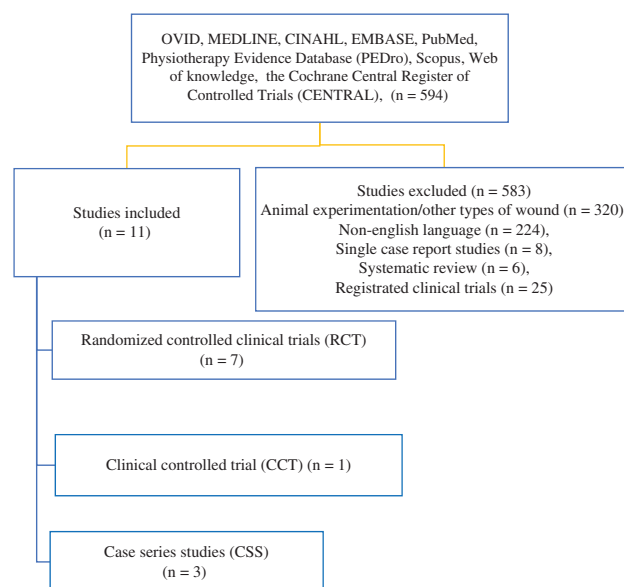
Figure 1 Study flow chart.

Participant characteristics

Table 2 summarises the participant characteristics and initial wound parameters. The number of participants included in the studies was 925 (range: 5–258), where 787 (85%) participants received ESWT, and 138 (15%) participants were placed in the comparison groups. The mean age of the participants was 59·5 years (range: 18–95 years). Gender distribution was not reported in two studies (32,34). However, the majority of the participants in the remaining nine studies were male (58%) (26–31,35–37).

A total of 947 lower limb ulcerations were available. These included diabetic foot ulcers (DFUs, $n = 376$; 39·6%), traumatic wounds (TWs, $n = 192$; 20·3%), venous leg ulcers (VLUs, $n = 115$; 12%), pressure ulcers (PUs, $n = 54$; 5·7%), arterial leg ulcers (ALUs, $n = 17$; 1·8%), acute burn wound (BWs, $n = 15$; 1·6%), disturbed wound healing (DWH, $n = 85$; 9%) and

Table 2 Summary of the participant characteristics and initial wound parameters of selected studies

Authors	Design Level of evidence	Groups (n)	Mean age, y (range) Male/female, n	Wound parameters		
				Types, n	Size (cm^2)	Duration (months)
Variji et al., 2015 (26)	CSS IV	ESWT group (n=5)	58·2 (33–75) 4/1	DFU, n=5	7·54±5·05	19±29
Omar et al., 2014 (27)	RCT II	ESWT group (n=19)	56 (45–65) 14/5	DFU, n=24	7·89±2·97	11·97±6·50
		Control group (n=19)	57 (45–65) 13/6	DFU, n=21	8·62±3·47	10·81±4·63
Wang et al., 2014 (28)	RCT II	DM group (n=29)	59·03 (33–81) 28/10	DFU, n=30	9·54±15·44	20·9±20·35
		NDM group (n=28)	60·75 (18–77) 15·14	Non-DFU, n=30	8·49±17·38	13·19±15·36
Nossair et al., 2013 (29)	RCT II	ESWT group (n=20)	56·6y (44–64) 15/5	DFU, n=20	8·86±3·41	N/A
		Control group (n=20)	55·15 (42–64) 14/6	DFU, n=20	8·32±3·88	N/A
Saggini et al., 2013 (30)	RCT II	ESWT group (n=62)	62 (28–80) 39/23	DFU, n=23; PU, n=10; TW, n=10; VLU, n=19	3·85	10 (3–24)
		ESWT group (n=40)	61 (33–77) 16/24	DFU, n=9; PU, n=1; TW, n=11; VLU, n=14; cryoglobulinemia, n=1	3·4	
Wolff et al., 2011 (31)	CSS III	ESWT group (n=258)	63·5 (46–79) 140/118	SW, n=93; decubital ulcer, n=13; TW, n=86; cast ulcer, n=9; VLU, n=38; AIU, n=11; BW, n=8	5 (0·5–300)	76·36% <3 12% >4 <12 10·85% > 12
Wang et al., 2011 (32)	RCT II	ESWT group (n=39)	60·51 (20–81) N/A	DFU, n=44	4 (1·5–9)	6 (3–16)
		HBOT group (n=38)	62·45 (23–88) N/A	DFU, n=40	7 (2–12)	6 (6–10)
Wang et al., 2009 (34)	RCT II	ESWT group (n=34)	58·6 (33–79) N/A	DFU, n=36	11·2±20	22·7±20·9
		HBOT group (n=36)	63·4 (39–81) N/A	DFU, n=36	10·5±20	19±19·5
Moretti et al., 2009 (35)	RCT II	ESWT group (n=15)	56·2 (47–66) 9/6	DFU, n=15	2·97±1·29	6 (3–24)
		Control group (n=15)	56·8 (43–68y) 8/7	DFU, n=15	2·45±1·09	
Saggini et al. 2008 (36)	CCT II	ESWT group (n=30)	58·5 (24–79) 18/12	VLU, n=12; TW, n=16; DFU, n=4 VLU, n=12; TW, n=16; DFU, n=4	5·15 (1–15·1)	5·34 (3–8)
Schaden et al., 2007 (37)	CSS III	Control group (n=10)	66·6 (55–78) 6/4	VLU, n=5; TW, n=2; DFU, n=3	6·12 (1·9–12·2)	5·2 (3–8)
		ESWT group (n=208)	61 (18–95) 109/99	DWH, n=82; AIU, n=6; TW, n=67BW, n=7; PU, n=21; VLU, n=14	8·76 (3·7–16·1)	79% ≤1 4% >1 <12 14% > 12

ALU, arterial leg ulcers; BW, burn wound; CCT, control clinical trial; CSS, control series studies; DFU, diabetic foot ulcer; DM, diabetes mellitus; DWH, disturbed wound healing; ESWT, extracorporeal shock wave therapy; HBOT, hyperbaric oxygen therapy; N/A, not available; NDM, non-diabetes mellitus; PU, pressure ulcers; RCT, randomised clinical trial; SW, surgical wound; TW, traumatic wound; VLU, venous leg ulcers.

Table 3 Therapeutic parameters of ESWT of the selected studies and follow-up time

Authors	ESWT source	ESWT generators	EFD (mJ/mm^2)	ESWT frequency (Hz)	Number of ESWT pulse (pulses/cm^2)	Number of sessions	Time interval between sessions	Duration/ follow-up
Variji *et al.*, 2015 (26)	Electromagnetic	Unfocused	0·25	N/A	600	6–8	N/A	6–8 wks/N/A
Omar *et al.*, 2014 (27)	Pneumatic	Unfocused	0·11	N/A	100	8	1 wk	8/20 wks
Wang *et al.*, 2014 (28)	Electromagnetic	Unfocused	0·11	4	At least 500	6		12/5 yrs
Nossair *et al.*, 2013 (29)	Pneumatic	Unfocused	0·1	N/A	At least 500	3	1 wk	12 wks/N/A
Saggini *et al.*, 2013 (30)	Electrohydraulic	Unfocused	0·1	4	300–600	7	1 wk	7 wks/N/A
			0·04					
Wolff *et al.*, 2011 (31)	Electrohydraulic	Unfocused	0·1	5	167 (100–300)	1–10	2 wks	15–17 wks /1 year
Wang *et al.*, 2011 (32)	Electromagnetic	Unfocused	0·23	4	at least 500	6		12 wks/N/A
Wang *et al.*, 2009 (34)	Electrohydraulic	Focused	0·11	N/A	300 + 100	3	2 wks	6 wks/N/A
Moretti *et al.*, 2009 (35)	Electromagnetic	Focused	0·03	N/A	100	3	3 days	20 wks/N/A
Saggini *et al.*, 2008 (36)	Electrohydraulic	Unfocused	0·037	4	100	4–10	2 wks	8–20 wks/NA
Schaden *et al.*, 2007 (37)	Electrohydraulic	Unfocused	0·1	5	100	3 (1–10)	2 wks	8 wks/N/A

EFD, energy flux density; ESWT, extracorporeal shock wave therapy; Hz, hertz; mJ/mm^2, mill joule per millimetre;N/A, not available; wk, week.

surgical wound (SWs, $n = 93$; 10%). The average size of wound surface area (WSA) was $6·83 ± 2·65$ cm^2 (range: $2·45–11·20$ cm^2). Non-significant differences in WSA ($6·79 ± 2·71$ and $6·86 ± 2·75$ cm^2, $P > 0·05$) were observed between ESWT and the comparison groups, respectively. The duration of lower limb ulceration was reported in all studies except one (29) and ranged between 1 and 22 months. There was variability in the wound types, duration and characteristics across the studies. The majority of the treated wounds were chronic (>3 months) except in one study (37), while five studies included wounds of mixed aetiology (28,30,31,36,37).

Intervention parameters

Table 3 provides details of therapeutic parameters of the selected studies and follow-up time. The majority of the studies included control groups. These groups received standard wound care (SWC) in four studies (27,29,35,36) and HBOT in two studies (32,34), while one study (30) compared two protocols of ESWT. In all studies (26–32,34–37), the wound dressing regimen and SWC remained unchanged after each treatment session.

The source of the ESWT generator was electrohydraulic in five studies (30,31,34,36,37), electromagnetic in four studies (26,28,32,35) and pneumatic in two studies (27,29). Two types of ESWT generator heads were detected: unfocused ESWT in the majority of the studies (26–32,36,37) and focused ESWT in two studies (34,35).

The dosage of ESW differs across the studies. It ranges between 0·03 and 0·25 mJ/mm^2, with the most regular value set at 0·1 mJ/mm^2 in four studies (29–31,37) and 0·11 mJ/mm^2 in three studies (27,28,34). The majority (82%) of reviewing studies (27–31,34–37) used low-energy ESW ($\leq 0·11$ mJ/mm^2), while only two studies (26,32) used medium-energy ESW (0·12–0·28 mmJ/mm^2).Frequency was set at 4 Hz in four studies (28,30,32,36) and 5 Hz in two studies (31,37), while five studies did not describe that parameter (26,27,29,34,35). In most of the studies, the number of pulses in a single ESWT session ranged from 100 to 500 pulses/cm^2 (27–29,31,32,34–37), with the most frequent value being 100 pulses/cm^2.The number

of treatment sessions ranged between three and eight sessions in most of the studies (26–30,32,34,35). However, in some studies (31,36,37), ESW application was continued for 10 sessions. The time interval between each session ranged from 3 days to 3 weeks, with a time interval of 1 and 2 weeks reported in 73% of the studies ((21,27,29–32,34,36,37)), while two studies used daily sessions of ESWT (28,35). In all studies, the ESWT was performed without anaesthesia, and the wound was covered with a sterile plastic barrier (27,28,30,32,34,37), single layer of sterilised gauze (36) or surgical draper over the wound (31,35), and ultrasound gel was applied to the area of skin in contact with ESWT.

Outcome measurements

Summary of outcome measurements is presented in Tables 4 and 5. Assessment of wound healing varied across the studies. A total of 10 studies (27–32,34–37) used percentage of wounds healed, while reduction of WSA was documented by four studies (26,27,29,30). Healing time was used by five studies (26,27,31,35,37), and blood flow was recorded in three studies (28,32,34). The safety and adverse effects of ESWT are described in most of the studies (26–28,30–32,34,36,37). None of the studies provided any information regarding the reliability and validity for the outcome measures used.

Proportion of wound healing

There was a great variability in the percentage of wound healing among the studies. In 2014, Omar *et al.* (27) showed significant ($P < 0·05$) differences in wounds completely healed (54% and 2·5%), improved (33·5% and 19%) and unchanged (12·5% and 52·5%) at 20 weeks follow-up in the ESWT group ($n = 19$) when compared to the control group ($n = 19$). Additionally, in the same year, Wang *et al.* (28) revealed the percentage of wounds that had healed completely (43% and 71%), had improved (3% and 6%) and were unchanged (27% and 13%) in diabetic and non-diabetic foot ulcers treated with unfocused ESWT at 5 years follow-up.

In 2013, Nossairet *et al.* (29) reported 83% wound closure in the ESWT-treated group ($n = 15$) compared to 49% in

Table 4 Summary of the outcome measurements of the controlled clinical studies

Authors	Mean time of reepithelisation (days)		Reduction in WSA		Proportion of wound healing (%)		Blood flow		Safety and adverse reaction
	ESWT	C-group	ESWT	C-group	ESWT	C-group	ESWT	C-group	
Omar et al., 2014 (27)	64·5 ± 8·06*	81·17 ± 4·35	83%*	63%	54% complete healing* 33·5% healed ≥50% 12·5% unchanged	28·5% completed healing 19% healed ≥50% 52·5% unchanged	N/A	N/A	Not observed
Wang et al., 2014 (28)	N/A	N/A	N/A	N/A	43% (DM group), 71% (NDM group) completed healing 3% (DM group), 6% (NDM group) healed ≥50% 27% (DM group), 10 (NDM group) unchanged 27% (DM group), 13 (NDM group) failure	completed	DM group 0·11 (0·04–0·3) NDM group 0·28* (0·07–0·8)	N/A	Not observed
Nossair et al., 2013 (29)	N/A	N/A	78%*	44%	83% complete healing*	49% complete healing	N/A	N/A	N/A
Saggini et al., 2013 (30)	N/A	N/A	80%*	67%	71% complete healing* 29% partially healed	40% completed healing 37·5% partially healed 22·5% unchanged	N/A	N/A	Not observed
Wang et al., 2011 (32)	N/A	N/A	N/A	N/A	57% complete healing* 32% healed ≥ 50% 11% unchanged	25% completed healing 15% healed ≥50% 60% unchanged	0·61* (0·40–0·79)	0·50 (0·11–0·53)	Not observed
Wang et al., 2009 (34)	N/A	N/A	N/A	N/A	31% complete healing* 58% improved 11% unchanged	22% completed healing 50% improved 28% unchanged	0·75* (0·46–1·28)	0·58 (0·51–0·66)	Not observed
Moretti et al., 2009 (35)	60·8 ± 4·7*	82·2 ± 4·7	N/A	N/A	53·3% complete healing*	33·3% complete healing	N/A	N/A	N/A
Saggini et al., 2008 (36)	N/A	N/A	N/A	N/A	53·3% complete healing*	10% complete healing	N/A	N/A	No adverse reaction

C-group, comparison group; DM, diabetes mellitus; ESWT, extracorporeal shock wave therapy; N/A, not available; NDM, non-diabetes mellitus; WSA, wound surface area.
* P value ≤ 0.05.

Table 5 Summary of the outcome measurements of case serious studies

	Mean time of reepithelisation (days)	Reduction in WSA	Proportion of compellation of wound healing (%)	Blood flow	Safety and adverse reaction
Variji *et al.*, 2015 (26)	6–8 weeks	Progressive reduction of WSA in four patients after 6–8 weekly treatment, mean reduction $(1 \cdot 21 \pm 0 \cdot 82$ cm^2)	N/A	N/A	Not observed
Wolff *et al.*, 2011 (31)	2 wks (1–288)	N/A	74% complete wound closure	N/A	Not observed
Schaden *et al.*, 2007 (37)	44 days (39·4 days for <10 cm^2, and 1 month duration – 164·6 days for wound > 10 cm^2, and duration > 1 month)	N/A	75% complete wound closure 81·0% complete wound closure in wound ≤10 cm^2 versus 61·8% complete wound closure in wound ≥10 cm^2 ($P < 0 \cdot 005$) 83·0% complete wound closure for wound ≤ 1 month versus 57·1% for wound ≥1 month old ($P < 0 \cdot 001$) 81·0% complete wound closure for acute wound versus 56·3% in chronic wound ($P < 0 \cdot 001$)	N/A	Not observed

N/A, not available; WSA, wound surface area.

the control group ($n = 15$) after 12 weeks of treatment. In the same year, Saggini *et al.* (30) reported complete wound healing in 71% and partial healing in 29% of cases in the unfocused ESWT-treated group ($n = 63$), with an energy flux density of 0·01 mJ/mm^2, compared with 40% completely healed, 37·5% improved and 22·5% unchanged in the unfocused ESWT group ($n = 40$), with energy density 0·04 mJ/mm^2.

In 2011, Wang *et al.* (32) revealed significant differences ($P = 0 \cdot 005$) in the proportion of wound healed; the authors reported completed healing in 57% and 25%, improved >50% (32% and 15%, $P = 0 \cdot 005$) and remained unchanged (11% and 60%, $P = 0 \cdot 071$) in ESWT when compared with HBOT groups. Wolf *et al.* (31) showed complete healing in 74% of total participants ($n = 258$) with mixed wounds who received ESWT. The rate of healing was affected by wound surface and duration as 81·0% of wounds healed completely with WSA ≤10 cm^2 versus 61·8% with WSA ≥10 cm^2. Significant ($P < 0 \cdot 001$) closure of the wounds was reported in 83·0% of cases with wound duration ≤1 month versus 57·1% with wound duration ≥1 month.

In a 2009 study by Wang *et al.* (34), the percentage of completely healed wounds was 31% and 22%, improved 58% and 50% and unchanged 11% and 28% in the ESWT and HBOT groups, respectively. Moreover, Moretti *et al.* (35) reported complete healing of DFU of 53·33% in the ESWT group ($n = 15$) compared with 33·33% in the control group ($n = 15$). Early work of Saggini *et al.* (36) reveals wound closure in 53·3% of the ESWT group ($n = 30$) compared to 10% in the control group ($n = 10$), while Schaden *et al.* (37) linked the completely healed wound with the wound area. The authors reported complete healing in 81% of wounds less than 10 cm^2 and 61·8% of wounds larger than 10 cm^2.

Time to healing

Time to complete healing was measured in days or months and presented as means with standard deviations or medians. Two randomised clinical trials by Omar *et al.* (27) and Moretti *et al.* (35) report short healing times in ESWT groups ($64 \cdot 50 \pm 8 \cdot 06$ days and $60 \cdot 80 \pm 4 \cdot 70$ days, respectively) compared with the control groups ($81 \cdot 17 \pm 4 \cdot 35$ and $82 \cdot 20 \pm 4 \cdot 70$ days, respectively). Early work of Schaden *et al.* (37) showed that the mean time to complete tissue epithelialisation is 44 days; the authors concluded that the time to complete healing was significantly associated with the wound surface area and duration of wound, where the time to complete healing was 39·4 days (WSA <10 cm^2 and 1 month wound duration) and 164·6 days (WSA > 10 cm^2 and duration >1 month). Moreover, Wolff *et al.* (31) reported complete healing of 74% of patients after a median duration of 31·8 months.

Reduction of wound surface area

A significant reduction of WSA was observed in four studies. Omar *et al.* (27) and Nossair *et al.* (29) reported reduction in WSA in the ESWT group (83% and 78%, respectively) when compared with the control group (63% and 44%, respectively). Saggini *et al.* (30) reported significant reduction in WSA of 80% in the ESWT group treated with energy flux density of 0·1 mJ/cm^2 compared with 67% in the ESWT group treated with energy flux density of 0·04 mJ/cm^2. A series case study reported mean reduction of WSA of $1 \cdot 21 \pm 0 \cdot 82$ cm^2 from initial wound area in four out of five patients treated with ESWT (26).

Blood flow

The blood flow perfusion rate as an indicator of tissue viability was measured using laser Doppler perfusion imaging in

Table 6 Quality assessment of the included studies according to the PEDro scale

	Authors	Vriji et al., 2015 (26)	Omar et al., 2014 (27)	Wang et al., 2014 (28)	Nossair et al., 2013 (29)	Saggini et al., 2013 (30)	Wolff et al., 2011 (31)	Wang et al., 2011 (32)	Wang et al., 2009 (34)	Moretti et al., 2009 (35)	Saggini et al., 2008 (36)	Schdaden et al., 2007 (37)
1	Eligibility criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
2	Random allocation	—	✓	—	✓	✓	—	✓	✓	✓	✓	—
3	Concealed allocation	—	✓	—	—	—	—	—	—	—	—	—
4	Baseline comparability	—	✓	✓	✓	✓	—	✓	✓	✓	✓	—
5	Blinded subjects	—	—	—	—	—	—	—	—	—	—	—
6	Blinded therapists	—	—	—	—	—	—	—	—	—	—	—
7	Blinded assessors	—	✓	—	—	✓	—	✓	✓	—	—	—
8	Adequate follow-up	✓	✓	✓	✓	—	✓	✓	✓	✓	✓	✓
9	Intention-to-treat analysis	—	—	—	—	—	—	—	—	—	—	—
10	Between-group analysis	—	✓	✓	✓	✓	—	✓	✓	✓	✓	—
11	Point estimates of variability	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Total scores (10)	2	7	4	5	5	2	6	6	5	5	2

three studies (28,32,34). Wang *et al.* (28) observed significant improvement in blood flow perfusion ($0{\cdot}07 \pm 0{\cdot}8$, $P < 0{\cdot}04$) in non-diabetic patients treated with ESW compared with diabetic patients ($0{\cdot}11 \pm 0{\cdot}10$) treated with the same protocol at 5-year follow-up, while there was no difference between groups at 1-year follow-up ($0{\cdot}67 \pm 0{\cdot}30$ vs $0{\cdot}65 \pm 0{\cdot}28$, $P = 0{\cdot}94$). Furthermore, Wang *et al.* (32) reported significant improvement in local blood perfusion in the participants with DFU and treated with ESW ($0{\cdot}61$, $P < 0{\cdot}002$) compared with those treated with HBOT ($0{\cdot}50$). The authors failed to show such an effect in their earlier study (34). However, the change in the blood perfusion rate from baseline was significant ($P < 0{\cdot}05$) in the ESWT group.

Safety and adverse effects of ESWT

Potential complications and adverse effects (e.g. pain, itching, skin irritation and pigmentation, infection) related to ESWT treatment were identified in all studies (26–28,30–32,34–37) except one (29). Moretti *et al.* (35) reported symptoms of local infection in both groups (ESWT and SWC), and oral antibiotics were prescribed. This complication was resolved within 5–7 days. In two studies by Wang *et al.* (32,34) comparing ESWT and HBOT, there were no adverse events and complications reported in the ESWT group. However, the HBOT group reported some complications, including middle ear barotraumas and sinus pain. All of these adverse reactions were resolved after the removal of chamber pressure. These results may reflect the superiority of ESWT.

Methodological quality

The methodological quality of the included studies according to the PEDro scale is shown in Table 6. The mean RCT score of PEDro is $5{\cdot}37$ (SD: $0{\cdot}91$, range: $4{-}7$) for 8 studies out of 11. Classification of the trials according to the total PEDro score revealed three studies classified as good (27,32,34) and five as fair (28–30,35,36), while the remaining three studies were poor (26,31,37). These scores represent multiple sources of bias.

In these studies, the worst scored criteria of quality were lack of blinding as all the studies (26–32,34–37) failed to obtain a positive score for both therapists blinding and subject blinding, and four studies reported assessors blinding (27,30,32,34). Moreover, intention-to-treat analysis achieved negative results in all studies (26–32,34–37), while concealed allocation was undertaken by one study (27). The best scored criteria were related to the statistical analysis of the results. All the studies reported between-group statistical analysis using both point measures and measures of variability except in three studies (26,31,37). Eight studies (27,29,30,32–36) reported random allocation. However, detailed explanations of randomisation were not reported adequately. Nine studies (27–30,32–36) had similar groups at baseline. Adequate follow-up was described in all studies except one (30), and two of them (28,29) had 100% follow-up because of the short duration of the study.

Discussion

The purpose of this systematic review is to evaluate evidence of effectiveness of ESWT on chronic lower limb ulcers. For

this purpose, 11 papers were evaluated. The evidence showed the clinical effectiveness regarding rate and time of wound healing and decreasing wound size. ESWT appears to be safe and associated with a low rate of complications during its application to treat chronic lower limb ulcers in both short- and mid-term follow-up periods.

The levels of evidence and the quality of the methodology of the identified studies must be considered before making conclusions about the effectiveness of ESWT for the management of chronic lower limb ulcers. In the current review, eight studies (27–30,32,34–36) with level II evidence showed mild to moderate methodological quality (score ≥ 5). There were no significant differences in patient demographics between the treatment groups in any of the eight included studies. The number of patients enrolled in each study ranged from 15 to 62, which is acceptable. Patient selection criteria were reported in all the included studies. This allows us to have confidence in the recommendations of these studies. However, two studies were graded as level III (31,37) because they were non-randomised clinical controlled studies. The final study (26) was graded as level V as it was reported as a clinical case series and had no controls. These findings do not suggest which treatment approach used in level III and V studies is less effective but only that the research designs used were less rigorous. Therefore, there is diminished confidence that the treatments themselves created the change in the outcome measures.

None of the 11 studies addressed all criteria of methodological quality suggested in this review. All studies are reported poor in blinding (therapist and patient), intention-to-treat analysis and concealed allocation except one (27). This might influence the internal validity of the studies and prevents researchers from incorporating expectations of the outcome while evaluating participants, and random allocation attempts to control extraneous factors in subject pools and balance variables throughout the groups.

Wound characteristics revealed the lack of uniform classification of ulceration (e.g., aetiology, duration, grade and size) across the identified studies. ESWs have been used to treat varieties of chronic wounds, such as DFU, PU, VLU, ALU and acute wounds, including BW, TW and SW. The duration of an ulcer varied across identified studies (1–24 months), and the initial ulcer size also varied (1 cm up to 10 cm^2). Although the included studies focus on the aetiology and duration of different wounds , the way in which they heal is similar (e.g. inflammation, proliferation, epithelialisation, etc.); therefore, it is appropriate to group them based on the measurement of the therapeutic effects of ESWT. However, the discrepancy across the studies represents the sources of bias.

In the current review, the relevant clinical outcomes were focused on wound healing and reepithelialisation time. However, the methods used to define them are varied. The common approach used to determine wound closure included observation and/or photographic documentation. The observation of wound closure and/or over 95% reepithelialisation was definecbd as the clinical endpoint by all studies (27–32,34–37) except one (26) during the follow-up and assessment period. In all studies, reepithelialisation and time to wound closure were significantly lower in the ESWT groups compared with standard therapy or HBOT. Additionally, the percentages of

reduction in WSA were calculated in four studies (26,27,29,30). The authors believe that using the rate of complete healing is clinically more useful than reporting the percentage of reduction in WSA.

Furthermore, blood flow perfusion was detected before and after the intervention in many studies (28,32,34). The reepithelialisation index that was quantified as mm^2 per day was used in the study by Moretti *et al.* (35). However, a clear definition of the reepithelialisation index has not been identified; therefore, it may be problematic to compare results across the included studies. All reported studies did not show validity or reliability of the data for the outcome measures chosen. Objective measures of wound healing are necessary to reduce bias and to determine whether the treatment findings are because of the ESWT intervention or whether they result from measurement error.

All included studies provide sufficient details to allow the repetition of the intervention protocol. However, there are differences in the generator, dosage, frequency and duration of ESW protocols. The heterogeneity in such parameters made it difficult to compare studies and standardise the application of different protocols. Intensity assessment is important for the analysis of ESWT study outcomes, and it is considered a major aspect of negative outcomes and adverse effects. To date, to our knowledge, no study has successfully achieved an intensity within the recommended range of the previous reports. Several other important aspects of ESWT should be considered for further analysis (e.g. total energy, frequency of intervention, types of ESW generators). Unfortunately, many key parameters are incompletely reported in the studies we reviewed, such as frequency. However, most of the studies suggest that low-intensity ESWT is a preferred treatment of chronic wounds. In addition, the follow-up period of all included trials is relatively short, except one study that had a 5-year follow-up (28). Therefore, the long-term efficacy remains unknown. Furthermore, the number of the trials comparing ESWT with other therapies is small, causing a lack of further understanding of the efficacy of ESWT.

None of the included studies reported adverse reactions secondary to ESWT application. However, one study (35) reported local signs of infection that has been resolved after 7 days of antibiotic administration. Even if none of the included studies have considered the cost-effectiveness of ESWT, all show a significant reduction in time required for wound closure when using ESWT. This might be administered to potentially reduce the need for prolonged wound dressing and care.

This review has some limitations. Even if not in our opinion, as a systematic review of small trials, it could be potentially unreliable in some fields of medicine for several reasons. This could be partly because of the restriction on English-language publications during the bibliographical research; thus, although we used a detailed search strategy, we still cannot be sure that all relevant trials were found. Selecting, publishing and reporting are other major causes of bias that should be considered. Probably not as a consequence of this, we included a limited number of studies (n = 11) with relatively small sample sizes. Although the quality of the studies included in this review was satisfactory, poor methodological quality of some studies could affect the reliability of our results and limit the overall conclusion about the efficacy of ESWT on managing chronic lower

limb ulcers; this highlights the importance of future research that should follow the standardised guidelines of clinical trials.

Conclusions

There is mild to moderate evidence to support the use of ESWT as an adjuvant therapy with a standardised wound care programme. This will promote wound closure and reepithelialisation, reduce WSA and improve blood flow perfusion and the time required to complete healing. However, it is difficult to draw firm conclusions about the efficacy of ESWT. Thus, future research with high methodological quality is required to assess the efficacy and cost-effectiveness of this relatively new physical therapy application.

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