Randomized control of extracorporeal shock wave therapy versus placebo for chronic decubitus ulceration

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Objective: To assess whether extracorporeal shock wave therapy increases the rate of healing in chronic decubitus ulceration.

Design: Double-blind randomized cross-over study.

Setting: A large, long-stay hospital specializing in the management of people with complex neurological disabilities.

Subjects: The total population of available patients with chronic neurological conditions and chronic decubitus ulceration who met the inclusion criteria.

Interventions: Ulcers were randomized into receiving either the extracorporeal shock wave therapy or the placebo for a four-week period, followed by a two-week 'washout' period followed by a four-week period of the cross-over treatment/placebo.

Main measures: Measurement of the area of the ulceration. For each observation the average of three measurements were taken.

Results: Nine ulcers (in eight patients) were included in the study: five on the buttocks/sacrum/trochanter and four on the feet/ankles. All those with static chronic ulcers showed improved healing starting 6–8 weeks after the start of extracorporeal shock wave therapy, whether treated first with the placebo or the therapy.

Conclusions: Extracorporeal shock wave therapy has a potential part to play in the treatment of chronic skin ulceration.

Introduction

Decubitus ulceration in severe disability occurs on all types of hospital wards, in nursing homes as well as in those cared for at home. They are painful, cause ill-health and are associated with increase in mortality rate.[1] They are very time-consuming for staff to treat and are costly in health care.

Experience in Austria suggests that patients treated with extracorporeal shock wave therapy for bone disorders seemed to have faster healing of associated skin wounds. In an uncontrolled trial[2] of 102 patients with 104 chronic skin lesions treated with extracorporeal shock wave therapy 74% showed complete healing, a further 10% had more than 50% epithelialization. It is of note that this used an unfocused form of shock wave using lower energies than are used in the treatment of pseudoarthosis or kidney stones.

There is also evidence of improved healing of chronic skin ulceration in diabetic patients following treatment with extracorporeal shock wave

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therapy,[3,4] in improving wound healing after vein harvesting[5] and in traumatic skin lesions.[6]

There is supportive evidence for wound healing from an animal study[7] showing that extracorporeal shock wave therapy can increase the vascularization in skin flaps, thus improving healing. There is also evidence[8,9] that extracorporeal shock wave therapy has an antibacterial effect, at least in the laboratory.

Chronic skin ulceration in long-term care, although uncommon, is a problem as it can delay rehabilitation, cause pain, is time-consuming and decreases the quality of life.

This study aimed to identify whether extracorporeal shock wave therapy could improve the rate of healing of chronic skin ulceration in people with severe and complex neurological disabilities.

Study design

The study design aimed to overcome three concerns:

- The Hawthorne effect – would the patients do something different because of the study?
- The Pygmalion effect[10,11] – would the staff do something different because of the study?
- If there was an effect was it because of the extracorporeal shock wave therapy or because of something else – such as the gel used as a coupling agent or the massaging of the extracorporeal shock wave therapy head?

In an attempt to overcome these concerns the manufacturers of the machine produced two heads for the machine – one that produced shockwaves and the other which did not (placebo) though the machine made the same noise whichever head was used. The equipment used was the Orthowave 180c (MTS Europe GmbH, Konstanz, Germany) with a non-focused head.

The ulcers were randomly allocated to one of two groups:

- group A where extracorporeal shock wave therapy started after the baseline observation period and
- group B where the placebo extracorporeal shock wave therapy started after the baseline observation period.

A three-week observation period with weekly measurements was carried out before the start of the interventions. After six weeks (including a two-week washout phase) the treatment and control groups crossed over so that those in the control group received treatment and those in the treatment group received placebo 'treatment'.

Randomization was by shuffled cards in sealed envelopes. All ulcers had equal opportunity of being included in the extracorporeal shock wave therapy-first or the placebo-first groups.

During the treatment and placebo phases the patients received one period of extracorporeal shock wave therapy/placebo each week for four weeks.

The cleaned wound was covered with sterile ultrasound gel and a sterile drape, over which further coupling gel was spread to provide an air-free contact for the extracorporeal shock wave therapy head. The head was then moved directly on the wound and shockwaves applied at a rate of five per second for $200 \text{ impulses} + 100$ impulses per cm^2 at 0.1 J/mm^2.

Following the procedure the type of dressing previously used by the patient was used to dress the wound (i.e. the patient treatment was not changed).

Where a patient had one or more ulcers these were counted as separate ulcers for the purpose of randomization (i.e. the ulcers were randomized rather than the patients).

The assessor carrying out the measurements was blind to which form of treatment/placebo was being given.

Study group

All patients in a large (250-bed) long-stay hospital who had decubitus ulceration and who did not have exclusion criteria were eligible for inclusion in the study irrespective of age, level of disability or diagnosis.

Nine patients (4 men and 5 women; average age 63.3 years, range 42–83 years) with decubitus ulceration met the criteria for inclusion in the study. They all had very severe physical disabilities (Barthel scores of less than 8/20, being non-ambulant, incontinent and totally dependent on others for daily activities). All had skin ulceration

lasting for longer than three months (average 54 weeks; range 12–156 weeks). Of these one had severe brain injury with cognitive impairment, five had late-stage multiple sclerosis, one bilateral strokes and one late-stage Friedreich's ataxia.

The patient with bilateral strokes had a chronic ulcer on each ankle (randomization resulted in one ulcer being in the treatment group first and the other in the placebo group first).

The ulcers fell into two groups – five central on buttocks/sacrum/trochanter and four were peripheral on ankles or feet.

The exclusion criteria were:

• Those patients declining to be involved after the study had been explained to them; or, in the case of those lacking mental capacity to make informed decisions, where their relatives declined for them to be involved in the study.
• Those with bleeding disorders or who were on anticoagulant therapy with coumarin.
• Decubitus ulceration of the chest wall (risk of lung damage); elbow creases (difficult to access) or ear (noise of machine too distressing).
• Those where the ulcer was healing prior to the start of the study.
• Those with small surface ulcers with deep sinuses.

Measurement

The area of the ulceration was recorded by tracing the outline of the ulcer onto an acetate sheet and measuring the area using a computerized grid system (Visitrak; Smith & Nephew, London, UK). For each observation the average of three measurements was taken.

Ethics

This trial received ethical approval from the National Research Ethics Service (ISRCTN88965832).

Where the patients were cognitively impaired because of their neurological disorder and were unable to give informed consent then their nearest

relative was informed of the study and asked whether the patient would have been likely to agree to the study and to express a view as to the best interest of the patient to be involved. None withheld or withdrew the patient from the study. The ward doctor who was not part of the study sought the first agreement for involvement and gained informed consent from the patient or informed agreement of the nearest relative.

Results

All the patients who met the criteria were included in the study. None (or their relatives when the patient lacked mental capacity to decide) refused and none were withdrawn (Figure 1).

The main finding was that those chronic ulcers which showed no healing over the three-week baseline observation period demonstrated healing following the introduction of extracorporeal shock wave therapy. Figure 2 shows the pattern of change in ulcer area following the start of extracorporeal shock wave therapy for those where the placebo phase was first (Figure 2a) and those where the therapy phase was first (Figure 2b).

Three ulcers increased in size following the start of extracorporeal shock wave therapy but then showed more rapid healing – one completely within nine weeks; the other two more slowly but progressively. One of these ulcers showed further deterioration after 12 weeks of improvement but responded again after the reintroduction of therapy. These three patients all had ulcers that were surrounded by ischaemic and vulnerable skin. The extracorporeal shock wave therapy seemed to cause the tissue with poor viability to break down (debridement) and then to heal more rapidly. Two of the ulcers were awaiting surgical debridement but this was not required following extracorporeal shock wave therapy.

To test the possibility that the ulcers were not healing because there was a new intervention (i.e. either the Hawthorne or Pygmalion effects), the healing patterns of the extracorporeal shock wave therapy-first group and the placebo-first groups were compared (Table 1). Although the earliest sign of change as seen in Figure 2 was about the third week after starting extracorporeal shock wave therapy this did not reach statistically
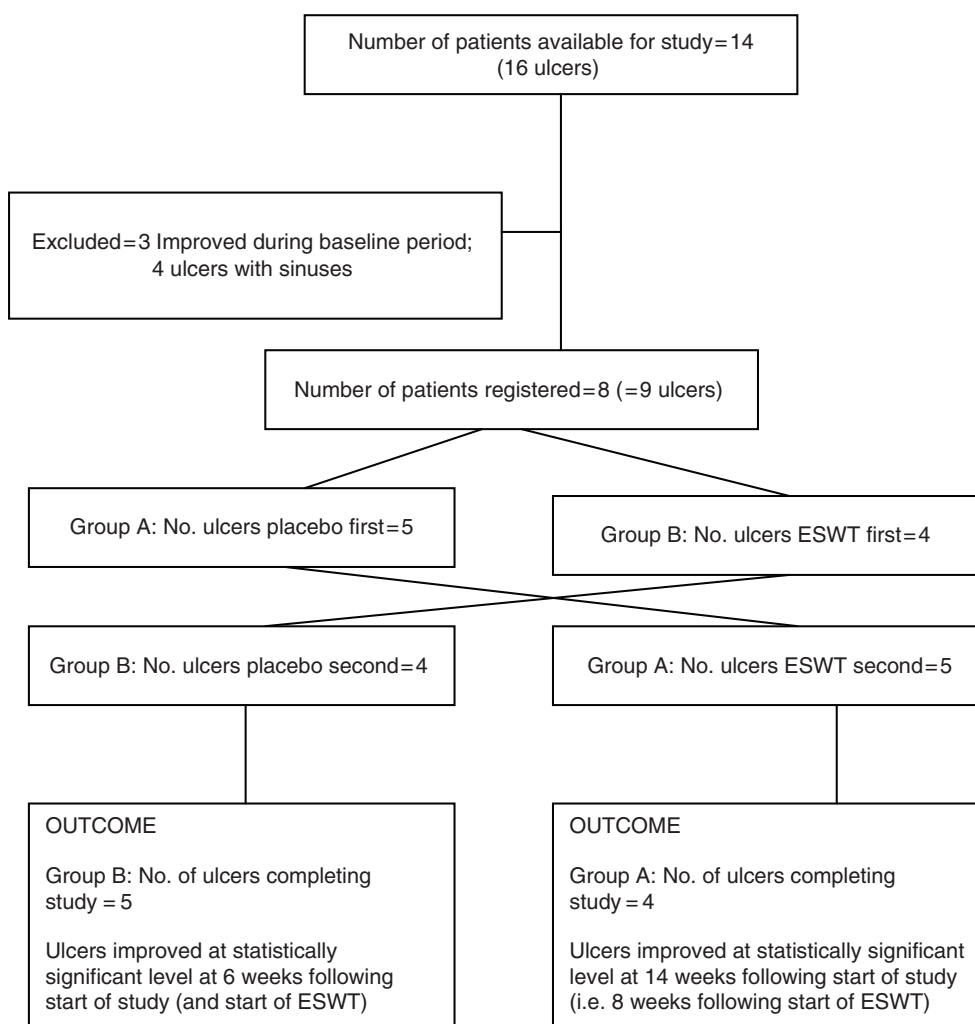
Number of patients available for study=14
(16 ulcers)

Excluded=3 Improved during baseline period;
4 ulcers with sinuses

Number of patients registered=8 (=9 ulcers)

Group A: No. ulcers placebo first=5

Group B: No. ulcers ESWT first=4

Group B: No. ulcers placebo second=4

Group A: No. ulcers ESWT second=5

OUTCOME

Group B: No. of ulcers completing
study = 5

Ulcers improved at statistically
significant level at 6 weeks following
start of study (and start of ESWT)

OUTCOME

Group A: No. of ulcers completing
study = 4

Ulcers improved at statistically significant
level at 14 weeks following start of study
(i.e. 8 weeks following start of ESWT)

Figure 1 Flowchart for the study.

significant levels until 6–8 weeks following the start of therapy (i.e. by week 6 in the extracorporeal shock wave therapy-treated first group and week 8 in the placebo-treated first group).

It is worth noting that one patient had ischaemic ulceration on both ankles, both present for about 15 months. The randomization resulted in one being in the placebo-first group and the other in the extracorporeal shock wave therapy-first group. In both cases the ulcers deteriorated in size once the extracorporeal shock wave therapy started and then began to improve (i.e. the extracorporeal shock wave therapy-first ulcer responded about six weeks before the placebo-first ulcer).

Discussion

We recognize that the number of patients is very small but this represents the total number of patients accumulated over a long period of time in a large (250-bed) long-stay hospital – equivalent to about 10 nursing homes. The inclusion of new
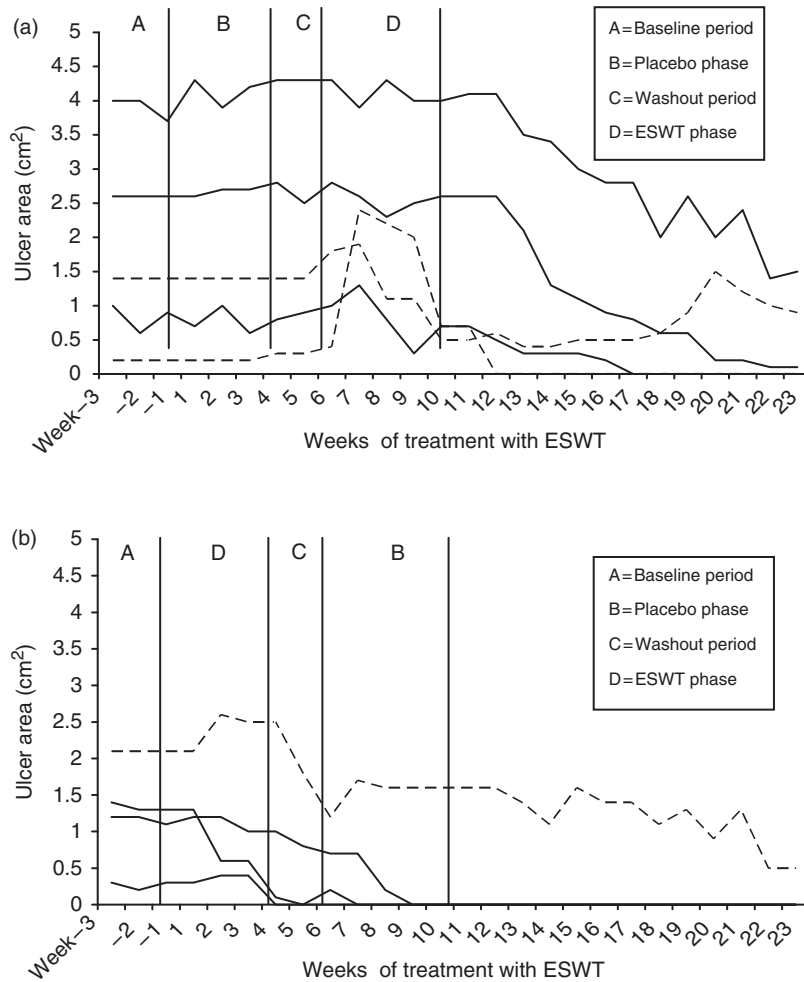
Figure 2 Patterns of change in size of ulceration. (a) Placebo-first group; (b) extracorporeal shock wave therapy (ESWT)-first group. Dashed line, patients whose ulcer increased in size following start of extracorporeal shock wave therapy; solid line, patients whose ulcer did not increase in size following start of extracorporeal shock wave therapy.

Table 1 Comparison between placebo-treated first and extracorporeal shock wave therapy-treated first groups

	Baseline ulcer size (cm^2)		Ulcer mean size difference (cm^2) from baseline across timepoints					
	Mean	SD	End of Placebo phase	2 weeks post placebo phase	End of ESWT phase	2 weeks post end ESWT phase	4 weeks post end ESWT phase	8 weeks post end of ESWT phase
Placebo first (*n* = 5)	1.79	1.48	0.13	0.27**	−0.09	−0.23	−0.71*	−1.15*
ESWT first (*n* = 4)	1.23	0.72			−0.33	−0.71*	−0.78*	−0.83*

*$P < 0.05$; **$P < 0.1$.
ESWT, extracorporeal shock wave therapy.

patients with ulcers that became chronic would take many years to accumulate sufficient numbers for a more satisfactory cohort size. A multicentre trial would be logistically difficult and complicated by the wide variety of methods of treating ulcers in different institutions.

Taking these concerns into account the study still provides support for the view that extracorporeal shock wave therapy can help heal chronic skin ulceration in severely disabled patients.

In this group of patients with chronic ulcers (ranging from being present for three months to three years) that were showing no evidence of healing in the three weeks prior to the study, all showed a response to the introduction of extracorporeal shock wave therapy. Where the placebo was used first, the response did not start until after the therapy had started thus supporting the view that it was the extracorporeal shock wave therapy that was having the effect rather than something else, such as the coupling gel or the Hawthorne/Pygmalion effect.

In some cases the response started within the first month of treatment but overall the statistically significant change occurred 6–8 weeks after the first dose of therapy (whether treated first with the placebo or extracorporeal shock wave therapy). There is some theoretical reasoning why this should be the case. Although the mechanism of the effect is only beginning to be understood shockwaves can increase cellular permeability, stimulate cellular division and stimulate cytokine production by cells.[12,13] There is evidence[14] that extracorporeal shock wave therapy activates cells that are sensitive to mechanical stimulation (e.g macrophages). Mechanisms such as increased motility of immune cells, increased attraction of immune cells,[15,16] increased phagocytosis, release of non-specific cytokines, interleukins and nitric oxide all may play a part and are likely to have a delayed effect. It is also possible that extracorporeal shock wave therapy produces shear stress/pressure resulting in stimulation of the capillary walls. Cells from the capillary walls (endothelial cells and smooth muscle cells) are under physiological conditions responding to shear laminal pressure of the capillaries.[17] A simple explanation of the phenomenon is that endothelial cells release nitric oxide[18] and smooth muscle cells release vascular endothelial growth factor.[19,20] The general outcome is increased blood flow and relaxation of the capillaries (immediate effect) and stimulation of angiogenesis (delayed effect) and induction of a long-lasting sustained effect. Our results are consistent with findings of Wang *et al.*[21] who have shown that extracorporeal shock wave therapy increased endothelial nitric oxide synthase and vascular endothelial growth factor production as much as three times the normal amount four weeks after treatment. This could explain the delayed and sustained effect of extracorporeal shock wave therapy on angiogenesis and the effect observed on pressure sores.

Three of the ulcers enlarged during the extracorporeal shock wave therapy phase. All of these were ulcers that were undermined and had ischaemic edges. For the purpose of the study the definition of ulcer size was the degree of broken skin, when in reality the true size was the area of ischaemic tissue and perhaps we should have considered this. If we had then there would have been no deterioration in the size of the ulcer. Of some clinical importance, two of these ulcers were waiting for surgical debridement but this was not required following extracorporeal shock wave therapy.

The patient with bilateral ischaemic ulcers offers additional anecdotal support for the benefit of extracorporeal shock wave therapy. Both ulcers had been present for the same length of time and both showed healing after the introduction of therapy – the placebo-first ulcer six weeks after extracorporeal shock wave therapy-first ulcer – the equivalent of four weeks of the placebo phase plus the two week washout period.

It is important to recognize that these ulcers were chronic and were not healing prior to the study. In view of the profundity of the disability of these patients and the chronicity of the ulcers it is unlikely that these ulcers would have healed during the period of this study.

It is still unclear how frequently the extracorporeal shock wave therapy needs to be provided. In this study four sessions at weekly intervals were provided. It is possible that one session of therapy would have been sufficient or perhaps the treatment would have been more effective if more frequent sessions were provided. Nevertheless the regime used here was effective for this group of patients.

This study supports clinical experience that extracorporeal shock wave therapy has potential benefit in healing chronic ulceration which is not only of benefit to the patient but is a considerable cost saving to healthcare organizations.

Clinical messages

- ESWT has a potential part to play in the treatment of chronic skin ulceration.
- ESWT improves healing of static chronic ulcers in people with complex neurological disabilities.

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