Treating venous leg ulcers with Extracorporeal Shockwave Technology (ESWT)

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Aims: Extracorporeal shockwave technology (ESWT) delivers high-energy acoustic shock waves to the body. With clinical applications in urolithiasis and orthopaedics, there is emerging evidence for its use to facilitate healing for diabetes related foot ulcers and burns. This study sought to examine the benefit of ESWT therapy on venous leg ulcers.
Method: A case series was conducted in 2016. During the study period, seven clinic patients were identified who met the eligibility criteria and consented to ESWT treatment; six of whom additionally provided written informed consent to have their details included in the case series.
Results: Participants (n=6) had a mean age of 78.67 years (SD=9.97) and wound duration of 34.80 weeks (SD=23.02). A reduction in wound size was observed for five patients. Only one patient, while achieving improved tissue quality, had an increased wound size and an alternative aetiology was subsequently considered. Client acceptability was high; pain was reported by only one patient during two of their five treatments and was concurrent with the pain at the dressing change in general. Capacity to implement the EWST as frequently as prescribed (weekly) was not feasible for most patients due to a combination of patient and clinic factors. The treatment was easy to implement for clinicians. **Discussion:** The case series suggests promising outcomes of ESWT therapy for venous leg ulcers that warrants further investigation using more controlled research methods.

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Extracorporeal shockwave technology (ESWT) — the application of shock waves to human tissue (Mittermayr et al, 2012) — was first introduced in the 1980s for the treatment of urolithiasis and continues to be gold standard for this disorder (Krokowicz et al, 2010). Other applications include muscloskeletal conditions involving connective tissues, tendon and ligament conditions, and it is also readily used in orthopaedics (Mittermayr et al, 2012); one study observing that ESWT could be used for relieving discomfort associated with plantar fasciitis (Metzner et al, 2010). It has further been argued that ESWT should be the first choice treatment for non-unions of the tibia (Haffner et al, 2016). In addition to these medical applications, the capacity for ESWT to facilitate wound healing is a burgeoning area of research and clinical application.

Much of the *in vivo* evidence in relation to ESWT and wound healing has emerged in relation to foot ulcers and diabetes related wounds (Wang et al, 2015). For example, one study examined the wound progress of 67 patients with chronic foot ulcers, 38 of which had a complication of diabetes mellitus, who received twice weekly ESWT

treatments for three weeks (Wang et al, 2014). Local blood perfusion increased for both groups 6 weeks and 1 year following treatment, before decreasing at the 5-year evaluation time point. The decline in perfusion was greater for diabetes mellitus associated foot ulcers. Historical controls were used to interpret wound outcomes with the clearest benefit of ESWT observed in the area of reduced amputation after one and five years.

Enhance blood flow perfusion was also detected in patients with diabetes related foot ulcers (DRFUs) who received a total of six ESWT treatments administered twice weekly for three weeks (n=39) compared to those undergoing 20 hyperbaric oxygen therapy (HBOT) (n=38) (Wang et al, 2011a; 2011b). In addition to requiring fewer presentations for ESWT treatment and having no adverse events compared to the HBOT group, histopathological findings demonstrated significantly greater cell proliferation, concentration and activity, and reduced cell apoptosis among DRFUs treated with ESWT compared to HBOT.

ESWT treated ulcers were more likely to heal (57%) compared to HBOT-treated wounds (25%) (Wang et al, 2011b). Biopsies further demonstrated that ESWT-treated wounds had significantly increased expression of positive immuno-activities of vWF, VEGF, eNOS, PCNA, EGF and reduced TUNEL expression compared to baseline results and the HBOT treated wounds (Wang et al, 2011a). More generally, *in vivo* research would suggest that ESWT is easy to implement clinically, is associated with few adverse events, and is a cost-effective treatment when contrasted with other DRFU therapies (Wang et al, 2014).

Research with other wound aetiologies suggest comparable benefits to those recorded with foot wounds. For example, positive healing outcomes and perfusion was observed after providing two ESWT for deep, partial or full-thickness burns (n=15), with significantly increased perfusion evident after a single treatment (Arnó et al, 2010). A small, blinded crossover randomised controlled trial using ESWT on pressure injuries in an acute setting (n=9) found wound size reductions in the intervention group that were continued after the crossover with a similar pattern of healing occurring in the control group upon commencement of ESWT (Larking et al, 2010). Schaden and colleagues (2007) conducted a prospective study among 208 non-healing acute and chronic wounds, the majority of which were 'disturbed healing' surgical wounds (39.4%) and post-traumatic necrosis (32.2%). An average of three ESWT were administered and treatment was generally well tolerated; a 15.4% drop out rate was reported. A logistic regression analysis was undertaken to predict healing, but as there was no control group, the number of ESWT treatments was included as an independent variable and did not emerge as a significant predictor of healing (Schaden et al, 2007).

Saggini et al (2008) treated wounds of post-traumatic (n=16), venous (n=12) and diabetic aetiology (n=4) that were unresponsive to conservative or advanced dressing treatment with two weekly ESWT treatments for between 4 to 10 treatments. Wound healing outcomes were compared to a control group (comprising posttraumatic (n=2), venous (n=5) and diabetic (n=3) wounds). The study showed a reduction of fibrin and necrotic tissue, and increased granulation tissue, significantly decreased pain, and reduced wound size (Saggini et al., 2008). The heterogeneity of aetiology, however, makes clarification of the benefit of ESWT for particular wounds difficult to discern.

There is a need for further research to increase the depth and breadth of evidence regarding the application and utility of ESWT to treat wounds of varying aetiology. Given the prevalence of venous leg ulcers — 0.05-1% in the community (Graves and Zheng, 2014), representing 50-60% of all lower leg wounds (Franks et al, 2016) and was estimated in 2014 as costing Australia $802.55 per annum (Graves and Zheng, 2014) — and given their propensity for delayed healing, the capacity for ESWT to foster wound healing warrants exploration. To expand evidence pertaining to ESWT and venous leg ulcers, a case series was conducted to examine wound-healing outcomes of patients with venous leg ulcers when treated with ESWT. The purpose of this case series was to ascertain if ESWT presents a feasible treatment for venous leg ulcers and if it was concurrently associated with positive healing outcomes.

Method

A case series of clients using ESWTs to facilitate healing of VLUs was conducted. The case series was implemented at a medical professional lead, multidisciplinary outpatient wound clinic in Melbourne, Australia. Patients were offered ESWT treatment if they met the indications for treatment. Written informed consent was provided for the use of their health information in the case series.

Sample

Patients of the clinic who were ≥18 years of age, had a venous leg ulcer on their lower leg, and were able to attend the clinic to receive treatment and for monitoring in the subsequent 3-month period (e.g., there were no planned absences)

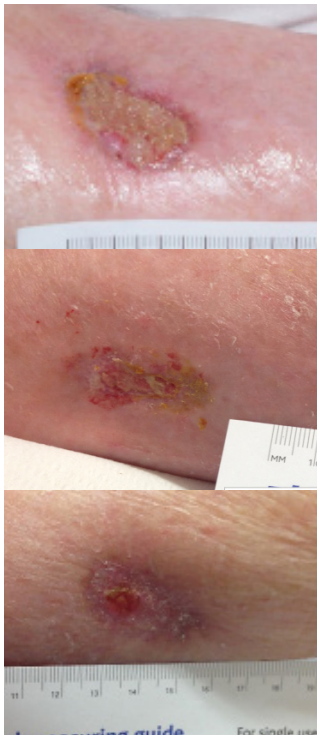

Figure 1. **(a) Week 2 of ESWT (b) Week 5 of ESWT (c) No treatment, 9 weeks after initial treatment.**

were considered for inclusion in the study. Exclusions or contraindications for use of ESWT or inclusion in a case series included:

1. An infected wound or active cellulitis at the site/in the surrounding area of the ulcer
2. Exposed bone, tendon or fascia in the wound bed
3. A diagnosis of any of the following conditions: Osteomyelitis, Coagulation disorders, sickle cell anaemia, malignancy, immunodeficiency disorder (e.g. AIDS)
4. Was receiving any of the following treatments: dialysis, chemotherapy within 60 days prior to the study, has history of radiation at the study site, target ulcer was treated with growth factors, prostaglandin therapy, negative pressure or vasodilator therapy within 2 weeks of the study, treated with wound dressings that include growth factors, engineered tissues, or skin substitutes (e.g., Regranex® (Smith & Nephew), Dermagraft® (Organogenesis), Apligraf® (Organogenesis), TheraSkin® (Soluble Solutions), GraftJacket® (Wright Medical Group), OASIS® (SIS Cookbiotech), Primatrix® (Integra), Matristem® (ACell)) within 30 days of the study.
5. Current pregnancy
6. People with pacemakers.

Outcome measures and data collection

The primary outcome measures were wound size (recorded on acetate grid tracing sheets) and wound healing (as indicated by wound appearance in digital wound images). Additional outcome measures included wound status, including the presence of tissues types, infection, and wound pain as per a Visual Analogue Scale (as recorded on wound assessment and wound progress notes). Demographics and diagnostic information was sourced from the electronic health record.

Procedure

The ESWT device in use was dermaPACE® (Sanuwave). This ESWT modality is Australian Therapeutic Goods Administration (TGA) registered for the application of PACE® (Pulsed Acoustic Cellular Expression) high-energy pressure shock waves to treat acute and chronic wounds. PACE treatment is one form of ESWT that produces high-energy acoustic shock waves to an affected area (Arno et al, 2010; Cwykiel et al, 2013). The console and hand-held applicator utilise PACE® technology, which is the proprietary form of ESWT. The treatment utilises high-energy acoustic pressure waves in the shock wave spectrum to produce compressive and tensile stresses on cells and tissue structures to elicit a series of biological responses (positive and negative pressure).

Treatment selection was an energy setting that dictates the voltage discharges of either E5 (0.299mJ/mm^2)/ E6 (0.305mJ/mm^2) delivered at a frequency of 240 pulses/min. This pulse count dictated by wound area (cm^2) as per the manufacturer's instructions, and as automatically programmed by the device. Individual treatment time, therefore, varied according to the surface area of the wound, with larger wounds requiring more time to treat than smaller wounds. The treatment protocol was one treatment delivered each week for 10 weeks.

Treatment involved placing a sterile sleeve over the applicator and ultrasonic conductive gel to the wound surface and 2 cm of periwound. The applicator was held perpendicular to the wound and periwound and the applicator was moved over the wound until the wound had been navigated completely. Once the treatment was complete, the applicator sleeve was discarded, the wound was cleaned of the gel, and topical moist wound care implemented, including as much compression therapy as the patient could tolerate.

Analysis

Study results are reported as anonymous case studies. Quantitative or qualitative analysis was

Table 1. Participant characteristics and wound history.

	P1	P2	P3	P4	P5	P6
Gender	Female	Female	Female	Female	Male	Female
Age (years)	86	85	87	61	74	79
Wound duration (weeks)	22	36	57	3	n/a*	56
Wound location	R) proximal gaiter	L) lateral malleolus/ gaiter	L) medial dorsum foot	L) medial malleolus	L) anterior ankle	R) lateral gaiter
ABPI	1.76	1.11	0.9	n/a*	n/a*	1.33

*data could not be located in patient healthcare record

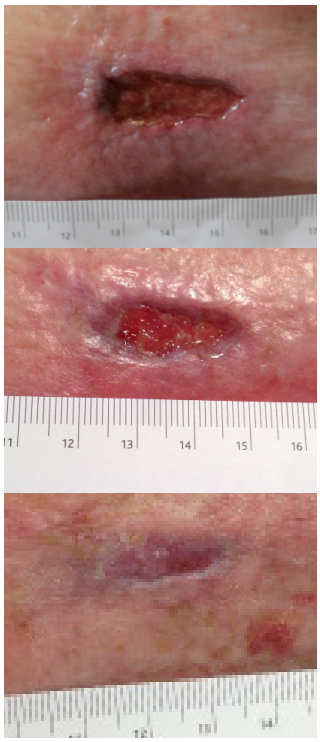

Figure 2. **(a) Prior to first ESWT (b) 3 weeks after commencing treatment (c) Final ESWT, week 11.**

not deemed appropriate for this research design although interpretation of case study results are presented in the discussion.

Results

During the study period there were seven patients who presented with venous leg ulcers that met the eligibility criteria for treatment and who agreed to receive ESWTs. Of the seven, six agreed to the inclusion of their health information in the case series. Reasons given by clinic patients who were suitable, but did not want the ESWT treatment related to the frequency of treatment, which was either untenable because the clinic was not in close proximity or the time commitment and inconvenience of attending the clinic on a regular basis.

All case series participants meet the eligibility of having a venous leg ulcer. Participant demographics and wound characteristics are presented in *Table 1*.

Patient 1

Patient 1 received their first ESWT on August 18, 2016 and received a further four treatments; once per week for the next 4 weeks. Due to a combination of patient cancelled visits or absence of staff who could provide the ESWT, no further treatments were administered. Thus, a total of five treatments were provided over a 5-week period. When the patient represented 9 weeks after the initial treatment the wound was close to healed and no further ESWTs were progressed for this reason.

At baseline the wound was 7cm^2 (baseline image missing; wound image from week 2 of treatment is shown in *Figure 1a*). Some discomfort was reported during the initial treatment although a biopsy had been attended immediately prior to treatment. Discomfort during treatment was reported once more during the third treatment, which coincided with the patient's report of intermittent and strong wound pain (8/10 VAS); wound pain was not subsequently reported. By the fifth week of consecutive treatments, the wound had reduced in size and wound tissue was healthier in appearance *[Figure 1b]*. At the final ESWT (September 15, 2016; *Figure 1c*) the wound bed demonstrated reduction of slough and increased granulation tissue. The patient did not attend the clinic again.

The patient's care plan involved treatment with an antimicrobial as a primary dressing. Secondary dressings were changed during the treatment timeframe and included absorbent, foam and silicone foam dressings. Compression therapy was three layers of straight tubigrip tubular bandage, which was subsequently reduced to two layers of straight tubigrip during the treatment period.

During the ESWT period, the wound showed steady reduction in size — approximately 1 cm^2 per week — and was 1 cm^2 at the final ESWT.

Patient 2

Patient 2 commenced ESWT on the September 1, 2016 when the wound was 2.5 cm^2 *[Figure 2a]*. The patient received four treatments in the first 5 weeks, had 2 weeks of no treatment before recommencing weekly treatments for 1 month. A total of eight ESWTs were received over an 11-week period.

The patient did not report wound pain generally and did not report any discomfort with the ESWT specifically. The patient's care plan during the treatment period included an antimicrobial as the primary dressing. Secondary dressings during the treatment period included either an absorbent or foam dressing. Compression therapy commenced with three layers of straight tubigrip which was subsequently changed to one layer of shaped tubigrip, increased to two layers of shaped tubigroup before changing to Coban 2 (3M).

A stable trend in wound size reduction was observed. After 3 weeks, the granulation tissue was less ruddy in appearance and the wound edges were no longer rolled *[Figure 2b]*. At the final ESWT *[Figure 2c]*, the wound was 1 cm^2 and close to healing. A follow-up visit attended 3 weeks after the final ESWT (November 24, 2016) described the wound status as "almost healed, only small superficial areas remain" and on January 16, 2017, approximately 16 weeks after the initial ESWT treatment, the wound was documented as healed.

Patient 3

Patient 3 received four ESWTs commencing on October 20, 2016 with treatments provided at fortnightly intervals thereafter. When ESWT was commenced the wound was 2 cm^2 *[Figure 3a]*. After 2 weeks of treatment, the wound had new areas of epithelisation tissue [*Figure 3b*]. At the final ESWT, the wound was 0.5 cm^2 *[Figure 3c]*. A follow-up visit on the December 15, 2016 recorded the wound as having achieved "100% epithelisation" according to the nursing documentation, and a "small wound" was recorded by the attending medical practitioner.

The patient's care plan during the ESWT was unchanged using an antimicrobial or low absorbent dressing, and their own compression therapy, the level of compression was not able to be established.

Wound pain on a VAS scale at baseline was not recorded, however, the patient reported at their

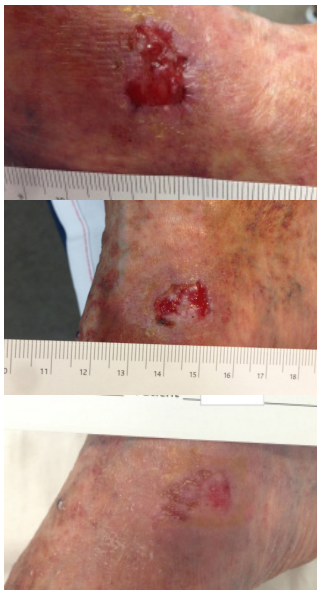

Figure 3. **(a) Prior to first ESWT (b) 2nd treatment, 2 weeks after treatment commenced (c) 4th and final ESWT, 6 weeks after treatment commenced.**

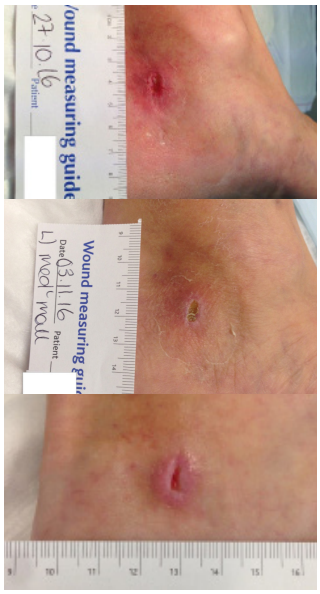

Figure 4. **(a) Prior to first ESWT (b) 2nd treatment, 1 week since commencing treatment (c) Fourth and final ESWT, 5 weeks since commencing treatment.**

third treatment that they had not experienced any wound-related pain since the first treatment. The patient did not experience pain during the ESWTs.

Patient 4

Patient 4 commenced ESWT on October 27, 2016 when the wound was 1 cm^2 *[Figure 4a]*. A second treatment was administered the following week *[Figure 4b]* and with two further treatments completed at fortnightly intervals thereafter. Thus, four ESWTs were provided over a 6-week period. At the final treatment the wound was assessed as being 0.25 cm^2 *[Figure 4c]*. A follow-up visit one week post the last ESWT (8/12/2016) documented the wound as "tiny". No further clinic visits were documented a month later.

During the treatment period the care plan included antimicrobial as the primary dressing, a foam dressing as the secondary dressing, and the use of the patients own stocking for which the level of compression could not be established. No discomfort during ESWTs or pain generally was recorded.

Patient 5

Patient 5 received an ESWT on October 27, 2016 when the wound was assessed as being 2.5 cm^2 *[Figure 5a]*. At the same visit, ultrasonic debridement (Sonica) was also attended prior to the ESWT. Although the patient returned to the clinic in subsequent weeks, only ultrasonic debridement was provided. The patient's wound was assessed at the next clinic visit prior to the conclusion of the case series 5 weeks post their ESWT as being 1.5 cm^2 *[Figure 5b]*. The patient did not attend the subsequent scheduled visit and nil further appointments were scheduled. The patient's care plan during this period of time included an antimicrobial and foam dressing, with one layer of shaped Tubigrip (Mölnlycke).

Patient 6

Patient 6 commenced ESWTs on November 17, 2016 and had treatments weekly for the next fortnight. Thus, a total of three ESWTs were provided over 3 weeks. The wound upon commencing treatment was assessed as being 1.5 cm^2 *[Figure 6a]*. The wound was assessed as showing an increase in size over the subsequent fortnight with a final wound size of 2.5 cm^2 *[Figure 6b]*. At the final treatment, the wound presented with a reduction in the extent of hypergranulation and a healthier wound margin *[Figure 6c]*. The patient did not report wound pain generally and experienced no discomfort during the actual ESWTs. At a follow-up visit 6 weeks after the final ESWT (January 12, 2017), Clinic staff felt that the wound's presentation was unusual and further investigations might ensure best care and although a biopsy had been attended previously, it was planned to re-biopsy the wound if the ulcer had not shown improvement.

Wound care during the treatment period included an antimicrobial as the primary dressing, an absorbent dressing as the secondary dressing. Compression therapy involved the use of three layers of straight Tubigrip for 2 of the 3 weeks, before being reduced to two layers.

Discussion

The purpose of this case series was to expand evidence regarding the viability and the concurrent healing outcomes when using ESWT to treat venous leg ulcers. Clinicians at the study site who had used the ESWT previously had found the therapy to be easy to learn and implement in the clinic setting. The capacity to deliver the scheduled weekly treatments was not, however, achieved in any instance. Participants did find the treatment to be acceptable. Pain was reported only twice and was concurrent to reports of wound pain during the dressing change or following a biopsy. As such, the experience of wound pain during a dressing change or following a procedure would be a reasonable indication as to whether the patient will find the ESWT painful and could be avoided or managed for patients who experience constant or intermittent wound pain. Positive wound healing trends were observed for five wounds, with the sixth revealing an initially increased presence of healthy tissue although plans for a biopsy to investigate the wound further were considered should the wound further deteriorate.

The recommended treatment regimen for the ESWT was weekly for 10 weeks. The active treatment itself would typically last for only 2-3 minutes with preparation and clean up also requiring only approximately five minutes of time, making ESWT an extremely practical therapy to implement in a busy clinic environment. However, the capacity to see patients weekly was difficult to realise. Reasons that prevented clients from considering the use of ESWT or from receiving the weekly care included their availability to attend the clinic weekly either due to a lack of close proximity to the clinic from the client's residence or due to competing life events and other appointments. Unexpected events, such as sickness, could also interrupt the treatment schedule. Weekly appointment time slots were not always available or feasible especially when the clinic was scheduled to operate at a half day when staff undertook afternoon training, when the clinic did not operate due to internal or external conferences, or when

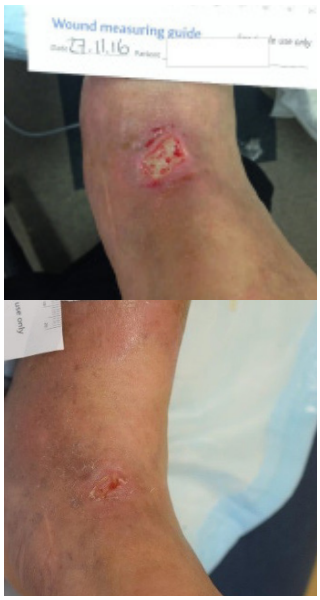

Figure 5. **(a) Prior to first ESWT (b) Week 5 follow up.**

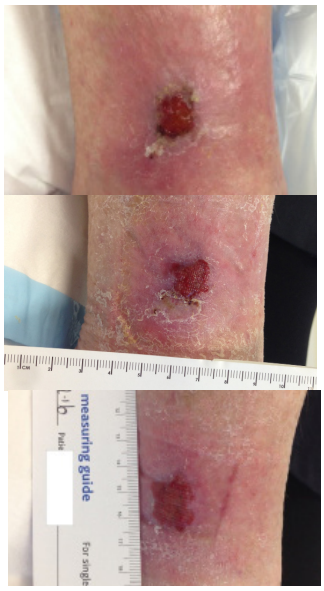

Figure 6. **(a) Prior to first ESWT (b) Second treatment, week 2 (c) Final ESWT, week 3.**

clinic staff trained in the use of the ESWT had a planned or unplanned absence.

Despite the inability to implement the treatment regimen as planned, positive wound healing effects were observed for the majority of client's receiving ESWT. Indeed, the majority of wounds at the conclusion of the case series were either healed or healing was anticipated in a subsequent visit. The rationale for ESWT treatment regimens would benefit from further research especially given that such varied treatment regimens are reported in the published literature and evidence of immediate biophysically changes after a single dose. For example, animal model research has demonstrated significantly improved wound-healing outcomes following even one treatment of ESWT compared to control and endothelial nitric oxide synthase (eNOS) knockout mice with increased expression of eNOS further observed in the ESWT group (Hayashi et al, 2012). Perfusion was also observed following a single ESWT among deep-partial or full-thickness burns (n=15) (Arnó et al, 2010).

More generally, the mechanism of ESWT is not widely understood (Mittermayr et al, 2012) potentially due to its multifactorial properties that impact understanding and prediction of clinical effects (Mittermayr et al, 2011). It has been shown, however, that ESWT increases angiogenesis and cell activity and decreases or normalises cell apoptosis in a localised area, therefore, improving tissue regeneration and which ultimately results in the acceleration of the wound healing process (Cwykiel et al, 2013). Positive variations to growth factors and cytokine levels at a cellular level have been acknowledged in previous studies and these variations are shown be present during regular wound healing (Krokowicz et al, 2010; Wang et al, 2011; Cwykiel et al, 2013). ESWT has also been observed enhance extracellular signal-regulation kinase 1/2 by activating the purinergic receptors in response to the release of cellular adenosine triphosphate (ATP) (Weihs et al, 2014). Furthermore, ESWT has been observed to assist in preventing muscle inflammatory responses during and following extended surgical procedures as well as promote angiogenesis and neovascularisation (Cwykiel et al, 2013; Mittermayr et al, 2011).

The optimal dosage and treatment regimen in relation to ESWT is an area of scientific research that, although not the persuasive clinical trials sought by clinicians to influence practice, will ensure the true benefit, should there be one, of ESWT can be identified when large clinical studies are progressed. Further research that can also identify the biophysical changes that occur in the wound will additional shed light on the mechanisms through which ESWT facilitate wound healing.

This study represents a low level of evidence regarding the viability and effect of ESWT in treating venous leg ulcers. The method which is characterised by a small sample and the absence of a comparison group and is a limitation in comparison to more rigorous research methodologies. The case series is, however, an appropriate research design for a burgeoning area of clinical enquiry where questions regarding feasibility, acceptability and effectiveness remain.

Conclusion

Given that chronic wounds represent a substantial economic burden (Graves and Zheng, 2014) and the ageing profile of many developed countries will further compound the volume and resources required to treat these wounds, the identification and execution of clinically effective care is central to heal wounds promptly. ESWT is utilised in a number of other clinical fields. To date, published literature regarding ESWT and wound healing is promising with the current study corroborating the feasibility and positive healing trends that have been reported. Given evidence that the treatment was easy to implement for clinicians, was generally acceptable for clients, and was concurrent to positive wound healing outcomes for the majority of participants, an evolving program of scientific enquiry that refines the treatment regimen and adopts more rigorous research designs warrants exploration. WINT

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