A Quantitative, Pooled Analysis and Systematic Review of Controlled Trials on the Impact of Electrical Stimulation Settings and Placement on Pressure Ulcer Healing Rates in Persons With Spinal Cord Injuries

Liang Liu, MBBS, PhD; Julie Moody, MSc, RCN; and Angela Gall, FRCP

Abstract

Pressure ulcers (PrUs) are among the most common secondary complications following spinal cord injury (SCI). External electrical current applied to a wound is believed to mimic the body's natural bioelectricity and to restart and stimulate endogenous electrical fields to promote wound healing. A systematic review was conducted to critically appraise and synthesize updated evidence on the impact of electrical stimulation (ES) versus standard wound care (comprising cleansing, dressing, nutrition, and debridement as necessary) and/or sham stimulation on PrU healing rates in persons with SCIs. Medline, Embase, the Cumulative Index for Nursing and Allied Health Literature (CINAHL), PsycINFO, and Cochrane Central were searched using the terms *spinal cord injury*, *electrical stimulation*, and *pressure ulcer* in free text and MESH terms. Publications were limited to peer-reviewed, randomized controlled trials (RCTs) and non-RCTs (CCTs) published in English from 1985 to 2014. The methodological quality of the RCTs was evaluated using the Jadad scale; CCTs were assessed using the Downs and Black tool. Pooled analyses were performed to calculate the mean difference (MD) for continuous data, odds ratio (OR) for dichotomous data, and 95% confidence intervals (CI). A total of 8 trials were reviewed — 6 RCTs and 2 CCTs included a total of 517 SCI participants who had at least 1 PrU. The number of patients per study ranged from 7 to 150 and the number of wounds from 7 to 192. Comparison models included ES irrespective of current type and placement of electrodes against sham/no ES (7 trials), ES delivered by electrodes overlaid on the ulcer versus sham/no ES (4 trials), ES delivered by electrodes placed on intact skin around the ulcer versus sham/no ES (4 trials), ES delivered by electrodes overlaid on the wound bed versus placed on intact skin around the ulcer (1 trial), ES with pulsed current versus sham/no ES (6 trials), ES with constant current versus sham/no ES (2 trials), pulsed current ES versus constant current ES (1 trial), number of PrUs closed (2 trials), and incidence of PrU worsened by ES versus sham/no ES (2 trials). The overall quality of studies was moderate; 2 trials were rated as good quality, 2 were poor quality, and 4 were moderate. Evidence showed ES increased the rate of PrU healing in patients with SCI (MD 4.97, 95% CI 1.97–7.98, $P = 0.00$; N = 7 studies and 559 ulcers), and a higher proportion of ulcers healed (OR 2.68, 95% CI 1.17–6.14, $P = 0.02$; N = 2 studies and 226 ulcers). The data suggest pulsed current ES increased the healing rate (MD 6.27, 95% CI 2.77–9.78, $P = 0.0005$; N = 6 studies and 509 ulcers) more than constant current (MD 4.50, 95% CI 1.19–10.18, $P = 0.12$; N = 2 studies and 200 ulcers). In addition, wounds with electrodes overlaying the wound bed seemed to heal ulcer faster than wounds with electrodes placed on intact skin around the ulcer. Future preclinical, *in vivo* models and clinical trials examining the impact of electrodes configuration for PrU healing are warranted.

Keywords: systematic review, electric stimulation, pressure ulcer, spinal cord injury

Index: *Ostomy Wound Management* 2016;62(7):16–34

Potential Conflicts of Interest: none disclosed

Dr. Liu is a research fellow, Centre for Critical Research in Nursing and Midwifery; and Ms. Moody is a senior lecture in adult nursing, Department of Adult, Child and Midwifery, School of Health and Education, Middlesex University, London, UK. Dr. Gall is a consultant physician, London Spinal Cord Injury Centre, Royal National Orthopaedic Hospital, London, UK. Please address correspondence to: Liang Q. Liu, MBBS, PhD, Middlesex University, London, UK, Department of Adult, Child and Midwifery, The Burrghs, Hendon Campus, London NW4 4BT UK; email: liangqinl@hotmail.com.

Ostomy Wound Management 2016;62(7):16–34

Key Points

- Some pressure ulcer (PrU) guidelines of care include the recommendation to augment good wound care with electrical stimulation (ES) in patients with spinal cord injury (SCI) if ulcers are extensive and/or refractory.
- However, guidance on ES settings and applications is less readily available.
- The authors conducted a quantitative meta-analysis using available study data to increase understanding of how different settings of ES affect PrU healing.
- The results suggest ES is more effective than control treatments for healing PrUs in patients with SCI and that pulsed current ES increases the healing rate more than constant current ES.
- Questions about the optimal electrode configuration remain largely unanswered by this study.

The National Pressure Ulcer Advisory Panel/European Pressure Ulcer Advisory Panel (NPUAP/EPUAP)[1] describes a pressure ulcer (PrU) as an area of localized damage to the skin as a result of prolonged pressure alone or pressure in combination with shearing forces. A PrU is typically categorized into 4 key stages depending on ulcer depth and severity. PrUs are among the most common secondary complications following spinal cord injury (SCI). According to the Model SCI System Statistical Centre,[2] the annual incidence rate of PrUs is 14.7% in the first post-injury year and noted to steadily increase thereafter. It is estimated that up to 85% of people living with SCI develop a PrU during their lifetime.[3-5]

According to the NPUAP/EPUAP guideline,[1] a systematic review of 12 studies,[6] and a survey[7] once a PrU has developed, it significantly increases the burden on the individual with SCI and/or his/her caregivers and has substantial detrimental impact on the quality of life, independence, and dignity of the patient. If a PrU is severe, it can lead to further disabilities, need for surgical interventions, and fatal infections. Krause et al[7] surveyed 1017 patients with SCI to examine the relationship between PrU and life adjustment after SCI and found PrUs adversely impacted nearly every area of life studied, including quality of life and independent living.

Apart from personal consequences, PrUs also represent a significant cost burden for health and social care systems. According to the National Institute of Health and Care Excellence (NICE) guideline,[8] in addition to the costs of standard care, the daily costs of treating a PrU are estimated to range from £43 to £374 in the United Kingdom. Resources required for treating a PrU include nursing time, dressings, antibiotics, diagnostic tests, and high-specification, pressure-redistributing devices. Although the exact cost of PrU management in SCI is unknown, the total cost of treating PrUs has been estimated to be between £1.4 billion and £2.1 billion per year; the average cost to treat 1 Stage IV PrU is £14,108 per episode in the general population.[9]

Treatment for PrUs can vary depending on the grade/stage of the ulcer. The standard care of PrUs varies across individual settings. Although the management of PrUs recommended by clinical guidelines[5,8] includes offloading, improving nutrition, cleansing, debridement, and dressing, the general principles of Stage I ulcer treatment incorporate pressure relief, careful clinical monitoring, cleansing, and dressings to promote hydration; Stage II ulcers may require pressure relief using a high-specification foam mattress/cushion or dynamic support surface and a moist dressing for reepithelialization; and Stage III and Stage IV ulcers usually require advanced nonsurgical or surgical treatment in addition to pressure relief; they also may require debridement and antibacterial treatment if systemic sepsis, cellulitis, or underlying osteomyelitis is clinically evident.

Electrical stimulation (ES) was proposed as a therapeutic modality for wound healing more than a century ago, and its use has been well documented in clinical studies since the 1960s, especially for wounds not responding to standard forms of treatment.[10-16] Despite the fact ES has been demonstrated in clinical studies[13-16] to accelerate wound healing compared to no ES as conjunctive therapy, the understanding of the exact physiological mechanism remains incomplete. Animal models and *in vitro* preclinical studies[9,17-31] provide some indication of the mechanism of ulcer healing enhanced by ES. Endogenous electrical fields (which measure electrical potentials) are known to naturally exist in the human body and are vital for tissue development and repair.[17-19] The electrical potential at the epidermis (transepithelial potential) is generated by intact skin through directional active ion transportation, leading to the concentration of negative chlorine ions at the surface and positive sodium and potassium ions in the tissues. The epithelial layer of intact skin acts as an electrical barrier. When a wound occurs, the epithelial barrier is broken, allowing the current to flow out of the wound. The transepithelial potential collapses and ions immediately begin to leak out, establishing a weak but measurable current between the skin and inner tissues (the current of injury). The current is thought to continue until the skin defect is repaired.[17-19]

Two main types of ES currents commonly noted in the literature are pulsed current (PC) and direct current (DC).[17] Constant, low-intensity DC involves applying continuous, unidirectional flow of current of low intensity (<1 mA) for at least 1 second. PC includes monophasic and biphasic waveforms: monophasic PC involves brief pulses of unidirectional flow of current followed by a finite off period, and biphasic PC consists of brief pulses of bidirectional current that has either a symmetric or asymmetrical biphasic waveform.[17] In symmetric biphasic PC, the bidirectional PC is equal and balanced, whereas asymmetric biphasic PC produces a bidirectional current that is unequal and may or may not be bal-

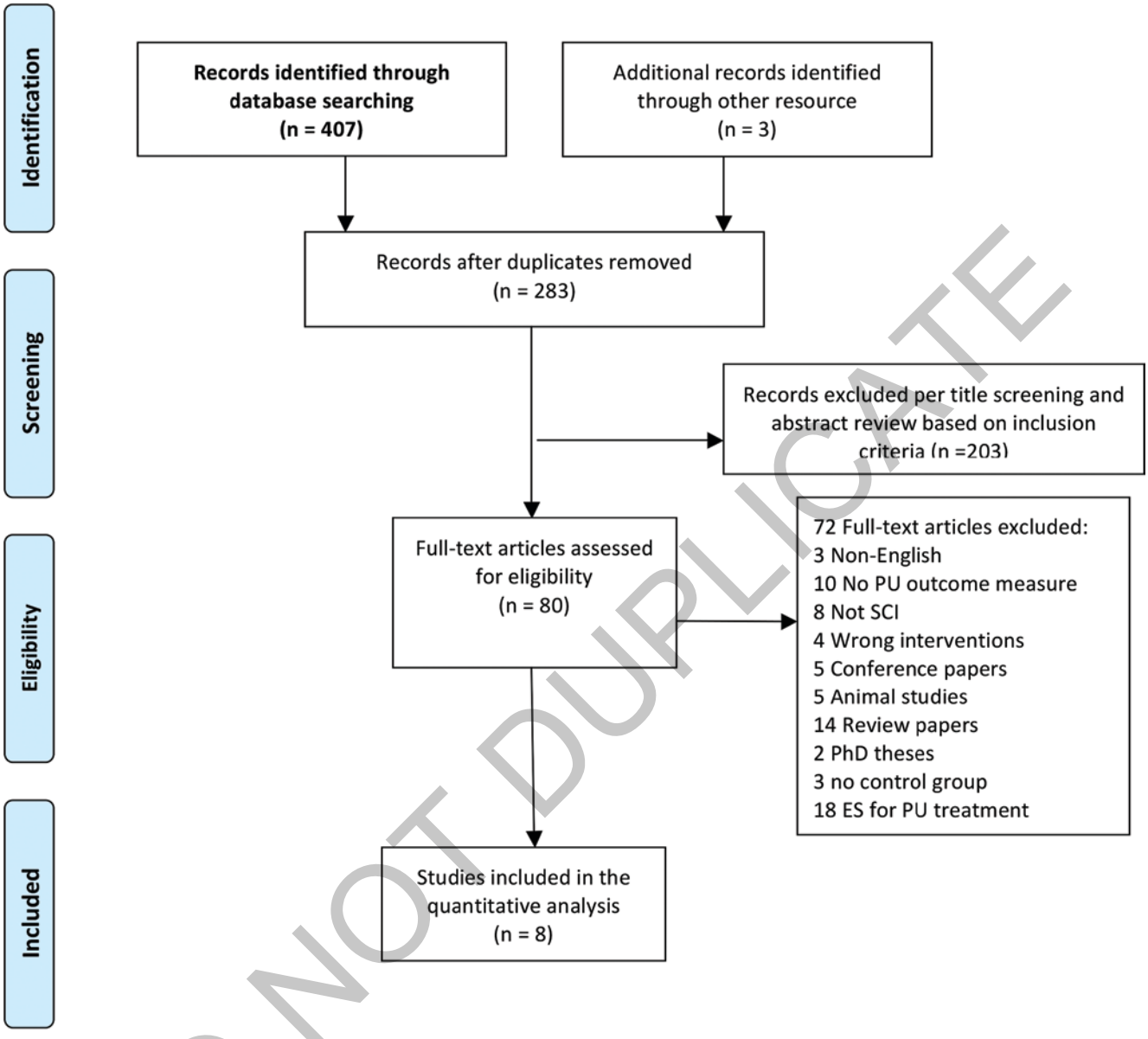

Figure 1. Literature search screening flow chart. *PU=pressure ulcer; SCI=spinal cord injury; ES=electrical stimulation*

anced. Balanced asymmetric biphasic PC has no net positive or negative charge; unbalanced asymmetric biphasic PC creates a net positive or negative charge over time.[17]

Application of an external electrical current to a wound is believed to mimic the body's natural bioelectricity and to restart and stimulate endogenous electrical fields and as such, promote wound healing.[20-22] ES has been demonstrated in both *in vitro*[23-26] and animal *in vivo*[27] studies to enhance cellular activities such as collagen and DNA synthesis, ATP concentration, and generation of chemotaxic factors.[24-27] ES also has been shown *in vitro* and *in vivo* studies[25,27-31] to increase tissue perfusion, decrease edema, and promote angiogenesis and galvanotaxis compared to no ES stimulation, directing and accelerating the process of endothelial migration in the wound tissue to promote wound healing.

In a clinical study, Baker et al[13] assessed 3 different forms of ES current for pressure healing among 192 PrUs in 80 patients with SCI who were treated for 45 minutes/day for 4 weeks. The authors reported ES enhanced PrU healing by measuring percentage changes of wound surface area per week in comparison with no ES in SCI. In addition, the authors identified asymmetric biphasic waveform of electrical current as the optimal wound healing protocol in comparison with microcurrent and without ES. Mittmann et al[32] constructed a decision analytic model over a 1-year period to determine the incremental cost effectiveness of ES plus standard wound care (SWC), typically comprised of nonsurgical procedures such as debridement, dressing, nutritional, physical

Table 1. Characteristics of studies reviewed

Author, year, reference, country	Number of patients (PrUs)	Comparison I=Intervention, C=control	Type of ES	ES parameters (pulse duration, frequency, intensity)	Electrode characteristics (location, material, size)	Study period	Outcome measures	Methodological quality
RCT								
Houghton et al (2010)[40] Canada	**34 (34)**	I: ES plus SWC program; C: SWC only without ES.	Pulsed current	50 µs, 100Hz and 10Hz, 50–150 V	On wound bed; NR, 4.8 cm x 10.2 cm	3 months	WSA	Low risk of bias Jadad 3, AC yes, ITT yes
Griffin et al (1991)[39] USA	**17 (17)**	I: ES plus standard nursing care program; C: Sham ES plus standard nursing care	Pulsed current	75 µs, 100 pps, 200v	On wound bed, aluminium plate; larger than ulcers	20 days	WSA	Low risk of bias Jadad 4, AC yes, ITT no
Adegoke et al (2001)[38] Nigeria	**7 (7)**	I: ES plus SWC; C: Sham ES plus SWC	Pulsed current	NR, 30Hz, submotor	On wound bed, aluminium plate; larger than ulcers' perimeters	4 weeks	WSA	Moderate bias Jadad 2, AC yes, ITT no
Baker et al (1996)[13] USA	**80 (192)**	I: asymmetric biphasic ES; II: symmetric biphasic ES; III: microcurrent ES; C: No ES treatment	Pulsed current	I: 100 µs, 50 Hz, submotor II: 300 µs, 50 Hz, submotor III: 10 µs, 1 Hz, 4mA	Edge of ulcer, carbon-rubber, 2.5 cm x 2.5 cm to 5 cm x 10 cm	4 weeks	Healing rate and WSA	Moderate bias Jadad 2, AC no, ITT no
Jercinovic et al (1994)[41] Slovenia	**73 (109)**	I: SWC plus ES; C: SWC. Crossover group after 4 weeks	Pulsed current.	250us, 40Hz, up to 45mA	Edge of ulcer, self-adhesive, 5 cm x 7.5 cm	4 weeks	Healing rate	Moderate bias Jadad 1, AC no, ITT yes
Karba et al (1997)[42] Slovenia	**50 (50)**	I: ES with positive electrode overlaid ulcer and 4 negative electrodes laid around ulcer; II: Same ES program with 2 electrodes laid on intact skin at the ulcer edge across wound; C: Sham ES. All groups received SWC	Constant direct current	NA, NA, 0.6 mA	I: Overlaid the ulcer; rubber electrodes; NR; II: edge of ulcer, self-adhesive electrodes, NR	Not reported	Relative healing rate	Moderate bias Jadad 2, AC no, ITT no

continued on next page

continued on next page

Table 1. Characteristics of studies reviewed

CCT							
Stefanovska (1993)[43] Slovenia	150 (150)	I: Conventional treatment plus constant direct currents (DC); II: Conventional treatment plus pulsed direct currents (PC); III: Conventional treatment only	Constant direct current and pulsed current	I: NA, NA, 600 µA; II: 0.25 ms, 40 Hz, 15–25 mA	Edge of ulcer, NR, NR	4 weeks or till wound closure	Healing rates	High risk of bias D&B score 13
Trontelj et al (1994)[44] Slovenia	106 (106)	I: ES plus conventional treatment; C: Conventional treatment only	Pulsed current	1.25 ms, 40 Hz, 15-25 mA	Edge of ulcer, self-adhesive, NR	8 weeks	Healing rate	High risk of bias D&B score 8

NA=not applicable; NR=not reported; ES=electrical stimulation; AC= allocation concealment; CCT=clinical control trial; D&B=modified Downs & Black score range from 0 to 28; ITT= intention to treat; Jadad score range from 0 to 5; PrU= pressure ulcer; RCT=randomized controlled trial; SCI= individual with spinal cord injury; SWC=Standard Wound Care/conventional treatment

therapies, and surgical procedures for the management of complications in comparison with SWC alone in SCI with Stage III and Stage IV (per the NPUAP) PrUs. The authors assessed PrU healing using healing rates, recurrence rates, and complication rates; ES also reduced the cost of care in the SCI population. Furthermore, the most recent NPUAP/EPUAP clinical guideline[5] recommends the use of ES to facilitate wound healing in recalcitrant Category/Stage II PrUs as well as any Category/Stage III and Stage IV PrUs in patients with SCI. However, the lack of consistency in the use of stimulation mode and parameters, together with the small sample size in the individual published trials, makes it difficult for health professionals and health providers to make clinical decisions on the implementation of ES treatment for PrU.

Purpose

The purpose of this quantitative meta-analysis was to increase understanding of how different settings of ES affect PrU healing. Pooled analysis that quantitatively calculates weighted averages of findings across multiple trials can increase the statistical power of the existing small sample size of individual studies, enriching understanding of inconsistent results encountered across individual studies.

The aims of this review were 1) to assess the effect of ES as an adjunctive therapy for PrU on the weekly healing rate in people with SCI when compared to sham stimulation or no ES treatment; 2) to explore whether different types of ES currents and electrode placement have any influence on the healing rate of PrUs; and 3) to examine whether ES treatment worsens PrU in SCI as compared to no ES treatment.

Methods

Literature search. The original systematic review protocol[33] registered in the PROSPERO database in July 2013 (www.crd.york.ac.uk/PROSPERO; registration number CRD42013005088) was updated to include more recent research up to July 3, 2014. Material from the original study plus new findings are analyzed. As before, full reports of randomized, controlled trials (RCTs) and nonrandomized, clinical controlled trials (CCTs) were identified through searches of the Medline, Embase, the Cumulative Index for Nursing and Allied Health Literature (CINAHL), PsycINFO, and the Cochrane Central Register of Controlled Trials without language restrictions. Search terms included *spinal cord injury*, *electrical stimulation*, and *pressure ulcer*. All searched hits were exported to Endnote (Endnote version X7 for Windows, Thomson Reuters). All titles and abstracts were screened for eligibility, and the full text of potentially relevant articles was retrieved and considered for inclusion by the first author. Each stage of the selection process was cross-checked by the second author. Any disagreement was discussed or consulted by the third author.

Literature inclusion/exclusion criteria.

Target population. Persons with SCI and any categorical grade or any number of PrUs irrespective of age, gender, and level and degree of severity of traumatic or nontraumatic injury were included. Studies with a mixed-study population that included individuals with SCI were included if the ulcer outcomes were reported/analyzed separately for SCI participants.

Type of intervention. All types of ES using 2 or more surface electrodes placed on the wound bed or in the edge of wound bed were

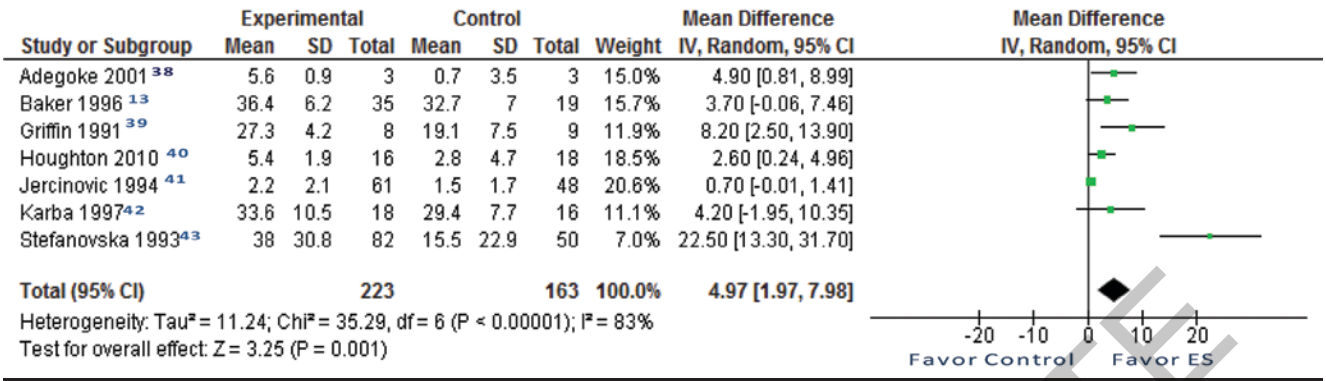

Figure 2. Weekly healing rate with electrical stimulation (ES) treatment versus without ES treatment in 7 studies.

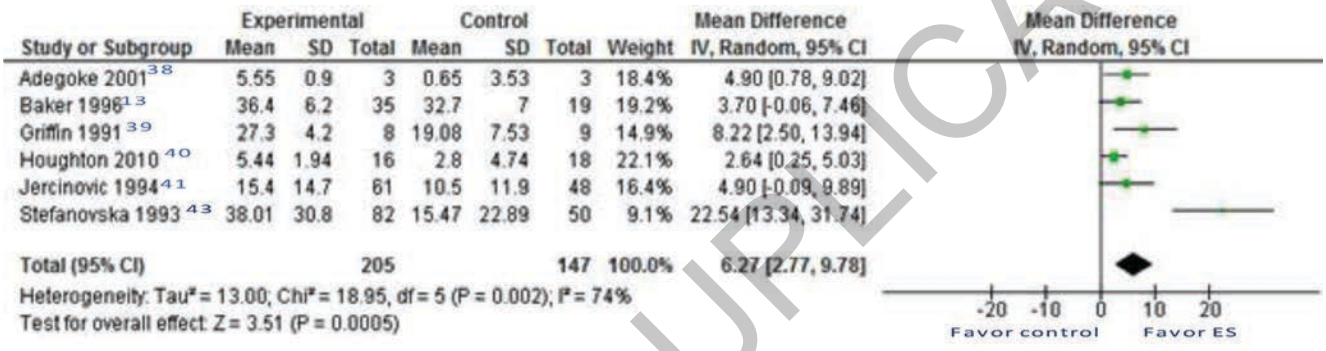

Figure 3. Weekly healing rate using pulsed current versus without electrical stimulation treatment.

included.

Type of studies. RCTs and CCTs that compared any type of ES against SWC consisting of cleansing, dressing, debridement and nutrition without ES or sham ES that were published in an indexed, peer-reviewed journal between January 1985 and July 2014 were included. Conference abstracts and university theses were excluded.

Outcome. The publication needed to report ulcer outcome measurement (eg, wound size or average healing rate per day, per week, or during whole study period).

Data extraction and methodological quality. The following data were extracted from eligible articles by 1 reviewer (LL) and cross-checked by the second reviewer: year of publication, country of author, and type of study design. All other data, including quality assessment, were assessed independently by 2 reviewers. This included sample size; participant age, gender, and type and level of SCI; the type of ES; the duration and pattern of stimulation; electrode placement; follow-up duration; and adverse events. Additionally, data extraction included outcome measures on the percentage change in wound surface area or changes in ulcer size. Any disagreement in assessed findings between the 2 independent reviewers was resolved by discussion or through consultation with a third reviewer.

Each publication was subjected to a quality assessment. For RCTs, a Jadad score (University of Oxford, Oxford, UK) was used together with the item allocation concealment and consideration as to whether the analysis was based on the randomized groups.[33-35] A modified Downs and Black tool (London School of Hygiene and Tropical Medicine, London, UK) was used for CCTs.[36,37] Both scales are well-established tools for assessing and reporting the quality of clinical and health-related studies in the literature. The Jadad score independently assesses the methodological quality of a clinical trial and has known reliability and external validity.[37] It contains an assessment — namely, risk of bias (selection bias, performance bias, detection bias, attrition bias) — and is relatively easy to use. The Jadad score addresses items relating to randomization, blinding, and description of withdrawals and dropouts, with scores ranging from 0 to 5 (trials scoring 3 or greater are considered to be of reasonably good quality). In addition to the Jadad score, 2 extra items were added: allocation concealment and intent-to-treat (ITT) analysis, which deal with reporting bias and performance bias for open-label (nonblinded) trials. Allocation concealment was considered adequate if patients and investigators who enrolled patients could not foresee treatment assignment. ITT is defined as an analysis that demonstrates inclusivity of all randomized participants based on specified criteria and includes all randomized patients in the groups to which they were randomly

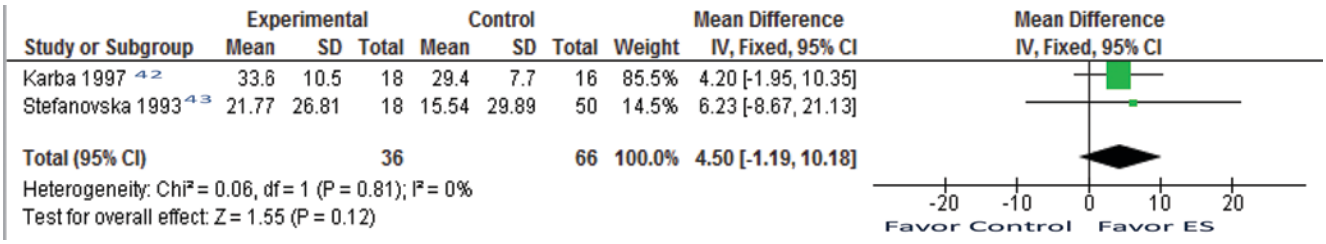

Figure 4. Weekly healing rate by constant direct electrical stimulation (ES) versus without ES treatment.

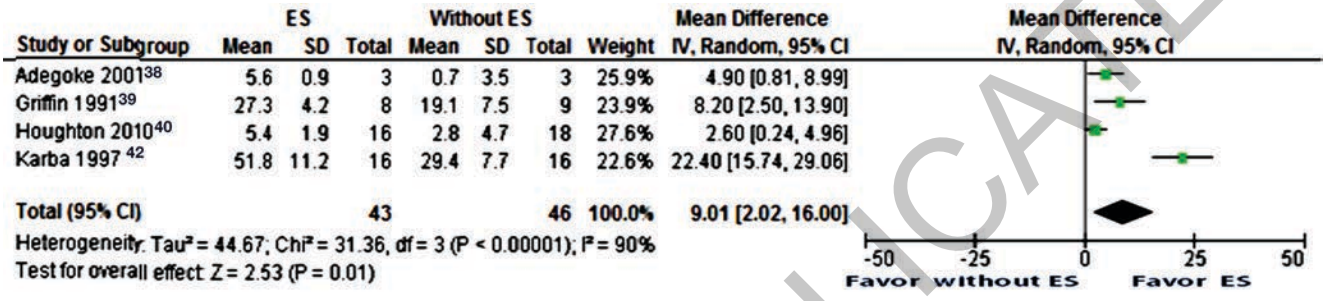

Figure 5. Weekly healing rate by electrical stimulation (ES) with electrode overlying wound versus without ES treatment.

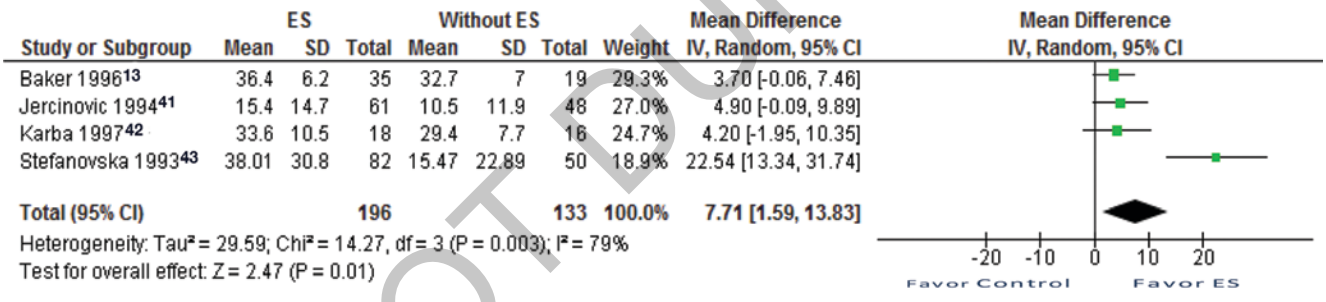

Figure 6. Weekly healing rate by electrical stimulation (ES) with both electrodes on intact skin versus without ES treatment.

assigned, regardless of 1) their adherence with the entry criteria, 2) the treatment they actually received, and 3) subsequent withdrawal from treatment or deviation from the protocol.[34] The Downs and Black tool[37] consists of 27 questions that evaluate the level of 4 domains: reporting, external validity, internal validity (both bias and confounding), and power. Each question was scored as Yes (1) or No/Unknown (0). Because question 5 addressed 2 components (Are the distributions of principal confounders in each group of subjects to be compared clearly described? A list of principal confounders is provided), the full score for the question was 2. Question 27 was modified slightly due to an ambiguity in the first component (Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is <5%? Sample sizes have been calculated?); only the second part of the question was assessed. For example, if the sample size was calculated by a trial, it was scored yes (1). The total score of the 27 questions was calculated by adding up the scores; thus, the highest score any reviewed article could receive was 28. It should be noted that scores increased in line with the methodological quality of the study; higher scores indicated higher methodological quality.[37]

Data analysis. Data were extracted to a spreadsheet. A quantitative pooled analysis was performed to estimate the pooled ES treatment effect on weekly healing rates, the number of ulcers healed, and the incidence of ulcers worsening. All trials included in this review defined ulcer healing in terms of changes in wound surface area either per week, per day, or during the whole study follow-up. Because the daily healing rate has limited clinical relevance, for those trials that reported percentage of ulcer decrease per day or during the whole study period, the weekly healing rate was calculated and used for pooled analysis. Weekly healing rate was defined as the mean percentage change in ulcer size per week. Review Manager (Review Manager (RevMan), Version 5.3. Copenha-

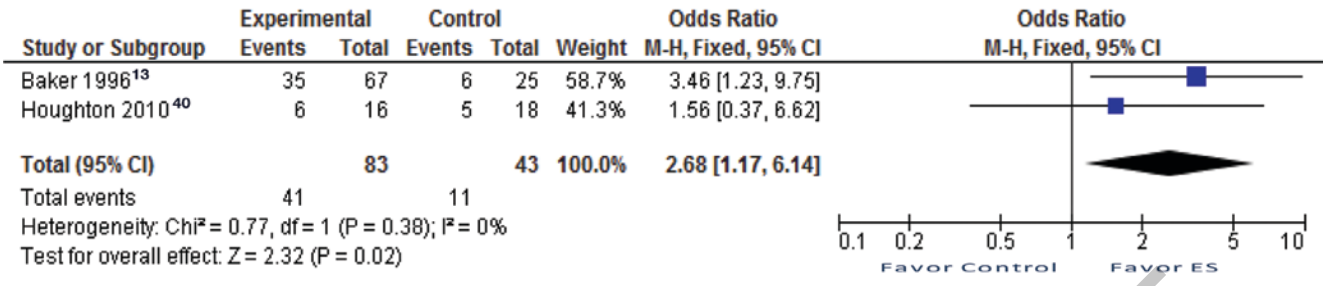

Figure 7. Number of pressure ulcers healed during study period with versus without electrical stimulation (ES) treatment.

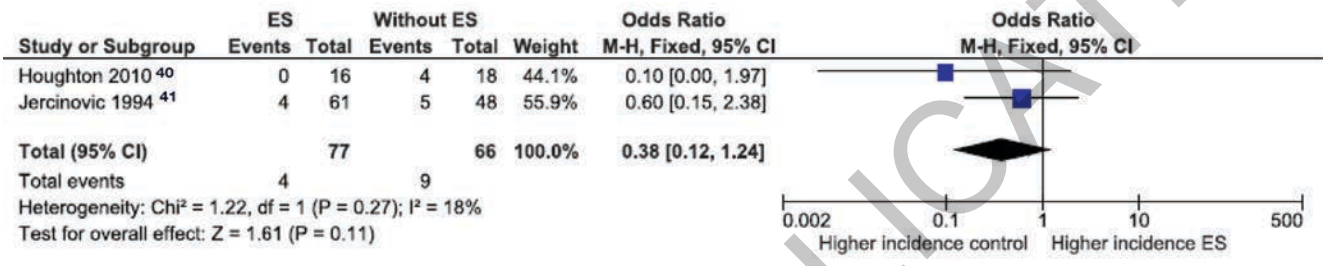

Figure 8. Incidence of pressure ulcers worsened with versus without electrical stimulation treatment .

gen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to pool the healing rate per week and the number of ulcers completely healed and ulcers that worsened among the studies.

All data irrespective of the length of treatment and follow-up were analyzed. Weekly healing rate was compared between patients who had ES and patients who had no ES treatment. Subgroup analysis was performed for good quality RCTs. The weekly healing rate between PC and constant DC and electrode overlaid versus placed at edge of ulcer were compared. For those trials with more than 2 arms, the ES arm with the largest sample was included for comparison with the control arm (no ES/sham ES). Treatment effect was significant if P <0.05. Heterogeneity between studies was tested with the use of the chi-square test (significant if P <0.1) and I^2 test (with substantial heterogeneity defined as values >50%). When studies showed significant heterogeneity (I^2 >50%), the Mantel–Haenszel random effects model was used to calculate mean difference. Otherwise, the fixed effects model (I^2 <50%) was used to calculate the pooled effect sizes when studies did not show heterogeneity.

Results

Studies. The literature search identified a total of 407 unique references; all were exported to Endnote, along with 3 additional articles identified from other sources. Of these 410 articles, 127 were identified as duplicates, resulting 283 abstracts and titles. These were further screened for eligibility, generating 80 potentially relevant abstracts that were retrieved and considered for inclusion in the final review. Of these, 8 (6 RCTs[13,38-42] and 2 nonrandomized CCTs[43,44]) met the inclusion criteria and were subjected to full-data extraction and quantitative analysis. Figure 1 provides a flow chart of the process and results for screening eligibility and study selection.

All 8 studies described the study target population as persons with SCIs who had at least 1 PrU. The number of patients per study ranged from 7 to 150, with the number of ulcers studied ranging from 7 to 192. Four (4) studies (N = 415 ulcers) measured mean daily percentage change in ulcer size,[41-44] 1 study (N = 192 ulcers) measured the mean weekly percentage change in ulcer size,[13] and 3 studies (N = 58 ulcers) measured mean percentage change in ulcer size across the entire study period.[38-40] Six (6) out of 8 trials (N = 509 ulcers) compared PC ES to sham/no ES treatment,[13,38-41,44] 1 trial (N = 50 ulcers) compared constant current ES to sham ES treatment,[42] and 1 (N = 150 ulcers) compared PC ES to constant current ES therapy or sham ES.[43] For stimulus pulse settings, stimulation varied from 40 Hz to 100 Hz in frequency and from 50 V to 150 V (or 4 mA to 45 mA) in intensity.

In terms of electrodes placement, in 3 studies[38-40] (N = 58 ulcers) the electrodes were overlaid on wound bed, in 4 studies (N = 557 ulcers) the electrodes were applied to intact skin around the wound,[13,41,43,44] and in 1 (N = 50 ulcers) ES treatment compared electrodes overlaid on the wound bed to electrodes placed on intact skin around the ulcers.[42] Details of sample characteristics are shown in Table 1.

Methodological quality. One (1) of the 6 RCTs described an appropriate method to generate the randomization sequence,[40] 2 were double-blinded and described the method

of double-blinding,[39,42] 3 adequately described allocation concealment,[38-40] and 2 used ITT to analyze the data.[40,41] Two (2) RCTs were considered to be of reasonably good methodological quality according to the Jadad score along with 2 other items; hence, they were classified as low risk of bias trials.[39,40] The remaining 4 RCTs were considered to exhibit moderate risk of bias.[13,38,41,42] Two (2) nonrandomized CCTs were assessed for their reporting quality using the Down and Black tool, scoring 13 and 8, respectively, out of a total achievable score of 28 and subsequently considered relative high risk of bias trials.[43,44]

Data pooling and meta-analysis.

Effectiveness of ES. ES effectiveness was assessed according to mean weekly healing rate (ie, average percentage change per week in ulcer size), the number of ulcers healed, and the incidence of ulcers worsening (defined as wound size increased during study period), comparing different ES settings and/or how ES performed versus sham or no treatment.

With regard to overall healing rate by ES versus sham/no ES, the pooled analyses of the 7 relevant trials showed people receiving ES treatment in addition to conventional wound treatment (which involved cleansing, dressing, nutrition, and debridement as necessary) reporting a higher weekly healing rate than those without ES treatment by 4.97% (MD 4.97, 95% CI 1.97-7.98, $P = 0.001$) (see Figure 2). However, heterogeneity among the studies was substantial ($I^2 = 83\%$, $P < 0.00001$). A subgroup analysis of RCTs considered to be of good methodological quality showed a trend toward a higher weekly healing rate in people treated with ES than people without ES treatment, but the pooled effect was not significant ($P = 0.07$).

When healing rate by PC ES versus sham/no ES was assessed, the pooled analysis of the 6 trials[13,38-41,43] showed a significantly higher weekly healing rate in people who were treated with PC ES than those without ES treatment (MD 6.27, 95% CI 2.77-9.78, $P = 0.0005$, $I^2 = 74\%$((see Figure 3).

When healing rate by constant DC versus sham/no ES was compared, the pooled analysis of the 2 trials in which constant current ES was applied showed a nonsignificantly higher weekly healing rate in people treated with constant current than those without ES (MD 4.50, 95% CI 1.19-10.18, $P = 0.12$, $I^2 = 0\%$ (see Figure 4).

With regard to healing rate by PC versus DC ES treatment, 1 CCT[43] compared PC ES treatment versus DC for PrU healing. A higher weekly healing rate was achieved by PC ES: 5.43% to 4.40% per day versus 3.11% to 3.83% per day, respectively ($P = 0.03$).

Healing rate by electrode placement also was assessed (ie, active electrode overlaid the wound bed versus sham/no ES). A meta-analysis of the 4 trials[38-40,42] that applied the active electrodes directly on the wound found a significantly higher rate with ES irrespective of current type than without ES (MD 9.01, 95% CI 2.02-16.00, $P = 0.01$, $I^2 = 90\%$) (see Figure 5).

When electrode placement on intact skin was analyzed, the pooled analysis of the healing rate for the 4 trials[13,41-43] where both electrodes were placed on intact skin/the edge of wound versus sham/no ES showed a significantly higher weekly healing rate in people who received ES than those who received no ES (MD 7.71, 95% CI 1.59-13.83; $P = 0.01$, I2 = 79%) (see Figure 6).

The healing rate when the active electrode overlaid the wound bed was compared to electrodes placed on intact skin/the edge of wound. One (1) study[42] compared the effect of ES delivered by applying the electrodes either directly on the wound bed or on the edge/intact skin around the ulcer versus sham ES treatment. In group 1, the positive electrode overlaid the ulcer and 4 negative electrodes were laid around the ulcer; in group 2, 2 electrodes were laid on intact skin at the ulcer edge across the wound; and in group 3, 2 electrodes were laid on intact skin at the ulcer edge across the wound without ES delivery. The authors reported electrodes that overlaid wound bed achieved a higher healing rate than electrodes placed on intact skin around the ulcer or sham ES group (1.6%/day overlaid versus 4.8±1.5%/day versus 4.2±11%/day).

Two (2) trials[13,40] addressed the number of ulcers completely healed by ES versus sham/no ES. Both trials reported a higher number of ulcers completely healed in the ES treatment group (52% and 37%, respectively[13,40]) compared to sham/no ES treatment (24% and 28%, respectively[13,40]). Pooled analysis of these 2 trials showed significantly higher numbers of ulcers (N = 226 ulcers) healed with ES treatment (OR 2.68, 95% CI 1.17–6.14, $P = 0.02$, $I^2 = 0\%$) (see Figure 7).

Two (2) studies[40,41] reported the incidence of ulcers that worsened during the study period compared to sham/no treatment. Both trials reported lower number of ulcers worsened in individuals who had ES treatment (N = 143 ulcers). However, the pooled analysis of these 2 trials showed the difference was nonsignificant (OR 0.38, 95% CI 0.12–1.24, $P = 0.11$, $I^2 = 18\%$) (see Figure 8).

Adverse events. Only 1 of the 8 studies[40] reported adverse events. The authors indicated some patients experienced minor adverse reactions related to ES, which included red, raised, itchy skin beneath the large dispersive electrode. One (1) patient had a persistent (>24 hour) redness or burn under the active electrode, presumably from too high a stimulus intensity, which resolved within 48 hours.

Discussion

ES has been recommended for use in the treatment of PrUs in recent (2014) NPUAP/EPUAP guidelines, yet the specifics for ES are not clear. The comparison of ES current types and placement of electrodes reported in the present review should provide new insights for clinicians who treat PrU in the SCI population. Of the 8 studies that met inclusion criteria and were included in this review, 6 were RCTs[13, 38-42] and

2 were nonrandomized CCTs.[43,44] Two (2) of the 6 RCTs[39,40] were classified as having good quality of evidence according to the Jadad scale; they used allocation concealment and ITT analysis. The other 4 RCTs[13,38,41,42] were classified as moderate quality, and the remaining 2 nonrandomized[43,44] CCTs provided a relatively low level of evidence. As a whole, the 8 trials provided a moderate level of evidence.

In terms of effectiveness, the quantitative pooled analysis of the 7 controlled trials showed an average higher weekly healing rate during the treatment period when patients received ES in addition to SWC of cleansing, dressing, nutrition, and debridement as necessary. Of the 8 trials included in the review, 2 studies[13,40] (N = 226 ulcers) reported the number of ulcers completely healed during the study period (OR 2.68, 95% CI 1.17–6.14); significantly more PrUs healed with ES treatment in comparison to sham ES or no ES treatment ($P = 0.02$). Two (2) trials[40,41] reported fewer ulcers worsening when patients received ES treatment. These 2 trials also showed a trend toward higher weekly healing in the ES group, although the difference was not significant between ES treatment and control groups.

In addition to supporting the recommendations of the most recent NPUAP/EPUAP clinical guidelines[5] regarding the application of ES for recalcitrant PrU healing in persons with SCI, the current findings are also in agreement with previous studies demonstrating ES enhances PrU healing in the SCI population[45] and chronic wound healing in the non-SCI population.[11-16] A systematic review conducted by Lala et al[45] reported the risk of PrU healing during the study period (20 days to 3 months) together with daily healing rate (percentage decreased per day) in SCI. The authors concluded ES seems to be an effective adjunctive therapy to accelerate and increase PrU closure in individuals with SCI. In the current review, the calculated weekly healing rate was anecdotally suggested by clinicians and tissue viability specialists to be more clinically relevant than simply describing the positive outcomes of previous research. In addition, the types of ES current and placements of electrodes, presented along with the incidence of worsening PrUs, should be of interest to clinicians.

The constant DC that involves unidirectional continuous flow of current for longer than 1 second has been associated with an antibacterial effect in PrU healing, but it can cause chemical and thermal burns.[46] This type of ES was employed in 2 of the studies[42,43] reviewed. The most commonly used ES for PrU healing in the review was PC that involved no sinusoidal, interrupted current flow for a brief period of time. It is suggested that PC ES more closely mimics the "current of injury" necessary for triggering tissue healing by sustained activation of the voltage-gated sodium channels in the surrounding tissues.[24] As compared with continuous DC stimulation, PC ES may carry a lower risk of possible skin burns and a greater depth of penetration.[10,24,46,47] PC ES was utilized in 6 out of 8 studies (N = 465 ulcers).[13,38-42] Pooled analysis of 6 trials showed PC ES significantly improved weekly healing rate compared with no ES.

Three (3) studies involved placing the active electrode directly on the wound bed and the negative electrode on the intact skin around the edge of the ulcer.[38-40] Four (4) studies reported the negative and positive electrodes were placed on opposite sides of the PrU on intact skin.[13,41,43,44] One (1) study[42] compared electrode placement (1 group of participants received ES by applying the ES with positive electrode overlaid on the ulcer and 4 negative electrodes laid around ulcer, while the other group received ES by applying same ES program with 2 electrodes laid on the intact skin at the ulcer edge across wound; the participants in the control group received sham ES treatment with 2 electrodes laid on the intact skin at the ulcer edge across wound). The authors found participants who received ES by electrodes overlaid on the wound bed had a higher healing rate than the participants who received ES by electrode placed surrounding the wound.

Electrode polarity has long been thought a complex issue in the literature. For instance, anodal stimulation was shown to increase fibroblast migration,[31,48] while cathode stimulation enhanced keratinocyte migration[22] and increased fibroblast proliferation.[46] Both anodal and cathode stimulation have an antibacterial effect, with cathode stimulation seeming to have greater antibacterial effects.[48,49] In the current endeavor, only 1 study[42] compared electrode configuration by either placing the active electrode in the wound and the dispersive electrode at a distance from the ulcer versus placing both electrodes on the edge of ulcer. Although the average weekly healing rate was significantly higher when active electrodes overlaid the wound surface than when electrodes were placed surrounding the wound, this study was not a RCT and was classified as low level of evidence with high risk of bias. Such results should be interpreted with caution. Thus, the assessment of the different effects between 2 types of electrodes placement for PrU healing is inconclusive. Future preclinical, *in vivo* models and clinical trials examining the impact of electrode configuration on PrU healing are warranted.

Limitations

Although systematic reviews and meta-analyses have their own merits in terms of increasing the statistical power of the small sample size of individual studies, conducting such analyses often presents a number of limitations. These include publication bias (particularly against negative findings), language restrictions, heterogeneity across each studies, and coding of keywords. The small number of relevant trials, together with substantial heterogeneity in this review, made it difficult to interpret some findings and draw firm conclusions. Higher heterogeneities evident across the trials in this review can be explained by the variation of study design and stimulation parameters (stimulation frequency, intensity, waveform) and stimulation device used.

Another limitation of the study was the use of the Jadad

scale for assessing methodology quality of RCTs. Although the Jadad scale is a well-established tool and is widely used for assessing and reporting the quality of clinical and health-related studies in the literature, it has shortcomings. The Jadad scale is criticized for being oversimplistic, placing too much emphasis on blinding and exhibiting low consistency between different raters. Furthermore, it does not take into account allocation concealment. However, in this review, 2 assessment items (allocation concealment and ITT analysis) were added. The methodological quality of CCTs was assessed using the Downs and Blacks tool, a well-established assessment tool used in SCI literature[35]; however, it features no cut-off point for definition of good or poor CCTs. Future reviews should consider using 1 assessment tool for both RCTs and CCTs. Nevertheless, the methodology for each article also was assessed independently by 2 authors, and consensus was achieved and disagreement was discussed between them.

A further limitation is the exclusion of non-English language literature. Although adding non-English articles may have strengthened the current review, the language restriction cannot be avoided due to lack of interpretation resources. To minimize the limitation, the authors adopted a well-structured search strategy that was approved by a clinical librarian, supplemented all "explode" functions, and utilized hand searches as well as contacting specialists to minimize the potential bias.

In addition to types of ES current and electrode placement, other parameters (such as material, size of electrodes, level of injury, quality of life, hospital stay, pain, and cost to patients and carers) also may have an impact on PrU healing. Unfortunately, incomplete reporting of such data was identified in the current review — for instance, only 1 trial[40] in this review reported the level of injury and the majority of trials failed to report the size or material of electrodes used for ES treatment. Such data should be reported in future clinical studies.

Conclusion

ES appears to help facilitate PrU healing in the SCI population. Pulsed DC ES confers better benefits for PrU healing than constant DC. PrUs in people who had ES treatment seem more likely to completely close and less likely to worsen than ulcers in people who had no ES treatment. ES has been recommended for Stage III and Stage IV ulcers and for recalcitrant Stage II PrU healing by the NPUAP/EPUAP, yet the NICE guideline[8] recommends not to use ES for PrU healing. Health professionals and the health service need well-designed clinical studies involving large sample populations to determine the optimal stimulation parameters and stimulation location with the most beneficial effect on the enhancement of PrU healing in SCI. Although an electrode directly placed on the wound bed may be more efficient than all electrodes placed on intact skin around the wound, more rigorous preclinical studies and clinical trials on determining the optimal stimulation parameters (eg, type of ES current — in particular, constant DC versus PC that were commonly used for PrU healing in SCI), locations of electrodes, material, and size of electrodes are warranted. To better understand the exact physiological basis of ES for enhancing PrU healing, research is urgently needed in the form of more preclinical *in vivo* models to identify the optimal mode of ES current and electrode placement (polarity). ■

References

1. Haesler E (ed). National Pressure Ulcer Advisory Panel, European Pressure Ulcer Advisory Panel and Pan Pacific Pressure Injury Alliance. *Prevention and Treatment of Pressure Ulcers: Quick Reference Guide*. Perth, Australia: Cambridge Media;2014.
2. McKinley WO, Jackson AB, Cardenas DD, DeVivo MJ. Long-term medical complications after traumatic spinal cord injury: a regional model systems analysis. *Arch Phys Med Rehabil*.1999;80(11):1402–1410.
3. Sumiya T, Kawamura K, Tokuhiro A, Takechi H, Ogata H. A survey of wheelchair use by paraplegic individuals in Japan. Part 2: Prevalence of pressure sores. *Spinal Cord*. 1997;35(9):595–598.
4. Byrne DW, Salzberg CA. Major risk factors for PUs in the spinal cord disabled: a literature review. *Spinal Cord*. 1996;34(5):255–263.
5. Ash D. An exploration of the occurrence of PUs in a British spinal injuries unit. *J Clin Nurs*. 2002;11(4):470–478.
6. Boakye M, Leigh BC, Skelly AC. Quality of life in persons with spinal cord injury: comparisons with other populations. *J Neurosurg Spine*. 2012;17(1 suppl):S29–S37.
7. Krause JS. Skin sores after spinal cord injury: relationship to life adjustment. *Spinal Cord*. 1998;36(1):51–56.
8. National Institute of Clinical Excellence (NICE) Guideline. Pressure Ulcers: Prevention and Management of Pressure Ulcers, April 2014. Available at: www.nice.org.uk/guidance/cg179. Accessed July 26, 2015.
9. Dealey C, Posnett J, Walker A. The cost of PUs in the United Kingdom. *J Wound Care*. 2012;21(6):261–266.
10. Kloth LC, Feedar JA. Acceleration of wound healing with high voltage, monophasic, pulsed current. *Phys Ther*. 1988;68(4):503–508.
11. Wolcott LE, Wheeler PC, Hardwicke HM, Rowley BA. Accelerated healing of skin ulcers by electrotherapy. *South Med J.* 1969;62(7):795–801.
12. Mulder GD. Treatment of open-skin wounds with electric stimulation. *Arch Phys Med Rehabil*. 1991;72(6):375–377.
13. Baker LL, Rubayi S, Villar F, Demuth SK. Effect of electrical stimulation waveform on healing of ulcers in human beings with spinal cord injury. *Wound Repair Regen*. 1996;4(1):21–28.
14. Adunsky A, Ohry AB. Decubitus direct current treatment (DDCT) of pressure ulcers: results of a randomized double-blinded placebo controlled study. *Arch Gerontol Geriatr.* 2005;41(3):261–269.
15. Wood JM, Evans PE III, Schallreuter KU, et al. A multicentre study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers. *Arch Dermatol.* 1993;129(8):999–1009.
16. Houghton PE, Kincaid CB, Lovell M, et al. Effect of electrical stimulation on chronic leg ulcer size and appearance. *Phys Ther.* 2003;83(1):17–28.
17. Kloth LC. Electrical stimulation for wound healing: a review of evidence from *in vitro* studies, animal experiments, and clinical trials. *Int J Low Extrem Wounds*. 2005;4(1):23–44.
18. McGinnis M, Vanable J Jr. Voltage gradients in newt limb stumps. *Prog Clin Biol Res*. 1986;210:231–238.
19. Stump R, Robinson K. Ionic current in Xenopus embryos during uroulation and wound healing. *Prog Clin Biol Res*. 1986;210:223–230.
20. Foulds IS, Barker AT. Human skin battery potentials and their possible role in wound healing. *Br J Dermatol.* 1983;109(5):515–522.
21. McCaig CD, Rajnicek AM, Song B, Zhao M. Controlling cell behavior electrically: current views and future potential. *Physiol Rev*. 2005;85(3):943–978.
22. Sussman C, Byl N. Electrical stimulation for wound healing. In: Sussman C, Bates-Jensen BM. *Wound Care Collaborative Practice Manual for Physical Therapists and Nurses*. New York, NY: Aspen Publishers;1998:577-624.
23. Kloth LC. Electrical stimulation for wound healing: a review of evidence from *in vitro* studies, animal experiments, and clinical trials. *Lower Extremity Wounds*. 2005;4(1):23–44.
24. Bourguignon GJ, Bourguignon LYW. Electric stimulation of protein and DNA synthesis in human fibroblasts. *FASEB J*. 1987;1(5):398–402.
25. Jennings J, Chen D, Feldman D. Transcriptional response of dermal fibroblasts in direct current electric fields. *Bioelectromagnetics*. 2008;29(5):394–405.

26. Sugimoto M, Maeshige N, Honda H, et al. Optimum microcurrent stimulation intensity for galvanotaxis in human fibroblasts. *J Wound Care*. 2012;21(1):5–10.
27. Alvarez OM, Mertz PM, Smerbeck RV, Eaglstein WH. The healing of superficial skin wounds is stimulated by externalelectrical current. *J Invest Dermatol*. 1983;81(2):144–148.
28. Kawasaki L, Mushahwar VK, Ho C, Dukelow SP, Chan LLH, Chan MK. The mechanisms and evidence of efficacy of electrical stimulation for healing of pressure ulcer: a systematic review. *Wound Repair Regen*. 2014;22(2):161–173.
29. Rouabhia M, Park H, Meng S, Derbali H, Zhang Z. Electrical stimulation promotes wound healing by enhancing dermal fibroblast activity and promoting myofibroblast transdifferentiation. *PLoS One.* 2013;8:e71660.
30. Zhao M, Song B, Pu J, et al. Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-gamma and PTEN. *Nature.* 2006;442(7101):457–460.
31. Guo A, Song B, Reid B, et al. Effects of physiological electric fields on migration of human dermal fibroblasts. *J Invest Dermatol.* 2010;130(9):2320–2327.
32. Mittmann N, Chan BC, Craven C, Isogai PK, Houghton P. Evaluation of the cost-effectiveness of electrical stimulation therapy for pressure ulcers in spinal cord injury. *Arch Phys Med Rehabil*. 2011;92(6):866–872.
33. Liu LQ, Moody J, Traynor M, Dyson S, Gall A. A systematic review of electrical stimulation for pressure ulcer prevention and treatment in people with spinal cord injuries. *J Spinal Cord Med*. 2014;37(6):703–718.
34. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials.* 1996;17(1):1–12.
35. Jadad AR, Murray E. *Randomized Controlled Trials: Questions, Answers and Musings*, 2nd ed. Oxford, UK: Blackwell Publishing;2007.
36. Regan MA, Teasell RW, Wolfe DL, Keast D, Mortenson WB, Aubut JL, for the Spinal Cord Injury Rehabilitation Evidence Research Team. A systematic review of therapeutic interventions for PUs after spinal cord injury. *Arch Phys Med Rehabil.* 2009;90(2):213–231.
37. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of healthcare interventions. *J Epidemiol Community Health*. 1998;52(6):377–384.
38. Adegoke BO, Badmos KA. Acceleration of pressure ulcer healing in spinal cord injured patients using interrupted direct current. *African J Med Medical Sci.* 2001;30(3):195–1977.
39. Griffin JW, Tooms RE, Mendius RA, Clifft JK, Vander Zwaag R, El-Zeky F. Efficacy of high voltage pulsed current for healing of PUs in patients with spinal cord injury. *Phys Ther.* 1991;71(6):433–442.
40. Houghton PE, Campbell KE, Fraser CH, et al. Electrical stimulation therapy increases rate of healing of PUs in community-dwelling people with spinal cord injury. *Arch Phys Med Rehabil.* 2010;91(5):669–678.
41. Jercinovic A, Karba R, Vodovnik L, et al. Low frequency pulsed current and pressure ulcer healing. *IEEE Transaction Rehabil Engineer*. 1994;2(4):225–233.
42. Karba R, Semrov D, Vodovnik L, Benko H, Savrin R. Direct current electrical stimulation for chronic wound healing enhancement. Part 1: Clinical study and determination of electrical field distribution in the numerical wound model. *Bioelectrochem Bioenergetics*. 1997;43(2):265–270.
43. Stefanovska A, Vodovnik L, Benko H, Turk R. Treatment of chronic wounds by means of electric and electromagnetic fields. Part 2. Value of FES parameters for pressure sore treatment. *Med Biologic Engineer Computing*. 1993;31(3):213–220.
44. Trontelj K, Karba R, Vodovnik L, Savrin R, Strukelj MP. Treatment of chronic wounds by lower frequency pulsed electrical current. *J Tissue Viability*. 1994;4(4):105–109.
45. Lala D, Spaulding SJ, Burke SM, Houghton PE. Electrical stimulation therapy for the treatment of pressure ulcers in individuals with spinal cord injury: a systematic review and meta-analysis. [Published online ahead of print April 13, 2015.] *Int Wound J*. doi:10.1111/iwj.12446.
46. Nishimura KY, Isseroff RR, Nuccitelli R. Human keratinocytes migrate to the negative pole in direct current electric fields comparable to those measured in mammalian wounds. *J Cell Sci.* 1996;109(1):199–207.
47. Bikson M, Datta A, Elwassif M. Establishing safety limits for transcranial direct current stimulation. *Clin Neurophysiol.* 2009;120(6):1033–1034.
48. Daeschlein G, Assadian O, Kloth LC, Meinl C, Ney F, Kramer A. Antibacterial activity of positive and negative polarity low voltage pulsed current (LVPC) on six typical Gram-positive and Gram-negative bacterial pathogens of chronic wounds. *Wound Repair Regen*. 2007;15(3):399–403.
49. Asadi MR, Torkaman G. Bacterial inhibition by electrical stimulation. *Adv Wound Care (New Rochelle)*. 2014;3(2):91–97.