COMPREHENSIVE INVITED REVIEW

Clinical Trials Involving Biphasic Pulsed Current, MicroCurrent, and/or Low-Intensity Direct Current

Pamela E. Houghton*

School of Physical Therapy, Western University, London, Canada.

Pamela E. Houghton, PT, PhD

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*Correspondence: School of Physical Therapy, Room 1588 Elborn college, 1201 Western Rd, Western University, London, Ontario N6G 1H1, Canada (e-mail: phoughto@uwo.ca).

Significance: This invited critical review will summarize an expansive body of literature regarding electrical stimulation (ES) and wound healing. Several clinical reports have been published in which ES has been evaluated as a therapy to speed the closure of chronic wounds. Different forms of ES have been applied in varying ways and described using inconsistent terminology by researchers and clinicians around the world. It is important to compile this research and to critically appraise the findings so that clinicians who are not familiar with this field can interpret the research.

Recent Advances: More recently, ES has been delivered at subsensory levels (termed microcurrent in this review) using very small electrical devices contained within wound dressing. While these newer technologies have obvious technical advances, what research has been published to date about these new devices has not produced findings that suggest this form of ES can accelerate wound closure.

Critical Issues: Reviewing a collection of published reports on this subject reveals that not all forms of ES produce beneficial results. Rather, only certain ES protocols such as monophasic pulsed current applied to the wound and biphasic pulsed current current that is applied for 2 h daily to periulcer skin at intensities which produce motor responses have consistently demonstrated positive results.

Future Directions: Optimal stimulus parameters and treatment schedule for ES used to treat chronic wounds need to be determined. Researchers publishing in this field should provide detailed information about their ES treatment protocol and use a similar terminology to describe the ES waveform and stimulus parameters.

SCOPE AND SIGNIFICANCE

This review summarizes clinical studies that have been published since 1960 about the effects of low-intensity direct current (LIDC), microcurrent (MC), and various forms of biphasic and monophasic pulsed current (MPC) on wound healing. It focuses on controlled clinical studies, prepost cohort studies, and case series that have examined the effects of these forms of electrical stimulation (ES) therapy on human subjects with open wounds due to common etiologies, including pressure ulcers, diabetic foot ulcers, venous and/or arterial leg ulcers, post traumatic, surgical wounds, and some other unique types of wounds (*e.g.,* leprosy). This review does not include studies involving people with burns, malignant wounds, skin grafts, donor sites, or post-surgical incisional wounds. The effects of ES applied to intact skin for people at risk of skin breakdown (pressure ulcer prevention) are also not covered in this review. The clinical trials summarized in this

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review include those that have employed a type of ES other than high-voltage pulsed current. For the purposes of this report, ES is considered an electrical current that is applied in contact with skin or tissues by at least two surface electrodes. This noninvasive or conservative form of ES is applied by placing at least two electrodes in direct contact with the skin or target tissue. Electrodes may be placed with (1) the active electrode in the wound and a larger return electrode on intact skin at some distance from the wound (monopolar technique); (2) using two or more electrodes on either the skin around the wound (peri-ulcer) or (3) on nerves or acupuncture points at a distance from the wound. All studies included here involved the application of ES for several minutes to hours over weeks or months with the intention of producing accelerated healing or, ultimately, wound closure.

TRANSLATIONAL RELEVANCE

This report summarizes the results from clinical trials in which ES therapy has been applied using common clinical procedures to subjects who are typically troubled with chronic, nonhealing wounds. In this way, the research results can be directly applied to relevant clinical settings that service similar patient populations. It is assumed that the changes in wound size measured in these clinical trials with and without ES application are caused by the cellular and physiological mechanisms investigated using *in vitro* cell cultures and appropriate animal models. For a comprehensive review of this research, we need to consult a review by Kloth.[1]

CLINICAL RELEVANCE

Based on the clinical trials included in this review, MPC applied directly to the wound using an identical treatment schedule consistently demonstrated ES accelerated healing. The application of LIDC described in earlier studies also produced positive results. However, these LIDC devices are no longer commercially available. Peri-ulcer application of Asymmetrical biphasic pulsed currents (Asym BiPC) may also be effective; however, this ES protocol requires higher intensities that produce visible muscle contractions and extended treatment times. Machines that produce MC lack strong clinical research evidence to recommend their use in clinical practice.

BACKGROUND

ES has been employed in clinical practice to accelerate wound closure for many decades. The effects of this form of bioelectrical energy on healing processes have been investigated by researchers from around the world. Several different ES waveforms, stimulus parameters, and treatment schedules have been employed. This international approach has led a wide base of clinical research evidence that supports the use of ES for the treatment of wounds in a variety of patient populations and different health-care systems. In fact, ES has been recommended for use in the treatment of chronic wounds, including pressure ulcers by several internationally based best practice guidelines.[2–5] However, the wide variations in ES protocols used around the world have left many clinicians wondering what application technique will work best. The confusion has been confounded by other forms of electrotherapy that are also used in the treatment of chronic wounds, including inductive forms of electricity such as pulsed electromagnetic fields (PEMFs). This review will summarize the research paying particular attention to the different types of ES currents/waveforms employed as well as other features of ES protocols.

Definition of different forms of ES therapy

For the purposes of this review, studies have been divided into four different groups based on the type of ES treatment employed. The types of ES current included biphasic pulsed current (BiPC), MPC, LIDC, and MC as previously defined[1] and consistent with the American Physical Therapy Association.[6] Most reports that described the ES waveform stated that the pulses were rectangular or square waves. Unfortunately, the terminology used by authors and equipment manufacturers to describe ES treatments is not consistent and many authors did not fully describe the ES waveform and/or stimulation protocol that they used. For the purpose of this review, ES protocols that employed waveforms with short duration pulses (typically micro- or millisecond pulse duration) which have either a unidirectional or a bidirectional flow of charged particles were considered "pulsed current" (PC) characterized as "brief unidirectional or bidirectional flow of charged particles in which each pulse is separated by a longer off period of no current flow."[1,6] In most instances, pulsed current was supplied via biphasic waveforms, where the electrical current flowed in both directions at some point during the pulse. This form of pulsed current involved either current flow that is equal and opposite (symmetrical [Sym] BiPC) or had two components in the pulse which are not similar (Asym BiPC) and, therefore, may or may not be charge

balanced. One device that was employed by several investigators reported in this review used rectangular-shaped MPC. Other forms of ES included in this review are LIDC, where low levels of current flow in one direction for one second or longer. Studies involving MC stimulation are also reviewed in this article. For the purposes of this review, MC was defined as those ES protocols involving either bidirectional or unidirectional flow of current at a level that would not usually produce sensory level stimulation (subsensory). Not included here are studies in which electromotive forces or electric fields are induced to occur in biological tissues indirectly via high-frequency modulated currents passed through a coil (*e.g.,* PEMFs). No studies in this review applied an alternating current (AC), which is considered in this review as a continuous bidirectional flow of charged particles in which a change in the direction of flow occurs at least once every second.

Evaluation of clinical research methods and quality of evidence

Each included study will be assigned a level of evidence (LOE) based on a modified Sackett scale.[7] Using this five-point scale (Table 1), low numbers are at the top of the scale and indicate better controlled intervention studies. A similar hierarchy of evidence scale has been used to evaluate research evidence available in stroke rehabilitation[8] and spinal cord injury (SCI)-related research.[9]

Table 1. *Hierarchy of evidence*

LOE = 1	Randomized controlled clinical trial (RCT) with good study design at multiple or single study sites
LOE = 2	Non-randomized, non-blinded (open), controlled clinical trial
LOE = 3a–d	Case control studies or RCTs with flawed study designs (see examples below)
LOE = 4	Pre-/post-studies or case series, retrospective analysis
LOE = 5	Case reports or observational studies
Examples of flawed study designs (assigned level of evidence)	
LOE 3a	Very small sample size ($n < 10$/group)
LOE 3b	Multiple wounds from single people were randomized and analyzed as independent data points
LOE 3c	High dropout rate (greater than 20% of originally enrolled subjects)

Modified from evidence-based reviews.[8,9] Level of evidence (LOE) assigned by single reviewer using modified Sackett's scale,[7–9] where lower numbers indicate better-designed clinical trials.

Nonblinded (open), a study in which assessor of wound outcomes was aware which treatment group subjects were allocated; RCT, randomized controlled clinical trial.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Several different types of ES have been employed to accelerate wound healing and promote wound closure of chronic wounds. Details of the relevant literature have been summarized for easy review in Table 2.[10–46,*]

Clinical trials using LIDC

Continuous LIDC is the type of current that was available in most ES prototype devices which were used in initial reports published in the 1960s (Table 2). The first report of the effects of ES on patients with non-healing wounds was published by Assimacopoulos in 1968.[10] He documented the benefits of ES on healing of long-standing chronic leg ulcers present in three clinical cases. This was followed by a clinical report of Wolcott *et al.*,[11] who treated 67 people with a total of 83 ulcers due to a variety of etiologies (pressure, venous, and arterial), including 53 people with SCI. They used LIDC set at an intensity between 200 and 800 μA based on the condition of the exudate, and applied directly to the wounds for an extended time (2 h on: 4 h off repeated thrice daily = 6 h per day) until wounds healed. They began with a negative electrode in the wound and continued cathode stimulation until the infection cleared, after which electrode polarity was switched every 3 days. Thirty-four of 75 ulcers treated with ES healed completely in an average of 7.7 weeks. The control group used for a comparison in this study only involved eight cases in which bilateral wounds were present in the same individual (on left and right ischial tuberosities). They reported that six of eight ulcers treated with LIDC had better outcomes, whereas none of the "identical" contralateral wounds healed. Gault & Gatens[12] repeated this case-controlled design in which 76 patients' ulcers due to mixed etiologies were treated with LIDC in an identical ES protocol as that employed by Wolcott *et al.*[11] They reported that 100 ulcers treated with LIDC had an 80.5% closure rate after 4.7 weeks of treatment. A very small number of subjects ($n = 6$) with bilateral matched wounds were used as a comparison group, and the healing rate of these untreated wounds was much less (27.3% in 4 weeks) than contralateral wounds treated at the same time with LIDC (74%).

Carley and Wainapel[13] published the first controlled clinical trial in which subjects with leg or

*Barczak M, Kluger P, Kluger J, Bauerle J, and Puhl W: Therapeutic effectiveness of electrical stimulation in paraplegic patients with pressure sores. Unpublished dissertation, Medical School of the University of Ulm, Ulm, Germany, 2001.

Table 2. *Chart of clinical studies*

Author (Year), Country	*Study Design*[a]*: Quality of Evidence; Control*[b]	*Wound Etiology*[c]*; Number of Ulcers (u) and Patients (p)*	*ES Waveform*[d]*; Stimulus Parameters*[e]*; Electrode*[f] *Placement and Polarity*	*ES Treatment Schedule*[g]	*Results*[h]		*Conclusion*[i]
					Control	*ES*	
Clinical studies using low-intensity direct current (LIDC)							
Assimacopoulos (1968),[10] Greece	CS: LOE = 5 CON: None	Venous leg ulcers *n* = 3 p	LIDC Sensory (50–100 μA) Monopolar wound, cathode	24 h/d until healed (25–42 d) = 168 h/wk Total hours = 600–1,008 h		LIDC *n* = 3 p; all healed (time to heal 25 d, 32 d, 42 d)	Yes
Wolcott *et al.* (1969),[11] USA	P/P: LOE = 4 CC: LOE = 3 CON: SWC	Mixed P/P: 75 u/67 p CC: Bilateral ulcers/8 p	LIDC Unknown sensation (200–800 μA, based on exudate) Monopolar wound, cathode for first 3 days then anode unless infected	2 h on 4 h off 3/d until healed (7.7 wks) = 42 h/wk Total hours = 323.4 h	CC: CON 8 u; 0 healed; 32% smaller @ 4 wks	P/P: LIDC 75 u; 81.8% smaller by 7.7 wks; 13.4%/wk CC: LIDC 8 u; 6 healed; 92.5% smaller @ 4 wks	P/P: Yes CC: Yes, ES > CON
Gault and Gatens (1976),[12] USA	P/P: LOE = 4 CC: LOE = 3 CON: SWC	Mixed P/P: 100 u/76 p CC: Bilateral ulcers/6 p	LIDC Sensory (200–800 μA, based on exudate) Monopolar wound, polarity same as Wolcott *et al.*[11]	2 h × 3/d × 4 wks = 42 h/wk Total hours = 168 h	CON *n* = 6 p; 27.3% smaller @ 4 wk; 14.7%/wk	P/P: LIDC 100 u; 80.5% smaller by 4.7 wks; 28.4%/wk CC: LIDC *n* = 6 p; 74% smaller @ 4 wks; 30%/wk	P/P: Yes CC: Yes, ES > CON
Barron *et al.* (1985),[14] USA	CS: LOE = 5 CON: None	Pressure geriatric *n* = 6 p	LIDC Micro-electro medical stimulation (MEMS); sensory (20–600 μA) Periulcer, probe applied to wound perimeter	3/wk × 3wk "until an effective treatment had been delivered." Unknown treatment schedule		LIDC *n* = 6 p; 30.5 ± 5.1 cm^2 to 3.0 ± 0.5 cm^2	Yes, significant reduction in wound size
Carley and Wainapel (1985),[13] USA	RCT: LOE = 2 CON: NA	Mixed, geriatric *n* = 30 p	LIDC Sensory (300–700 μA = 30–110 $\mu A/cm^2$) Monopolar wound cathode × 3 days then anode; repeat if plateau	2 h × 2/d × 5 d/wk × 5 wks = 20 h/wk Total hours = 100 h	CON *n* = 30 p 3.92 ± 1.24 @ 0 wk 2.6 ± 1.0 cm^2 @ 3 wks 2.5 ± 0.9 cm^2 @ 4 wks 2.2 ± 0.9 cm^2 @ 5 wks	LIDC *n* = 30 4.74 ± 1.39 @ 0 wk 1.1 ± 0.4 cm^2 @ 3 wks 0.7 ± 0.3 cm^2 @ 4 wks 0.5 ± 0.2 cm^2 @ 5 wks	Yes, ES > CON
Wood *et al.* (1993),[15] USA	Multi-site (4) RCT: LOE = 1 CON: Placebo	SII–III pressure 74 u/71 p	LIDC Harbour Instruments; 3 treatments @ 300 μA, 0.5 pps, then 3 treatments @ 600 μA, 0.5 pps Periulcer	3 treatments/d × 3/wk × 8 wks = 0.6 h/wk Total hours = 4.8 h	CON 31 u/30 p; 3% healed @ 8 wks	LIDC 43 u/41 p; 58% healed @ 8 wks	Yes, ES > CON
Stefanovska *et al.* (1993),[16] Slovenia	Retro: LOE = 4 CON: SWC	Pressure, SCI Total, *n* = 150 p CON, *n* = 50 p LIDC, *n* = 18 p BiPC, *n* = 82 p	LIDC Sensory (600 μA) Periulcer	2 h/d × 4 wks = 14 h/wk Total hours = 56 h	CON *n* = 50 p; 2.87% ± 3.12%/d	LIDC *n* = 18 p; 4.62% ± 3.29%/d	No difference
Cukjati *et al.* (2001),[17] Slovenia	Retro: LOE = 4; duplicate cases CON: SWC sham	Mixed Total, 300 u/214 p CON, 54 u Sham, 23 u LIDC, 42 u BiPC, 181 u	LIDC Sensory (600 μA) Monopolar wound, anode	0.5–2 h/d × 60 wks = 3.5–14 h/wk Total hours = 210–840 h	CON 54 u; 0.145 (0.026–0.261) mm/d Sham 23 u; 0.162 (−0.046 to 0.205) mm/d	LIDC 42 u; 0.168 (0.089–0.424) mm/d	No difference

(*continued*)

Table 2. *(Continued)*

Author (Year), Country	*Study Design*[a]*: Quality of Evidence; Control*[b]	*Wound Etiology*[c]*; Number of Ulcers (u) and Patients (p)*	*ES Waveform*[d]*; Stimulus Parameters*[e]*; Electrode*[f] *Placement and Polarity*	*ES Treatment Schedule*[g]	*Results*[h]		*Conclusion*[i]
					Control	*ES*	
Clinical studies using microcurrent (MC)							
Katelaris *et al.* (1987),[18] Australia	RCT: LOE = 3a CON: Saline or povidine-iodine (PI) in microfoam	Venous leg ulcers *n* = 24 p	MC Subsensory (20 μA) Monopolar wound, cathode	24 h/d until healed (46–85.3 d) = 168 h/wk Total hours = 1104–2047 h	Saline *n* = 4 p; 46.1 ± 7.2 d to heal PI *n* = 11 p; 49.2 ± 4.3 d to heal	ES + saline *n* = 5 p; 45.9 + 6.4 d to heal ES + PI *n* = 4 p; 85.3 ± 7.2 d to heal	No, suggests deleterious effect of combining ES with PI
Karba *et al.* (1997),[19] Slovenia	RCT: LOE = 2 CON: Sham ES—power source disconnected	SIII–IV pressure, SCI *n* = 50 p	MC Subsensory (600 μA) DC + monopolar wound, anode DC +/− periulcer	2 h/d until healed (6–14 wks) = 14 h/wk Total hours = 84–196 h	Sham *n* = 16; 4.2%/d	DC + mono *n* = 16 p; 7.4%/d DC +/− peri *n* = 18 p; 4.8%/d	DC + mono: Yes, ES > CON DC +/− peri: No difference
Baker *et al.* (1996),[20] USA	RCT: LOE = 3b CON: Sham—leads cut	Pressure, SCI Total, 192 u/80 p CON, 25 u/19 p MC, 42 u/20 p BiPC Asym, 67 u/20 p BiPC Sym, 58 u/21 p	MC Biphasic square wave, unknown sensation "at such low levels as to have no therapeutic benefit" = 4 mA, 10 μs, 1 pps, 7:7 on:off ratio Periulcer, cathode proximal	30 min × 3/days × 5 d/wk until closure (32–52 d) = 7.5 h/wk Total hours = 240–390 h	CON 25 u/19 p; 29.2% ± 8.1%/wk	MC 42 u/20 p; 38.5% ± 5.8%/wk	No difference
Baker *et al.* (1997),[21] USA	RCT: LOE = 3b CON: Sham—leads cut	Diabetic foot ulcers Total, 114 u/80 p CON, 25 u/19 p MC, 28 u/20 p BiPC Asym, 33 u/21 p BiPC Sym, 28 u/20 p	MC Stimulus same as Baker *et al.*[20] Periulcer, cathode proximal	30 min × 3/d × 5 d/wk until closure (32–52 d) = 7.5 h/wk Total hours = 240–390 h	CON 25 u/19 p; 12/25 ulcers healed by 36 ± 4 days; 17.3% ± 2.3%/wk	MC 28 u/20 p; 10/28 ulcers healed by 47 ± 7 days; 17.2% ± 4.8%/wk	No difference
Adunsky and Ohry (2005),[22] Israel	Multi-site RCT: LOE = 3c CON: Placebo DDCT	SIII pressure, geriatric, SCI *n* = 63 p	MC DDCT, Lifewave Medical Devices Company; subsensory, automated Periulcer	20 min × 3/d × 2 wks + 20 min × 2/d × 6 wks = 7 h/wk Total hours = 42 h	CON *n* = 28 p; 1/18 healed @ 57 d; 10/28 (35.7%) healed @ 147 d; 89.7 ± 9.2 d to heal	ES *n* = 35 p; 5/19 healed @ 57 d; 9/35 (25.7%) healed @ 147 d; 63.4 ± 15.1 d to heal	Mixed depending on healing outcome and day of evaluation
Hampton and King (2005),[24] United Kingdom	Case: LOE = 5 CON: None	Post Sx *n* = 1 p	MC Posifect dressing; subsensory Monopolar wound, cathode	24 h/d × 7 d/wk × 3 wk + 1 wk off × 8 wks = 168 h/wk Total hours = 1,008 h		Healed in 4 months	Yes
Ullah (2007),[23] Belgium	Multi-site (6) RCT: LOE = 2 CON: Placebo	Pressure 114 u/60 p	MC MET parameters not described, < 1 mA Electrode details unknown	24 h/d × 12 wks = 168 h/wk Total hours = 2016 h	CON 60 u/30 p; 0.9455 ± 0.0760 mm/wk	ES 54 u/30 p; 0.9002 ± 0803 mm/wk	No

(*continued*)

Table 2. *(Continued)*

Author (Year), Country	Study Design[a]: Quality of Evidence; Control[b]	Wound Etiology[c]; Number of Ulcers (u) and Patients (p)	ES Waveform[d]; Stimulus Parameters[e]; Electrode[f] Placement and Polarity	ES Treatment Schedule[g]	Results[h]		Conclusion[i]
					Control	ES	
Clinical studies using monophasic pulsed current (MPC)							
Feedar *et al.* (1991),[25] USA Mulder (1991),[26] USA	Multi-site (9) RCT: LOE = 1 CON: Placebo	Mixed 50 u/47 p	MPC Varapulse, Staodyn Inc.; submotor (38 mA max), 64–128 pps, 132–140 μs, 249.6–499.2 μC/s Monopolar wound, alternate polarity q3d	30 min × 2/d × 4 wks = 7 h/wk Total hours = 28 h	CON 24 u; 44% initial WSA @ 4 wks; 14%/wk	ES 26 u; 67% initial WSA @ 4 wks; 8.25%/wk	Yes, ES > CON
Gentzkow *et al.* (1991)[27] USA	Multi-site (9) RCT: LOE = 1 CON: Placebo	SIII–IV pressure, geriatric 40 u/37 p	MPC Dermapulse, Staodyn Inc.; stimulus same as Feedar *et al.*[25] Monopolar wound, polarity same as Feedar *et al.*[25]	30 min × 2/d × 4 wks = 7 h/wk Total hours = 28 h	CON 19 u; 23.4% @ wks; 5.8%/wk	ES 21 u; 49.8% @ 4 wks; 12.5%/wk	Yes, ES > CON
Gentzkow *et al.* (1993),[28] USA	P/P: LOE = 4 CON: Historical (4 wks)	SIII–IV pressure, geriatric 78 u/68 p	MPC Dermapulse, Staodyn Inc.; stimulus same as Feedar *et al.*[25] Monopolar wound, cathode til debride then alternate polarity every 3 d	30 min × 2/d × 4 wks = 7 h/wk Total hours = 28 h		41/78 (52.6%) improved @ 2 wks 57/78 (73.1%) improved @ 4 wks	Yes
Barczak *et al.* (2001),* Germany	RCT: LOE = 1 CON: Placebo	Pressure, SCI 33 u/24 p	MPC Dermapulse, Staodyn Inc.; stimulus same as Feedar *et al.*[25] Monopolar wound, alternate polarity same as Feedar *et al.*[25]	30 min × 2/d × 12 wks = 7 h/wk Total hours = 84 h	CON 17 u/14 p; 1.1%/d; 38% initial WSA @ 4 wk; 9/13 (69%) healed @ 12 wk	ES 16 u/10 p; 2.0%/d; 65% initial WSA @ 4 wk; 14/14 (100%) healed @ 12 wk	Yes, ES > CON
Junger *et al.* (2008),[29] Germany	RCT: LOE = 1 CON: Sham—nonconductive leads	Venous leg ulcers 40 u/39 p	MPC woundEL, Gerromed, Germany; stimulus same as Feedar *et al.*[25] Monopolar wound, cathode × 7 d then alternate polarity every 3 d	30 min × 2/d × 7/wk × 16 wks = 7 h/wk Total hours = 116 h	CON n = na; 542 to 346 mm^2 @ 16 wks (p = n.s.)	ES n = na; 550 to 80mm^2 @ 16 wks (p = 0.03)	Mixed Yes, ES over time No, ES vs. CON
Adegoke and Badmos (2001),[30] Nigeria	RCT: LOE = 3a CON: Sham—set at zero	SIV pressure n = 7 p	MPC Duffield Mk 7, Duffield Medical Equip Ltd.; sensory, 30 pps, 2:1 on:off ratio Monopolar wound, unknown polarity	45 min × 3/wk × 4 wks = 2.25 h/wk Total hours = 900 h	CON n = 3 p; 2.6% @ 4 wks	ES n = 4 p; 22.2% @ 4 wks	Yes, ES > CON
Clinical studies using biphasic pulsed current (BiPC)							
Stefanovska *et al.* (1987),[31] Yugoslavia	P/P: LOE = 4 CON: None	Pressure, SCI 13 u/10 p	BiPC Stimulus same as Karba *et al.*[32] Periulcer	30 min/d × 4 wks = 3.5 h/wk Total hours = 14 h		BiPC n = 10 p; time constant of rate of healing; 2.4 wks sacral; 4.7 wks trochanter	Unclear, depended on patient sex and wound location

(*continued*)

Table 2. *(Continued)*

Author (Year), Country	*Study Design*[a]*: Quality of Evidence; Control*[b]	*Wound Etiology*[c]*; Number of Ulcers (u) and Patients (p)*	*ES Waveform*[d]*; Stimulus Parameters*[e]*; Electrode*[f] *Placement and Polarity*	*ES Treatment Schedule*[g]	*Results*[h]		*Conclusion*[i]
					Control	*ES*	
Karba *et al.* (1990),[32] Yugoslavia Karba *et al.* (1991),[33] Yugoslavia	P/P: LOE = 4 CON: Historical (several months)	Mixed *n* = 63 p	BiPC Asym (balanced, 250 μs pulse duration) Motor (15–25 mA), 4 sec pulse train @40 pps, 50:50 on:off ratio Periulcer	1 h/d × 7/d × na wks = 7 h/wk Total hours = unknown		BiPC 60/63 healed	Yes
Karba *et al.* (1995),[34] Slovenia	CCT: LOE = 3a CON: SWC	Pressure, SCI *n* = 13 p	BiPC Stimulus same as Karba *et al.*[32] Periulcer	60 min/d until healed (44.1 d) = 7 h/wk Total hours = 44.1 h	CON 0/7 healed	BiPC 6/6 healed	Yes, ES > CON
Jercinovic *et al.* (1994),[35] Slovenia	RCT: LOE = 2 CON: SWC	Presssure, SCI *n* = 73 p	BiPC Stimulus same as Karba *et al.*[32] Periulcer	2 h/d × 5 d/wk × 4 wks = 10 h/wk Total hours = 40 h	CON *n* = 31 p; 2.7%/d	BiPC *n* = 42 p; 5.7%/d	Yes, ES > CON based on exponential healing model
Trontelj *et al.* (1994),[36] Slovenia	CCT: LOE = 2; duplicate cases CON: SWC	Pressure, geriatric, SCI *n* = 106 p	BiPC Stimulus same as Karba *et al.*[32] Periulcer	2 h/d until healed (6–14 wks) = 14 h/wk Total hours = 84–196 h	CON *n* = 43 p; 2.6% ± 2.6%/d	BiPC *n* = 63 p; 4.89% ± 3.8%/d	Yes, ES > CON
Stefanovska *et al.* (1993),[16] Slovenia	Retro: LOE = 4 CON: SWC	Pressure, SCI Total, *n* = 150 p CON, *n* = 50 p BiPC, *n* = 82 p LIDC, *n* = 18 p	BiPC Stimulus same as Karba *et al.*[32] Periulcer	2 h/d × 4 wks = 14 h/wk Total hours = 56 h	CON *n* = 50 p; 2.21% ± 3.27%/d	BiPC *n* = 82 p; 5.43% ± 4.4%/d	Yes
Cukjati *et al.* (2001),[17] Slovenia	Retro: LOE = 4; duplicate cases CON: SWC (*n* = 54) + sham ES (*n* = 23)	Mixed Total, −300 u/214 p CON, 54 u Sham, 23 u LIDC, 42 u BiPC, 181 u	BiPC Stimulus same as Karba *et al.*[32] Periulcer	1 h/d × 60 wks = 7 h/wk Total hours = 420 h	CON 54 u; 0.145 (0.026–0.261) mm/d Sham 23 u; 0.162 (0.046–0.205) mm/d	BiPC 178 u; 0.190 (0.114–0.328) mm/d	Yes
Lundeberg *et al.* (1992),[37] Sweden	RCT: LOE = 1 CON: Placebo	Diabetic and venous leg ulcers *n* = 64 p	Unknown waveform Delft Instruments/Henley Healthcare, Sugar Land, TX; submotor, 80 pps, 1 ms Periulcer, alternate polarity after each treatment	20 min × 2/d × 12 wks = 4.6 h/wk Total hours = 56 h	CON *n* = 32 p; 15% heal @ 12 wks	ES *n* = 32 p; 42% healed @ 12 wks	Yes, ES > CON
Thurman and Christian (1971),[38] USA	Case: LOE = 5 CON: None	Diabetic foot ulcer *n* = 1 p	Unknown waveform Dynawave motor, 5 pulses/min Wound, polarity unknown	20 min × 2/d × 5 d + 20 min/d × 2 d/wk × 4 wks = 6.6 h/wk Total hours = 6 h		ES, healed 4 months post discharge	Yes, healed and prevented amputation
Baker *et al.* (1996),[20] USA	RCT: LOE = 3b CON: Sham—leads cut	Pressure, SCI Total, 192 u/80 p CON, 25 u/19 p MC, 42 u/20 p BiPC Asym, 67 u/20 p BiPC Sym, 58 u/21 p	BiPC Asym (100 μs; 50 pps; 7:7 on:off ratio; 62.8–64.9 mA submotor); BiPC Sym (300 μs; 50 pps; 7:7 on:off ratio; 62.8–64.9 mA submotor) Ultrastim, Henley Healthcare, Sugar Land, TX Periulcer, cathode proximal	30 min × 3/d × 5 d/wk until closure (20–42 d) = 7.5 h/wk Total hours = 150–390 h	CON 25 u/19 p; 29.2% ± 8.1%/wk;	BiPC ASym 67 u/20 p; 63.7% ± 7.2%/wk BiPC Sym 58 u/21 p; 50.6% ± 5.6%/wk	No, when data from all subjects analyzed in original (4) separate groups

(*continued*)

Table 2. *(Continued)*

Author (Year), Country	*Study Design*[a]*: Quality of Evidence; Control*[b]	*Wound Etiology*[c]*; Number of Ulcers (u) and Patients (p)*	*ES Waveform*[d]*; Stimulus Parameters*[e]*; Electrode*[f] *Placement and Polarity*	*ES Treatment Schedule*[g]	*Results*[h]		*Conclusion*[i]
					Control	*ES*	
Baker *et al.* (1997),[21] USA	RCT: LOE = 3b CON: Sham—leads cut	Diabetic foot ulcers Total, 114 u/80 p CON, 25 u/19 p MC, 28 u/20 p BiPC Asym, 33 u/21 p BiPC Sym, 28 u/20 p	BiPC Sym; BiPC Asym (balanced) Stimulus same as Baker *et al.*[20] Periulcer, cathode proximal	30 min × 3/d × 5 d/wk until closure (32–52 d) = 7.5 h/wk Total hours = 240–390 h	CON 25 u/19 p; 17.3% ± 2.3%/wk	BiPC ASym 33 u/21 p; 27% ± 4%/wk BiPC Sym 28 u/20 p; 16.4 ± 6.1%/wk	No, when data from all subjects analyzed in original (4) separate groups
Jankovic and Binic (2008),[39] Serbia	RCT: LOE = 2 CON: Unknown	Venous leg ulcers 42 u/35 p	BiPC Asym (balanced) FREMS, Lorenz Biotech, Italy; sensory threshold (100–170 μA set by patient) Periulcer, 4 channels applied along limb	40 min/d × 5 d/wk × 3 wks = 3.3 h/wk Total hours = 600 h	CON 19 u/15 p; values not reported	BiPC 24 u/20 p; values not reported	Yes, WSA (cm^2) smaller @ 3, 4, and 8 wks
Petrofsky *et al.* (2010),[40] USA	RCT: LOE = 2 CON: Local dry heat 37°C	Diabetic foot ulcers *n* = 20 p	BiPC Sym Stimulus same as Suh *et al.*[41] Periulcer, electrodes same as Suh *et al.*[41]	30 min × 3/wk × 4 wks = 1.5 h/wk Total hours = 6 h	CON *n* = 10 p; 30.1% ± 6.7% initial WSA @ 4 wks	BiPC + heat *n* = 10 p; 68.4% ± 28.6% initial WSA @ 4 wks	Yes
Suh *et al.* (2009),[41] USA	P/P: LOE = 4 CON: Local dry heat 37°C	Mixed *n* = 18 p	BiPC Sym Challenge 8000 A, Max Performance Biometric Technologies, Reno, NV; sensory (20 mA), 30 pps, 250 μs Periulcer, 3 electrodes rotated position around the wound	30 min × 3/wk × 4 wks = 1.5 h/wk Total hours = 6 h		BiPC + heat *n* = 18 p; 43.4% ± 44.5% @ 4 wks	Yes, significant reduction in wound size
Clinical studies using other ES protocols							
Ogrin *et al.* (2004),[42] Australia	RCT: LOE = 1 CON: Placebo	Venous leg ulcers *n* = 29 p	Unknown waveform Subsensory (4 mA), 5 pps Limb, peroneal nerves	5 min × 2/d × 12 wks = 1.16 h/wk Total hours = 13.9 h	CON *n* = 15 p; 10 (66%) healed @ 6 wks	ES *n* = 14 p; 8 (57%)healed	No difference
Kaada (1983),[43] Norway	P/P: LOE = 4 CON: Historical (several months)	Mixed *n* = 10 p	BiPC, unknown waveform Em-set, TNS 4736; motor (25–50 mA), 2 pps (five pulses @ 100 pps), 200 μs Hand, cathode placed in web space	30–45 min × 3/d until healed (6–22 wks) = 10.5–15.75 h/wk Total hours = 63–346 h		ES *n* = 10 p; 10 healed	Yes, all healed
Kaada and Emru (1988),[44] Norway	P/P: LOE = 4 CON: Historical (15 months)	Leprous ulcers *n* = 32 p	BiPC Stimulus same as Kaada[43] Above and below ankle	30 min × 11/wk until healed (5.2 wks) = 2.75 h/wk Total hours = 28.6 h		ES *n* = 32 p; 19 healed	Yes, all subjects who were compliant with ES protocol healed
Asbjornsen *et al.* (1990),[45] Norway	RCT: LOE = 2 CON: Placebo	Pressure, geriatric *n* = 16 p	Unknown waveform Decapuls, Denmark; motor, 3 pps (85ms burst @ 100 pps) Hand, cathode placed in web space	30 min × 2/d × 5 d/wk × 6 wks = 5 h/wk Total hours = 30 h	CON *n* = 9 p; 2 healed @ 4 wks, 9/9 smaller	ES *n* = 7 p; 0 healed @ 4 wks, 4/7 smaller	No difference

(*continued*)

Table 2. *(Continued)*

Author (Year), Country	Study Design[a]: Quality of Evidence; Control[b]	Wound Etiology[c]; Number of Ulcers (u) and Patients (p)	ES Waveform[d]; Stimulus Parameters[e]; Electrode[f] Placement and Polarity	ES Treatment Schedule[g]	Results[h]		Conclusion[i]
					Control	ES	
Chalker (1983),[46] USA	Case: LOE = 5 CON: None	SIII pressure, SCI *n* = 1 p	Unknown waveform Electro-Acuscope 80; subsensory, automated Periulcer, probe applied to wound perimeter	20 min × 3/d until healed (10–15 d) = 7 h/wk Total hours = 10–15 h		ES *n* = 1 p; healed @ 15 d	Yes, healed

[a]***Study Design:*** **case,** a single subject; **CS,** case series—selected patients who are treated with ES that may or may not be the same protocol or over the same time period (no control group); **CC,** case–control, a clinical study in which individual cases had a matched control from which to compare; **P/P,** pre-/post-, an uncontrolled study in which all subjects received ES treatments (no control group was followed prospectively); **CT,** a controlled trial in which a control group was used for comparison, but the subjects in the control group were not randomly selected and/or equal in number; **RCT,** a study with two equal and similar groups which were created from a pool of subjects who were assigned using an acceptable randomization procedure; **multi-site RCT,** several clinical or academic centres recruited subjects using similar criteria in a study with RCT design; **retro,** retrospective analysis where a large number of patients who were treated as a part of clinical service before commencing the research (the information is obtained from charts or databases).

[b]***Control:*** **SWC,** standard wound care that typically includes regular dressing changes and management of wound infection; **placebo,** an identical ES unit without electrical output was used to deliver ES treatment that was undetected by therapist or patient; **sham,** therapist provided a treatment that did not result in ES delivery (not blinded); **historical,** subjects had a history of no healing in chronic wounds; **none,** no control group was included in the study.

[c]***Wound Etiology:*** **mixed,** a study in which subjects with wounds of different etiologies are included; **pressure, geriatric,** pressure ulcers occurring in individuals who are > 60 years of age; **pressure, SCI,** pressure ulcers occurring in individuals with spinal cord injury; **SII, SIII, SIV,** stage 2, 3, or 4 pressure ulcers as defined by National Pressure Ulcer Panel (NPUAP), 2007.

[d]***Waveform:*** **BiPC,** electrical current flows in both directions for short and separate pulses; **BIPC Sym,** bidirectional flow of pulsed current that is equal and opposite (the waveform is assumed to be rectangular); **BiPC Asym (balanced),** electrical current flowed in both directions and was not similar in shape but was balanced where no net current flow occurred; **LIDC,** low-intensity direct current that produces current flows in one direction for at least one second and a sensory level stimulation; **MPC,** monophasic pulsed current–unidirectional flow of current within short individual pulses separated by a finite off period; **MC,** ES protocols involving either bidirectional or unidirectional flow of current at a level that would not usually produce sensory-level stimulation (sub-sensory); **TENS,** ES applied to surface electrodes over nerves or acupuncture points (away from the wound) at a level that produces sensory parathesia (sensory) or muscle twitches (motor).

[e]***Stimulus Parameters:*** **subsensory,** intensity set at a level that would not usually produce any perceptible sensation; **sensory,** intensity set at a level that would produce tingling sensation or sensory paresthesia in normally innervated skin; **submotor,** intensity is set by increasing intensity until visible muscle contractions occur under the electrode and then, intensity is reduced until the motor response is no longer observed; **motor,** intensity is set at a level that produces muscle contraction; **pps,** pulses per second.

[f]***Electrode:*** **monopolar,** electrode was placed directly over the wound; **periulcer,** all electrodes were placed at the wound edge; **cathode,** negatively charged electrode; **anode,** positively charged electrode; **polarity,** refers to the net charge produced under the active electrode typically placed within the wound.

[g]***Treatment Schedule:*** duration of each treatment (minutes or hours) × number of treatments per week (daily treatments were assumed to be 7 days per week) × number of weeks.

[h]***Result:*** **control,** result provided for ulcers treated with standard wound care with or without sham or placebo ES; **ES,** electrical stimulation, waveforms previously defined were applied to subjects/ulcers in this category; **% initial WSA @ 4 wks,** percentage of initial wound surface area (WSA) measured at 4 weeks; **%/wk,** percentage decrease in wound size per week; **%/d,** rate of healing expressed as % size reduction per day; **% healed by # wks,** the proportion of total number of subjects treated in this group whose wound healed by the specified number (#) of weeks.

[i]***Conclusion:*** **yes,** a significant difference between ES and control-treated wounds was found in favor of ES treatment protocol, and/or the authors concluded that ES was effective in accelerating wound closure; .**no difference,** no statistically significant difference was found between ES and control-treated wounds, and/or authors concluded that there was no notable difference in people treated with ES; **yes, ES > CON,** healing outcome was better/faster in the ES-treated wounds compared with the control.

*Barczak M, Kluger P, Kluger J, Bauerle J, and Puhl W: Therapeutic effectiveness of electrical stimulation in paraplegic patients with pressure sores. Unpublished dissertation, Medical School of the University of Ulm, Ulm, Germany, 2001.

LOE, level of evidence assigned using modified Sackett's scale;[7–9] CON, control; *n*, number of patients included in the study group; u, ulcers; p, patients; NA, data not available; DDTC, decubitis direct current treatment; FREMS, frequency rhythmic electrical modulation system.

sacral wounds were either randomized to receive LIDC or to continue standard wound care. ES treatment involved a direct wound application of LIDC at an intensity level that produced a strong sensory stimulus, for 2 h twice daily, 5 days a week for 5 weeks, or until the ulcer healed, whichever occurred first. Weekly measurements of wound size by an unblended assessor revealed consistently and significantly smaller wounds in the LIDC treated versus control-treated subjects. Barron *et al*.[14] produced a clinical report around the same time when good healing outcomes were reported in six cases when they delivered nine treatments at an intensity level sufficient to produce a "tingling sensation" (20–600 μA, 50 V) through a pair of probes that were placed within 2 cm of the wound edge and moved around the circumference of the wound 'until an effective treatment had been delivered across the entire surface".[14] However, the exact treatment times employed in this report were not provided. They described this "highly sophisticated device" as "nongalvanic" and "modified biphasic square wave," and the frequency of stimulation could be adjusted between 0.5 and 990 pps. Since the authors selected the lowest pulse frequency (0.5 pps), this reviewer considered this LIDC. Wood *et al.*, 1993[15] described a double-blinded, placebo-controlled study that was conducted in four academic centers in the United States where peri-ulcer application ES at an intensity of 600 μA was given thrice a week to stage II and III pressure ulcers (NPUAP 2007) for an undisclosed treatment time.[47] Again, these authors termed this type of current "pulsed LIDC"; however, with fewer than 1 pps, this form of current has been categorized as LIDC. In this review, statistical analysis revealed that a significantly greater number of ulcers were healed after 8 weeks of treatment with active LIDC units (58% healed) compared with placebo LIDC units (3% of wounds healed at 8 weeks).

While these early reports which employed LIDC produced very promising results and supported the notion of topical application of ES directly to the wound and/or periulcer skin, these ES devices are no longer clinically used. This change may have occurred due to the high potential for skin irritation that could occur under electrodes. In addition, some researchers who compared the results of different types of ES current were finding that superior results with a newer form of current called pulsed current (PC) were available. For example, in 1993,[16] Stefanovska reviewed healing outcomes in 150 cases and compared the effects of LIDC (600 μA) applied within the wound versus peri-ulcer stimulation using a biphasic charge balanced pulsed current (Asym BiPC balanced). They found superior healing outcomes in this population of predominantly SCI individuals with pressure ulcers when they were treated with Asym BiPC—which they unfortunately referred to as "AC" or alternating current. When other variables known to affect healing outcomes were factored into their analysis (initial wound size, wound duration, and age of patient), only the Asym BiPC treatment protocol (0.25 ms, 40 pps, 4 s pulse train delivered via a 50% duty cycle, 15–25 mA), and not treatments using LIDC, was found to be significantly different than controls. The suggestion that differences seen in healing outcomes were related to the type of ES used was confounded by many other variables which were different between groups in this non-randomized controlled clinical trial; most notably was the very small sample size of subjects that received direct current ($n = 18$) relative to the number in the BiPC ($n = 82$) and control ($n = 50$) groups. Since electrodes were placed either within or outside the wound with LIDC and Asym BiPC protocols, respectively, it also not clear whether different healing responses were due to electrode location.

A more recent report by authors from the same university involved a retrospective analysis of a large database that included 214 patients with more than 300 wounds of mixed etiology.[17] Cukjati *et al.*[17] also concluded that the type of ES current was one of the five prognostic factors which determined wound-healing rates measured in these patients While this large retrospective study adds to the theory that the type of ES waveform and mode ES delivery are important determinants of healing outcomes, it is likely that these results include data taken from subjects previously reported by members of this research group.[16] It will be important for other researchers to independently confirm these interesting findings.

Clinical trials using MC

For the purpose of this review, all studies that used an ES protocol which delivered sub-sensory levels of ES were considered MC regardless of the direction of current flow or the shape of the waveform. While earlier reports used LIDC applied at a very low amplitude (20 μA),[18] more recently, clinical trials have employed automated devices that continuously deliver low levels of electrical current to the wound bed or peri-ulcer skin. More recently, MC devices have been miniaturized so that they are incorporated within the wound dressing.

In 1987, Katelaris[18] found that by applying LIDC (20 μA) using a self-contained unit which was placed directly within the dressing produced deleterious results if iodine-based antiseptic solutions were applied concurrently. Although the patient's perception was not reported when this device was applied directly to their venous ulcers, it is assumed that this low level of current (20 μA) would not be detectable and, therefore, considered MC for the purposes of this review. The authors surmised that the slower healing rates seen in wounds treated with povidone-iodine solution plus ES occurred, because the cathode drove the negatively charged iodine molecules into the tissues, where they became intracellular toxins. Current practice advocates the use of more physiologically balanced products in healable wounds and recommends that clinicians avoid using ES in conjunction with wound care products, which include ionically active substances such as free iodine, silver, or other charged ions.

Karba[19] evaluated the effects of low levels of DC applied below detectable sensory levels (considered MC) on wound-healing rates. They used mathematical modeling in 50 patients with pressure ulcers and SCI to demonstrate that changing the position of electrodes changed the distribution of the electrical field in and around the wound. Specifically, placement of the positive electrode (anode) in the wound and negatively charged electrodes surrounding the wound perimeter produced an electric field more similar to endogenous or naturally occurring bio-potentials and was associated with accelerated healing rates. By contrast, the use of two oppositely electrodes placed on either side of the wound is quite different from the endogenous field and is not associated with clinically important increases in wound healing.

Baker *et al.* conducted two clinical trials involving patients with SCI[20] or diabetes.[21] In both studies, a group of subjects were treated with what the authors termed "microcurrent." The MC protocol applied 4 mA of bidirectional current via 10 μs pulses and a 50% duty cycle (7 s on then 7 s off) at the wound edge for 1.5 h per day for an average of 38–47 days. Whether these parameters represent MC is debatable, as the sensation produced by this MC protocol was not described. However, since the authors selected this MC protocol because it was "not expected to have a therapeutic benefit," this reviewer assumed that the intensity was applied at a subsensory level. Not surprisingly, neither of these studies conducted by Baker *et al.*[20,21] found that MC stimulation produced a significant change in wound-healing outcomes. In fact, in one study involving people with SCI,[20] the MC and control groups were combined, as there was little difference in the treatment response noted in either group.

Adunsky and Ohry[22] described the results of a multicenter trial involving grade III pressure ulcers treated in 11 centers across Israel. They used a "decubitus direct current treatment" (DDCT) that was linked to computerized technology to deliver a customized amount of current to the wound base. Since this is a "proprietary waveform," less information is available about the ES waveform. While this device is referred to as LIDC, it is described as providing both DC and AC currents. No information about the patient's perceptions was provided; however, the device was designed to simulate electrical activity measured around healing wounds. Therefore, it was assumed to be MC that was undetectable to the patient (subsensory). In this study, DDCT was applied to peri-ulcer skin of chronic pressure ulcers for 20 min twice or thrice a day for 8 weeks. They reported significantly better wound-healing outcomes (absolute wound size and percentage area reduction) at day 47 while ES treatments were being administered. However, these differences were not sustained when wound size was re-evaluated at the end of stimulation (day 57) nor at the 90 day follow-up time point (day 147), which was 12 weeks after ES treatments had stopped.. While Adunsky and Ohry[22] stated that higher dropout rates are "quite usual in pressure ulcer studies," this reviewer is skeptical of data from only 38 of 63 (60%) enrolled subjects.

Ullah *et al.*[23] described the results of using ES, which they called microcurrent electrical therapy (MET) in six centers in Belgium. MET therapy was described as a low-frequency current of less than 1 mA; however, the location of the electrodes and how long the stimulation was supplied was not described. Weekly wound size measurements for 114 patients over a 12 week observation period were expressed as a regression model and did not appear different between MET and control wounds. Although evidence of a statistical comparison was not provided, results were quite variable and seemed to depend to a great extent on which of the hospitals provided the wound treatment. Although the study involved a large number of subjects ($n = 114$), the scarcity of detail in the report regarding wound and patient characteristics and unclear and variable results limit this reviewer's ability to evaluate the true effect of this form of MC.

Several case reports have been published[24,48] to describe the use of a relatively new technology that

delivers ES via a small device which is contained within a single use dressing that has an anode ring applied around the wound and a small cathode tab that produces a small amount of negatively charged DC within the wound bed. This form of MC produces sub-sensory stimulation continuously in the wound. The ES protocol recommended 3 weeks of constant stimulation followed by 1 week cessation over a period of 8 weeks. This is believed to kick start the wound-healing process and is, therefore, no longer needed after two cycles of 3 week treatments. Complete healing was reported in these cases with very recalcitrant wounds.[24] A comparison of this device to an appropriate control group has not yet been published.

Other recent reports tested ultra-low MC device which delivered DC at a maximum of 3 mA using electrodes that switched current direction (polarity) every 11.5 min.[49] The treatments were applied to 12 people with diabetes and hypertension for 3.5 h per day for 5 days a week over 2–4 months. Laboratory findings suggested normalization of diabetic symptoms such as glycosylated hemoglobin concentration and blood pressure. Two of the twelve people reported in this publication had foot ulcers, both of which healed. Wound-healing outcomes were not the focus of this case report, and there were no statistical comparisons or control group included in the publication.[49]

In general, recent studies employing subsensory levels of MC[18,19,22,23] have not provided sufficient evidence to confirm that MC treatments can promote increased rate of healing of chronic wounds. The two studies performed by Baker[20,21] were really not designed to evaluate the MC protocol, as the stimulus parameters were not designed to produce optimal treatment outcomes. Only two of seven published clinical studies[19,22] included a control group from which to compare healing outcomes. Adunsky *et al.* employed a well-designed multi-randomized controlled study design; however, results were conflicting and 40% of the enrolled subjects did not complete the study.[22] In 1997, Karba showed in a study with 50 subjects with SCI and pressure ulcers that the effects of sub-sensory levels of DC depended on electrode orientation and position[19] with better results occurring when the active electrode was placed directly in the wound. Preliminary results using commercially available ES units that fit directly in the wound[23,24,48] show promising results. Until further research using well-designed clinical trials are available, the effect of MC on healing rates of chronic wounds is not known.

Clinical trials using MPC

There are several published reports that employed an ES device which delivers MPC using a standard treatment protocol (Table 2).[25–29,*] The ES device, initially named Varapulse, then Dermapulse, and, most recently, the woundEL device produced in Germany, delivers rectangular-shaped pulses of 132–140 μs duration at a pulse rate of either 64 pps or 128 pps. A similar ES protocol was used in all these studies employing MPC.[25–29,*] The higher frequency stimulation was applied first using negative polarity; later, polarity was switched and the frequency was reduced to 64 pps. The amplitude of stimulation was set for each patient at an intensity between 20 and 40 mA (average 29.2 mA), which was just below where small muscle twitches (submotor or sensory level) of stimulation were observed. Prefabricated, single-use electrodes that were placed directly over the open wound and resulted in an accumulated pulse charge of 249.6–499.2 μC/s at low- and high-frequency settings, respectively. All investigators applied the same treatment schedule, which involved 30 min sessions twice daily separated by at least 4 h. Treatments were given every day (7 days a week) for at least 4 weeks and up to 16 weeks in some studies. How many days between electrode polarity change and the criteria for changing the charge of the active electrode placed in the wound was also slightly different between studies (Table 2).[25–29,*]

Using a well-designed, multi-site, randomized, placebo-controlled, double-blinded study design, Feedar *et al.* reported a reduction in wound size that was significantly faster than placebo-treated wounds reported after 4 weeks of ES treatment using this device.[25] Significant improvements in all wound-healing outcomes were tracked over 4 weeks for 59 patients with 63 wounds of mixed etiology, including stage II-IV pressure ulcers (NPUAP, 2007) or postoperative wounds. Identical results from these nine investigational sites in the United States were reported in a second published report written by Mulder in the same year.[26] Gentzkow *et al.* (1991)[27] also reported better healing outcomes when this device was used to treat 37 people with 40 pressure ulcers. Gentzkow also published a second report in 1993 that involved data compiled from three other sites in the United States, where 78 pressure ulcers in 68 subjects were treated with the Dermapulse device using the 2:4 h daily treatment schedule.[28] Wound appearance was evaluated using an eight-point wound

*Barczak M, *et al.* (unpublished dissertation).

characterization system. Significant improvement in wound appearance, denoted as an increase in wound characterization of at least two levels, occurred in 52.6% of wounds evaluated after 2 weeks and 78.9% of wounds evaluated after 4 weeks of treatment.[28] These estimates included 17 subjects who did not complete at least 4 weeks of ES treatment. Despite this intention to treat analysis, 23% of the wounds were completely healed after 4 weeks of ES treatment. Gentzkow and co-authors[28] called their study a baseline controlled study, as wounds included in this study had no evidence of improvement for at least 4 weeks before starting ES treatment. However, since data were not prospectively collected from an independent control group, these conclusions were assigned a lower level of evidence (LOE = 4).

Barczak *et al.* wrote a doctoral dissertation about a controlled study conducted in Germany that specifically focused on pressure ulcers in people with SCI.* Healing rates were faster after 28 days of treatment using MPC. They also reported that all (100%) ulcers treated preoperatively with ES healed after surgical closure, whereas 31% of wounds in the control group remained open at 12 weeks post op. Surgical complication rates and hospital length of stay were similar between groups, suggesting that these outcomes were influenced by factors other than preoperative treatment with ES.*

In 2008, Junger and *et al.*[29] examined the effects of MPC in a well-designed RCT involving a small group of patients ($n = 39$) with leg ulcers due to chronic venous insufficiency. All subjects also used short stretch compression therapy for leg edema. Overall, there was no difference between ES and sham-treated wounds over a 4 month observation period. A statistically significant reduction in wound size over 4 months was shown in wounds treated with real ES but not in those receiving sham ES treatments. These researchers[29] found that ES treatment was associated with greater pain reduction in these leg ulcers; therefore, they concluded that ES is a "viable treatment option for therapy-resistant venous leg ulcers." Junger *et al.*[29] did not report a power calculation before conducting this trial; however, given the significant reduction in wound size observed after 4 months of ES treatment but not control treatments, it is likely that a relatively small sample size ($n = 39$) might explain why these authors were unable to detect a statistical difference between treatment groups.

Adegoke and Badmos performed a randomized controlled clinical trial on people living with SCI and pressure ulcers in Nigeria.[30] They used what they called "interrupted direct current" that was applied at a frequency of 30 pps directly to the wound at a sensory level for 45 min thrice a week. Unfortunately, details about the waveform, electrode polarity, and other stimulus parameters were not provided in their report. They found a marked and statistically significant difference in the percentage wound reduction between ES and placebo treatment groups after 4 weeks of treatment (2.6% vs. 22.2%). While these results are impressive, the extremely small sample sizes in each group ($n = 3$–4 patients) limit the ability to extrapolate these results to clinical practice.

Overall, initial reports from the United States that used the "Dermapulse" device which supplies MPC were associated with marked improvement in healing rates.[25–29] Unfortunately, this device has limited availability in the United States or Canada. A more recent report from Europe that used a newer MPC device (woundEL, Gerromed, Germany) has not produced statistically significant improvements in wound-healing rates.[29] Further clinical trials involving larger sample sizes are warranted to evaluate the effects of this MPC device on people with chronic wounds.

Clinical trials using BiPC

Several studies have been published from a group of researchers in Slovenia (Table 2).[16,17,19,31–36,50] In all these studies, BiPC with balanced charge was applied to the wound edge at a level that produced visible muscle twitches. In 1997, Semrov documented using mathematical modeling the electrical field that was produced using this ES protocol.[50] The stimulus parameters were all set to deliver 250 μs pulses in 4 s pulse train 40 times per second (40 pps) in a 50:50 on-off ratio. Treatments were given for 2 h a day at least 5 days a week until complete wound closure was achieved. Initial reports published in the late 1980s and early 1990s involved various wound etiologies, including pressure ulcers, vascular leg wounds, and postsurgical or post-trauma wounds, that were successfully treated with this ES protocol.[31–33] In these case series,[32,33] very few wounds (3 of 63) did not heal completely. Mean healing times were dependent on the type of wound being treated with longer treatments required for vascular wounds (10 weeks) compared with traumatic wounds (4.5 weeks) or pressure ulcers (5.5 weeks).[32] Similar results were reproduced in another publication by the same authors.[33] Subsequent clinical reports involved prospective and controlled clinical trials and targeted pressure ulcers occurring in people with SCI.[16,31,34,35] It appears that some of the data presented in these

*Barczak M, *et al*. (unpublished dissertation).

reports which came from the same research group may have been duplicated.[17,33,36] In all the reports from Slovenia, results were presented using an exponential curve-fitting model, and significantly faster healing rates were found in ES treated compared with sham controls. Since ES was applied at a higher intensity that resulted in visible muscle contractions, the researchers and patients could not be blinded to treatment allocation, and details about wound measurement and method of randomization were not clearly described.

Cukjati and *et al.*[17] reviewed a database of more than 300 subjects that had been treated using the same BiPC protocol. Since this research group is located within a rehabilitation institute, 71% of these patients had pressure ulcers and SCI.[17] They identified wound characteristics that were associated with better responses to ES treatment provided they are followed for at least 4 weeks. These predictive factors included initial wound size, wound duration, location on the body, and the age of the patient.

Collectively, these studies produced by researchers in Slovenia suggest that healing can be accelerated when BiPC is applied for 2 h a day to periulcer skin at a relatively high intensity which produces muscle stimulation.[16,17,19,31–36,50] This research group has produced increased healing rates in a population of patients with SCI who are commonly affected by pressure ulcers. Positive healing outcomes resulting from this ES protocol using BiPC has yet to be reproduced by other research groups.

Several different research groups used BiPC applied at a sensory level to periulcer skin to treat people with diabetic foot wounds,[21,37,38] chronic painful leg ulcers,[39] and pressure ulcers in SCI.[20] Each of these studies (Table 2) were prospective randomized clinical trials that included an appropriate control group in which subjects were treated with conventional wound care[39] and, in some instances, also a placebo ES unit.[37]

Baker *et al.* published two large clinical trials that involved a group of patients with pressure ulcers and SCI,[20] and another recruited subjects with diabetic foot ulcers.[21] In both these reports, the study began with four treatment groups: a control group that did not get ES, and three groups which received different forms of ES applied in 30 min treatment sessions applied thrice daily. One group received MC that produced subsensory level stimulation, and the other two groups at high-frequency (50 pps) BiPC using either a biphasic symmetrical square waveform (Sym BiPC) and an asymmetrical biphasic but charge balanced waveform (Asym BiPC) which had a short (100 μs) perceptible initial pulse followed by a longer (20 ms) subsensory pulse flowing in the opposite direction. Patients receiving some form of ES were treated until wound closure, and mean time to healing was recorded for these groups. Subjects initially assigned to the control group were treated for 4 weeks and then offered ES treatment (single cross over design). Both reports involving diabetic foot wounds[21] or pressure ulcers[20] indicated faster healing rates when the AsymBiPC waveform was applied rather than the SymBiPC waveform or the MC therapy.

An impressive number of wounds were included in reports by Baker *et al.* in 1996 (192 wounds)[20] and 1997 (114 wounds);[21] however, several patients (21% and 42%) enrolled in the studies had multiple wounds or recurrent wounds and each wound was randomized to a particular group. This resulted in data from the same patient recorded more than once and confounded results reported by patients who would be aware that wounds were being treated differently. Baker and colleagues concluded that biphasic current using asymmetrical waveform produced better wound-healing outcomes; however, this was based on *post hoc* analysis where data from control and the MC treatment groups were combined.[20] They only included in the analysis wounds that were on patients who were considered "semi-compliant" (received at least 45 min of ES treatment per day). When all results were analyzed in the four groups that were initially (and randomly) assigned, no significant difference was detected between groups. A similar approach was adopted in the 1997 study published by Baker *et al.*,[21] where a significant difference in healing rates was detected between pressure ulcers treated with control versus Asym BiPC. Again, this difference was only detectable in a subgroup of wounds that were considered "good responders" and were compliant with ES treatments. This data manipulation was conducted to reduce the large variability in the data.[21] However, it may also suggest that this ES treatment protocol using Asym BiPC is effective in only a particular group of subjects who comply with daily ES treatments and have wound characteristics which make them good responders.

Lundeberg conducted a well-designed randomized clinical trial on 64 subjects with diabetic foot ulcers.[37] The ES protocol involved applying 1 ms pulses at a rate of 80 pps to the peri-ulcer skin at an intensity sufficient to produce sensory paresthesia for 20 min twice daily for 12 weeks. Changes in wound area and the number of healed ulcers measured at 8 and 12 weeks were significantly

better for ES compared with placebo-treated wounds. Therefore, the authors concluded that this report provided strong evidence that ES produced better healing rates in people with diabetic foot ulcers.

In 2010, Petrofsky and Lawson conducted a randomized controlled trial with 20 subjects who had diabetic foot ulcers.[40] In this study, BiPC (200 μs, 30 pps, and 20 mA) ES was applied to periulcer skin for 30 min, thrice a week for 4 weeks.[40] This group uses a unique electrode arrangement that includes three electrodes placed around the wound, and the stimulator automatically alternates current flow between two electrodes every second throughout the treatment. A previous work has shown that this three-electrode set-up produces a more uniform field in both the wound base and at the edge of the wound.[41] They compared the effect of ES when combined with dry heat (infrared heat lamp) versus a control group that received standard wound care and dry heat and found significantly greater wound size reduction in ES and heat-treated wounds.[41] These results were consistent with a previous report by the same researchers when they used this ES protocol to produce significant improvements in local blood flow measured around the wounds.[51] Unfortunately, in studies performed by both Suh *et al.*[41] and Petrofsky.[40] the effects of ES were confounded by concurrent treatment with a heat lamp.

Jankovic and Binic[39] recently reported the effects of a new ES device that delivers high-frequency (1,000 pps) BiPC which is modulated to produce varying sensations over a 40 min treatment. This frequency-modulated electrical stimulation (FREMS) is applied using four channels that are located around the wound and along peripheral nerves.[39] Changes in wound size measured in people with chronic painful leg ulcers due to venous (80%) or arterial insufficiency after 3 weeks of FREMS treatment produced significantly faster healing rates compared with sham-treated control wounds. The authors also reported better pain intensity scores in those receiving FREMS. Some details about the study were limited, and it seems that standard wound care for subjects with venous insufficiency ulcers did not include compression therapy.

Clinical trials using other ES protocols

Ogrin *et al.* used a very unique ES treatment protocol to stimulate sensory nerves of people with venous ulcers (Table 2).[42] This was a well-designed, prospective, randomized, placebo-controlled, and double-blinded clinical trial. The ES treatment included extremely low levels (4 mA, 5 pps) that were applied at a sub-sensory level to peripheral sensory nerves of the limb in 5 min treatment sessions applied twice a day for 12 weeks. The type of waveform used in this patent-pending device was not revealed. Their results were inconclusive with little difference in healing rates detected between groups.[42] Researchers observed an improvement in microvascular blood flow, transcutaneous partial pressure of oxygen, and flare response to capsaicin in ES-treated limbs; however, these changes were not significantly different than placebo-treated controls.[42] Perhaps a trial of longer or more frequent or longer ES treatment is worth investigating.

Another application technique that has been used to treat chronic wounds involves applying a traditional transcutaneous electrical nerve stimulation (TENS) machine which produces two bursts of five 200 μs pulses at an intensity which causes tetanic muscle contraction.[43–45] The active electrode (cathode) is placed over acupuncture points that are located in the hand or foot. Although the specific waveform delivered from this device was not described, it is presumed to be BiPC with no net charge under either electrode (balanced). Two clinical reports from the same group in Norway found that complete healing could be produced when this ES protocol was applied to people with recalcitrant wounds of mixed etiology[43] and due to leprosy.[44] Another group of researchers in Norway performed a small controlled study and did not find significant differences in healing rates when they applied a similar acupuncture-like TENS protocol to hand muscles of patients with pressure ulcers located on the sacrum or heels.[45] Since this study included only 16 subjects, it is not known whether they had sufficient power to detect differences in wound healing. Therefore, the benefits of this unique type of ES applied at some distance to the wound remain to be determined.

SUMMARY

This systematic review revealed a total of 36 clinical studies in which direct current or different forms of pulsed current were applied and healing outcomes were evaluated in a total of 1,432 people. Twenty of these studies ($n = 862$ subjects) included a control group in which either placebo ES or standard wound care was compared with subjects treated with some form of ES. There were also five case reports ($n = 11$), eight uncontrolled clinical reports ($n = 344$ subjects), three case controlled studies,[11,12,34] and two large retrospective analyses

involving at least 300 patients.[16,17] If the results of this group of studies are evaluated collectively and simplistically, the results appear conflicting and confusing. Eleven well-designed controlled studies ($n = 490$ subjects) reported a significantly faster healing rate compared with control subjects. However, four studies with 144 subjects found no added benefit of ES on healing outcomes.[23,29,42,45] An examination of the methodological quality of these clinical reports identified that five randomized controlled studies ($n = 238$ subjects with 350 ulcers) had serious design flaws.[18,20–22,30] Four of these five poorly conducted studies[18,20–22] did not find a difference between ES and control-treated wounds.

A closer examination of the ES protocols employed in these published reports revealed that the results depended on the type of ES waveform employed in the study. Initial reports using very rudimentary devices that delivered LIDC produced promising results in terms of ulcer-healing rates. These devices were replaced by ones that provided some form of PC, where short (microseconds in duration) pulses were delivered in distinct units or pulses followed by periods of no stimulation or rest. When BiPC was applied to the peri-ulcer skin at levels sufficient to produce motor stimulation, ES was found to significantly and consistently produce faster wound closure rates. This ES protocol was applied by a large group of researchers working in Slovenia who were predominantly involved in treating people with pressure ulcers and SCI.[31–36] When this group compared healing outcomes produced by ES applied using motor level stimulation of BiPC waveform, they found significantly better results than those patients who had previously been treated with LIDC.[16,17] Several research groups from many locations around the world have used BiPC at a sensory level applied to the peri-ulcer skin.[20,21,37–40] The treatment schedule and stimulus parameters used in these studies[20,21,37–40] were quite varied and, understandably, the effects of ES reported in these studies were conflicting. The application of MPC applied directly to the wound bed have produced more consistent and positive results;[25–28,*] however, a recent report that employs the only device which remains commercially available did not find statistically significant differences between MPC and control-treated wounds.[29] Sub-sensory levels of ES, termed MC in this review, have generally not produced evidence to suggest that this type of ES can stimulate wound closure.[18–24]

*Barczak M, *et al.* (unpublished dissertation).

TAKE-HOME MESSAGES

- Published clinical reports that examined the effects of ES on healing rates have employed different forms of electrical current and a variety of ES protocols (intensity and treatment schedule).
- Several researchers have consistently reported that MPC can accelerate healing.
- A protocol developed by a group in Slovenia that involves the use of BiPC applied at a higher intensity sufficient to produce muscle stimulation warrants evaluation by other investigators.
- There is insufficient evidence to support the use of ES protocols that deliver sub-sensory levels of ES (termed microcurrent (MC) in this review).

Based on the results from this review, it is apparent that several different types of ES have been employed to accelerate wound healing and promote wound closure of chronic wounds. It seems that the results are dependent on the type of ES waveform employed. Clinicians also need to consider the strength of the research study design and the stimulus parameters such as the amplitude or intensity, the treatment schedule, and where the electrodes are placed. These details have been summarized for easy review in Table 2.

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ABOUT THE AUTHOR

Dr. Pamela E. Houghton is Full Professor in the School of Physical Therapy at Western University. She developed the Masters of Clinical Science program in the field of wound healing in 2007. This program provides specialized training for health-care professionals treating people with chronic wounds using distance education methods. Dr. Houghton leads an active research program at Western that is dedicated to evaluating therapeutic modalities such as electrical stimulation for the treatment of people with chronic wounds. Pamela is a licensed Physical Therapist with the College of Physiotherapists of Ontario.

REFERENCES

1. 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:** 23.
2. European Pressure Ulcer Advisory Panel and National Pressure Ulcer Advisory Panel: Pressure ulcer prevention: quick reference guide. Washington, DC: National Pressure Ulcer Advisory Panel, 2009. www.epuap.org/guidelines/Final_Quick_Prevention.pdf (accessed November 20, 2011).
3. Consortium for Spinal Cord Medicine Clinical Practice Guidelines: Pressure ulcer prevention and treatment following spinal cord injury: a clinical practice guideline for health-care professionals. J Spinal Cord Med 2001; **24 (Suppl 1):** S40.
4. Registered Nurses of Ontario (RNAO) Assessment and Treatment of Stage I to IV pressure ulcers. 2007. www.rnao.org/Storage/29/2371_BPG_Pressure_Ulcers_I_to_IV.pdf (accessed Jan 30, 2013).
5. Houghton PE and Campbell KE; CPG Panel: Canadian Best Practice Guidelines for the prevention, assessment and treatment of pressure ulcers in people with spinal cord injury: a resource handbook for clinicians. http://onf.org/system/attachments/168/original/Pressure_Ulcers_Best_Practice_Guideline_Final_web4.pdf (accessed June 30, 2013).
6. American Physical Therapy Association: *Electrotherapeutic Termnology in Physical Therapy*. Alexandria, VA: APTA Publications, 1990.
7. Straus SE, Richardson WS, Glasziou P, Haynes RB: *Evidence-Based Medicine: How to Practice and Teach EBM*. 3rd Ed. Toronto: Elsevier Churchill Livingstone, 2005.
8. Teasell RW, Foley NC, Bhogal SK, and Speechley MR: An evidence-based review of stroke rehabilitation. Top Stroke Rehabil 2003; **10:** 29.
9. Regan M, Teasell RW, Keast D, Aubut JL, Foulon BL, Mehta S: Pressure ulcers following spinal cord injury. In: *Spinal Cord Injury Rehabilitation Evidence*. Version 4.0, edited by Eng JJ, Teasell RW, Miller WC, *et al.* 2012. www.scireproject.com/rehabilitation-evidence/pressure-ulcers (accessed December 2, 2013).
10. Assimacopoulos D: Low intensity negative electric current in the treatment of ulcers of the leg due to chronic venous insufficiency. Am J Surg 1968; **115:** 683.
11. Wolcott L., Wheeler PL, Hardwicke H, and Rowley B: Accelerated healing of skin ulcers by electrotherapy. South Med J 1969; **62:** 795.
12. Gault W and Gatens P: Use of low intensity direct current in management of ischemic skin ulcers. Phys Ther 1976; **56:** 265.
13. Carley P and Wainapel S: Electrotherapy for acceleration of wound healing: low intensity direct current. Arch Phys Med Rehabil 1985; **66:** 443.
14. Barron J, Jacobson W, and Tidd G: Treatment of decubitus ulcers a new approach. Minn Med 1985; **68:** 103
15. Wood J, Evans P 3rd, Schallreuter K, *et al.*: A multicenter study on the use of pulsed low-intensity direct current for healing chronic stage II and stage III decubitus ulcers. Arch Dermatol 1993; **129:** 999.
16. Stefanovska A, Vodovnik L, Benko H, and Turk R: Treatment of chronic wounds by means of electric and electromagnetic fields. Part 2, Value of FES parameters for pressure sore treatment. Med Biol Eng Comp 1993; **31:** 213.
17. Cukjati D, Robnik-Sikonja M, Rebersek S, Kononenko I, and Miklavcic D: Prognostic factors in the prediction of chronic wound healing by electrical stimulation. Med Biol Eng Comput 2001; **39:** 542.
18. Katelaris P, Fletcher J, Little J, McEntyre R, and Jeffcoate K: Electrical stimulation in the treatment of chronic venous ulceration. Aust NZ J Surg. 1987; **57:** 605.
19. Karba R, Semrov D, Vodovnik L, Benko H, and Savrin R: DC electrical stimulation for chronic wound healing enhancement. Part 1. Clincial study and determination of electrical field distribution in the numerical wound model. Bioelectrochem Bioenerg 1997; **43:** 265.
20. Baker L, Rubayi S, Villar F, and Demuth S: Effect of electrical stimulation waveform on healing of ulcers in human beings with spinal cord injury. Wound Rep Reg 1996; **4:** 21.
21. Baker L, Chambers R, DeMuth S, and Villar F: Effects of electrical stimulation on wound healing in patients with diabetic ulcers. Diabetes Care 1997; **20:** 405.
22. Adunsky A and Ohry A: Decubitus direct current treatment (DDCT) of pressure ulcers: results of a randomized double-blinded placebo controlled study. Arch Gerontol Geriatr 2005; **41:** 261.
23. Ullah M: A study to detect the efficacy of microcurrent electrical therapy on decubitus wound. J Med Sci 2007; **7:** 1320.
24. Hampton S and King L: Healing an intractable wound using bio-electrical stimulation therapy. Br J Nurs 2005; **14:** S30.
25. Feedar J, Kloth L, and Gentzkow G: Chronic dermal ulcer healing enhanced with monophasic pulsed electrical stimulation. Phys Ther 1991; **71:** 639.
26. Mulder G: Treatment of open-skin wound with electrical stimulation. Arch Phys Med Rehabil 1991; **72:** 375.
27. Gentzkow G, Pollack S, Kloth L, and Stubbs H: Improved healing of pressure ulcers using Dermapulse, a new electrical stimulation device. Wounds 1991; **3:** 158.
28. Gentzkow G, Alon G, Taler G, Eltorai I, and Montroy R: Healing of refractory stage III and IV pressure ulcers by a new electrical stimulation device. Wounds 1993; **5:** 160.
29. Junger M, Arnold A, Zuder D, Stahl H, and Heising S: Local therapy and treatment costs of chronic, venous leg ulcers with electrical stimulation (Dermapulse): a prospective, placebo controlled, double blind trial. Wound Rep Reg 2008; **16:** 480.
30. Adegoke B and Badmos K: Acceleration of pressure ulcer healing in spinal cord injured patients using interrupted direct current. Afr J Med Med Sci 2001; **30:** 195.
31. Stefanovska A, Vodovnik L, Benko H, *et al.*: Enhancement of ulcerated tissue healing by electrical stimulation. *Proceedings of the Resna 10th Annual Conference*, San Jose, CA, 1987.
32. Karba R, Presern-Strukeij M, Vodovnik BL, and Klesnik M: Accelerated wound healing of lower extremities by means of electrical stimulation. Adv External Control Hum Extremities 1990; **8:** 509.
33. Karba R, Vodovnik BL, Presern-Strukeij M, and Klesnik M: Promoted healing of chronic wounds due to electrical stimulation. Wounds 1991; **3:** 16.
34. Karba R, Benko H, Savrin R, and Vodovnik L: Combination of occlusive dressings and electrical stimulation in pressure ulcer treatment. Med Sci Res 1995; **23:** 671.
35. Jercinovic A, Karba R, Vodovnik L, *et al.*: Low frequency pulsed current and pressure ulcer healing. IEEE Trans Rehabil Eng 1994; **2:** 225.
36. Trontelj K, Karba R, Vodovnik L, Savrin R, and Presern Strukelj M: Treatment of chronic wounds by low frequency pulsed electrical current. J Tissue Viability 1994; **4:** 105.
37. Lundeberg T, Eriksson S, and Malm M: Electrical nerve stimulation improves healing of diabetic ulcers. Ann Plast Surg 1992; **29:** 328.
38. Thurman B and Christian E: Response of a serious circulatory lesion to electrical stimulation. Phys Ther 1971; **51:** 1107.
39. Jankovic A and Binic I: Frequency rhythmic electrical modulation system in the treatment of chronic painful leg ulcers. Arch Dermatol Res 2008; **300:** 377.
40. Petrofsky J, Lawson D, Berk L, and Suh H: Enhanced healing of diabetic foot ulcers using local heat and electrical stimulation for 30 min three times per week. J Diabetes 2010; **2:** 41.
41. Suh H, Petrofsky J, Fish A, *et al.*: A new electrode design to improve outcomes in the treatment of chronic non-healing wounds in diabetes. Diabetes Technol Ther 2009; **11:** 315.
42. Ogrin R, Darzins P, and Khalil Z: The use of sensory nerve stimulation and compression bandaging to improve sensory nerve function and healing of chronic venous leg ulcers. Curr Aging Sci 2009; **2:** 72.
43. Kaada B: Promoted healing of chronic ulceration by transcutaneous nerve stimulation (TNS). VASA 1983; **12:** 262.

44. Kaada B and Emru M: Promoted healing of leprous ulcers by transcutaneous nerve stimulation. Acupunct Electrother Res Int J 1988; **13:** 165.

45. Asbjornsen G, Hernaes B, and Molvaer G: The effect of transcutaneous electrical nerve stimulation on pressure sores in geriatric patients. J Clin Exp Gerontol 1990; **12:** 209.

46. Chalker M: Healing of decubitus ulcers of patients in neuro-kinesthetic program with the electro-acuscope 80. Crit Care Update 1983; **10:** 50.

47. Black J, Baharestani M, Cuddigan J, *et al.*; National Pressure Ulcer Advisory Panel: National Pressure Ulcer Advisory Panel's updated pressure ulcer staging system. Dermatol Nurs 2007; **19:** 343.

48. Hampton S and Collins F: Treating a pressure ulcer with bio-electric stimulation therapy. Br J Nurs 2006; **15:** S14.

49. Lee B, Al-Waili N, Stubbs D, *et al.*: Ultra-low microcurrent in the management of diabetes mellitus, hypertension and chronic wounds: report of twelve cases and discussion of mechanism of action. Int J Med Sci 2009; **7:** 29.

50. Semrov D, Karba R, and Valencic V: DC electrical stimulation for chronic wound healing enhancement: Part 2. Parameter determination by numerical modeling. Bioelectrochem Bioenerg 1997; **43:** 271.

51. Lawson D and Petrofsky J: A randomized control study on the effect of biphasic electrical stimulation in a warm room on skin blood flow and healing rates in chronic wounds of patients with and without diabetes. Med Sci Monit 2007; **13:** CR258.

Abbreviations and Acronyms

AC = alternating current
Asym BiPC = asymmetrical biphasic pulsed current
Asym BiPC balanced = asymmetrical biphasic charge balanced pulsed current
BiPC = biphasic pulsed current
DC = direct current
DDCT = decubitus direct current treatment
ES = electrical stimulation
FREMS = frequency modulated electrical stimulation
HVPC = high-voltage pulsed (galvanic) current
LIDC = low-intensity direct current
LOE = level of evidence
MC = microcurrent
MET = microcurrent electrical therapy
MPC = monophasic pulsed current
PC = pulsed current
PEMFs = pulsed electromagnetic fields
SCI = spinal cord injury
Stage II, III, or IV (NPUAP, 2007) = stage 2, 3, 4 pressure ulcer staging as per National Pressure Ulcer Panel guidelines, 2007
Sym BiPC = symmetrical biphasic pulsed current
TENS = transcutaneous electrical nerve stimulation