The Efficacy of Pressure Ulcer Treatment With Cathodal and Cathodal-Anodal High-Voltage Monophasic Pulsed Current: A Prospective, Randomized, Controlled Clinical Trial

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Background. Studies show that anode and cathode electrical stimulation (ES) promotes the healing of wounds, but specific protocols for both electrodes are not available.

Objective. To compare the effectiveness of cathodal versus cathodal+anodal ES in the treatment of Category II-IV pressure ulcers (PrUs).

Design. Prospective, randomized, controlled, clinical study.

Setting. Three nursing and care centers.

Patients. Sixty-three participants with PrUs were randomly formed into a cathodal ES group (CG: N = 23; mean age of 79.35; SD 8.48), a cathodal+anodal ES group (CAG: N = 20; mean age of 79.65; SD 11.44) and a placebo ES group (PG: N = 20; mean age of 76.75; SD 12.24).

Intervention. All patients were treated with standard wound care and high-voltage monophasic pulsed current (HVMPC; twin-peak impulses; 154 μs; 100 pps; 0.25 A; 250 μC/s) for 50 minutes per day, 5 times a week, for 6 weeks. The CG, CAG, and PG received, respectively, cathodal, cathodal+anodal, and sham ES through electrodes placed on a moist gauze pad. The treatment electrode was placed on the wound, and the return electrode was positioned on healthy skin at least 20 cm from the PrU.

Measurements. Measurements were made at baseline, and after each of the 6 weeks of treatment. Primary outcome was percentage wound surface area reduction at week 6.

Results. Wound surface area decreased in the CG by 82.34% (95% confidence interval [CI] 70.06-94.63) and in the CAG by 70.77% (95% CI 53.51-88.04). These reductions were significantly greater than in the PG (40.53%; 95% CI 23.60-57.46). The CG and CAG were not statistically significantly different regarding treatment results.

Limitations. The time of treatment proved insufficient for PrUs to close.

Conclusions. Cathodal and cathodal+anodal HVMPC similarly reduced the area of Category II-IV PrUs.
Clinical practice guidelines recognize electrical stimulation (ES) as therapeutically useful in treating Category II, III, and IV pressure ulcers (PrUs).\cite{1,2}

Electric currents used in wound studies include direct and pulsed microamperage current (<1 mA),\cite{3-7} low-voltage biphasic pulsed current,\cite{8-10} low-voltage monophasic pulsed current,\cite{11-15} and high-voltage monophasic pulsed current (HVMPC).\cite{16-24} The authors of the 2014 reviews\cite{25,26} concluded that both low-voltage biphasic and monophasic currents and HVMPC can produce consistently positive results in patients with chronic wounds. However, optimal ES protocols for wound treatment are not available yet.

Authors of clinical studies used HVMPC to treat venous leg ulcers,\cite{16-18,20,22-24} PrUs,\cite{16-17,21-24} and diabetic foot ulcers,\cite{19} applying also standard wound care (SWC) for ethical reasons. Treatment results were compared with control groups (SWC alone)\cite{18,21-23} or SWC+sham HVMPC.\cite{16,17,19,20,24} The outcomes of the studies\cite{16-24} indicated that HVMPC promoted the healing of wounds, decreasing their area more in the SWC+HVMPC groups than in controls.

The cited clinical studies are similar regarding the selection of HVMPC parameters.\cite{16-24} Their authors used twin-peak monophasic pulses,\cite{16-24} pulse duration of 50–154 µs,\cite{16-18,24} and pulse frequency of 100–105 pps.\cite{16-24} with the current evoking only sensory, sub-motor reactions.\cite{16-24} HVMPC was usually applied for 3.75 to 7 hours a week.\cite{16,18,20,22-24} In most studies, treatment sessions of 45–60 minutes were held 5–7 days a week. The treatment electrode was always placed on the wound\cite{16-24} and the return electrode on healthy skin at least 15–20 cm from it.\cite{16,18,20,22-24}

At the same time, the studies differ in the selection of the treatment electrode polarity. Some authors only used the anode or the cathode to deliver HVMPC.\cite{17,20,24} Others used cathodal stimulation and anodal stimulation,\cite{18,21-25} but varied the duration of their application. Wounds were first treated with cathodal stimulation for a period of 1–3\textsuperscript{18} or 1–2 weeks, and then anodal stimulation was applied until the end of treatment. In some studies with HVMPC, treatment started with negative polarity that was changed every week.\cite{21}

The authors of studies who treated wounds with low-voltage rectangular monophasic pulsed current also varied in the use of cathode and anode.\cite{11-15} In one study, only the anode was used as the treatment electrode.\cite{11} In others, both electrodes were used, but cathodal stimulation was always applied first.\cite{12,14} Some researchers chose to reverse the treatment electrode polarity every three days.\cite{12,14} The authors of one study coordinated it with healing progress—after the first 1–2 weeks of cathodal stimulation, they introduced anodal stimulation for 3–10 days and then changed polarity again.\cite{15}

The different use of anode and cathode in the cited studies implies that specific protocols showing how the electrodes should be applied to human wounds are yet to be created.

Authors of the reviews of clinical\cite{27,28} and epidemiological studies\cite{29} consider wound closure the crucial endpoint in evaluating treatment efficacy, but clinical studies with ES rarely go on until it is achieved. We have found only one study in which all PrUs were treated with HVMPC until full closure.\cite{16} In trials that terminate before wounds are closed, the percentage wound area reduction (PAR) from baseline after treatment lasting 4, 6, or 12 weeks is crucial.\cite{17,24} The time over which PrU surface area decreases from baseline by at least 50% is also important as an indicator of treatment efficacy.\cite{27,29}

**Aim of Study**

The study was designed to determine more information regarding the effect of HVMPC delivered through the cathode or the cathode and anode on the healing of PrUs. Clinical trials comparing these two types of ES applied to PrUs are not available in the literature.

Two research hypotheses were formulated for the study. The first states that HVMPC delivered only by the cathode or by the cathode subsequently replaced by the anode can effectively promote the healing of PrUs. According to the second hypothesis, the cathode and anode are similarly effective in treating PrUs, regardless of how they are applied.

Both hypotheses were formulated based on the results of clinical\cite{17-24} and preclinical studies.\cite{29-42}

Clinical studies\cite{16-24} provide evidence that HVMPC promotes the healing of chronic wounds. This effect can be observed when such wounds are stimulated only by the cathode,\cite{17,20,24} and when cathodal stimulation used at the beginning of treatment is replaced by anodal stimulation.\cite{18,22,23}

Similar conclusions can be drawn from preclinical studies,\cite{29-42} which show that in cell cultures human fibroblasts,\cite{30,31} keratinocytes,\cite{32,33} microvascular endothelial cells,\cite{34} and epithelial cells\cite{35} migrate directionally toward the cathode. Cathodal stimulation has been observed in vitro to increase DNA synthesis in human fibroblasts,\cite{32,33} and in vivo studies have demonstrated that cathodal stimulation increases the release of vascular endothelial growth factor in animal skin.\cite{36} These results imply that cathodal stimulation can intensify cell proliferation in the wounds. From in vivo studies with animals,\cite{34,35,37,38,39} it is known that also treating wounds first with the cathode and then with the anode is effective. The authors of the studies observed increased wound epithelialization,\cite{34,35,37,38,39} tensile strength,\cite{30} mRNAs expression of collagen-I and transforming growth factor-β1,\cite{41} reduced wound inflammation,\cite{35} improved cell proliferation, and the remodeling of wounds.\cite{37}

**Methods**

**Study Design**

A prospective, randomized, controlled, clinical trial was designed to compare PrU closure after 6 weeks of treatment between 3 parallel groups of patients receiving SWC plus cathodal ES, cathodal-anodal ES, or sham ES. Ethical approval was granted by the Academy Bioethics Commission. The trial
was prospectively registered with the Australian-New Zealand Clinical Trials Registry: ANZCTR 1261400092606.

Setting and Participants
The trial screening procedure was applied to patients in 3 nursing care centers, whose eligibility to participate was assessed by their physician against the following criteria: aged 60+; high risk of PrU development (below 14 points on the Norton scale), Category II, III, or IV PrU of at least 0.5 cm², and duration from 1 to 12 months located on the pelvic girdle. The trial focused on chronic PrUs in elderly persons who frequently have co-morbidities impeding normal wound healing. All treated ulcers were located on the pelvic girdle to ensure the comparability of treatment results.

Patients who could not receive ES (cancer, electronic implants, malignancy, tunneling, necrotic wounds, osteomyelitis, PrU requiring surgical intervention, metal implants in the PrU area) and patients with conditions impeding wound healing (diabetes HbA1C > 7%, critical wound infection, allergies to standard wound treatment, alcoholism) were excluded from the trial. After the study was registered with ANZCTR but before patient recruitment began, the exclusion criteria were extended to factors that could disturb wound healing process or inhibit the use of ES or pharmacological therapy.

Patients’ demographics were obtained from standard interviews, physical examinations, and medical records. Their physical and mental condition, mobility, and incontinence were evaluated using the Norton scale. The risk of friction and shear, wound moisture, sensory perception, physical activity, and mobility were measured with the Braden scale. The patients’ diet was reviewed, and their intake of healthy and unhealthy nutrients and fluid losses was assessed. The nutritional status of patients was quantified using the Nutritional Risk Score (NRS—2002).

Wound severity at enrollment was determined by a physician using the National Pressure Ulcer Advisory Panel criteria (Category II PrUs = partial-thickness loss of the dermis presenting as a shallow open ulcer with a red pink wound bed, no slough; Category III PrUs = full-thickness tissue loss; subcutaneous fat possibly visible, but not the bone, tendon, or muscles; Category IV PrUs = full-thickness tissue loss; muscle/bone exposed).

Randomization
Three groups were formed of patients who consented to participate in the study (or whose legal guardians accepted their participation).

Group assignment was performed using the block randomization method. In each of the 3 nursing care centers, a person uninvolved in the trial generated 4 blocks of 6 letters (combinations of A, B, and C) using computer software. To conceal the allocation sequence, consecutively numbered, opaque, and sealed envelopes were used. The principal investigator opened them to assign patients to the appropriate group following the completion of baseline measurements.

Blinding
All patients, medical personnel, and researchers were blinded. The exception was the main investigator and principal physical therapist, who set the equipment to apply active or sham ES. The person responsible for wound surface area measurements and statistical analysis was blinded too.

Interventions
Standard wound care program administered to all groups. All patients in the cathodal ES, cathodal+anodal ES, and placebo groups received SWC comprising prevention measures, wound care, and physical treatment under the supervision of the physician and principal investigator following best practices. Each patient was assessed by an interdisciplinary team consisting of a physician, nurse, physical therapist, and dietician in order to develop individual wound prevention and treatment programs addressing patients’ needs for PrU prevention and nutritional intervention, the optimization of the wound dressing protocol, and incontinence management.

Treatments preventing the development of more PrUs in the patients were applied, such as pressure-redistribution surfaces, devices, and pillows. The immobile patients were repositioned by a nurse or physical therapist at least every 2 hours. Those who could move were requested to change position as often as they could.

Blood samples were tested to screen patients for nutritional status markers and metabolic disorders, such as different types of anemia, thyroid dysfunction, impaired glycemic control, dehydration, protein deficit, and hypoalbuminemia.

The malnourished patients received individual nutritional support. A nurse or medical assistant helped them with meals and monitored whether the quantity and quality of food and liquids they ingested followed the dietician’s guidelines. Nutritional supplementation was used when necessary to ensure that the patients received the recommended quantity of proteins, vitamins, and minerals. Patients who could not take in sufficient amounts of food were fed enterally or parentally.

Patients’ wounds were regularly examined by a physician to determine the types of topical treatments that were necessary. Interventions included tissue debridement, infection and inflammation control, maintaining moisture balance, and monitoring wound edges and epithelization. Wounds were cleaned with antiseptics or covered with hydrogel and hydrocolloid dressings to trigger autolysis.

Necrotic tissue was cleaned enzymatically, and infected wounds were rinsed with antiseptics: Octenilin Wound Gel, Schulke, Germany (Compounds: Octenidine dichlorohydrochloride; Aqua purificata; Propylene Glycol, Hydroxyethylcellulose); Octenisept solution, Schulke, Germany (Compounds: Octenidini dichlorohydrochloride 0.1%; Phenoxyethanol 2%;...
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Cocamidopropyl betaine, CAPB; sodium D-glucurate 30% solution; Glycerol 85% solution; sodium hydroxide; sodium chloride; purified water; Actelocoll W Solution/Gel, Polvet Healthcare Teodorowski SJ (Compounds: Polyhexamethylene biguanide PHMB 0.1%; carrier substances; purified water).

Additionally, skin in the wound area was cleaned with Kodan Tinktur forte solution, Schülke, Germany (Compounds: 2-Propanolum 45%; 1-Propanolum 10%; 2-Biphenylol 0.2%; hydrogen peroxide; purified water) and Skinsidept, Ecolab, Germany (Compounds: ethanol 46%; isopropyl alcohol 27%; benzyl alcohol 1%; hydrogen peroxide; purified water).

Patients with elevated leukocyte levels received antibiotics indicated by the results of microbiological culture and sensitivity tests. Topical dressings were selected depending on the stage of wound, the presence of infection, and the intensity of exudation. Clean wounds with granulation tissue were covered with dressings moistened with 0.9% sodium chloride, hydrocolloid, or polyurethane foam dressings. Wounds with necrotic tissue or considerable exudation had hydrogel or alginate dressings applied. All immobile patients received low-molecular-weight heparin.

Cathodal electrical stimulation group (CG). Patients in the CG received SWC and cathodal HVMPC delivered by the Intelect Advanced Combo unit (Chattanooga, Tennessee), generating a twin-peak monophasic pulse (154 µs) consisting of two 77-µs exponential pulses in rapid succession. Pulse frequency was 100 pps, and voltage was set above 100 V for amperage of 0.25 A that did not elicit motor reactions. The charge delivered by the electrodes was 250 µC per second. Patients participated in five 50-minute sessions a week (Monday-Friday). This protocol was adopted because of positive results of earlier clinical trials on PrUs and venous leg ulcers.

Each patient was assigned a personal set of conductive carbon-rubber electrodes. The treatment electrode (5.0 × 10.0 cm) was placed on an aseptic gauze pad saturated with physiological saline overlying the wound site, and the return electrode (10.0 × 10.0 cm) was attached to healthy skin, at least 20 cm from the PrU (on a gauze pad saturated with physiological saline).

Patients' PrUs were stimulated with the cathode once a day, in keeping with clinical studies that found that cathodal stimulation accelerated the healing of PrUs and venous leg ulcers. The results of in vitro studies show that cathodal stimulation induces electrotaxis, causing human fibroblasts, keratinocytes, microvascular endothelial cells, and epithelial cells to migrate directionally toward the cathode. The results of Bourguignon et al's in vitro study with human fibroblasts show that cathodal stimulation can increase the rate of protein and DNA synthesis. The in vivo study by Asadi et al has provided evidence that cathodal sensory-level ES increases the release of vascular endothelial growth factor in skin. In clinical trials performed by Franek et al, cathodal ES improved granulation tissue growth in VLUs. The results of cited studies lead to a conclusion that cathodal ES can promote granulation tissue formation and epithelialization.

Cathodal plus anodal electrical stimulation group (CAG). Patients in the CAG received SWC and cathodal-anodal HVMPC. The HVMPC protocols designed for the CAG and CG were only different in that the CAG received cathodal stimulation in the first week and anodal stimulation for the remaining 5 weeks.

The ES protocol for the CAG was prepared, taking into account the results of in vivo studies with animals and clinical studies showing that wounds stimulated first with the cathode and then with the anode heal more readily. In in vivo studies with animals, experimental wounds were treated by applying HVMPC and microamperage direct current (200–300 µA) for 7–15 days with cathodal stimulation being replaced after the first 3 days, with anodal stimulation for the rest of treatment. A comparison between the results obtained for the treated groups and controls (receiving sham ES or no ES) showed that in the treated groups wounds closed significantly faster, and epithelialization was more advanced and the mean number of fibroblasts at day 7 was significantly greater as well as mean tissue tensile strength at day 15. The authors of the studies also noted increased mRNA expression of collagen-I, -smooth muscle actin, and transforming growth factor-β1 as well as decreased duration of the inflammatory phase and more advanced wound proliferative and maturation phases of healing.

The authors of clinical studies applied HVMPC to VLUs and PrUs for a period of 6–22 weeks. After the first 1–2 weeks, cathodal stimulation was replaced with anodal stimulation. The duration of cathodal stimulation was adjusted, taking into account the amount of pus in the wound and the rate of granulation tissue formation. Junger et al, who used low-voltage monophasic pulsed current to treat VLUs, also adjusted the length of cathodal stimulation and anodal stimulation following changes in wound severity. After the first 1–2 weeks, cathode was replaced by anode for 3 to 10 days, and then the polarity of the treatment electrode was changed to negative again. The overall average wound treatment time was 38 days.

In our study, PrUs were of necrotic tissue with approved enzymes in preparation for the application of ES. Thus, purulence was not present in the wounds, granulation tissue was just beginning to form, and all patients received cathodal stimulation in the first week only (5 sessions). This approach is relatively similar to those used in animal studies, in which the authors applied cathodal stimulation for the first 3 days. It is also consistent with the methodology...
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of clinical trials and ensured that all patients in the CAG received uniform treatment.

Placebo electrical stimulation group (PG). In the PG, SWC and sham ES were applied. The positioning of the electrodes did not differ from that in the ES groups, and the monitor showed all parameters, but electrical current was not delivered.

All patients were treated using an ES device with 2 independent electrical circuits, of which only 1 was active. The person connecting the electrodes and selecting the polarity of the treatment electrode was the chief physical therapist. The procedure was performed in an inconspicuous manner so that neither the patient nor the medical team members could see whether real or sham ES was applied.

Amperage in the active ES groups was set to 0.25 A. The value was also displayed for the patients receiving sham ES. Active ES did not cause muscle contractions in the patients, evoking only weak tactile sensations. However most patients in all groups had tactile sensory problems and were unable to feel the current, so patients in the sham ES group were not aware of receiving sham therapy.

Sham ES in the PG and active ES in the ES groups were applied following the same protocol (a daily session of 50 minutes, 5 times a week).

Before and after each ES or placebo ES session, electrodes were sterilized in approved disinfectant solution Incidin Liquid, Ecolab, Germany (Compounds: 2-Propanolum 35%; 1-Propanolum 25%; amphoteric surface active bactericidal agents 0.375%), and with Sani-Cloth Active, Ecolab, Germany (Compounds: didecylmionium chloride 0.45%). After sessions, wounds were thoroughly cleansed with a 0.9% sodium chloride solution and covered with SWC dressings (see above).

In designing the trial, it was assumed that wound healing would be monitored in all groups for 6 weeks, ie, an average period of a patient staying in the facility. Patients hospitalized longer than 6 weeks were to receive the same treatments, and healing progress was to be assessed as before. Data obtained during the trial and the follow-up periods were subjected to the Kaplan-Meier analysis to determine the percentages of wounds that did not close in particular groups.

In patients with more than 1 PrU, all wounds were treated, but only the most severe ones were analyzed statistically.

Measures
At least 7 weekly measurements were made before the trial and after each week of treatment to evaluate each patient’s wound surface area (WSA cm²). If a PrU closed before week 6 ended, the date of closure was recorded.

To determine the surface area of the wounds (WSA), their shapes were first traced onto acetate sheets and then onto rigid, transparent film to be measured with a planimeter. The obtained data were processed by a digitizer (Mutoh Kurta XGT, ALTEK Information Technology Inc, Spokane, Washington) connected to a personal computer with software C-GEO (version 4.0, Nadowski SoftLine, Poland) that was also used for making computations and storing the results. A similar method was used by the authors of other clinical trials.

Measurement errors caused by irregular wound shapes ranged from 2.7% (PrUs 70 cm²) to 37.9% (PrUs ulcers <1 cm²). The method for calculating measurement errors has been presented in the earlier study.

Outcomes
The primary study outcome was wound severity at week 6, as indicated by percentage change in WSA (PAR6) from baseline.

PAR6 were calculated as:

$\text{PAR6} = \frac{\text{initial WSA (cm}^2\text{)} - \text{WSA (cm}^2\text{) at week 6}}{\text{Initial WSA (cm}^2\text{)}} \times 100\%$

The secondary outcome was the rate at which wound severity changed. To estimate it, the approximate amount of time that would be needed for PrU area to decrease from baseline by 50% ($T_{0.5}$) was calculated. The amount of time during which WSA was likely to decrease from baseline by 50% ($T_{0.5}$) was estimated by means of nonlinear approximation. First, to make sure that the WSA change rates were comparable regardless of treatment length, the nonlinear approximation of relative wound area ($WSA_{rel}$) was calculated:

$WSA_{rel} = WSA (t) / WSA (t = 0)$

where $WSA_{rel}$ – the relative wound area; $WSA (t) – the wound area at week’s end; $WSA (t = 0) – the baseline wound area. Accordingly, the relative wound area of a wound area of 20 cm² at week 0 (baseline) is calculated as $WSA_{rel}(0) = WSA (0) / WSA (t = 0) = 20 cm² / 20 cm² = 1$. For a wound area of 15 cm², at week 1, the relative area is $WSA_{rel}(1) = WSA (1) / WSA (t = 0) = 15 cm² / 20 cm² = 0.75 cm²$.

The nonlinear approximation was given by the following exponential model:

$WSA_{rel} = e^{\frac{t}{T_{0.5}}}$

where $t$ – week of treatment; $T_{0.5}$ – approximate time over which wound area decreases by half.

At week 6, we also calculated as secondary outcomes the percentages of PrUs that closed and the percentages of PrUs the WSA of which increased from baseline.

In planning the trial, it was assumed that changes in wound severity would be monitored for a period of 6 weeks, and that all members of the study groups remaining in the facility beyond this point would continue to receive treatment. The probabilities of wound non-closure
were estimated for all 3 groups using the Kaplan-Meier analysis and individual (real) lengths of treatment, which ranged from 3 to 17 weeks.

**Statistical Analysis**

To determine group sizes for the trial, a pilot study was prepared, in which 3 groups of 8 patients with PrUs were treated with cathodal stimulation (CG), cathodal stimulation followed by anodal stimulation (CAG), and placebo ES (PG). At week 6, percentage changes in wound surface area from baseline (PAR6) were compared between CG and PG and CAG and PG. The greatest standard deviation of PAR6 calculated for the groups (37.88%) and the smallest between-group difference for PAR6 (21.52%) indicated that statistically significant between-group differences in PAR6 could be obtained (at $P < .05$) with study groups of at least 18 participants. Because of the likelihood that some patients would withdraw from the study, we decided to add 2 extra persons to each group, which finally consisted of 20 persons.

Because wound surface areas measured at the end of treatment varied more than in the pilot study, statistical analysis focused on the relative wound area to minimize the risk of baseline interpatient differences biasing the study results. The relative wound areas were used to determine percentage change in WSA at week 6 (PAR6) and to perform nonlinear approximation to estimate the pace of changes in WSA ($WSA_\text{rel}(t)$).

To retain data of all randomly allocated participants, an intention-to-treat analysis was conducted. To account for the missing data, statistical analysis focused on the relative wound area to minimize the risk of baseline interpatient differences biasing the study results. The relative wound areas were used to determine percentage change in WSA at week 6 (PAR6) and to perform nonlinear approximation to estimate the pace of changes in WSA ($WSA_\text{rel}(t)$).

The within-group homogeneity of patients’ characteristics before treatment was tested using the 2-sided Fisher exact test, the ANOVA Kruskal-Wallis test, and the Kruskal-Wallis post-hoc test.

The between-group comparisons of mean PAR6 were made using the ANOVA Kruskal-Wallis test and Kruskal-Wallis post-hoc test.

The amount of time necessary for wound area to decrease from baseline by at least 50% was estimated using nonlinear approximation and an exponential model (1).

The percentages of PrUs that closed and the percentages of PrUs the surface area of which increased were compared between the groups at week 6 using the 2-sided Fisher exact test.

The Kaplan-Meier percentages of PrUs that did not close during treatment were compared between the 3 trial groups using the chi-square test. The within-group differences were tested for statistical significance by means of the Gehan-Wilcoxon test.

In all cases the level of significance was $P < .05$. All statistical analyses were performed by a blinded person using the Statistica software (version 10.0, StatSoft Polska Sp. z o.o.).

**Results**

Between September 21, 2014, and June 1, 2015, a group of 71 persons was screened for the trial. Eight individuals were excluded for meeting the inclusion criteria, and the remaining 63 persons were randomly allocated to the following groups: CG (23), CAG (20), and PG (20). Six patients (9.52%) dropped out before the end of treatment, but all patients were treated for 3 weeks minimum.

The flow of participants through the trial is illustrated in Figure 1.

The between-group comparisons of PAR6 and the estimations of the amount of time during which PrUs might decrease by half (non-linear approximations) were made using data on all patients, including those who dropped out from the study (63 patients). In the Kaplan-Meier analysis the actual data were used because this analysis can be performed on the base of complete observations (closed wounds) and cut-off observations (patients who drop out of the study).

**Baseline Characteristics**

The demographic and wound characteristics of patients in the 3 comparative groups show (Tables 1 and 2) that at baseline the groups were not statistically significantly different for any of the considered variables.

The sample consisted of 52 female patients (82.53%) and 11 male patients (17.46%) aged 60 to 95 years, mostly older than 80 years (35; 55.51%) were immobile. Forty-one patients (65.08%) were malnourished. Forty-one patients (65.08%) were diagnosed with generalized atherosclerosis, 27 (42.86%) had type 2 diabetes (HbA1C < 7%), and 24 (38.09%) were cerebral stroke patients. In 19 malnourished patients (30.16%), nutrition therapy was applied.

The patients had a total of 63 PrUs ranging in size from 0.5 to 39.10 cm$^2$; 36 PrUs were Category II (57.14%), 25 Category III (39.68%), and 6 Category IV (9.52%). Thirty-seven (58.73%) developed in Category II, 11 (17.46%) aged 60 to 95 years, most

**Research Funding Source**

The study was funded by the Academy of Physical Education.
ischial tuberosity, and 16 (25.4%) on the trochanter. Sixteen patients (25.4%) had multiple PrUs, and in 37 (58.73%) recurrent PrUs were diagnosed. The pre-trial duration of patients’ PrUs was 1–8 months, mostly 1–3 months (36; 57.14%).

The groups did not differ at baseline for any patients’ characteristics (\( P > .05; \) Tables 1 and 2).

**Primary outcome.** The cumulative change indicated by PAR6 was 82.34% (95% CI 70.06-94.63) in the CG, 70.77% (95% CI 53.51-88.04) in the CAG, and 40.53% (95% CI 23.60-57.46) in the PG. Results obtained for CG were statistically more significant than those obtained for PG. The CG and CAG were not statistically significantly different from each other (Table 3).

**Secondary outcomes.** According to nonlinear approximation results, in the CG WSA would decrease from baseline by half (\( T_{1/2} \)) over 1.92 (95% CI 1.62-2.23) week of treatment, 2.60 (95% CI 2.08-3.13) weeks in the CAG, and 10.60 (95% CI 7.25-13.95) in the PG. The analysis of confidence intervals for \( T_{1/2} \) showed that the periods were statistically significant different between CG and PG and between CAG and PG, but not between CG and CAG (Figure 2; eTable, available at academic.oup.com/ptj).

More PrUs closed during the 6 weeks of treatment in the CG (11 of 23 = 47.83%) and the CAG (9 of 20 = 45%) than in the PG (0 of 20 = 0%); \( P = .013 \) and \( P = .045 \), respectively. The percentages of PrUs that closed in the CG and CAG were not statistically significantly different (\( P = .48 \)). Measurements at week 6 showed that unlike the CG, where no PrUs had increased in size from baseline, in the CAG and PG 1 and 2 PrUs, respectively, were larger. The differences between groups were not statistically significant (\( P > .05 \)).

CG accounted for the smallest ratio of PrUs that did not close (Figure 3) and PG for the highest. CG and CAG were not statistically significantly different in that respect. Statistically significant differences were found between CG and PG and between CAG and PG in favor of CG and CAG. The result of the chi-square test for all 3 groups was \( P < .01 \). The results of between-group comparisons made with
Table 1.
Baseline Patient Characteristics (No. of patients = 63)\textsuperscript{a}

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cathode ES group (n = 23)</th>
<th>Cathode + anode ES group (n = 20)</th>
<th>Placebo ES group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender [n (%)]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>17 (73.91%)</td>
<td>18 (80%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (26.09%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Age [years]: Average (SD)</td>
<td>79.35 (8.48)</td>
<td>79.65 (11.44)</td>
<td>77.55 (12.24)</td>
</tr>
<tr>
<td>No. of people in age [years (%)]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69 years</td>
<td>2 (8.7%)</td>
<td>4 (20%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>70–79 years</td>
<td>9 (39.13%)</td>
<td>4 (20%)</td>
<td>5 (25%)</td>
</tr>
<tr>
<td>≥80 years</td>
<td>12 (52.17%)</td>
<td>12 (60%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>BMI [no. of patients (%)]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &gt; 30</td>
<td>2 (8.7%)</td>
<td>3 (15%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>BMI &lt; 19</td>
<td>2 (8.7%)</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Unable to change position unaided [no. of patients (%)]:</td>
<td>18 (78.26%)</td>
<td>16 (80%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Concomitant diseases [no. of patients (%)]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General atherosclerosis</td>
<td>15 (65.22%)</td>
<td>11 (55%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Diabetes (HbA1C &lt; 7%)</td>
<td>10 (43.48%)</td>
<td>11 (55%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>Cerebral strokes</td>
<td>7 (30.43%)</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>No. of patients with malnutrition (%)</td>
<td>7 (30.43%)</td>
<td>5 (25%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>No. of patients with multiple PrUs (%)</td>
<td>7 (30.43%)</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

\textsuperscript{aBMI = body mass index, PrUs = pressure ulcers.}

Table 2.
Baseline PrU Characteristics (No. of patients = 63)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cathode ES group (n = 23)</th>
<th>Cathode + anode ES group (n = 20)</th>
<th>Placebo ES group (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WSA of PrUs [cm\textsuperscript{2}]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>9.59 (10.48)</td>
<td>7.37 (5.95)</td>
<td>8.90 (7.21)</td>
</tr>
<tr>
<td>Duration of PrUs [months]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean (SD)</td>
<td>2.41 (1.68)</td>
<td>2.65 (2.20)</td>
<td>3.03 (2.22)</td>
</tr>
<tr>
<td>No. of PrUs of duration (%):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 months</td>
<td>14 (60.87%)</td>
<td>12 (60%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>3.1–6 months</td>
<td>7 (30.43%)</td>
<td>6 (30%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>6.1–12 months</td>
<td>2 (8.7%)</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>PrU severity according to NPUAP scale [no. of patients (%)]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Category II\textsuperscript{a}</td>
<td>12 (52.17%)</td>
<td>11 (55%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Category III\textsuperscript{a}</td>
<td>9 (39.13%)</td>
<td>6 (30%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>Category IV\textsuperscript{a}</td>
<td>2 (8.7%)</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Location [no. of PrUs (%)]:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sacrum</td>
<td>11 (47.83%)</td>
<td>13 (65%)</td>
<td>13 (65%)</td>
</tr>
<tr>
<td>Ischial tuberosity</td>
<td>4 (17.39%)</td>
<td>3 (15%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Trochanter major</td>
<td>8 (34.78%)</td>
<td>4 (20%)</td>
<td>4 (20%)</td>
</tr>
</tbody>
</table>

\textsuperscript{aPrU(s) = pressure ulcer(s), WSA = wound surface area, NPUAP = National Pressure Ulcer Advisory Panel.}

the Gehan-Wilcoxon test were $P = .64$ (CG vs. CAG); $P < .01$ (CG vs. PG); and $P < .01$ (CAG vs. PG).

**Discussion**

**Statement and Principal Findings**

The trial has showed that in elderly persons an SWC program enhanced by HVMPC can reduce PrU surface area statistically significantly more than SWC alone. In both groups receiving electrical stimulation PrUs decreased by half statistically significantly faster, more PrUs closed by the end of treatment (week 6), and the probability of PrUs not closing within a period of 3 to 17 weeks was lower (Kaplan-Meier Analysis) than in the placebo group. This supports our hypothesis that SWC combined with HVMPC programs is more effective in treating PrUs than SWC alone.

The results of in vitro and in vivo studies show that the polarity of the
treatment electrode is important to wound healing, but protocols specifying how the cathode and the anode should be applied to chronic wounds in humans are yet to be developed. In this trial, 1 group received cathodal stimulation for 6 weeks, and in the second group cathodal stimulation was replaced after the first week with anodal stimulation, which was applied for the remaining 5 weeks. Treatment results between groups treated with HVMPC were not statistically significantly different, which supports the second hypothesis stating that cathodal stimulation applied to PrUs for a period of 6 weeks and cathodal stimulation used in the first week and anodal stimulation during the next 5 weeks offer similar therapeutic effects.

Clinical studies comparing the influence of cathodal and cathodal plus anodal HVPMPC on the healing of PrUs are not available, but according to some reports both types of ES can be effective. For instance, Griffin et al, Houghton et al, and Polak et al chose cathodal stimulation to treat PrUs and VLUs. Franek et al treated wounds using cathodal stimulation during the first 1–3 weeks (VLUs) and 1–2 weeks (PrUs). In both studies, it was replaced by anodal stimulation until treatment end. Houghton et al treated PrUs with cathodal stimulation in the first week and then changed polarity every 3 days or, depending on healing progress, used cathodal stimulation during the first 1–2 weeks, anodal stimulation for the next 3–10 days, and then changed polarity to negative again.

The authors of many studies who treated PrUs and VLUs with low-voltage rectangular monophasic pulsed current also used the cathode and anode as the treatment electrode, always starting therapy with cathodal stimulation. They changed the polarity of the treatment electrode every 3 days or, depending on healing progress, used cathodal stimulation during the first 1–2 weeks, anodal stimulation for the next 3–10 days, and then changed polarity to negative again.
Notwithstanding this variety of protocols, positive effects of ES are consistently reported. This seems to imply that the polarity of the treatment electrode can be selected for the stage of wound healing rather than following a standard protocol.

Both in vitro and in vivo studies have demonstrated that the cathode and anode can induce electrotaxis, causing cells important for wound healing to travel toward the wound. Anodal stimulation facilitates the electrotaxis of macrophages and neutrophiles for autolysis and reactivation of the inflammatory phase of healing, as well as promoting the electrotaxis of vascular fibroblasts, vascular smooth muscle cells, and umbilical vein endothelial cells for angiogenesis.

Fibroblasts, keratinocytes, microvascular endothelial cells, and epithelial cells migrate toward the cathode, which enhances the proliferative phase of wound healing.

Becker has found anodal stimulation to be able to amplify the local positive injury content. In the in vivo study by Talebi et al, the anode restored wound potential in acute skin wounds to the preinjury level and acute skin wounds closed faster. Borba et al have observed in rats improved neangiogenesis in the early stage of acute wound healing under the influence of anodal stimulation.

The authors of in vitro studies have shown that cathodal stimulation improves collagen synthesis in fibroblasts and in vivo studies its ability to increase the release of vascular endothelial growth factor in skin has been demonstrated.

Reports from in vivo studies where a combination of cathodal and anodal stimulation was used point to faster wound epithelialization and greater wound tensile strength, as well as to increased mRNAs expression of collagen-1, α-smooth muscle action, and transforming growth factor-β1. In the study by Demir et al, cathodal stimulation followed by anodal stimulation reduced the number of polymorphonuclear leukocytes, macrophages, and mast cells in the wounds, thus...
shortening the inflammatory stage. By increasing the number of fibroblasts and stimulating collagen synthesis and maturation, they also supported wound proliferation and remodeling.

**Strengths and weaknesses of the study.** The main strengths of the trial include the blinding of the research team (physicians, nurses, physical therapists), the person measuring WSA, and the statistician; the trial participants were hospitalized, so PrU prevention measures and treatment could be uniformly applied under the supervision of the medical staff and the ES protocol was consistently observed; valid and reliable acetate tracings were used to measure wound sizes; the drop-out rate was relatively low; and in the intention-to-treat analysis the exponential regression function was used, with which WSA decreases can be precisely represented.

**Limitations**

The major limitation of the trial is that most PrUs were treated not longer than 6 weeks. The period was too short for all PrUs to close. Consequently, we could not determine how long cathodal or cathodal+anodal HVMPC should be applied to cause the closure of Category II-IV PrUs. Monitoring the healing of patients' PrUs after the trial was not possible either, because some were discharged from the hospital to be treated at homes, and a number of others were moved to other wards for treatment for concomitant diseases.

The PrU prevention and treatment program for all 3 groups generally followed the same best practice recommendations, but its specific solutions addressed the needs of individual patients. The blinding rate of patients and assessors was not assessed.

**Strengths and weaknesses in relation to other studies; important differences in results.** Our results are consistent with the results obtained by other researchers treating PrUs with HVMPC, but its specific solutions addressed the needs of individual patients. The blinding rate of patients and assessors was not assessed.

The primary research outcome in our trial was percentage decrease in wound surface area, which was also used in other clinical studies to evaluate the efficacy of wound treatment. We found the WSA of Category II-IV PrUs to be smaller at week 6 by 82.34% and 70.77% in the cathodal ES group and the cathodal+anodal ES group, respectively. These results are comparable with the results obtained by other authors who also used HVMPC. Griffin et al described 80% decrease in the area of Category II-IV PrUs after 3 weeks of cathodal ES. Polak et al reported an 80.31% decrease in the area of Category II-III PrUs after 6 weeks of cathodal ES. In Franek et al and Polak et al, studies on Category II-IV PrUs, 6 weeks of intervention with cathodal+anodal ES, yielded PAR of 88.9% and 76.19%, respectively. Sixteen Category II-IV PrUs (mostly Category III-IV PrUs (93.73%)) in Houghton et al decreased after 12 weeks of treatment with cathode plus anode by an average of 70.0%.

The reviews of clinical studies point also to wound closure as another important surrogate endpoint. In our trial, 47.83% (CG) and 45% (CAG) of PrUs treated with HVMPC closed after 6 weeks (mostly Category II PrUs and only 1 Category III-IV PrU in each ES group). In the study by Houghton et al, 37.5% of PrUs closed after 12 weeks of treatment, but it needs to be noticed that in the ES group as much as 81.25% of them were Category III-IV. In this study, Category III-IV PrUs accounted for 47.83% and 40% in the CG and CAG, respectively.

**Significance of the Study: Possible Explanations and Implications for Clinicians and Policymakers**

Our HVMPC protocol was designed following those used by other authors. The sterilized treatment electrode was placed on the wound and the return electrode on intact periwound skin about 20 cm from the wound edge. The electrodes were separated from the tissue by sterile gauze pads moistened with physiological saline to improve electrical conductivity and maintain moist wound environment.

HVMPC with twin-peaked pulses of 154 μs, frequency of 100 pps, 0.25 A, and electric charge of 250 μC/sec in the voltage range from 100 to 150 V that we and other authors selected to treat PrUs, venous leg ulcers, and diabetic foot ulcers is reported to be effective. Following the protocols used by other researchers, we applied amperage that only caused sub-motor reactions.

Most authors treated PrUs with HVMPC for 45–60 minutes, once a day, 5–7 days a week, so the total duration of ES in their studies ranged from 3.75 to 7 hours per week. Our sessions were similar in duration (50-minutes 5 days/week; total treatment time of 4.16 hours of a week).

**Side effects.** Neither we nor other researchers found HVMPC to have adverse effects.

Our patients, elderly individuals at high risk of PrU development, were relatively similar at baseline regarding wound healing determinants such as age, wound duration, severity, and size. The treatment we applied proved effective despite these unfavorable circumstances. Patients in the ES groups received also an interdisciplinary wound management program consistent with the best practice guidelines on PrU treatment.

**Unanswered questions and future research.** There are many preclinical studies, the results of which show that the polarity of the treatment electrode is important in treating chronic wounds. Our clinical trial appears, however, to be the first one that compares the healing of PrUs treated with HVMPC delivered according to 2 different polarity protocols. Further clinical studies are necessary to determine how the specific polarity of the treatment electrode influences wound healing processes.

**Conclusions**

Our trial has shown that HVMPC (154 μs; 100 pps; 150 V; 250 μC/sec) applied 50 minutes a day, 5 times a week, with the cathode as the only treatment electrode or the cathode in the first week and then the anode, is effective in treating Category II-IV PrUs. Both types of ES reduced the surface area of PrUs and accelerated their healing.
Electrical Stimulation With Cathodal Versus Cathodal Plus Anodal Polarities for Pressure Ulcers

Our results are consistent with the results of other researchers who found HVMPC to improve the healing of chronic wounds, including PrUs.

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Disclosures

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

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