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Electrostimulation: Current Status, Strength of Evidence Guidelines, and Meta-Analysis

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Abbreviations and Acronyms

DFU = diabetic foot ulcers

EBM = evidence-based medicine

EF = electric field

EPUAP = European Pressure Ulcer Advisory Panel

ES = electrical stimulation

ET = electrotherapy

NPUAP = National Pressure Ulcer Advisory Panel

PAR4 = percentage area reduction in 4 weeks

PU = pressure ulcers

RCT = randomized controlled trial

SR = systematic review

SWC = standard wound care

TEP = transepithelial potential

VLU = venous leg ulcers

Significance: Delayed healing of skin wounds is a serious problem for the patients, clinicians, and society. The application of interventions with proven effectiveness to increase wound healing is relevant.

Recent Advances: This article summarizes the results of effect studies with the application of electrostimulation (ES) as additional treatment to standard wound care (SWC). Therefore, five published narrative reviews are discussed. In addition, 15 studies with a clear randomized controlled trial design are analyzed systematically and the results are presented in four forest plots. The healing rate is expressed in the outcome measure percentage area reduction in 4 weeks of treatment (PAR4). This leads to a continuous measure with mean differences between the percentage healing in the experimental group (SWC plus ES) and in the control group (SWC alone or SWC plus placebo ES). Adding ES to SWC in all wound types increases PAR4 by an extra 26.7% (95% confidence interval [CI] 15.6, 37.8); adding unidirectional ES to SWC increases PAR4 by 30.8% (95% CI 20.9, 40.6) and adding unidirectional ES to the treatment of pressure ulcers increases PAR4 by 42.7% (95% CI 32.0, 53.3).

Critical Issues: There is a discrepancy between the proven effectiveness of ES as additional treatment to SWC and the application of ES in real practice. Possible drawbacks are the lack of clinical expertise concerning the proper application of ES and the extra time effort and necessary equipment that are needed.

Future Directions: Clinicians concerned about the optimal treatment of patients with delayed wound healing should improve their practical competency to be able to apply ES.

SCOPE AND SIGNIFICANCE

CHRONIC WOUNDS ARE a serious problem for patients, clinicians, and society. This review focuses on the clinical effectiveness and practicality of the application of electrostimulation (ES) as an additional treatment in wound care.

Electrotherapy (ET) is sometimes defined in a broad way gathering all modalities developed with an electrical apparatus that is applied to a patient with therapeutic objectives (like ultrasound, laser, shortwave, or shockwave therapy); however, in this review, ET is defined in a smaller way

meaning those therapies that apply an electrical stimulus to the patient. ET can be classified in three categories: low frequency (<1,000 Hz), medium frequency (1,000–300,000 Hz), and high frequency (>300,000 Hz). Stimulation of neuromuscular tissues is just possible with low- and medium-frequency ET and that is why these forms are also indicated as ES. In this review, the effectiveness of low-frequency ES on wound healing is evaluated. In low-frequency ES, at least two electrodes are attached to the body to realize an electric circuit leading to an internal electric field

(EF) with physiological responses of the body. The placement of the electrodes is often one in the wound and the other one opposite to it or with both electrodes just around the wound. Two forms of low-frequency ES should be distinguished; unidirectional ES with a fixed cathode (negative pole) and anode (positive pole) leading to an EF in the same direction, or bidirectional ES with biphasic pulses and with alternating cathode and anode and an also alternating EF.

The effectiveness of different types of ES (unidirectional and bidirectional ES) on different wound types as pressure ulcers (PU), venous leg ulcers (VLU), and diabetic foot ulcers (DFU) will be described by summarizing the results presented in effect studies with high methodological quality.

TRANSLATIONAL RELEVANCE

Basic science research has shown that in living organisms, endogenous EFs play a vital role in the regulation of several physiological processes, including wound healing. Well-known measurable electrical phenomena include action potentials in the neuromuscular system, positioning of proteins in connective tissue, electroencephalogram, electrocardiogram, and electroretinogram. Mammalian skin layers have voltage gradients, which in the case of a skin wound lead to the development of the transepithelial potential (TEP) that plays a leading role in the generation of the endogenous integumentary EF.^{1,2} The EF has a stimulating effect on epidermal stem cells relevant for wound healing.^{3,4}

CLINICAL RELEVANCE

Chronic wounds of the skin and subcutaneous tissues are often a significant problem for patients in that, they often contribute to decreased mobility, wound-related pain, and infection. The costs for caring of chronic wounds in many societies have reached almost insurmountable levels.⁵ In the industrialized world, the high prevalence of chronic wounds is significantly related to aging and to the higher occurrence of comorbidities like diabetes mellitus and stroke. Unfortunately, it appears that the number of people with chronic wounds will continue to increase. The application of interventions with proven effectiveness and efficacy is relevant.

DISCUSSION OF FINDINGS AND RELEVANT LITERATURE

Current status

Levels of evidence. In 2011, the Oxford Center of Evidence Based Medicine (EBM) published the

new version of the GRADE system for classifying the levels of external evidence.⁶ For interventions like ES used in the treatment of chronic wounds, five levels of evidence are distinguished; the highest level 1 means that a systematic review (SR) of several effect studies with a proper randomized controlled trial (RCT) design is available. Level 2 evidence is based on studies with the RCT design, level 3 on controlled, but nonrandomized studies, level 4 on case series or case-control studies, and level 5 on mechanism or theory-based therapy.

An SR is based on a thorough literature search, applies clear criteria to include studies, weighs the studies for methodological quality and for possible risk of bias, and performs the analysis and statistical pooling with transparent and valid methods. An SR ends with a recommendation for clinical practice; sometimes a clear recommendation can be formulated; but very often it is, due to inconsistent results described in the effect studies, not possible to come up with a clear overall result. At the Cochrane website (www.cochrane.org [the main source for SRs]), about 25 SRs on topical treatments for wound healing can be assessed. Evaluating reviews concerning several topical wound treatments leads to the conclusion that at best, no clear evidence is available for most of the treatments like dressings,^{7,8} silver,^{9,10} honey,¹¹ negative pressure treatment,¹² or ultrasound therapy.¹³ In fact, only two clear conclusions are made; in VLU, compression improves healing¹⁴ and cleaning a wound with tap water does not increase the chance for contamination.¹⁵

Quality of effect studies regarding bioelectric fields and wound healing. Searching the scientific literature leads to the positive conclusion that, in this field, a sufficient number of studies are performed. That counts for fundamental research on the rationale of ES for wound healing, for uncontrolled case studies as well for effect studies with the RCT design. In the next paragraph, the published reviews will be discussed; at the moment, there is no SR available.

Availability and quality of reviews. Recently, a number of narrative reviews have been published concerning the topic, "Does ES stimulate wound healing?"¹⁶⁻²⁰ Four of the five review authors evaluated the effects of ES to be positive and consider ES as a "potentially useful, accessible, and cheap intervention,"¹⁸ but "further research is desired."^{16,19} Only the judgment of Collins *et al.*²⁰ is less positive. Including 13 studies with the RCT design, the authors conclude that they "...failed to

find statistically significant differences in wound healing between patients treated with ES and controls in the majority of reports.”²⁰ All five reviews have a narrative design, which means (1) they are written by experts, (2) studies are included without clear selection criteria, (3) studies are evaluated without transparency in the research methodology, and (4) conclusions are still based on authority and have nonoptimal generalizability. Narrative reviewing is a reason why different reviews reviewing the same topic, sometimes even based on the same effect studies, can arrive at different interpretations and conclusions. In the next paragraph, a SR on the effects of ES on the acceleration of wound healing is described.

Translation to guidelines. Despite the fact that many good quality studies are available in most clinical guidelines, ES is not mentioned as one of the options for proper treatment. An exception has to be made for the guideline for PU, the type of wound that is most frequently studied. The combined European Pressure Ulcer Advisory Panel (EPUAP)/National Pressure Ulcer Advisory Panel (NPUAP) reference guideline is clearly positive about the application of ES to improve the healing of PU.²¹ In that guideline for clinicians, the strength of evidence is classified from A (strong) to B (moderate) and C (weak), and on page 35, the application of ES is described as follows: “..... consider the use of direct contact ES in the management of recalcitrant stage II, as well as stage III and IV PU to facilitate wound healing (strength of evidence = A).”

New systematic analysis of studies on healing rate

Selection of high-quality effect studies. A literature search in the available databases like Medline, Embase, and Cinahl was performed with appropriate search/MESH terms. All chronic wound types were included, the intervention had to be low-frequency ES, the design was RCT, and the primary outcome measure was the healing rate.

The authors were very strict to categorize a study as an RCT study only if the study states that the allocation was random. The precise method of randomization need not be specified. Procedures such as coin-tossing and dice-rolling should be considered as random. Quasi-randomization allocation procedures such as allocation by hospital record number, birth date, participating institute (in a multicenter study), or alternation, do not satisfy this criterion.

To be sure to select only high-quality RCTs, we further applied the inclusion and exclusion criteria listed in Table 1.

This very strict selection, independently performed by two authors, led to the inclusion of 15 high-quality studies.^{22–36} The analysis is described in the next section.

Expression of healing rates in percentage area reduction in 4 weeks. The 15 RCTs have treatment times ranging from 3 weeks to 16 weeks (average treatment time is 6.5 weeks; most of the time with five treatments per week) and the studies describe the wound surface in cm² at the start of the study (A0) and at the end of the study (A1). In this review, the percentage area reduction (PAR) will be used to express the healing rate. The PAR is a sensitive measure that corrects for possible differences in the initial wound surface area.³⁷ PAR is calculated as $[(A0 - A1)/A0] \times 100\%$, where in A0 is the initial wound area and A1 the wound area at the end of the treatment period.

Clinicians are advised to use the PAR at 4 weeks as a relevant predictor for wound closure, so in this review, the percentage area reduction in 4 weeks (PAR4) is used as a continuous outcome measure.^{38–40} Expressing healing rates in PAR4 values makes it possible to compare the effects of different studies with different treatment periods. The information in the 15 RCTs was good enough allowing the authors of this review to calculate the PAR4 values from the original data.

Analysis of PAR4 leads to a weighted mean difference between ES groups (standard wound care [SWC] plus ES) and control groups (SWC with

Table 1. The inclusion and exclusion criteria for effect studies with randomized controlled trial design to enter the systematic review

Inclusion Criteria	Exclusion Criteria
Good RCT design, experimental group with SWC plus ES and control group of the same SWC without ES or with sham ES	No selection bias (random sequence generation and concealed allocation)
Appropriate blinding of observers who perform the measurement	No reporting bias, so methods paragraph and results paragraph are consistent
Clear description of the form of ES	Loss to follow-up larger than 20%
Number of wounds, at least 20	Involvement of ES manufacturers

ES, electrostimulation; RCT, randomized controlled trial; SWC, standard wound care.

placebo ES or SWC alone). Wounds with poor healing progress at 4 weeks were highly likely to remain unhealed after 8 weeks of additional treatment. Cardinal *et al.*⁴⁰ analyzed retrospectively the effects of topical wound care in 306 VLU and 241 DFU and found the following characteristics of PAR4 as a predictor of complete ulcer healing at 12 weeks. Selecting a cutoff point of PAR4=37.7%, the positive predictive value for complete healing was 70.6% and the likelihood ratio was 6.15; meaning that patients (wounds) who reach at least PAR4 37.7% have a 6.15 greater chance of total healing in 12 weeks than wounds that do not reach a PAR4 of 37.7%.

In the Supplementary Data (available online at www.liebertpub.com/wound), the calculations for the PAR4 in the 15 studies and the standard deviations for those new PAR4 samples are presented. The method of calculation is described. Table 2 presents the PAR4 values of the 15 included studies.

Results of the meta-analysis. The descriptive statistics in Table 2 shows that the 379 wounds treated with SWC (SWC alone or SWC combined with placebo ES) reduced their surface area in 4 weeks of treatment by 29.3%. Needless to say, many variables have an influence on wound healing, for example, ulcer duration, initial surface area, and comorbidities are prognostic factors related to treatment results; so different studies include different patients with different wounds and

different results. PAR4 values vary from 3.0%³³ to 56.4%³²; both studies concern VLU, but Junger *et al.*³³ included wounds with a mean duration of 42 months, whereas Jankovic *et al.*³² included wounds with a mean duration of 10 weeks. The mean PAR4 in the 15 studies that applied ES was 57.0%; so the application of additional ES increases wound reduction by an extra 27.7%. The forest plot of these comparisons, all wounds with all types of ES with SWC+ES and SWC alone is presented in Fig. 1.

Fig. 1 shows that 14 of 15 studies have a positive mean difference (mean wound reduction of SWC with additional ES—mean wound reduction of SWC alone). In seven studies, the 95% confidence interval is completely positive (above 0), meaning that the probability that the increased healing is based on coincidence is smaller than 5% ($p < 0.05$). The sum of the mean differences divided by the number of studies is +26.7% with a 95% confidence interval of +15.6 to +37.8%, meaning that this difference in favor of ES is both clinically relevant (it almost doubles the healing rate) and statistically significant ($p < 0.05$). Many factors like wound prognosis, type of skin wound, duration at the start, type of ES, ES stimulus characteristics, possible comorbidities, and method of measurement have an influence on the results, so heterogeneous results can be predicted. This clinical heterogeneity caused by the above-mentioned differences in clinical trials can also lead to statistical heterogeneity. Statistical heterogeneity quantifies if the amount of differences between the

Table 2. Details of the 15 included randomized controlled trial studies

Characteristics of RCT Studies						Exp (SWC+ES)		Control (SWC – ES)	
Ref.	Study, Year of Publication	N total	Type of Ulcer	Type of ES	Weeks	N Exp.	PAR4 (%)	N Ctr.	PAR4 (%)
22	Ahmad, 2008	60	PU	Uni	5	45	62.35	15	20.76
23	Baker/Rubayi, 1996	192	DFU	Bi	4	125	38.49	67	51.00
24	Baker/Chambers, 1997	114	PU	Bi	4	61	64.77	53	41.78
25	Barczak, 2001	33	PU	Uni	4	16	69.21	17	44.04
26	Carley, 1985	30	Mixed	Uni	5	15	83.46	15	37.92
27	Feedar, Kloth, 1991	50	Mixed	Uni	4	26	56.18	24	32.82
28	Franek, 2006	55	VLU	Uni	7	28	42.05	27	28.27
29	Franek, 2012	50	PU	Uni	6	26	68.83	24	23.24
30	Houghton, 2003	42	VLU	Uni	4	22	44.30	20	16.00
31	Houghton, 2010	34	PU	Uni	12	16	37.02	18	13.83
32	Jankovic, 2008	43	VLU	Bi	3	24	89.62	19	56.42
33	Junger, 2008	39	VLU	Uni	16	20	15.11	19	3.04
34	Peters, 2001	40	DFU	Uni	12	20	56.09	20	34.17
35	Petrofsky, 2010	20	DFU	Bi	4	10	68.40	10	30.10
36	Wood, 1993	74	PU	Uni	8	43	60.37	31	6.77
	Total/average	876	PU: 6 VLU: 4 DFU: 3 Mixed: 2	Uni: 11 Bi: 4	6.53	497	57.08	379	29.34

Ctr, control group; DFU, diabetic foot ulcers; Exp, experimental group; PAR4, percentage area reduction in 4 weeks; PU, pressure ulcers; VLU, venous leg ulcers.

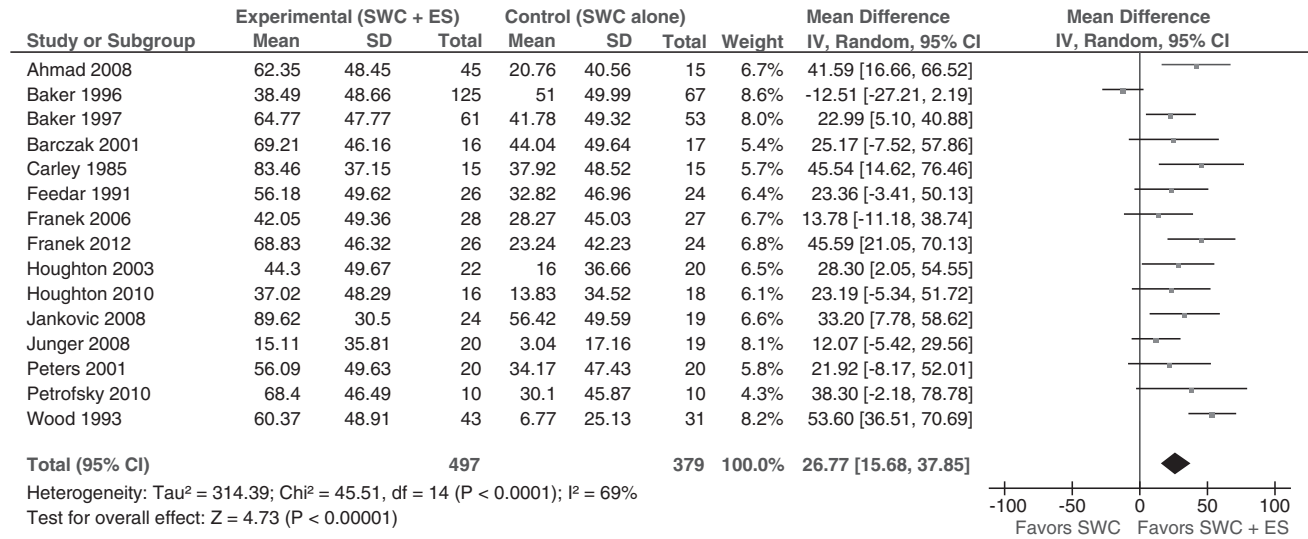


Figure 1. Forest plot with the results of all 15 studies (left column)²²⁻³⁶ on all wound types comparing the mean differences between the experimental group (SWC plus ES) and the control group (SWC alone or SWC plus placebo ES). ES, electrostimulation; SWC, standard wound care; CI, confidence interval.

results of effect studies is larger than one would expect is based on coincidence (random error). To determine the statistical heterogeneity, the Chi² test is included to assess whether differences are based on coincidence or not; in case of a low *p*-value (*p* < 0.1), the differences are not based on coincidence, but statistical heterogeneity is present.⁴¹ Another way to quantify inconsistency is to determine the I² test by relating the Chi² to the number of included effect studies (I² = [Chi² - n/Chi²] × 100%); if I² is higher than 50%, substantial heterogeneity is present.⁴² So, in fact, analyzing different clinical studies in a context of healing wounds with many variables, a certain amount of heterogeneity is inevitable. Strategies to address heterogeneity are the application of a more con-

servative random effects meta analysis.⁴¹ In addition, the challenge is rising to evaluate if heterogeneity disappears in stratified subgroup analyses. The type of ES waveform (unidirectional or bidirectional) is one of the key factors that influences the results and the fact that the rationale for ES is more related to unidirectional ES, stratified analyses were performed with the 11 RCT studies that applied unidirectional ES and the 4 studies that applied bidirectional ES (Table 2, 5th column). The forest plots for both ES waveform types are presented in Figs. 2 and 3 and show that the results of unidirectional ES (extra PAR4 = 30.8%; 95% confidence interval [CI] 20.9, 40.6) are clearly better than for bidirectional ES (extra PAR4 = 18.3%; 95% CI - 7.1, 43.7). In the analysis

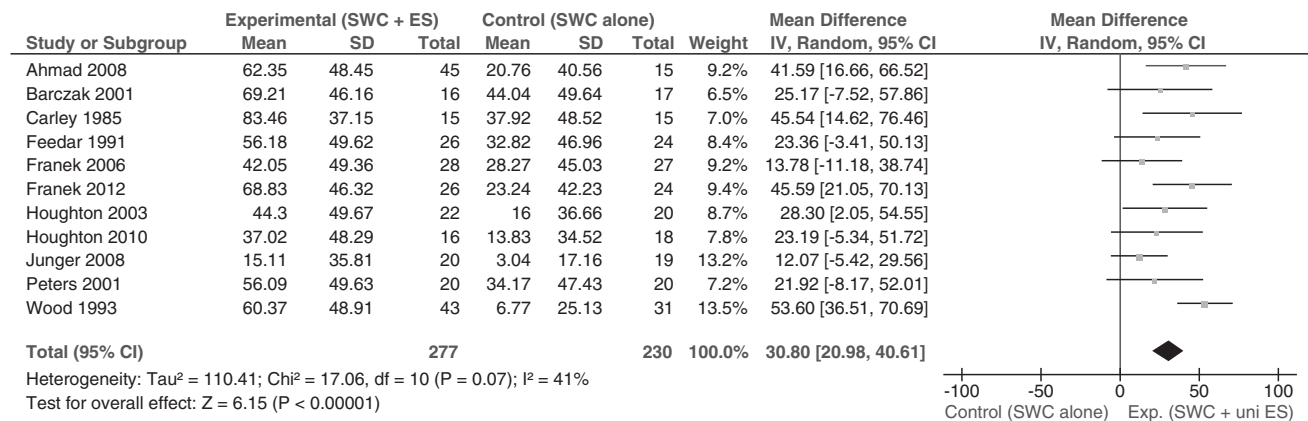


Figure 2. Forest plot with the results of the 11 studies (left column)^{22,25-31,33,34,36} that applied unidirectional ES on all wound types comparing the mean differences between the experimental group (SWC plus ES) and the control group (SWC alone or SWC plus placebo ES).

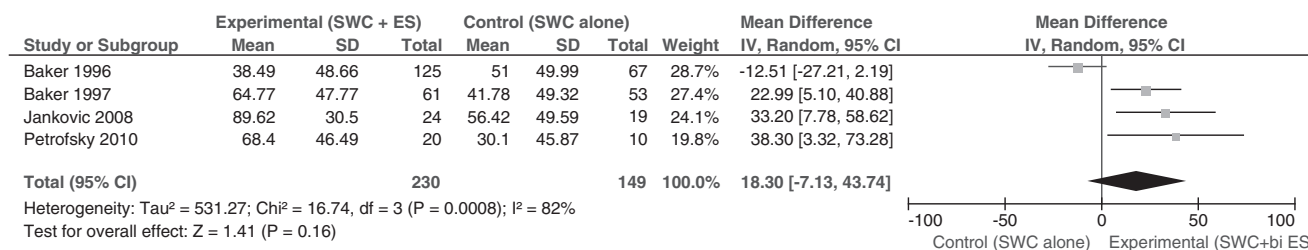


Figure 3. Forest plot with the results of the four studies (left column)^{23,24,32,35} that applied bidirectional ES on all wound types comparing the mean differences between the experimental group (SWC plus ES) and the control group (SWC alone or SWC plus placebo ES).

of unidirectional ES in all wound types (Fig. 2), heterogeneity is decreased ($p = 0.07$; $I^2 = 41\%$), but the analysis is still performed randomly.

The most evaluated wound type is PU. Table 2 (4th column) shows six RCTs, where ES was used in the treatment of PU, five studies applied unidirectional ES (Ahmad 2008, Barczak 2001, Franek 2012, Houghton 2008, Wood 1993), and one study applied bidirectional ES (Baker 1997). The forest plot of that compared SWC plus additional unidirectional ES with SWC without unidirectional ES is presented in Fig. 4 and shows homogeneous results ($p = 0.34$, $I^2 = 12\%$; fixed analysis performed) of an extra wound-healing effect of 42.7% after 4 weeks treatment with unidirectional ES (95% CI 32.0, 53.3).

The mean PAR4 in the SWC group was 21.6%, whereas the mean PAR4 in the SWC + unidirectional ES was 59.5%. In the forest plot with corrections for the weight of the studies, the mean difference was more than 40%. In all five studies, the unidirectional ES was applied with the active electrode directly in the wound.

Discrepancy between current status/evidence and practical use

Based on a large number of RCTs, five reviews and the analysis described in paragraph 3, ES is

an intervention with satisfying external evidence. Nonetheless, in wound-healing practice settings, ES is not generally used in a systematic way and also appears not to be an important topic described in guidelines or presented at plenary sessions at wound-healing congresses. In EBM, there are, beside external evidence, two other factors described: clinical expertise and expectations and preferences of practitioners and patients.⁴³ If a practitioner is uncertain as to how to apply an intervention, and is not familiar with the theory and practice of that intervention and if patients and practitioners have no experience, there also are no positive expectations. These two last mentioned factors of EBM can hinder an intervention with just convincing external evidence as the main characteristic. In daily practice, other factors have a significant influence on the choice of interventions included in the treatment plan. Factors like having the proper equipment plus accessories, is the treatment time sufficient to use the intervention, can the patient or partner of the patient apply the intervention, and is the patient's insurance plan willing to pay for the intervention, are all important issues in the clinical reasoning process.

Many of these accompanying factors negatively effect whether ES will be utilized for wound-healing

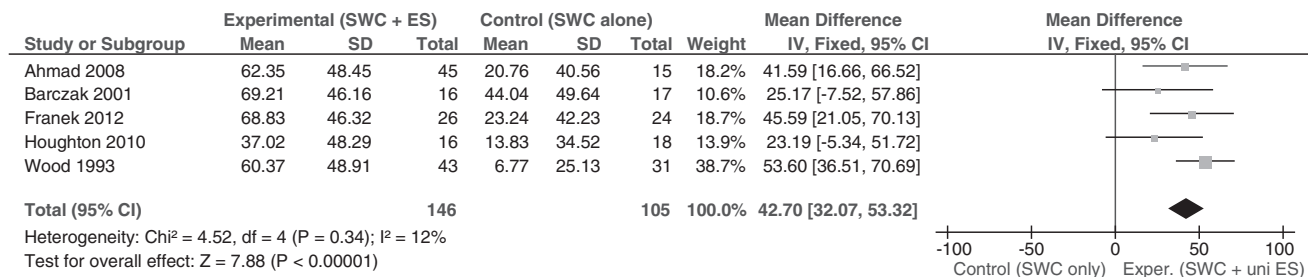


Figure 4. Forest plot with the results of the five studies (left column)^{22,25,29,31,36} that applied unidirectional ES on pressure ulcers comparing the mean differences between the experimental group (SWC plus ES) and the control group (SWC alone or SWC plus placebo ES).

treatment. In most countries, the health care professionals who receive formal education about ES are physical therapists who often are not intensively involved in wound treatment, whereas the professionals most frequently involved in the treatment of patients with wounds are specialized wound nurses or medical specialists who are not familiar with the application of ES. So translating the external research findings to clinical practice is imperative in moving the use of ES forward in wound-healing practice. Clinicians should improve practical competences to be able to apply ES appropriately.

SWC or extra interventions needed

SWC should be well known in theory and practice, easy to apply, and clearly described in guidelines. SWC should be the first choice treatment in the majority of patients. Wounds tend to become a chronic problem and because the treatment time is very often long, patients and therapists should estimate early in the treatment process if SWC alone is expected to be effective. If in 4 weeks a wound area decreases more than 40%, there is a good chance that wound closure will occur with an additional 8 weeks of treatment.⁴⁰ That is our motivation to describe the PAR4 as a simultaneous outcome measure and a prognostic factor. If the clinician has measurement tools with satisfying agreement, the evaluation of PAR4 is a helpful strategy to determine if SWC alone is satisfying or if an extra intervention with ES to increase wound healing is indicated.^{44–46}

CONCLUSIONS

Summary of results

Applying additional unidirectional ES to a program of SWC increases the reduction in the wound surface area in 4 weeks of treatment by an extra 30% (95% CI 20.9, 40.6). In the best studied wound type (PU), these results increase to an extra wound reduction in 4 weeks of treatment by 42.7% (95% CI 32.0, 53.3). In PU care, there is clear motivation to apply unidirectional ES; in other wound types like VLU and DFU, also bidirectional ES can realize positive results.

Pros and cons of clinical application of ES

The main motivation for the application of ES is its proven effectiveness for wound healing expressed in increased healing rates. Further, ES is a safe treatment with minimal if any adverse effects.

TAKE-HOME MESSAGES

A clear and positive recommendation is available regarding the effectiveness of ES to increase wound healing. The application of unidirectional ES directly in the wound in the treatment of PU is most effective by increasing wound area reduction with an extra 40% in 4 weeks of treatment.

If SWC has disappointing effects that can be quantified as an initial wound healing in 4 weeks of less than 40%, the clinician should choose additional treatment and among the options, ES is an evidence-based application with proven effectiveness.

If appropriate equipment is available, patients, with the help of partners, can apply part of the treatment self. Besides the improved wound healing, many patients also have reported a decrease of wound-related pain.^{32,33}

Drawbacks for ES are the time needed to set up treatment and the fact that aside from physical therapists, not many clinicians are competent or have the appropriate equipment to apply the intervention correctly. Education and training will be necessary to apply ES in wound healing in a systematic way.

AUTHOR DISCLOSURE AND GHOSTWRITING

For both authors, there are no conflicts of interest and no financial interests exist. The text was expressly written by the two authors. No ghostwriters were used to write this article.

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