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The Effects of Electrical Stimulation on Chronic Wound Healing: A Systematic Review

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ABSTRACT:

BACKGROUND AND PURPOSE

Electrical stimulation (ES) is an adjunct modality used to facilitate healing of chronic wounds. Current literature suggests electrical stimulation has some net benefit, although best-practice protocols have yet to be substantiated. The purpose of this systematic review is to analyze the existing literature about the use of ES to facilitate the treatment of chronic wounds. Key questions include: 1) What is the effect of ES on healing rates of chronic wounds when compared with standard care, 2) What parameters of ES are most beneficial, 3) Is the response to ES wound-etiology specific, and 4) Do the benefits of ES continue to outweigh the harms?

METHODS

Cochrane, Cinahl and Medline were electronically searched using keywords "electrical stimulation" and/or "wound healing" from 1973 through 2014 resulting in a total of 1858 hits. Through title and abstraction review by multiple researchers, 1796 articles were eliminated with 62 remaining articles found appropriate for review. Of these, 34 were accessible for this study (11 randomized controlled trials, 5 clinical trials, 5 systematic reviews, 4 literature reviews, and 9 case reports). Statistical analysis was conducted using Review Manager software for the 11 RCTs.

RESULTS

Of the 11 RCT evaluated, 5 comparisons examined the relative strength of treatment effect based on wound type, ES protocol, and outcome measures. Although the results are mixed, studies examining the use of biphasic ES's effect on healing rate and those examining the use of high voltage pulsed current's (HVPC) effect on total surface area change showed results in favor of the experimental groups. Comparisons for ES on pressure ulcers showed favor for experimental groups in regards to closure rate outcome measures, and comparisons regarding diabetic ulcer healing rate with electrical stimulation treatment favored the experiment group.

CONCLUSIONS

Given the variability in wound type, ES parameters, and outcomes evaluated, few comparisons could be analyzed. Based on the available evidence, ES has a modest positive effect on healing rates when compared with standard care alone. Biphasic ES was most commonly studied for use in treatment of diabetic ulcers (4/4 studies), whereas pressure ulcers were managed with both biphasic (2/5 studies) and HVPC (3/5 studies) ES. More consistent outcome reporting is required to make direct comparisons. Finally, ES appears to be a safe adjunctive treatment with no adverse events reported in the studies analyzed.

RESEARCH ADVISOR FINAL APPROVAL FORM

The undersigned certify that they have read, and recommended approval of the research project entitled

The Effects of Electrical Stimulation on Chronic Wound Healing: A Systematic Review

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in partial fulfillment of the requirements for the Doctor of Physical Therapy Program

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INTRODUCTION

Wound management is a function of health care that can be especially challenging when wounds become chronic, meaning that they do not progress in the healing process with standard wound care.[1] An estimated $25 billion dollars is spent on chronic wounds annually in the United States, and that figure is projected to rise with the increasing prevalence of diabetes, obesity, and adults over the age of 65.[2] The average chronic wound requires $7,439 to $70,000 to medically manage, and 90% of patients with chronic pressure ulcers are being cared for by government funding.[2]

Chronic wounds are also debilitating for the patient. In a study by Sen et al in 2009, 12% of those with venous ulcers had to take early retirement due to their wounds and over 75% of chronic wound patients felt their mobility was limited due to their wound.[2] Nursing Times literature has reported impaired mobility to be caused by wound pain in a 2004 study.[3] Pain is often reported as a top disadvantage of having an ulcer.[2] Sen et al also reported that this pain causes sleep disturbance in up to 73% of people, as well as depression.[2] Nursing Times linked wound leakage and odor with social isolation and low self-esteem of patients.[3] Caring for chronic wounds can be painful and can significantly interrupt normal life, with some patients having to choose between work and wound care.[2] Time spent on dressing changes (typically 4-5x/wk, 16 minutes/time) correlated with reduced quality of life in one study of 530 patients.[4] Quality of life includes the emotional impact of a condition, and 68% of chronic wound patients report the ulcer has an emotional impact.[2] Fear, depression, social isolation, anger, resentment and a negative self-image often accompany chronic wounds.[2]

Due to their complex and long-lasting nature, a specialized team approach is recommended to facilitate and expedite the healing process. A Physical Therapist (PT) is a key member of this wound care team because of their unique set of skills that includes training specific to wound care, unique adjunct modalities, and training as a movement specialist that together can support the health and function of the entire individual.[5] Chronic wounds are not ameliorated with traditional treatment and thus require adjunct therapies such as electrical stimulation (ES) to facilitate healing and wound closure.[6] This paper aims to analyze the existing literature about the use of electrical stimulation to facilitate the treatment of chronic wounds

Background

Normal Healing Process

Many of the pathologies that cause wounds, especially chronic wounds, impair the healing process. The complex and coordinated response to injury or trauma is the inflammation and repair process. Purposefully designed, this process works to eliminate the cause of injury and restore function through the repair of damaged tissue and regeneration of tissue structures. The foundation of wound healing requires an understanding of normal healing processes, pathologies that complicate healing, and specific interventions that can facilitate healing. The process of healing can be broken down into 3 phases (Inflammatory, Proliferation, and Maturation), each with varying durations and events with the ultimate goal of preparing a wound area to lay down new tissue and circulatory vessels that strengthen and mature over time to return tissue to its prior function.[6]

What are Chronic Wounds?

In a healthy person, a wound typically heals in three to four weeks, with microscopic tissue remodeling over the next year. If a wound does not heal normally, it may become “stuck” in one of the phases of healing and become chronic. Chronic wounds are defined as “wounds which have failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result.” [7]

Pathophysiology of Chronic Wounds

Wounds can originate from a variety of causes: both from impaired body systems (pathology) and external insult (trauma). Wounds originating from pathology can be caused by impaired immune and nervous system function, or impaired blood supply and nutrient/oxygen delivery to the tissue. Chronic medical conditions such as diabetes, atherosclerosis, deep vein thrombosis, peripheral vascular disease, and obesity are leading factors in pathological wounds.[1,2,6] External wounds often result from non-penetrating trauma such as friction, abrasions, contusions, and lacerations, or penetrating trauma where the full skin depth is broken through such as stab and surgical wounds. In addition, external injuries can also arise from chemical burns, thermal extremes, electrical wounds, and animal bites or stings.[6]

The development of a wound into a chronic, non-healing wound is specifically associated with persons with one or more pathologies. Some risk factors that impair healing and thus promote chronicity include: diabetes, older age, immobility, reduced sensation, peripheral vascular disease, obesity, and other chronic diseases. In addition to those with chronic disease, people with weakened immune systems (eg. AIDS, radiation therapy, bone marrow transplant, etc.) often have a more difficult healing process.[6, 8]

Common complications of wounds throughout the healing process include: infection, scarring, loss of tissue function, and chronic inflammation. Due to the multifactorial nature of wound healing, it is imperative for a clinician to consider all possible barriers to proper wound healing.[6,7]

Pathologic Factors

Systemic factors such as age, disease, medication, and nutrition also affect wound healing. As one ages, healing rate slows down because of a decrease in density and cross-linking of collagen which results in decreased tensile strength, numbers of mast cells and fibroblasts, and rate of epithelization of tissue. Decreased organization of cutaneous vessels in elders causes poorer wound healing as well due to altered circulation.

Different diseases can also alter tissue healing. Diabetes mellitus impairs collagen synthesis, increases one's risk of infection, and causes decreased phagocytosis. Diabetes also leads to decreased peripheral vascularization, which affects blood flow to an area. Circulation problems due to an impaired cardiovascular system can delay wound healing as proper nutrients cannot be delivered to the wound area as efficiently.

Additionally, there are some medications that, while being used to treat disease, can actually affect how a wound will heal. Typically, corticosteroids are used to treat diseases of inflammation such as arthritis, colitis, or asthma due to their anti-inflammatory properties. However, corticosteroids can be used in wound healing as they are able to block the inflammatory cascade necessary for bringing blood flow and healing factors to the wound area. Corticosteroids can decrease margination, migration, and accumulation of monocytes at the site of inflammation and can induce the anti-inflammatory properties of monocytes.

Finally, nutrition has a huge impact on how a wound will heal as well. Being deficient in important amino acids, vitamins, minerals, or water can cause delayed wound healing as healing is a hypermetabolic state that without necessary nutrients, cannot proceed optimally. Vitamin A deficiency specifically can slow the rate of epithelialization, collagen synthesis, and cross-linking of tissue. Thiamine deficiency decreases collagen formation, and vitamin C deficiency impairs collagen synthesis while increasing susceptibility of infection.[6]

Interventions

Current Interventions for Chronic Wounds

Typically, physical therapists or wound care nurses use standard interventions to facilitate wound healing, such as: keeping the wound moist, cleaning and moisturizing the wound and periwound area, using dressings designed to facilitate healing, selective and non-selective therapeutic debridement to remove necrotic tissue, and immobilization or positioning techniques to reduce pressure on the wound area in addition to therapeutic exercise and patient/caregiver education on how to care for the wound at home.[9] Combinations of these interventions allow for a proper environment for chronic wounds to heal.

Adjunctive Therapy

When wounds do not heal with standard treatment or are healing slowly, adjunctive therapies may be used. Reputable wound-healing textbooks describe studies that have shown that therapeutic technologies such as hyperbaric oxygen, negative pressure wound therapy, intermittent compression, laser therapy, ultrasound, and electrical stimulation can be effective treatments to facilitate tissue healing for chronic wounds.[6] Adjunctive therapies typically work to improve healing through enhanced environment control (i.e. reducing bacterial load, removing necrotic tissue, etc.) or direct physiological support of the patient's own healing process (i.e. through enhanced cell stimulation, improved wound oxygenation, etc.). Electrical stimulation is a well-researched adjunctive modality that works through multiple facets to promote healing.[10]

Electrical Stimulation

Electrical stimulation (ES), defined as "the use of direct contact electrodes applied to the skin or wound surface," originated as a pain modality in the late 1800's, and has experienced various applications since, including use in wound healing.[11] Research has shown ES to improve healing rates in a variety of patients under various parameters. A 1999 meta-analysis by Gardner et al stated the net effect of ES throughout the studies analyzed was a 13% increase in healing rate per week compared to a control of standard wound care.[6]

Multiple studies are now looking at innovative ways to decrease wound healing time by using different modalities to improve the rate of the healing process.[12,13,14] Electrical stimulation has been growing in popularity for use in conjunction with standard treatment to expedite healing in a variety of wounds, both chronic and acute, from both injury and pathology, and is currently recognized as an evidence-based modality for tissue healing.[11] Specifically, increased protein synthesis and cell migration, increased blood flow and subsequent tissue oxygenation, and antibacterial effects are among the major ES mechanisms utilized by clinicians to facilitate healing.[6]

Antibacterial Effect

Early ES in vitro showed that a current could reduce infection rates in animals. Rowley et al tested a microorganism in rabbit wounds and found that infection was inhibited by stimulated copper electrodes. A synergistic effect was noted when ES was added to antibiotic treatment.[15]

Current research supports ES's contribution to the reduction of infection. The stimulation of nitric oxide (NO) release via calcium ion (Ca^{++}) influx has an antibiotic influence at the wound site as NO is an oxidizing molecule.[16] Additionally, restoring the natural charge of the skin can attract white blood cells and repel bacterial molecules. CD3+ lymphocytes specifically are both activated and attracted by the ES negative charge.[6,17] Direct bacterial killing effects, however, are not able to be observed in treatment due to the fact that the high voltages that required would damage healthy patient cells as well.[6] The most commonly reported ES used to reduce infection successfully is monophasic currents including microA direct current (DC) and high voltage pulsed current (HVPC), but not alternating current (AC).[6]

Cell Migration

Galvanotaxis is the process of attraction of cells by an electric charge; specifically charged cells such as neutrophils, macrophages, lymphocytes, and fibroblasts.[6] A negative electrode is used to promote healing of inflamed or infected wounds since it attracts neutrophils, lymphocytes, platelets, mast cells, and fibroblasts to the wound area. When present, these cells clear debris and synthesize proteins needed in preparation of future healing. A positive electrode can promote healing of wounds in the absence of inflammation or necrosis by attracting macrophages and epidermal cells, which work to restructure the injury site for closure. Additionally, positive charges inactivate neutrophils and allow for uninterrupted healing.[18]

Protein Synthesis

ES is believed to promote wound healing by improving cell function; specifically increasing protein synthesis and fibroblast replication for an increased production of collagen. Electrical current triggers the calcium channels along fibroblast membranes to open, which increases the flow of calcium (Ca^{++}) into the cell. An in vitro study of human fibroblasts by Bourguignon et al has demonstrated increased Ca^{++} influx with ES can enhance membrane display of insulin receptors.[19] Using high voltage galvanized stimulation (HVGS) on human fibroblasts, Bourguignon et al's experiment found that ES opens voltage-gated Ca^{++} channels in fibroblast membranes, creating a Ca^{++} influx that can stimulate the transition of insulin channels to the membrane and promote insulin uptake into the cell. High voltage direct current (HVDC) has been shown to open voltage gated channels at 60-80V.[6] An increase in insulin uptake can be correlated with additional ATP availability and use, as well as enhanced DNA synthesis and collagen production.[18,20] Early practice found this improvement in DNA synthesis and ATP availability as a mechanism for ES's ability to increase fibroblast activity, angiogenesis, epithelization and subsequent healing rates.[18, 19, 20]

Increased Blood Flow

Another proposed mechanism of accelerated healing through ES is improved blood circulation to the tissue via stimulation of vasodilator neurotransmitter release. Petrofsky et al has found that ES's ability to increase blood flow can be linked to the Ca^{++} influx it produces. A

Ca^{++} influx triggers the NO mechanism of vasodilation in normal tissue.[23] More blood at the healing site translates to more nutrients, cells, and proteins delivered and more debris and wastes cleared.

Improved healing rates however, have not always held true for more challenging patient populations, such as those with diabetic foot ulcers.[21] This population has damaged nerves, impaired insulin sensitivity, generally reduced circulation and a defective NO mechanism of vasodilation, which each provide a barrier to wound healing.[22] Recent research by Petrofsky et al shows promise in this area by investigating the mechanism of ES effect in detail.[16] In normal tissue, vasodilation and constriction are balanced by the sympathetic nervous system (SNS), insulin and the NO mechanism. In diabetics, nerves are damaged, cells respond to insulin only to produce vasoconstriction (not balanced by vasodilation, as would be normal), and have a generally dysfunctional NO mechanism. Diabetic tissue responds to the Ca^{++} influx produced by ES with normal NO release, however the response is blunted by the strong vasoconstriction imposed by the SNS and defective insulin.[23] To combat the SNS and encourage vasodilation, Petrofsky et al and Lawson and Petrofsky in separate trials, have treated patients with ES in a warm room (32°C) or with local heat.[16, 22] The effect has been synergistic increases in blood flow to the wound. By altering the environment, ES can be effective at enhancing blood flow, which can thereby enhance healing through the delivery of nutrients and oxygen and the removal of wastes. Research supports biphasic ES for improved blood flow and ultimately improve healing rates.[16, 22] HVPC, however, has also been shown to improve wound blood flow, although likely though a different mechanism which utilizes different ES parameters.[18]

REVIEW OF CURRENT LITERATURE

While the quantity of evidence studying the effects of electrical stimulation is fairly large compared to other adjunct modalities such as laser therapy, the quality of trials is lacking. Two recent systematic reviews discuss this, acknowledging that further research is needed to confirm claims of ES's effects.

A recent systematic review by Kwan et al in 2013 analyzed RCTs using multiple databases to find articles from 1966-2011 that used adjunct modalities to treat diabetic foot ulcers. Including ES, low-level laser therapy, ultrasound and electromagnetic therapy the author's search produced 8 RCTs with 325 participants. Of these, Kwan et al found 5 on ES and statistically analyzed the results of 3 RCTs.[12]

> "All studies reported that the experimental group was significantly more favourable than the control or sham group. The pooled estimate of the number of healed ulcers of the three studies on electrical stimulation compared to the control or sham electrical stimulation showed statistical significance [mean difference of 2·8 (95% CI = 1·5–5·5, p = 0·002] in favour of electrical stimulation."

Kwan went on to state that the small number, poor quality, and protocol heterogeneity of studies limited the ability to make a strong recommendation for the use of ES. Larger studies are needed to rule out potential risks of ES.[12]

A similar statement of limitations is reported by Thakral et al in a 2013 systematic review of the use of ES on wound healing finding a variety of ES applications. This 2013 review, published after the inception of this review reviewed 21 RCTs, of which 16 were appropriate for analysis as the others had less than 8 subjects. Despite acknowledged limitations, Thakral et al concluded that; "Electrical stimulation was associated with faster wound area reduction or a higher proportion of wounds that healed in 14 out of 16 wound randomized clinical trials." No adverse effects were reported and thus the suggestion for future research lies in determining the appropriate dosage, timing and type of ES for clinical application.[13]

The existing literature demonstrates the effectiveness of electrical stimulation as an adjunct to standard wound healing as a whole, with no known adverse side effects. However this conclusion is limited by few high-quality RCTs with appropriately large sample sizes and specific methodological parameters regarding electrical stimulation types, doses, durations, and applications.

Purpose

In light of the large impact of chronic wounds on patient physical health, mental health and overall quality of life, as well as the societal cost of long-term wound management, it is imperative to develop best practices in wound management. While there is a plethora of literature available in the realm of wound healing and electrical stimulation, there is a lack of consensus in parameters, dosage or etiology-specific treatments. The purpose of this study is to examine the available literature about electrical stimulation. The effect of electrical stimulation on chronic wound healing will be analyzed, and an attempt to consolidate the best information for more safe and effective clinical utilization will be made. Specific questions examined in this paper include: 1) Compared to standard wound care, what is the effect of ES on healing rates? 2) What are the most beneficial types of ES for wound healing? 3) Is the response to ES wound-etiology specific? 4) Do the benefits of ES continue to outweigh the harms in regards to chronic wound healing?

METHODS

Literature Search

In order to determine search parameters, a researchable question was created using the PICOT method; whereby a population, intervention, control treatment, outcome measure, and time period are defined for studies to be accepted for review. The specific parameters of this PICOT question are discussed below. Studies for this systematic review were acquired through a computerized database search focusing on the use of electrical stimulation for chronic wound healing. The electronic databases used in this study included Cochrane, Medline, and Cinahl, with search terms “electrical stimulation” AND/OR “wound healing” from database origin to March 2014. An initial combined search of each database yielded 1,858 hits that were divided between three individuals with two of those individuals reviewing each hit to determine eligibility for abstraction based on original PICOT criteria. The process used to determine articles included for analysis is depicted in Figure 1. Specific database searches included the following: **Cochrane**: 3 hits with MeSh terms “wound healing” exploded AND “electrical stimulation” exploded, 1480 hits with MeSh term “electrical stimulation” exploded; **Cinahl**: 100 hits by searching “wound healing” AND “electrical stimulation” with no search limits (year 1991-2013 by natural preset). **Medline**: 275 hits with “electrical stimulation” AND “wound healing” with no search limits (year 1973-2014 by natural preset).

Articles were reviewed and included or excluded based on title, abstract, duplicate articles, language, and availability via library systems. Any confusion regarding inclusion or exclusion was addressed through researcher consensus. One thousand eight hundred and twenty-four articles were removed in total, leaving 34 articles for abstraction. These 34 articles consisted of a mixture of systematic reviews, literature reviews, case reports, clinical trials, and randomized control trials. Figure 1 summarizes the inclusion and exclusion process of articles for abstraction and thorough review. A detailed description of how articles were selected for the abstraction process is described below.

Study Selection

Articles were considered appropriate for inclusion if the following criteria were met:

Study Design: All study designs were eligible for inclusion. Randomized control trials were utilized for potential statistical analysis following abstraction. Case reports, clinical trials, and systematic reviews/literature reviews were included for introductory information and for trend assessment. Only full articles were included, any abstracts or unpublished articles were excluded from this study.

Study Population: An article was included in this systematic review if it included human patients that were 18 years of age or older who were dealing with one or more chronic wounds (unless serving as a control). Articles involving bone healing or traumatic injury were excluded. All animal trial articles were excluded following title or abstract review.

Language and Accessibility: Any studies that were written in a language other than English were excluded from this study. Also, any articles that were not available through the St. Catherine University database or through the interlibrary loan system were excluded.

Intervention: All articles using electrical stimulation were included in this study. No specific parameters were set as a part of the aim of this study was to determine if particular parameters of electrical stimulation were preferred over the others. For randomized control trials, studies were included if the control group was standard care or a sham wound treatment, but not another type of electrical stimulation.

Outcome Measures: A variety of outcome measures that evaluated wound healing were included, such as: wound area, granulation area, healing rate, total surface area change, closure rate, wound depth, and wound volume. Any and all outcome measures were included in order to foster as many comparisons between articles as possible.

Length of Study: Articles with any length of follow-up were chosen to observe if electrical stimulation treatment had any long-term benefit compared to standard wound care. However, studies with only one treatment session were not accepted.

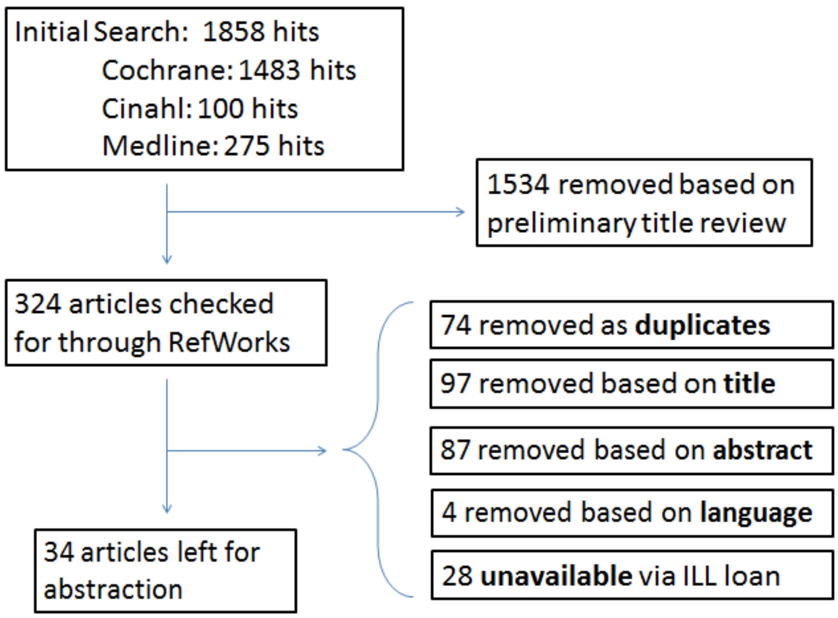

Figure 1: Process of article elimination to yield articles used for abstraction and analysis.

Data Abstraction

Thirty-four articles were selected for complete review and abstraction. These articles were divided between three researchers to read independently and abstract. The articles were then reviewed by one additional researcher to ensure efficient and accurate abstraction. Any discrepancies were settled by researcher discussion with thorough re-evaluation of the article. A table was created in which specific information regarding subjects, wound types, intervention techniques, and outcomes were recorded for eventual comparison. Reviewers were not blinded to article type, title, author, or journal. Articles were separated based on evidence type (randomized control trials, systematic reviews, literature reviews, and case reports) for ease of abstraction and organization.

Data Analysis

Prior to data analysis, 11 randomized control trial articles were grouped together to find comparable data. Groupings were made by wound type to determine if articles reported synonymous outcome measures needed for meta-analysis. One article that included multiple types of wounds (i.e.: pressure sores and diabetic ulcers) was excluded from full data extraction as it could not be placed in a wound-specific comparison. Groupings were also made by electrical stimulation type to find if synonymous outcome measures were present for meta-analysis. One article was excluded from comparison here as it studied the effect of TENS while no other article did.

The 11 RCTs were analyzed using Review Manager Software, which has been validated by The Cochrane Collaboration.[24] To statistically compare articles, each had to report a similar outcome measure with the mean and standard deviation for both the control and experimental groups (at both baseline and follow-up, where applicable). Statistical significance was defined by a z-score of greater than 1.96, a p-value of less than 0.05, or a 95% confidence interval that did not cross zero. These cut-offs were chosen as they are commonly used in statistical analysis to indicate that the results found are not likely due to chance.[24] Using the groupings mentioned above, meta-analysis was conducted. Comparisons were limited by the number of articles that provided comprehensive data for both experimental and control groups. In total, outcomes were analyzed from 11 articles to create six forest plots regarding comparable outcome measures.

RESULTS

Randomized Controlled Trials

Following abstraction of the randomized control trials (RCTs), 11 studies were examined based on wound etiology and electrical stimulation type. Biphasic electrical stimulation treatment was represented in six out of 11 studies--more than any other type of ES, especially in the treatment of diabetic ulcers (4/11). Pressure ulcers were treated with both biphasic and high voltage pulsed current (HVPC) electrical stimulation (2/11 and 3/11, respectively). The remaining two RCTs contained wounds of mixed etiology, using HVPC and TENS treatments and thus had limited comparability. Due to heterogeneous outcome measure reporting, no meta-analysis pooling about all ES types and wound types was able to be made. Overall, 69% percent of the articles abstracted contained enough data for comparison with another article; with 73% percent of those articles then actually having an article with matching outcome measures against which to compare. Results will be presented based on electrical stimulation type, then wound etiology type, a summary of each article can be found in Table 2.

Analysis by Electrical Stimulation Parameters

Three studies were identified as using HVPC for the treatment of chronic wounds, with the following parameter ranges reported: 100-120 Hz, 1-1.75 V, 50-255 microsec, 30-50 minutes/session, 5 sessions/week. All of the HVPC studies reported overall positive results with no adverse events.[18, 24, 25]

The first meta-analysis includes two studies regarding HVPC to treat pressure ulcers with the outcome measure of complete wound closure. Each included study reported the number of patients with wound closure as defined by a patient obtaining complete closure of the wound within the study follow-up. A good quality study by Kloth, and a poor quality study by Edsberg were compared and produced an overall effect in favor of electrical stimulation. The z-score, p-value and 95% confidence interval were each statistically significant and the forest plot can be found in Figure 2.[25, 26]

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Edsberg 2002	2	3	4	5	97.3%	0.50 [0.02, 12.90]
Kloth 1988	9	9	0	7	2.7%	285.00 [5.04, 16117.07]
Total (95% CI)		**12**		**12**	**100.0%**	**8.19 [1.37, 49.08]**
Total events	11		4			

Heterogeneity: Chi² = 5.82, df = 1 (P = 0.02); I² = 83%
Test for overall effect: Z = 2.30 (P = 0.02)

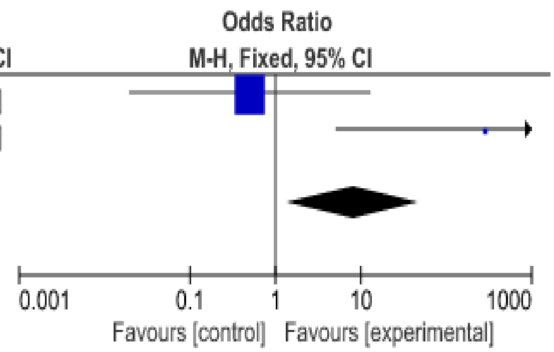

Figure 2: HVPC and Pressure Ulcer Closure Rate

Figure 3 compares two studies in regards to the relationship between HVPC treatment and wound surface area. Kloth, a good quality study, and Franek, an excellent quality study were included. Edsberg, while a study using HVPC, was not included as it did not report wound surface area change in a comparable fashion. Due to the 100% surface area change (full closure) reported by Kloth, there was no standard deviation and therefore a 0.1 standard deviation was used for calculation purposes due to Review Manager software requirements. The overall effect results of this comparison were statistically significant in favor of the electrical stimulation group and can be found in Figure 3.[18, 25]

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Franek 2012	88.9	14	26	44.4	63.1	24	86.9%	44.50 [18.69, 70.31]
Kloth 1988	100	0.1	9	28.93	89.8	7	13.1%	71.07 [4.55, 137.59]
Total (95% CI)			**35**			**31**	**100.0%**	**47.98 [23.91, 72.04]**

Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.91 (P < 0.0001)

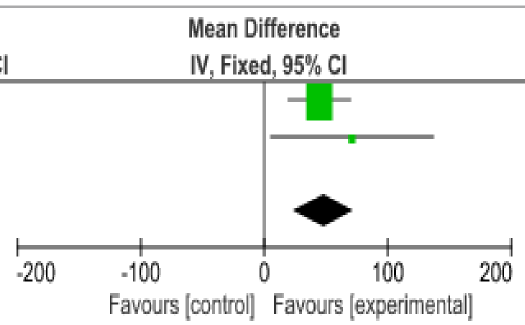

Figure 3: HVPC and Total Surface Area Change

Five studies were identified as using biphasic electrical stimulation for the treatment of chronic wounds, with the following parameter ranges reported: 1-80 Hz, 0.004-0.2 V, 1-300 microsec, 20-50 minutes/session, 3-15 sessions/week. All of the biphasic studies reported overall positive results and none reported adverse reactions related to the electrical stimulation treatment. [16, 21, 22, 27, 28]

Wound healing rate was compared with two studies using biphasic electrical stimulation. A good quality study by Baker (1997) and a poor quality study by Lawson were compared. Since each treatment group in Baker had a different, defined protocol and was independently compared to a separate control group, analysis was conducted as though there were three separate studies--shown as Baker 1997-A, -B, and -MC in the forest plot. The overall effect results are statistically significant in favor of electrical stimulation treatment, as found in the Figure 4 forest plot.[22, 27]

	Experimental			Control				Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI
Baker 1997-A	27	4	33	17.3	2.3	25	47.0%	9.70 [8.06, 11.34]
Baker 1997-B	16.4	6.1	28	17.3	2.3	25	21.2%	-0.90 [-3.33, 1.53]
Baker 1997-MC	17.2	4.8	28	17.3	2.3	25	31.6%	-0.10 [-2.09, 1.89]
Lawson 2007	70	32.3	10	38.4	22.3	10	0.2%	31.60 [7.27, 55.93]
Total (95% CI)			**99**			**85**	**100.0%**	**4.40 [3.28, 5.52]**

Heterogeneity: $Chi^2 = 82.95$, $df = 3$ ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 7.69$ ($P < 0.00001$)

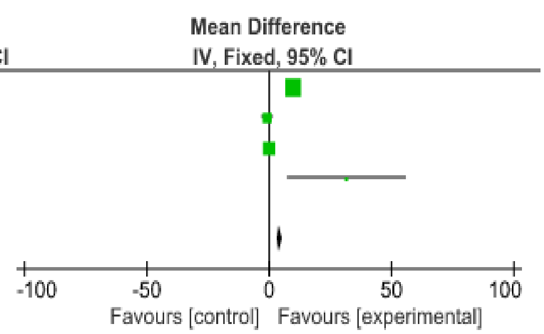

Figure 4: Biphasic and Healing Rate

The second meta-analysis for biphasic electrical stimulation focuses on the outcome measure of total surface area change. Three good quality studies are included in this comparison: Baker (1996), Lundeberg, and Petrofsky. Baker (1996) also utilized a three treatment group protocol where each treatment group used a defined protocol independently compared to a separate control group, and thus analysis was conducted as though there were three separate studies--shown as Baker 1996-A, -B, and -MC in the forest plot. The overall effect statistics can be found in Figure 5; the effect produced did not favor either group and was not statistically significant.[16, 21, 28]

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Baker 1996-A	36.4	6.2	67	32.7	7	25	30.0%	3.70 [0.58, 6.82]
Baker 1996-B	29.7	5.1	58	32.7	7	25	31.5%	-3.00 [-6.04, 0.04]
Baker 1996-MC	23.3	4.8	42	32.7	7	25	30.3%	-9.40 [-12.50, -6.30]
Lundeberg 1992	61	14	32	41	11	32	7.7%	20.00 [13.83, 26.17]
Petrofsky 2010	68.4	28.6	10	30.1	22.6	10	0.6%	38.30 [15.71, 60.89]
Total (95% CI)			**209**			**117**	**100.0%**	**-0.93 [-2.64, 0.78]**

Heterogeneity: Chi² = 94.64, df = 4 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.07 (P = 0.29)

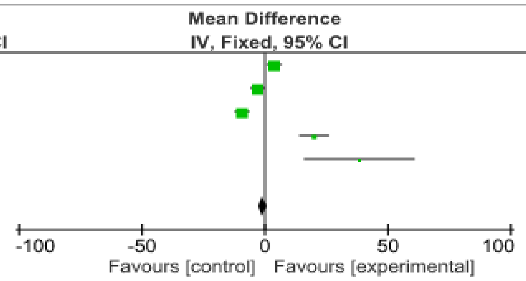

Figure 5: Biphasic and Total Surface Area

The next two meta-analyses demonstrate the effect of electrical stimulation on specific wound etiologies, regardless of electrical stimulation type. Pressure ulcer total surface area change was compared between 3 studies; a good quality study by Baker (1996), a good quality study by Kloth and an excellent quality study by Franek. Statistically significant results can be found in Figure 6, with the overall effect favoring the control group.[18, 25, 28]

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Baker 1996-A	36.4	6.2	67	32.7	7	25	32.5%	3.70 [0.58, 6.82]
Baker 1996-B	29.7	5.1	58	32.7	7	25	34.2%	-3.00 [-6.04, 0.04]
Baker 1996-MC	23.3	4.8	42	32.7	7	25	32.8%	-9.40 [-12.50, -6.30]
Franek 2012	88.9	14	26	44.4	63.1	24	0.5%	44.50 [18.69, 70.31]
Kloth 1988	100	0.1	9	28.93	89.8	7	0.1%	71.07 [4.55, 137.59]
Total (95% CI)			**202**			**106**	**100.0%**	**-2.65 [-4.42, -0.87]**

Heterogeneity: Chi² = 51.66, df = 4 (P < 0.00001); I² = 92%
Test for overall effect: Z = 2.92 (P = 0.004)

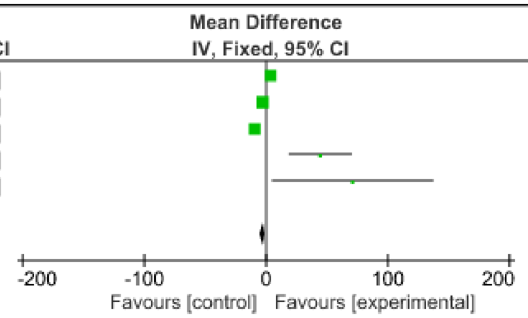

Figure 6: Pressure Ulcer and Total Surface Area Change

A final analysis regarding the healing rate of diabetic ulcers when treated with electrical stimulation was desired, however only the three treatment groups from Baker (1997) could be compared. This limited analysis was due to the fact that the other RCT focusing on diabetic ulcers by Petrofsky et al reported wound healing rates per month, not per week. Statistical significance for the overall effect was found in favor of the electrical stimulation group, see Figure 7.[16, 27]

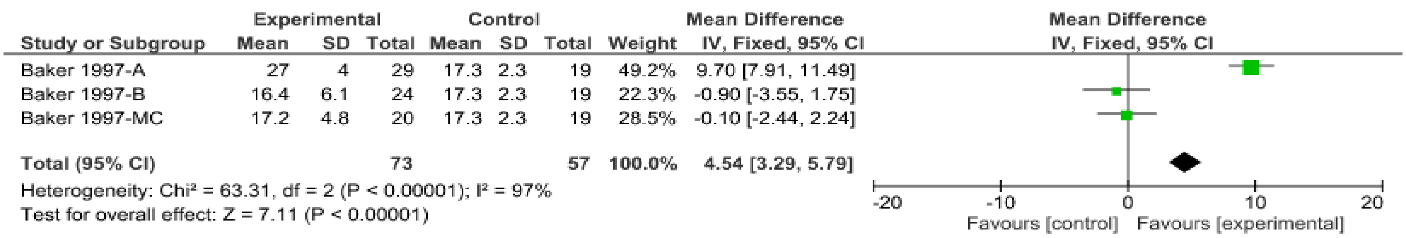

Figure 7: Diabetic Ulcers and Healing Rate

Quality Assessment (of Randomized Controlled Trials)

The Physiotherapy Evidence Database scale (PEDro), a well-accepted RCT quality assessment scale consisting of 11 yes or no questions, was used to analyze the quality of each of the 11 RCTs used in the forest plot comparisons above.[24] Article quality is graded out of 10, with a score of 9-10 considered excellent, 6-8 good, 4-5 fair, and less than 4 poor quality. High quality studies do not necessarily support the control or experimental group, but rather have high quality methodology.[29]

Of the 11 RCTs used in analysis, 1 was considered “excellent”, 6 were “good” and the remaining 4 were “fair to poor” quality. Many of the abstracted articles did not address PEDro scale items and thus received “no’s” by default. The PEDro qualifiers with the highest percentages of articles were the “intent to treat” and “between group statistical analysis” at 81 and 90% respectively. Limitations involved “concealed randomization of participants” and “blinded assessors” at with only 18% and 27% of articles reporting these actions, respectively. A summary of the PEDro analysis can be found in Table 1.

Table 1: Qualitative Analysis of RCT using the PEDro Scale

PEDro scale item	**% "Yes" (out of 11 RCT)**
1 Eligibility specified	72%
2 Random assignment	72%
3 Concealed randomization	27%
4 Baseline comparability	63%
5 Blinded subjects	63%
6 Blinded therapists	18%
7 Blinded assessors	36%
8 Drop out <15%	63%
9 Intention to treat analysis	81%
10 Between-group statistical analysis	90%
11 Point Measures	81%

Case Reports and Case Series

Nine articles were found suitable for review under the category of case report or case series. Five of these were individual patient case reports, 3 using HVPC, 1 using monophasic electrical stimulation, and one using wireless microcurrent electrical stimulation. Four articles were case series reports; 3 using HVPC (16 patients total) and 1 using bioelectrical stimulation (11 patients total). Ricci's modality description for "bioelectrical stimulation" was consistent with an electrical stimulation device; however, the researchers utilized unique protocol parameters which are detailed in Table 3.

HVPC was the most common type of treatment reported (6/9 articles). Parameter ranges for HVPC were: 50-120 Hz, 0.1-150 V, 10-400 microsec, 2-5 days/week, and 30-60 minutes/session. The mode of patient treatment parameters were: 100 Hz, 100 V, unknown microsec pulse duration, 5 days/week, for 60 minutes per session. Article follow-ups were between 8 and 22 weeks with the most common outcome measure utilized was total surface area change.

Pressure ulcers were the most common wound etiology documented, with 5 studies reporting on patients with pressure ulcers.[30, 33, 34, 37, 38] One case report focused on diabetic ulcers and the three remaining articles contained mixed etiology wounds.[31;32,35,36] A full summary of the case articles can be found in Table 3.

All of the case reports and case series reported at least some positive results with the use of electrical stimulation treatment. One article did however stop ES therapy before full wound closure (at 95% wound healing per the article's unique protocol) and reported wound closure ensued shortly thereafter.[34] Between all the articles, one report of dropout due to skin irritation was noted.[35]

DISCUSSION

Randomized Controlled Trials

This systematic review evaluated 11 randomized controlled trials that used a variety of ES applications in the treatment of chronic wounds. The initial aim was to describe research supporting electrical stimulation by type and by wound etiology. These comparisons favored HVPC for both closure rate and surface area; however, there were mixed results for biphasic ES and wound etiology.

One source of ambiguity may be related to the challenges when broadening comparisons to include additional studies. For example, when comparing HVPC's effect on total surface area, only 2 studies were included. This comparison yielded support for electrical stimulation. However, if the comparison is broadened to include biphasic ES through the addition of one study; the effect of any type of ES on wound healing produced mixed results. The increased number of patients treated, or the combining of ES types through the addition of one article, may have skewed the results in a more neutral direction. Therefore HVPC may be more effective than biphasic ES in the treatment of chronic wounds.

Secondly, the acceptance of any electrical stimulation treatment for the experimental group is reflected in the mixed results. Specifically, Baker studies in 1996 and 1997 had a substantial microcurrent treatment group that was treated with ES, but described by Baker as a "current too small in amplitude to have a therapeutic effect".[27, 28] The authors intended the group to be a sham treatment but given its apparent therapeutic effect, was included as an experimental group. By including this microcurrent group, the results may be biased in comparisons involving Baker. A closer look at the forest plots produced (Figure 5 and Figure 6) demonstrates that the microcurrent group was a main contributor favoring the control, thus potentially skewing the results.

Another comparison confounded by accepting any ES treatment group would be that of HVPC's effect on pressure ulcers, which included a study by Edsberg where both control and experimental groups received Hyperbaric Oxygen Therapy in addition to their standard wound care. Hyperbaric Oxygen Therapy is a different adjunct modality often cited for its ability to facilitate the healing of chronic wounds.[26] Our search parameters allowed for this inclusion as it is not another form of electrical stimulation and was applied to both treatment groups, being considered part of standard care for this study. However, it should be noted that Hyperbaric Oxygen Therapy is not a sham treatment, nor considered typical standard treatment, but rather is usually an adjunct optional modality.

The results and limitations of this systematic review align closely with that of previous literature in that ES may improve wound healing however, direct comparisons are difficult due to inconsistent parameters and data reporting. A systematic review performed in 2008 by Hinchliffe et al. found 2 randomized control trials that examined the effects of electrical stimulation on diabetic foot ulcers. One article, noted to be methodologically weak, saw no benefit with the use of electrical stimulation, while the other did see a trend toward increased healing.[39] Another systematic review by Kwan et al in 2012 assessed the efficacy of ES in the treatment of diabetic ulcers.[12] Kwan goes on to say that, "Results of studies to date provide no conclusive remarks on its use, especially whether electrophysical [electrical stimulation] therapy is better used as an adjunct therapy or alone." The most recent systematic review by Thakral et al. published after the initiation of this project, examined 16 randomized control trials to evaluate the use of electrical stimulation for chronic wound healing.[13] Although results from their analysis suggest that electrical stimulation accelerates overall wound healing, specific parameters and treatment duration vary. These systematic reviews show that there are holes in the literature regarding electrical stimulation effectiveness and best parameters for practice.

Overall, the common factors limiting a consensus statement about electrical stimulation use in previous systematic reviews surround quality and applicability. Franek et al points out that the variety of variables emphasized (i.e. wound type, individual ES parameters) have produced a large, yet strongly diverse, body of research on the modality.[18] In addition to RCTs presenting a variety of protocols, reviews have often noted many RCTs have small sample sizes and lack power calculations whereas others are of insufficient treatment length or provide inconsistent follow-up data.

The limitations of recent systematic reviews included quality and heterogeneity of randomized control trials. Poor and fair quality studies were used in this analysis because each did provide the data needed for Review Manager software analysis, allowing this study to make more comparisons than that of the existing literature. This poor methodological input limits the confidence of results presented here; while more numerous, they cannot be generalized with the full confidence of more stringent systematic reviews. The results reported here were similar to previous studies, with more comparisons made than in most reviews by looking at a wide range of wound etiologies and ES types. No meta-analysis was able to be made regarding diabetic ulcer healing, as the two available studies reported different outcome measures.

There were multiple limitations of this systematic review. Quality of life and functional outcome measures were not investigated nor were they reported. An exhaustive search was unable to be performed as only the available electronic search engines were used, and further articles were not hand-selected from those referenced in previous reports. Additionally, 28 articles were inaccessible. Finally, inconsistent data reporting by researchers in the field was a main limiter in calculating meta-analyses.

Case Reports and Case Series

Five case reports and four case series were analyzed for trends. HVPC was the most often studied, which is in contrast to the RCTs analyzed where biphasic electrical stimulation was most often studied. In light of the RCT meta-analysis, however, HVPC appears to have more consistently positive results than biphasic electrical stimulation, thus individual case reports may be trying to further develop a case for this effective, yet less-studied electrical stimulation type.

Concurrent modalities may skew the case report and case series results, case reports/series often look into lesser reported clinical protocols and document the results. Two articles reviewed utilized concurrent modalities with electrical stimulation treatment and standard wound care. A case report by Edsberg et al used Hyperbaric Oxygen Therapy (HBO) for 60 minutes, 7 days/week in addition to 5 days/week HVPC ES and documented complete healing of the patient wound.[30] A case series by Lasko et al, however, used Acoustic Pressure Therapy for 2-18 minutes 2-3 days/week in addition to 3 days/week of electrical stimulation and found only 60% of 10 lower extremity wounds healed.[35] If the electrical stimulation parameters for these studies were more similar, theories could be developed as to the effectiveness of electrical stimulation with each concurrent modality, however the basic ES parameters are different and thus it cannot be discerned as to whether the differing results are related to the different ES protocols or the different adjunctive therapies.

The benefit of the case reports reviewed includes the addition of novel protocols that do not necessarily follow traditional precautions. Pollack et al, for example, used electrical stimulation to the point of muscle stimulation surrounding the wound site for the stimulation of healing and reported successful healing in 13 weeks.[33] In India, Ramadhinara and Poulas used wireless microcurrent stimulation on a foot wound positive for osteomyelitis with healing in 45 days.[31]

The limitations of the case reports reviewed parallels that of the RCTs analyzed. Researchers did not consistently report electrical stimulation parameters or wound outcome measures. Some simply stated the ES machine used and one aspect of the wound. Others stopped treatment before full closure was achieved. Still, the main issue of comparison was inconsistent parameters, as noted with the wide range of parameters reported in the results section and Table 3.

Finally, the nature of publishing may create bias in case reports. Since there are fewer patients in a case report/series and no pre-determined protocol, if a patient does not respond to treatment, a report will likely not be generated.

CONCLUSION

The results of this study showed that electrical stimulation has a mixed effect on chronic wound healing. Positive results were shown in meta-analyses of HVPC and pressure ulcers, HVPC and surface area, biphasic and wound healing rate, and diabetic ulcers and healing rate shown in Figures 2, 3, 4, and 7 respectively. The meta-analysis regarding biphasic ES and total surface area shown in Figure 5 was not statistically significant. Negative results were shown in meta-analyses of pressure ulcer and total surface area change in Figure 6. HVPC protocols including: 100-120 Hz, 1-1.75 V, 50-255 microsec, 30-50 minute sessions, 5 days per week, and positive, negative, or alternating polarity have supported chronic wound healing over 4-16 weeks of treatment in 3 RCT systematically analyzed.[18,25,26] Additionally, biphasic protocols including: 1-80 Hz, 4-20 mA (0.004-0.2 V), 1-300 microsec, 20-30 minutes per session, 1-3 sessions per day, 3-7 days per week have supported chronic wound healing over 3-12 weeks of treatment in 5 RCT systematically analyzed.[16,21,22,27,28] Currently, a meta-analysis of HVPC ES has the most consistent evidence in support of its use for wound healing. Despite limited statistical analysis and significant findings, it can be seen that electrical stimulation is a useful modality in treating chronic wounds of multiple etiologies. However, there were not enough comparable studies found in this systematic review to determine if ES is wound-etiology specific. The results of this study suggest that the potential benefits of ES continue to outweigh the harms as only 1 of the RCT analyzed reported any adverse events during treatment, and this was due to a mild allergy. While it has been shown to be beneficial in comparison to standard or sham treatment, it is unknown just how beneficial this intervention is.

Future research is needed to incorporate more standardized outcome measure reporting and better statistical reporting to allow for further comparisons. A more in-depth look into the most effective parameters per ES type would also be beneficial for clinical application.

Table 2: Summary of Studies included in RCT Analysis [16, 18, 21, 22, 25, 26, 27, 28]

Randomized Controlled Trial	ES Type	Treatment Dose	Frequency Amplitude Duration Charge	Outcome	PEDRO Score	Comments
Edsberg (2002)	HVPC	5x/wk; 30'/session 150'/wk	120 Hz 1.5 V 255 µs Monopolar	Ave. 8wks to closure; 16-22wk for large area	3 (poor)	• n=8 • pressure ulcer
Kloth (1988)	HVPC	5x/wk; 45'/session 225'/wk	105 Hz 1-1.75 V 50 µs Changed daily if plateaued	100% of patients fully closed; ave. 7.3wks	7 (good)	• n=16 • pressure ulcer
Franek (2012)	HVPC	5x/wk; 50'/session 250'/wk	100 Hz Sensory V 100 µs 1-2 wk neg. 3-6 wk pos	6wk = sig. closure	9 (excellent)	• n=50 • pressure ulcer
Baker (1997-A)	Biphasic	15x/wk; 3x/d; 30'/session 450'/wk	50 Hz No contraction 100 µs N/A	Ave. discharge at 6 wks	7 (good)	• n=grp A+ control=58 wounds • diabetic ulcer
Baker (1997-B)	Biphasic	15x/wk; 3x/d; 30'/session 450'/wk	50 Hz No contraction 300 µs N/A	Ave. discharge at 6 wks	7 (good)	• n=grp B+ control=53 wounds • diabetic ulcer
Baker (1997-MC)	Biphasic	15x/wk; 3x/d; 30'/session 450'/wk	1 Hz 0.004 V (4mA) 10 µs N/A	Ave. discharge at 6 wks	7 (good)	• n=grp MC+ control=53 wounds • diabetic ulcer
Lawson (2007)	Biphasic	3x/wk; 30'/session	30 Hz 0.2 V (20mA) 200 µs N/A		3 (poor)	• n=20 • pressure ulcer
Baker (1996-A)	Biphasic	15x/wk; 3x/d; 30'/session 450'/wk	50 Hz No contraction 100 µs N/A	Ave. discharge at 3-5 wks	8 (good)	• n=grp A+ control=92 wounds • pressure ulcer (SCI patients)
Baker (1996-B)	Biphasic	15x/wk; 3x/d; 30'/session 450'/wk	50 Hz No contraction 300 µs N/A	Ave. discharge at 3-5 wks	8 (good)	• n=grp B+ control=83 wounds • pressure ulcer (SCI patients)
Baker (1996-MC)	Biphasic	15x/wk; 3x/d; 30'/session 450'/wk	1 Hz 0.004 V (4mA) 10 µs N/A	Ave. discharge at 3-5 wks	8 (good)	• n=grp MC+ control=67 wounds • pressure ulcer (SCI patients)
Lundeberg (1992)	Biphasic	7x/wk; 20'/session	80 Hz Sensory 1 µs Changed daily		6 (good)	• n=64 • diabetic ulcer
Petrofsky (2010)	Biphasic	3x/wk; 30'/session	30 Hz 0.02 V (20mA) 250 µs N/A		7 (good)	• n=20 • diabetic ulcer

Table 3: Summary of Case Studies Analysis [30, 31, 32, 33, 34, 35, 36, 37, 38]

Case Reports	ES Type	Treatment Dose	Frequency Amplitude Duration Charge	Outcome	Comments
Edsberg (2002) pressure ulcer	HVPC + Hyperbaric Oxygen Therapy for 60`bid x7	5d/wk 30`/session 150'/wk	120 Hz 150V 255 pulse pair intervals --	13wks = closure	• healed • Hyperbaric Oxygen co-treatment
Jacques (1997) pressure ulcer	HVPC	5d/wk 30`/session 150'/wk	-- -- -- --	8wks = closure	• healed • parameters lacking
Pollack (2004) pressure ulcer	Monophasic (ES bike)	2x/wk 10`/session 20'/wk	60 Hz Muscle stim 400 µs N/A	13wks = closure	• healed • abnormal protocol • parameters lacking
Ramadhinara (2013) diabetic ulcer	WMCS (Wireless microcurrent stimulation)	7x/wk, 60`/session 420`/wk	-- 0.0000015 -- N/A	6.4wk = closure	• no adverse effects with osteomyelitis • healed • parameters lacking
Fitzgerald (1993)	HVPC	5x/wk, 60`/session 300`/wk	100 Hz 100-120V -- (-) 20'; (+) 40'	10wk = closure	• healed • thoracic wound
Case Series	**ES Type**	**Treatment Dose**	**Frequency Amplitude Duration Charge**	**Outcome**	**Comments**
Lasko (2010)	HVPC + Acoustic Pressure Therapy	3d/wk, 60`/session 180`/1wk	50-80 Hz 100-150V -- (-) until necrotic then (+)	13.5wks = 60% of patients fully closed	• 10 patients • unique protocol (low dose) • Acoustic Pressure co-treatment • 60% of pts healed
Silva (2010) -A, B, C	HVPC	2x/wk, 30`/session  60`/wk for 15wks	-- 100V -- (-)	A: 19% closure B: 30% closure C: 85% closure	• 3 patients • parameters lacking • unique protocol • limited healing
Recio (2012) -A, B, C pressure ulcer	HVPC	3-5x/wk, 60`/session 180-300`/wk	100 Hz 0.1V 10 µs Changed weekly	A: 16wks = 95% closure B: 22wks = 96%	• 3 patients • 1yr f/u healed • stopped treatment at 95% healing

				closure ______________ C: 6wks = full closure	
Ricci (2010) pressure ulcer	Bioelectrical Stimulation Therapy (ES)	tid, 7x/wk, 30'/session 630'/wk	2 Hz 12V 0.04 μs N/A	5wks = 45% of patients fully closed	• 11 patients • 30d f/u • short treatment length • unique protocol

Key: N/A: not applicable; --: not reported; (+): positive; (-): negative

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