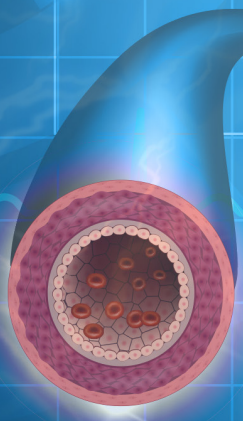
THE EFFECTS OF LOW FREQUENCY NERVE STIMULATION TO SUPPORT THE HEALING OF VENOUS LEG ULCERS



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The goal of this document is to provide a narrative overview of the existing literature and review expert opinion for the use of low frequency nerve stimulation (LFNS) of the common peroneal nerve as an adjunct to best practice treatment of venous leg ulcers.

Introduction

The use of electrical stimulation in health care is far from novel and there is an expansive literature base investigating the physiology behind its clinical effectiveness. It is currently used in many forms to encourage changes in muscle action and function, increase strength and range of motion, reduce edema, enhance blood flow, heal tissue and decrease pain. The physiological effect produced is dependent upon the parameters of the electrical stimulation used.

Broadly speaking, electrical stimulation devices fall into three categories: neuromuscular electrical stimulation (NMES), transcutaneous electrical nerve stimulation (TENS) and functional electrical stimulation (FES).[1] Unfortunately, these terms are often used interchangeably in the literature, which can result in confusion. Therefore, it is important to look at the parameters of the machine in order to determine its effects rather than category labels, as demonstrated in Table 1. For example, low frequency nerve stimulation (LFNS) harnesses the positive effects of pain modulation, circulation augmentation and autonomic nerve stimulation.

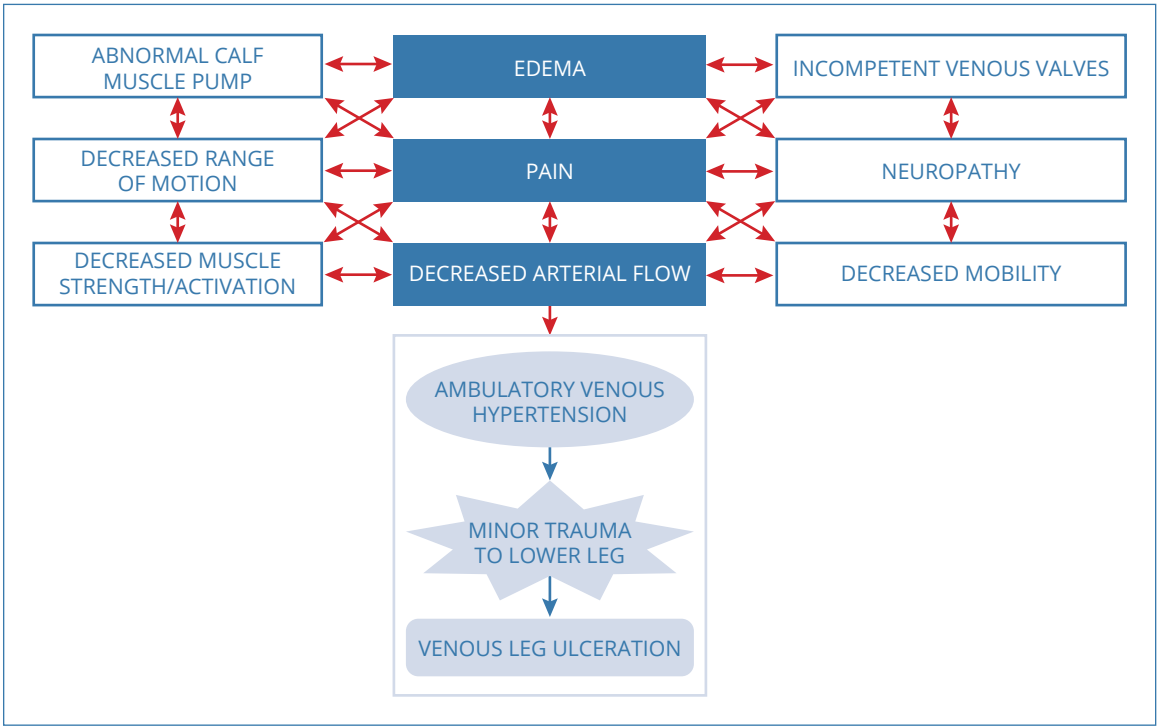
TABLE 1: Types of Electrical Stimulation

TYPE	TYPICAL FREQUENCY	TYPICAL EFFECT
Neuromuscular Electrical Stimulation (NMES)	NMES is typically used at frequencies between 20 and 50 Hz as these are frequencies that activate muscle and motor nerve fibres.	The purpose of NMES is to produce full-range-of-motion muscle contraction.[1]
Functional Electrical Stimulation (FES)		FES refers to pairing traditional NMES with a functional task such as stimulating tibialis anterior and walking.[1]
Transcutaneous Electrical Nerve Stimulation (TENS)	TENS traditionally is administered at frequencies higher than 50 Hz or at low frequencies (1 – 10 Hz) with the goal of providing pain relief. The frequency chosen depends on which mechanisms of pain relief is the focus.[2]	TENS propagates along smaller afferent sensory fibres specifically to override pain impulses. When low frequencies are used, TENS specifically targets sensory nerve fibres and does not activate motor nerve fibres so a full muscle contraction is not produced.[1-2] By stimulating sensory nerves, TENS can also impact autonomic functions such as circulation.[2]

As a result of the positive and cumulative effects demonstrated when applying low frequency nerve stimulation, the ability to enhance healing of venous leg ulcers is now being investigated.

Figure 1 illustrates the complex interplay of factors involved in the development and chronicity of venous leg ulcers and demonstrates that LFNS can impact various stages of the leg and wound physiology to manage odema, pain, blood flow and ultimately healing.

FIGURE 1: Factors that can lead to Venous Leg Ulceration



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Objectives

This paper specifically addresses the use of low frequency nerve stimulation of the common peroneal nerve and its potential to produce some of the previously mentioned physiological effects to enhance wound healing in the lower leg.

Method

A literature search was conducted to gain a better understanding of the evidence describing the physiological effects that LFNS may have on the body. Terms used included *electrical stimulation, leg ulcer, NMES* and *TENS*. The result is a narrative review based on a selected sample of articles based on convenience from that initial search. It is by no means meant to be exhaustive. Instead, it is intended to provide an overview of this area of emerging research and clinical practice.

Overview of the Technology

Nerve stimulation can be delivered using a small self-contained, portable, single-patient-use device that applies stimulation at 1 Hz over the common peroneal nerve in the lower leg. Once the self-adhesive electrodes are applied, the level of intensity is increased, allowing for patient comfort, which causes a small, local muscle involuntary contraction. This is observed as visible twitching in the muscle. The device does not produce full-range-of-motion muscle contraction in the same manner as devices using 20 – 50 Hz stimulation. When this technology has been used to augment healing, current practice is for patients to wear the device for up to six hours daily and wear it on both legs. This technology does not restrict activity or movement and allows patients to continue with their established routines.

Current Research on LFNS and VLU

The current research demonstrates a number of attributes that may directly affect many of the areas of concern outlined in Figure 1. The following sections focus on the specific issues that LFNS have been demonstrated to have had some impact relating to the successful management of venous leg ulcers.

BENEFITS OF LOW FREQUENCY NERVE STIMULATION

1. Improve blood flow
2. Reduce edema
3. Reduce pain

Increased Blood Flow and Improved Circulation

LFNS appears to have positive effects on blood flow in healthy volunteers. As of yet there is limited research in patients with chronic venous insufficiency. To date, the majority of the studies have focused on inflow. Most studies also used treatment times much lower than the six hours that is currently advocated by the manufacturer for use in patients with wounds. More investigation on the physiological effects that occur when the machine is applied for longer periods is warranted. Table 2 provides an overview of the research relating to increased blood flow.

TABLE 2: Evidence For Increased Blood Flow and Improved Circulation

STUDY	PATIENT NUMBERS	SUMMARY OF STUDY AND FINDINGS
Tucker et al.[9]	30 healthy volunteers	Tucker et al. did an initial investigation on the ability of LFNS over the common peroneal nerve to change blood flow in 30 healthy volunteers.[9] The study was conducted while the subjects were in a sitting position. One leg had the device and the other acted as a control. Fifteen sequential sessions of stimulation were applied for five minutes each, with a 10-minute rest period in between for recovery. Different frequencies of stimulation were investigated (1 Hz, 3 Hz and 5 Hz). Blood flow was assessed before, during and after stimulation. Microcirculation and blood flow all increased significantly with stimulation, at all frequencies, and increased as intensity of stimulation increased. Blood flow in the veins specifically also increased with stimulation. The amount of improvement in blood flow increased as more muscle twitch was elicited. Of note is that stimulation at a frequency of 1 Hz had the least effect on blood flow and elicited barely 50% of full dorsiflexion at the ankle.
Williams et al.[10]	10 healthy volunteers	Williams et al. compared LFNS over the common peroneal nerve and intermittent pneumatic compression (IPC) in 10 healthy volunteers to change blood flow.[10] IPC is a technique that is frequently used to augment edema management, blood flow and as a method for DVT prophylaxsis. They found that IPC improved peak venous velocity by 51%, time-averaged velocity by 5% and volume flow by 3%. Stimulation had improvements of 103%, 101% and 101% respectively. Only stimulation was found to improve arterial measures in this study. There is some confusion regarding methods of this study, however. Initially it is stated that the device used has a frequency of 1 Hz, then later it is stated the device has a frequency of 60 Hz. These frequencies would elicit very different physiological effects and have a significant impact on the results of this paper.
Jawad et al.[11]	10 healthy volunteers	Jawad et al. investigated the effect LFNS over the common peroneal nerve had on hemodynamics in 10 healthy volunteers and compared this with two different IPC machines.[11] LFNS increased venous and arterial blood flow by 30%. Microcirculatory blood velocity improved by 370%.
Zhang et al.[12]	14 healthy volunteers	Zhang et al. investigated the effect of LFNS over the common peroneal nerve on force generation, oxygenation and blood flow volume on the immobilized leg of 14 healthy volunteers.[12] The authors also stimulated venous stasis by applying a blood pressure cuff to the leg. The force created in the muscle by stimulation was 2.25 N and was 119 N with active muscle activation. The device created only 2% of the force generated by voluntary contraction. The device caused muscle activation in tibialis anterior and peroneus longus. There was some artifact noted in extensor hallucis brevis and medial gastrocs. Blood volume was increased during the simulated venous stasis by 4–9%.

STUDY	PATIENT NUMBERS	SUMMARY OF STUDY AND FINDINGS
Warwick et al.[13]	10 healthy volunteers	Warwick et al. measured the characteristics of venous flow in 10 healthy volunteers using LFNS over the common peroneal nerve with and without a plaster cast applied to the leg.[13] Venous blood flow had a mean difference of 11.5 cm/second when the device was paired with a cast and 7.7 cm/second without the cast. The device did improve venous flow in both situations but was more effective when combined with the compressive effect of the cast.
Yilmaz et al.[14]	15 patients	LFNS over the common peroneal nerve was applied to 15 patients undergoing total knee replacement surgery in combination with compression stockings and heparin. Venous blood flow was compared with 15 patients who received compression and heparin alone. Those who received stimulation plus conventional therapy had increased peak blood flow velocity that was significantly higher. There was no difference in edema measures.[14]
Barnes et al.[15]	77 patients	In this study of 77 vascular patients, use of LFNS demonstrated a significant reduction in plasma PAI-1 levels, suggesting that it may have a role in augmenting fibrinolysis.[15] LFNS over the common peroneal nerve may also have cellular effects that could enhance blood flow. Patients with lower limb vascular disease often have prothrombotic tendencies, resulting in an increased risk for blood clot formation. Tissue plasminogen activator (t-PA) promotes fibrinolysis (breakdown of clots) through the conversion of plasminogen to plasmin. t-PA is usually inhibited by plasminogen activator inhibitors (PAI) 1 and 2.

Pain Control

Low frequency nerve stimulation causes the release of endogenous opiates and hormones within the body, thereby activating the body's own pain-relief mechanisms.[16] Endogenous opiates and hormones tend to have longer-lasting effects and can also have a whole-body effect when compared with other methods of electrical stimulation used for pain relief. This pain relief, in turn, encourages an increase in patient mobility, thereby reducing the deleterious effects of immobility on venous blood flow (Personal communication via e-mail, Keith Harding, MD, October 2016).

Several of the studies utilizing LFNS reported decreased pain as one of the outcomes (see Table 3).

TABLE 3: Evidence For Pain Control

TYPE	TYPICAL FREQUENCY	TYPICAL EFFECT
Ferguson et al.[16]	21 healthy males	The benefits of LFNS were assessed in professional athletes relating to improving recovery times following strenuous training, extended travel and short rest periods between sporting events.[16-18] The combined use of compression socks with LFNS of the common peroneal nerve accelerated the return of the creatine kinase (CK) level to baseline following two pre-season rugby games, demonstrating the potential for the technique to be used to improve recovery-stress state in professional athletes.[17]
Beaven et al.[17]	25 professional rugby players	
Forst et al.[19]	19 patients	Forst et al. investigated the uses of LFNS in 19 patients with mild to moderate diabetic neuropathy in a double-blind randomized study.[19] One group received treatment using the technology while the other group received a placebo treatment with an inactive device. It was hypothesized that the patients with neuropathy would not be able to feel the treatment. These patients were reassessed at six and 12 weeks of treatment. There was significant improvement (42%) of the neuropathy total symptom score after six weeks and a further 32% after 12 weeks. A component of this score is pain and when analyzed, this sub-component also improved significantly.
Taylor et al.[18]	28 professional rugby and football players	The use of LFNS following an intensive training session with professional rugby and football players resulted in significantly lower perception of muscle soreness ($P = 0.02$) and CK concentrations ($P<0.001$) 24 hours post-sprints.[18] In this case there could be a potential placebo effect because the athletes were aware of which treatment group they were a part of for these studies.
Ivins et al.[5]	10 patients	Several case studies that utilized LFNS as a treatment for long-standing chronic lower leg wounds of varying etiologies noted that up to 90% of individuals indicated a marked reduction in pain and a subsequent reduction in narcotic usage.[5-6]
Brooke et al.[6]	3 patients	

While there is sparse research into the use of LFNS specifically in patients with venous leg ulceration to address their pain, the use of low frequency stimulation is well known to reduce pain from many different etiologies. It is used in a variety of health-care settings to do so. Therefore this modality could have the potential to do the same with this patient population. An emerging area of further research could be the effect this technology has on neuropathy of various etiologies.

Venous Stasis

It is well established in the literature that a complex interplay of factors in the lower leg can contribute to chronic venous insufficiency (see Figure 1). Among these factors are DVT, incompetent valves, impaired calf muscle pump and inactivity. Impaired venous outflow and edema then lead to further complications; this is cyclical in nature. Investigations into the ability of the LFNS approach to address this are underway.

TABLE 4: Evidence in Support of Venous Stasis

STUDY	PATIENT NUMBERS	SUMMARY OF STUDY AND FINDINGS
Wou et al.[20]	10 healthy volunteers	Wou et al. compared the effectiveness of grade 2 graduated compression stockings and two different LFNS devices in managing the dependent edema of 10 healthy subjects.[20] Measurements of leg volume using ultrasound were taken at the beginning of the day and again six hours later to establish change in edema. Subjects wore each intervention on different days. The graduated compression stockings were found to be most effective in managing edema. No difference was found between the LFNS devices.
Wainwright et al.[21]	NK	Wainwright et al. compared the effect of LFNS to the use of knee-high thromboembolic deterrent stockings (TEDS) in managing edema in patients who underwent total hip replacement.[21] It was found that the patients who used electrical stimulation technology had a mean change in swelling of 1.5 cm (+/- 0.3 cm) and those who used TEDS had an increase of 2.9 cm (+/- 0.6) cm. No information was given on the number of patients in this trial. Of note is that TEDS are not designed to manage edema in patients who do not spend the majority of their day in bed and no information was given on activity levels of the patients; thus it is difficult to make a true comparison.
Griffin et al.[22]	18 healthy volunteers	Many of the studies investigating blood flow changes using LFNS technology focus on inflow. Changes in outflow are more indicative of an intervention's ability to change edema. Griffin et al., however, did investigate the volume of ejected blood in a single-centre open-label intra-subject study in 18 healthy volunteers using LFNS.[22] They found that the ejected volume of blood per stimulus (while the device was active) was increased by 113% in the peroneal vein, by 38% in the posterior tibial vein and by 50% in the gastrocnemial vein. No information was given regarding parameters.

Further study is required to elucidate the mechanisms behind improved venous blood flow with the use of LFNS over the common peroneal nerve. Assessment of ejection fraction and direct comparison between use of LFNS over the common peroneal nerve and full-force contraction of the gastroc and soleus calf-muscle pump would be beneficial to help determine the actual physiological effects behind the demonstrated improvements in edema.

Wound Healing

Direct electrical stimulation to the wound bed has been used to stimulate wound healing by creating an electrical field across the wound that is understood to encourage cellular growth and, hence, wound healing. In application, electrodes are placed either adjacent to or in the wound.[23] There is meta-analysis evidence to support its use to support healing of wounds.[24]

This use of direct electrical stimulation is not the same as the application of the LFNS to the lower extremity with the goal of edema management, pain relief and/or increased blood flow. The aim of LFNS is to optimize these conditions for wound healing, as outlined above, while direct electrical stimulation stimulates the wound itself.

TABLE 5: Evidence for Wound Healing

STUDY	PATIENT NUMBERS	SUMMARY OF STUDY AND FINDINGS
Ogrin et al.[4]	14 older adults	Ogrin et al. showed increased C-fibre activation with the use of LFNS applied to the common peroneal nerve and high-level compression over high-level compression alone in a small double-blind, placebo-controlled randomized trial in 14 older adults with chronic venous leg ulcers.[4] Microvascular improvement was similar in both groups. They did not demonstrate improved healing between the groups. However, when the size and chronicity of the wounds was taken into consideration, the largest and longest wounds had a trend to heal more quickly with the electrical stimulation and compression. The treatment with the device also only lasted five minutes twice daily. This may have not been long enough to elicit effects. While the study size was small, this research is intriguing because C- fibre activation is important in the inflammatory response that promotes healing. Therefore, methods to improve this activation in patients with venous disease could benefit healing outcomes. The improvement of C-fibre activation is also an indicator of the reversal of the neuropathy that may have developed as a result of chronic edema.
Ivins et al.[5]	10 patients	Ivins et al. evaluated an LFNS device on individuals (n=10) with differing lower limb wounds (venous leg ulcerations, mixed leg ulcers, diabetic foot ulcers).[5] The reported preliminary findings were suggestive of potential acceleration of wound healing with the use of LFNS therapy over the common peroneal nerve.
Brooke and Loney[6]	3 patients	Brooke and Loney reviewed the use of a LFNS device on challenging, refractory (non-healing for up to 10 years) venous leg ulcer and diabetic foot ulcer patients from the community setting.[6] These individuals received LFNS stimulation over the common peroneal nerve for several hours at a time. Individuals were deemed to be their own controls as no other modalities/ treatments had been successful in closing their particular wounds. The authors reported a marked improvement up to and including wound closure and discharge from service.

STUDY	PATIENT NUMBERS	SUMMARY OF STUDY AND FINDINGS
Ingrves et al.[7]	2 patients	Ingrves et al. presented two case studies involving patients with multifactorial and refractory leg edema who also suffered from wounds to their legs.[7] After 10-week trials using LFNS to the common peroneal nerve, there was a visual improvement of edema based on photographs and a modest decrease in wound size.
Williams et al.[8]	3 patients	Williams et al. reported a series of three case studies involving patients with lower leg ulcers of mixed venous and arterial etiology.[8] These patients also showed modest improvement in ulcer characteristics and wound surface area after treatment using LFNS to the common peroneal nerve.

At this time, literature to support the use of LFNS over the common peroneal nerve and wound healing specifically in venous legs ulceration is limited and in general is company-specific. Many of the reported case studies included multiple wound types and it is therefore difficult to discern how the therapy impacted venous leg ulceration specifically.

Although current literature is inconclusive, the evidence presented above does demonstrate that this modality does have benefit in addressing pain and neuropathy, venous stasis and blood flow. These impairments have important impact on a patient's ability to heal, particularly in patients with venous leg ulcers.

Indications for Use and Patient Selection

The premise of LFNS, as discussed above, is to aid in the improvement of venous and arterial blood flow and reduce pain in individuals with chronic lower leg edema of mixed etiology. As optimization of the patient's status is a necessity for wound healing, clinicians might consider this technology as a part of their toolkit for the prevention and treatment of lower leg ulcers.

While further research is required to fully explore the potential of LFNS as a wound healing modality, clinicians should consider its use in challenging and refractory wounds that are not responding to traditional treatments.

Patient Selection

There is no clear patient selection guidance provided in the literature because much of the emerging evidence is from case studies or involves healthy participants. However, clinicians could consider the use of LFNS:

- to benefit patients who are at risk for developing DVT
- to manage lower leg edema that is contributing to reported pain
- to manage stalled, chronic lower leg wounds that are not progressing along the expected healing trajectory
- in conjunction with compression or when compression cannot be tolerated
- to benefit patients who have lower leg neuropathy
- for patients with fixed ankle joints, those who are bed ridden or those who have limited mobility

Warnings and Precautions

Regarding electrical stimulation in general the following warnings and precautions for use are:[25]

- on areas where it could cause malfunction of electronic devices, such as cardiac pacemakers
- to acupuncture points of pregnant women
- to regions of known or suspected malignancy
- on persons with active DVT or thrombophlebitis
- on actively bleeding tissue or on persons with untreated hemorrhagic disorders
- to infected tissues
- on persons with tuberculosis
- to wounds with underlying untreated osteomyelitis
- to recently irradiated tissues
- to damaged or at-risk skin areas that would result in uneven conduction of current (excluding open wounds where the specific intent is to use electrical stimulation for tissue healing)
- over areas that maybe unstable due to recent surgery, bone fracture or osteoporosis

Safety

Some modalities can cause a skin reaction but these rarely require the discontinuance of therapy and can be managed with routine skin care. While skin reactions could be considered mild adverse reactions, they need to be of concern in patients who have impaired skin integrity.

Another potential concern for any electrical device (which to date has not been reported with this therapy) is the causing of ischemic pain. This pain could potentially be caused by creating a draw for blood flow that the body is unable to supply due to artery calcification and actually increasing edema by causing increased arterial flow in patients who are not able to return that blood back to the heart.[25]

In general, LFNS appears to be well tolerated with adverse effects limited to muscle soreness and in some cases, localized skin reactions.

Recommendations for Use

The literature on LFNS use is still sparse and studies using the technology have used varying protocols. Therefore, an optimal protocol for the use of LFNS in the management of venous leg ulcers has yet to be determined. The majority of studies used healthy volunteers, and time of stimulus has been short when compared with the manufactures' recommendations for use in patients with chronic venous insufficiency. Further research needs to be done in order to determine optimal parameters for this patient population. Early expert opinion would suggest that an evaluation over a four-week period, and beginning cautiously, would be a good starting point to determine if LFNS has a patient-specific benefit.

Conclusion

Despite the widespread use of LFNS for the treatment of acute muscle injuries and the prevention of venous thromboembolism,[13-14] there is limited literature pertaining to the use of LFNS in the management of venous leg ulcerations. Numerous case studies presented at national conferences have reported the potential role of LFNS in wound healing and serve to highlight the need for further research into this modality.

Although the literature is limited, stimulation of the common peroneal nerve in the lower leg using LFNS may be a comfortable and practical method to support healing of venous leg ulcers. The cumulative effects of using LFNS — of improving circulation (arterial and venous) as well as reducing pain and associated improved mobility — have shown to have positive effects on wound healing.

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