Original Article

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Effects of Electrical Stimulation on the Management of Ischemic Diabetic Foot Ulcers

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ABSTRACT

BACKGROUND AND OBJECTIVE: Diabetic foot ulcer is a major complication caused by diabetes. Electrical stimulation is considered as an efficient modality of diabetic wound healing. This study aimed to investigate the effects of direct-current stimulation of cathodal on skin temperature and acceleration of ischemic diabetic foot ulcer closing.

METHODS: This randomized, single-blinded, clinical trial was conducted from November 2013 to September 2014 on 20 patients with type II diabetes suffering from ischemic diabetic foot ulcers. Subjects were randomly divided into two groups of electrical stimulation and placebo. The electrical stimulation group received direct-current cathodal stimulation to the wound for one hour a day, repeating three days a week (4 weeks, 12 sessions), and the placebo group underwent the same procedure with zero-intensity electrical stimulation. Skin surface temperature was measured in the plantar and dorsal areas of the diabetic foot before and after the intervention at sessions one, six and twelve. In addition, the surface of ulcer area was measured at the same intervals (IRCT: 2014110819854 N1).

FINDINGS: Comparison of the study groups indicated the mean of skin temperature changes to be significantly higher in the stimulation group compared to the placebo group at sessions one (p=0.01, 0.41±0.2 and 0.75±0.26), six (p=0.01, 0.25±0.27 and 0.6±0.21) and twelve (p=0.007, 0.25±0.27 and 0.66±0.23), respectively. In addition, reduction of the wounded area was considerably higher in the electrical stimulation group (52.68%) compared to the placebo group (38.39%) at session 12 (p=0.02).

CONCLUSION: According to the results of this study, direct-current cathodal stimulation could improve skin temperature and accelerate wound closing in ischemic diabetic ulcers.

KEY WORDS: Electrical stimulation, Leg ulcers, Diabetic foot, Wound healing, Skin ulcers, Diabetes.

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Introduction

Diabetic foot ulcer (DFU) is a major complication caused by diabetes. Approximately 15% of all diabetic patients experience DFU at least once during the course of their disease, and mismanagement of wound treatment may lead to amputation in 7-20% of these patients (1, 2). DFU and amputation affect the daily performance of patients leaving a substantial economic burden on the health care system of a country.

Therefore, prevention of DFU and amputation has to be prioritized by the medical experts of a society. So far, treatments used to enhance the healingprocess of diabetic ulcers have not yielded the desirable outcomes;thus, scientific efforts continue as to discover the appropriate treatmentsfor rapid diabetic wound healing. Electrical stimulation is a modality proposed to accelerate the healing process of chronic wounds (3-5).

This method increasesthe density of capillaries andblood circulation in human wounds(6-8). In one study, Petrofsky et al.reported that blood circulation would increase after the induction of electrical stimulation in patients with grade 3 and 4 DFU. According to their findings,blood flow increasesby 53% in the wound surface area and remains the same after the stimulation (8).

In another study, researchers evaluated the role of electrical stimulation and heat separately in the healing process of chronic wounds. They concluded that the combination of heat and electrical stimulation was more effective in increasingblood circulation,reducing the severity of chronic wounds and improving the healing process of wounds compared to the separateuse of each of these parameters (7). In addition, they observed that in normal skin,wound fringes,oxygen levels and skin perfusion increased before and after the induction of electrical stimulation (transcutaneous oxygen pressure: TcPo2) (9, 10).

In several studies performed on animal models,biopsy of scar tissuesindicated that electrical stimulation could increase the expression of angiogenic factors, density of capillaries and angiogenesis of scar tissues(11-13). In a systematic review,it was stated that despite the potential advantages of electrical stimulation in the treatment of diabetic ulcers, interpretation and generalization of the results to all diabetic patients should be performed with caution due to the lack of sufficient and high-quality clinical studies, as well as the different etiologies of diabetic wounds in these studies(14).

Although the differences in the etiology of diabetic ulcers could affect the treatment outcomes of electrical modalities used forwound healing, there is insufficient information on the precise etiology of diabetic ulcers in most of the studies in this regard. Furthermore,it is unclear whether the wound improvement caused by the use of electrical stimulation could be achieved in case of other ulcers with different etiologies (14). Since blood perfusion and inadequate circulationcould significantly delaythe healing process of diabetic ischemic wounds (15), conducting clinical studies in order to evaluate the exact effects of electrical stimulation on the acceleration ofischemic DFU seems necessary. Previous studies have indicated that direct-current cathodal stimulation could increase the expression of angiogenic factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2), in the cut wounds of animal models. Moreover, this method could enhancethe plasma levels of VEGF and nitric oxide (NO) in DFU patients (11,13,16). The present study aimed to evaluate the effects of direct-current cathodal stimulation on the temperature of foot skin surfaceand acceleration of ischemic DFU.

Methods

This single-blinded, randomized, clinical trial was conducted on patients with type II diabetes and ischemic DFU referring to Hajar Hospital from September 2013 to December 2014 (registration number: IRCT: 1N2014110819854). After obtaining permission from the Ethics Committee of Tarbiat Modarres University, written informed consent was provided from the patients. Inclusion criteria for ischemic DFU were as follows:1) lacking or decreasedpulse dorsalis pedis artery and posterior tibial artery (0.5<ankle-brachial index<0.9) (grade 2 based on Wagner Ulcer Classification)(17) under the ankle (HbA1c<8.2);2) lack of participation in other research projects within thepast month or at the time of this study and 3) presence of mild-to-moderate neuropathy according to the Diabetes Foot Screening table (UK). Exclusion criteria were the presence of

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severe wound infections with purulent discharge, previous angioplasty, osteomyelitis, skin diseases andhistory of drug abuse. Sample size of the study was calculated with 80% power and5% margin of error (α) consisting of 10 patients based on the results of previous studies in this regard (8). In total, 24 patients (male and female) with type II diabetes and ischemic DFUwere enrolled in this study in accordance with the inclusion criteria, and 4 were excluded from the studydue to disagreement to receive treatment or hospitalization. The remaining 20 patients were randomly divided into two groups of electrical stimulation (N=10) andplacebo (N=10).

Anthropometric features of the subject sinc luding age, gender, height, weight, type of wound or ulcer, neuropathic severity and wound duration were recorded. Before the intervention, the dressing on the wound was removed and thesurrounding areaswere sterilized usingserum and gauze.The electrical stimulation group received direct-current stimulation with sensory threshold implemented for one hour per session three times a week (12 sessions). Parameters used in this study were determined based on the criteria of previous studies (11,13,16,18,19).

Due to the possibility of disabilitiescaused by neuropathy in diabetic patients, a pilot study was conducted to estimate the sensory threshold ratio of the frontal forearm to the frontalleg,and the frontal thigh to the frontal anterior leg in four healthy subjects.Obtained ratios were used to determine the sensory threshold of the patients in the electrical stimulation group. During the first session and before the intervention, sensory thresholdsof the anterior thigh and forearm were recorded and calculated, and the severity of sensory threshold of legs was determinedbased on the ratios obtained fromthe healthy volunteers in the pilot study. To install the electrodes,the negative electrode (cathode) was placed near the wound and secured with a strap, and the positive electrode (anode) was installed in the proximal tibia (fig 1).

In order to avoid the complications of direct-current stimulation, such as chemical burns,the surface under the electrodes was controlled regularly, and the electrodes were moved around the wounds every 10 minutes. The placebo group underwent the same procedures as the stimulation group without the induction of any electrical stimulation. Since this was a single-blinded study, all intervention processeswere identical between the two groups ofelectrical stimulation and placebo, and the patients remained unaware of treatments.

Figure 1. Electrode Installation: Cathode installed nearthe Wound (Ulcer located on the First DorsalMetatarsal Artery)/Anode placed in the Proximal Tibia

During the study, all the patients received standard treatmentsconsisting ofwound cleaning with saline and gauze dressing, and the staff in charge wasuninformed on the type of interventions as well. All the stages of interventions, as well as the calculation of different parameters, were performedby the principal researcher in both study groups.Skin surface temperature was measured at sessionsone, 6 and 12before and after the intervention using a thermometer (model: HT-3006, LUTRON, Taiwan). In addition, plantar and dorsal foot skin temperatures were measured at five different spots in both extremities(16). Skin temperature measurements were repeated twice, andthe mean of temperature was calculated for each section.To measure the wound surface, we applied a two-dimensional measurement technique using a standard ruler; thevalidity of this method has been approvedby previous studies (20).In this technique,the standard ruler was placed at the length of the ulcer, as well as its width, and images of the wound were captured using a digital camera (Casio Exilim QV-R200, Japan). Wound surface area was calculated in square centimeters(cm^2) inDesign CAD software, andwound area measurementswere performed at days one, 6 and 12 of the study in both groups (16). At the 6^{th} and 12^{th} sessions, the reduction in the wound surface was calculated using the following formula:

$$([S1^{st} - S6^{st}(\text{or } 12^{st})]/S1^{st}) \times 100$$

$$\text{Wound area at first day} = S1^{st}$$

$$\text{Wound area atdays 6 and 12} = S6^{st}(12^{st})$$

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Data analysis was performed using SPSS V.16,and Kolmogorov-Smirnov test was used to determine the normal distribution of the quantitative data. According to the results of this test, the data had a normal distribution. For the comparison of results between the two groups at different intervals, independent T-test was used, and to compare the qualitative variables of the demographic data, we used the Chi-square test (2χ). In this study, $p<0.05$ was considered as significant.

Results

In this study, no statistically significant difference was observed between the two groups in the comparison of demographic data (table 1). Mean of wound surface area in the stimulation and placebo groups reduced from 4.05±2.01 and 4.27±2.3 cm^2at the first session to 3.12±1.3 and 3.6±1.6 cm^2 at the 6th session, respectively. At session 12, wound diameters were calculated to be 1.01±0.8 and 2.6±1.1cm^2 in the stimulation and placebo groups, respectively. Comparison of the wound surface areas at sessions one and six showed no significant differences between the two groups.

Table 1. Demographic Characteristics of Patients in the Stimulation and Placebo Groups

Variables \ Groups	Electrical Stimulation Mean±SD	Placebo Mean±SD
Age(year)	60±5.7	59.33±4.2
Gender(%)	Male(63.3%)	Male(50%)
*BMI(kg/m^2)	24.5±3.31	22.08±1.2
Duration of Disease(years)	9.1±3.31	10.3±2.4
Wound Duration (months)	3.4±0.96	2.9±0.97
History of Foot Ulcer(%)	20	10
Wound Surface(cm)	4.05±2.01	4.27±3.2
Severity of Neuropathy		
Mild(%)	30	40
Moderate(%)	70	60
**FBS(mg/dL)	138.1±37.3	136.6±31.41
Glycosylated Hemoglobin (HbA1c)(%)	0.8±0.3	0.75±0.1
Creatinine(mg/dL)	1.1±0.29	1.15±0.21
***ABI	0.88±0.05	0.87±0.07

No significant difference in demographicsbetween the groups,*Body Mass Index, **Fasting blood sugar, ***Ankle-brachial index

However, the mean of wound area had a significant reduction in the stimulation group compared to the placebo group at session 12(p=0.06). Reduction in the wound area at the6thsessionin the stimulation and placebo groups was calculated to be 20.89% and 13.53%, respectively and 52.68% and 38.39% at session 12, respectively. Comparison of wound surface reduction between the two groups at the 12th sessionwas indicative of a statistically significant difference (p=0.02) (fig 2).

Mean of skin temperature changes in the stimulation and placebo groups at sessions one, 6 and 12was 0.75 ±0.26 and 0.41 ±0.2,0.6 ±0.21 and 0.25 ±0.27 and 0.66 ±0.23 and 0.25 ±0.27°C, respectively. During all the three sessions, changes of skin temperature were more significant in the stimulation group compared to the placebo group (p=0.01, p=0.01 and p=0.007, respectively). Compared to the first session (before intervention),mean of skin temperature changesat sessions6 and 12(before intervention) in the stimulation group was 0.18 ±0.1 and 1 ±0.13°C, respectively, and 0.16 ±0.1 and 0.56 ±0.15°C in the placebo group, respectively. Changes in the skin temperature at session12 were more significant in the stimulation group compared to the first session; however, this difference was not considered to be statistically significant (fig 3).

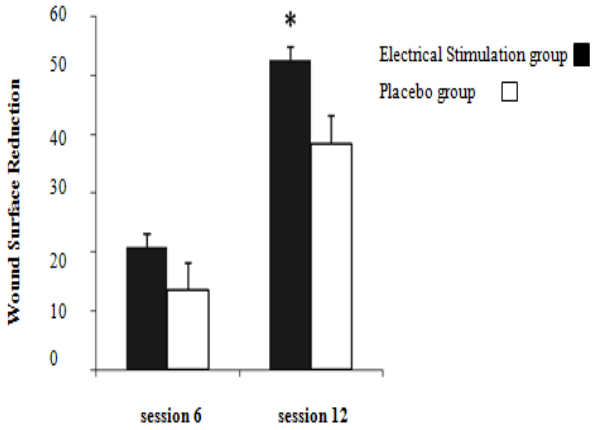

Figure 2. Wound Surface Reduction in Electrical Stimulation and Placebo Groups. *Values presented in Mean±SD. Wound reduction at session 12 was significantly higher in the electrical stimulation group compared to the placebo group($p<0.05$)

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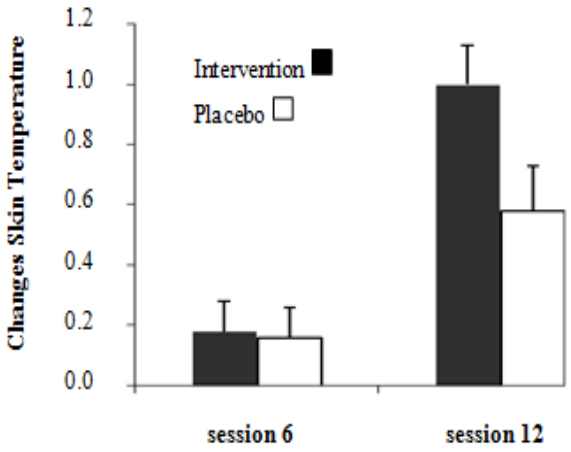

Figure 2. Changes in Skin Temperature at Sessions 6 and 12compared to the First Session (before intervention)

Discussion

According to the results of this study, electrical stimulation could increase foot skin temperature in ischemic DFU. Furthermore,analysis of skin temperature changes immediately after the use of electrical stimulation in the stimulation group indicated that electrical stimulation could steadily increase the skin temperature of the diabetic foot. Furthermore, comparison ofskin temperature changes at session 12(before intervention)with the first session (before intervention) indicated that electrical stimulation could cause a more significant increase in the rate of skin temperature changes in the stimulation group compared to the placebo group;however, this increase was not statistically significant.The findings of the present study are compatible with a study conducted by Mohajeri-Tehrani et al. According to their results, electrical stimulation increased the skin temperature of leg surface in DFUpatients (16). In another study, Aldayel et al.reported that skin temperature in healthy individuals significantly increased within10 minutes after the induction of electrical stimulation on the quadriceps muscles compared to the control group (21). Similarly, Motieollah et al.observed that the use of high voltage direct-current stimulation (340 volts) could result in an increase in the skin temperature of healthy adults by causing relaxation in the vascular walls and enhancing blood circulation(22).On the other hand, evidence suggests thatdirect-current stimulation has no effects on skin temperature and blood circulation. However, it should be noted that in most of the studies supporting this argument, electrical stimulation has been applied on healthy skin tissues rather than skin wounds or ulcers.

In one study, Sandberg et al. reported that induction of biphasic current stimulation on the trapezius muscle ofhealthy individuals for 15 minutes could increase blood circulation in the muscle, while exerting no effects on the temperature of the overlying skin and blood flow (23). In addition, Chen et al. claimed that applying transcutaneous electrical nerve stimulation(TENS) on the forearm skin of healthy individuals had no effects on the blood circulation and temperature of the skin (24). As previously noted, these findings mainly apply to healthy skins,which differ from the pathology and physiological responses of wounds to electrical stimulation. Moreover, the conflicting results of these studiesmight be due to the differences in the type of the electrical current or use of short-term electrical stimulation. Regarding the fact thatskin temperature is directly affected by the blood flow under the skin (25), it seems that the observed increase in the temperature immediately after the stimulation, as well as the temporary effects of electrical stimulation on skin temperature, could be associated withthe vasodilation caused by electrical stimulation on blood vessels.By releasingNO, as a coronary vasodilator, or inhibitingsympathetic vasoconstriction tone, electrical stimulation may cause increased blood circulation (25).

In the present study, it seems that the increasein skin temperature immediately after the induction of electrical stimulationoccurred due to the temporary increasein skin blood flowin the stimulation group.Before intervention, increased skin temperature at session 12 compared to the first session,which was indicative of the permanent effects of electrical stimulation on skin temperature, could be caused bythe angiogenic effects of electrical stimulation in the wound surface area. Several studies have confirmed that byreleasingangiogenic factors, such as VEGF and FGF-2, electrical stimulation could enhance angiogenesis in wound repair in animal and human models (11-13, 16, 29, 30). It is probable that in the current study,the increase in skin temperature of the stimulation group at session 12 compared to the first session was due to the increasedangiogenesis caused by the induction of electrical stimulation in

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the wound surface area. However, lack of statistically significant differencesin skin temperature changes at sessions 6 and 12compared to the first session might be due to the limited number of investigated samples. Therefore, repeating this experiment on a larger sample size with DFUcould yield data that are more reliable. Another important finding of the current study was the significant wound surface reduction at sessions 6 and 12 in the stimulation group compared to the placebo subjects, and this difference was observed to be significant at the 12th session of the study. Only a few clinical studies have reportedthe use of electrical stimulation,along with standard wound therapy,toaccelerate the process of wound repair in DFUpatients (7, 9, 31-33);this finding is consistent with the results of the present study. In a case presentation, Yarboro et al.appliedelectrical stimulation (TENS) on the right foot of a patient with ischemic DFUfor three months.After4 weeks,wounddiametersdeclined by 45% and 12 weeks later, the wound closed completely (34). In another study, Lawson et al. reported that using biphasic current stimulationfor 4 weeks reducedDFU (grade 3 and 4) by 70% (35). In addition, Petrofsky et al.demonstrated that biphasic current stimulation along with local heat accelerated the reduction of wound area in patients with DFU (7).

The findings of Baker et al. (31) and Lundeberg et al. (32) were indicative of a significant reduction in DFUcaused by the use of electrical stimulation. Similarly, Mohajeri-Tehrani et al. reported that the use of cathodal DC polarization for 12 sessions decreased wound surface area ofDFUsby 31% in the stimulation group compared to the control group (9%) (16). One of the limitations in studies conducted in this regard isthe unclear ischemic and neuropathic origins of ulcers, which could affect theobtained results;in the present study, all the examined wounds were of the ischemic type. Since natural bioelectric currents may be disrupted in chronic wounds, induction of low-intensity direct-current stimulationcould facilitate the process of wound healing by simulating the natural bioelectric current (36). Fibroblasts, epithelial cells and keratinocytesplaya pivotal role in collagen releaseand wound closing. In the electric field, these cellstend to movetowards the negative pole (i.e. cathode) (37,38), and the migration and proliferation of these cells are impaired in the presence of diabetic ulcers (15). Consequently, it seems that by simulating the natural bioelectric currents in the wounds, cathodal DC polarization was able tofacilitate the migration of these cells (fibroblasts, epithelial cells and keratinocytes) to the diabetic wounds and accelerate the process of wound closing in this study.

According to the results ofthe present and previous studies, electrical stimulation could increase the blood supply in wounded tissues,leading to temporary wound repairthrough vasodilation or permanent repair through angiogenesis.Therefore, it seems that the increased blood flow caused by the use of electrical stimulation in ischemic diabetic ulcers was the most important contributing factor to wound surface reduction in the stimulation group in the present study. Some of the limitations of this studywere the small sample sizeand lack of the direct measurement of blood flow in the woundedareaand TcPo2of the skin. In this regard, Doppler laser and measurement of skin oxygen pressure are recommended for a closer examination of the effects of electrical stimulation on blood circulation in ischemic diabetic ulcers.

Furthermore, examination of the angiogenic factors and their receptors located in the wound areas of human models could be useful in determining the angiogenic effects of electrical stimulation on the process of wound healing.In conclusion, the results of the present study indicated that induction of electrical stimulation based on the parameters used in this studycould improve the blood circulation and skin temperature around wounds,leading to the acceleration of wound closing in patients with ischemic diabetic ulcers..

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