Effect of Low Intensity Cathodal Direct Current on Rate of Healing and Quality Of Life in Diabetic Patients with Ischemic Foot Ulcer

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Submitted: 2016-02-18; **Accepted**: 2016-06-25

Introduction: Adjunctive treatment using electrical stimulation has recently been shown to promote healing in patients with diabetic foot ulcer. The aim of the present study was to evaluate whether low intensity cathodal direct current electrical stimulation improves healing rate of foot ulcers and health related quality of life in diabetic patients. **Materials and methods:** A total of 30 type 2 diabetic patients with ischemic foot ulcer were included in the present randomized, single-blind, placebo controlled trial. Participants were randomly assigned to receive either electrical stimulation therapy (direct current with low intensity, ES group, n=15) or sham treatment (placebo group, n=15) for 1 h/day, 3 days/week, for 4 weeks (12 sessions). Improvement ratio of wound and quality of life was evaluated at the 1st and 12th sessions. The quality of life was assessed using SF-36 questionnaire. **Results:** The mean of improvement ratio was significantly higher in the electrical stimulation group (59.4%) compared with that of the placebo group (27.07%) at the 12th session (P=0.02). Overall score of quality of life significantly increased in the electrical stimulation group as compared with that for the placebo group (0.01). **Conclusion:** By promotion of wound healing, applied low intensity cathodal direct current may increase the health-related quality of life in diabetic patients with ischemic foot ulcer.

Key words: Diabetics, Ischemic foot ulcers, Low intensity direct current, Wound improvement rate, Quality of life

Please cite this paper as: Asadi MR, Torkaman G, Hedayati M, Mohajeri-Tehrani. MR Effect of Low Intensity Cathodal Direct Current on Rate of Healing and Quality of Life in Diabetic Patients with Ischemic Foot Ulcer. J Clin Physio Res. 2016; 1(2): 68-72. Doi: 10.22037/jcpr.2016.05

Introduction

Diabetic Foot Ulcer (DFU) is one of the most serious complications of diabetes mellitus and 15% of the individuals with diabetes mellitus will experience this complication during their lifetime (1). There is evidence to show that the presence of DFUs has a serious deleterious effect on the Quality of Life (QoL) for both the individuals affected and their careers (2).

The previous studies have reported that QoL is significantly lower in patients with current DFUs than in patients with healed ulcers (3). Improved techniques and interventions that result in more effective and rapid healing of DFUs could reduce both the period of mobility restriction and patient's dependency on their careers. Faster foot ulcer healing would have important positive psychological effects. It seems that improved management of DFUs could have major QoL benefits for both the individuals affected by the condition and their careers not to mention its obvious positive effects on general health (3).

Meanwhile, numerous reports (4-6) demonstrated that Electrical Stimulation (ES) used adjunctively with other standard wound care enhanced wound healing rate in animal and human wounds. ES therapy involves the transfer of electrical current across wound tissues, usually via two electrodes. The net effect of this current is to induce a flow of ions through the wound bed. It has been proposed that an external ES mimics the human body's endogenous bioelectric systems that attract neutrocytes, leukocytes, macrophages, and fibroblasts toward wound site, and also improves collagen synthesis (7). Some studies have shown that ES increases blood flow to the skin and promotes wound healing (8-10). The mechanisms by which ES increases the healing of chronic wound are not still well-known, but it seems that ES has the potential to accelerate wound healing by stimulating some physiological processes that are effective to the recruitment of related cells and chemical mediators in different phases of healing.

ES is also shown to improve the healing rates of chronic wounds due to different etiologic status, such as diabetes and arterial or venous insufficiency (8, 9, 11-14). In a systematic review, Barnes *et al.* (15) reported that ES appears to increase the rate of ulcer healing and may be superior to standard care for ulcer treatment. Impaired healing in ischemic diabetic ulcers reduces daily living activity of patients and their QoL. Thus, there is a hypothesis that promotion of healing rate in patients with ischemic DFU may have positive effects on various aspects of their QoL.

The primary objective of the current study was to further evaluate the clinical effect of ES on the promotion of wound healing rate and health-related QoL in DFU patients.

Methods and Materials

Design overview

All type 2 diabetic patients with foot ulcer treated at Hajar Hospital in Tehran, Iran, between November 2013 and September 2014 were eligible to participate in the current single-blind, randomized controlled trial. The study was approved by the medical ethics committee at Tarbiat Modares University (Ethical reference number: د/52/2570).

Study population

The inclusion criteria were type 2 diabetic patients who had ischemic DFU (ischemia were diagnosed with 0.5<ankle-brachial index<0.9, absence or decrease of pulse rate in dorsalispedis, and tibialis posterior artery), wound size >2cm^2, light neuropathy (based on UK scale), and wound with grade two according to Wagner foot classification. Participants were excluded if they had osteomyelitis, cardiac pacemaker, angioplasty, severe infection, cancer, kidney failure, skin diseases, and any medical condition for which ES is contraindicated. Participants signed the written informed consent prior to entering the study.

Randomization and intervention

Randomized allocation of the participants was managed by trial investigators. Eligible participants were randomly assigned to either ES or placebo groups using permuted blocks (blocks of four, allocation ratio 1:1). Participants were blind to treatment allocation.

In the ES group, patients received cathodal direct current with sensory threshold intensity for 12 sessions, 1 h/d, 3 d/wk during a 4-wk period. To determine the sensory threshold intensity of patients in the ES group, we used the guidelines from our previous study (16). In the present study, negative pole (cathode) of direct current was set to be the active electrode during the treatment period. ES (direct current) was applied to wound site through carbon rubberized electrode (3 × 4 cm) placed near the edges of the ulcer, over the intact skin. Passive electrode (positive pole, 4 × 6 cm) was placed approximately 20 cm proximal to the active electrode and far from the wound on the leg. In the placebo group, all of the study protocol was similar to that described for the ES group, but the current intensity was zero. Standard treatments (included debridement, cleaning of the wound with saline, and ordinary dressing) were applied for all the patients (ES and placebo) during the treatment period. The BTL-5000 series (BTL Industries, Ltd; Staffordshire, United Kingdom) was used as the ES device. Parameters used in the present study were selected according to those used in the previous studies (16-18).

Study outcomes

In order to measure wound surface area (WSA), a digital photograph was taken using a digital camera (Casio Exilim EX-H5, CASIO COMPUTER CO., Ltd, Japan) with a standard metric ruler placed next to the ulcer. Wound surface area was calculated using design CAD software, version 23.0 (IMSI/Design, LLC, Novato, CA). The Mean improvement ratio (MIR) was calculated for each patient using the following formulae: MIR = [(initial WSA–WSA on last session)/initial WSA] ×100.

In order to measure QoL, all the patients completed a self-reported health measurement questionnaire (SF-36) to evaluate their physical and mental function and their QoL both before intervention at the first session and after 12 ES sessions. The SF-36 questionnaire measures eight domains, including physical functioning, bodily pain, general health perception, vitality, social functioning, and role limitations due to physical, emotional, and mental health. Evaluation of reliability and predictive validity of SF-36 indicated that SF-36 includes frequently represented health concepts (19).

Sample Size and Statistical Analysis

According to our previous study and with α equal to 0.05 and a power of 80%, sample size was determined to be 10 patients with DFU in each group. To compensate for the loss of patients, more samples were included in the study (16).

The Kolmogorov-Smirnov test demonstrated that the data was normally distributed in the groups ($P>0.05$). Therefore, paired *t*-tests (to compare data in each group), and independent *t*-tests (to compare data in the two groups) were run for data analysis. Statistical analysis was performed using SPSS (v. 16.0) (IBM Corporation; Armonk, New York). Statistical significance was set at $P<0.05$.

Table 1. Demographic characteristic of participants

	ES group (n=13)	Placebo group (n=11)	*P*-value
Age (year)	60.8 (5.5)	60.1 (6.4)	*P*=0.7
BMI (kg/m²)	24.8 (3.2)	23.6 (2.7)	*P*=0.3
Sex (%)	%63 (Male)	%55 (Male)	*P*=0.1
Duration of diabetes (year)	9.5 (3.3)	10.3 (2.4)	*P*=0.5
Duration of DFU (month)	3.3 (1)	2.3 (1.1)	*P*=0.07
History of DFU (%)	%20	%10	*P*=0.2
Initial WSA (cm²)	4.19 (2.2)	3.82 (1.7)	*P*=0.7
Fasting blood glucose (mg/dL)	137.9 (35.6)	136.6 (31.4)	*P*=0.9
HbA_{1c} (%)	8.1 (1.1)	7.5 (1)	*P*=0.3
Creatinine (mg/dL)	1.2 (0.28)	1.1 (.21)	*P*=0.7
ABI	0.88 (0.06)	0.89 (.14)	*P*=0.4

Table 2. SF-36 domains scores in participants

	First session			Last session		
	ES group (n=13)	**Placebo group (n=11)**	***P*-value**	**ES group (n=13)**	**Placebo group (n=11)**	***P*-value**
Physical functioning	32.91 (5.95)	29.16 (7.35)	0.3	46.53 (5.15)	42.5 (5.24)	0.1
Role limitation due to physical health	38.16 (9.02)	34.37 (6.55)	0.3	52.85 (4.85)	45.95 (6.14)	0.1
Bodily pain	50.42 (11.64)	48.16 (10.2)	0.2	62.65 (12.66)	56.66 (7.35)	0.2
General health	45 (11.6)	36.66 (9.3)	0.1	57.3 (10.72)	46.66 (6.83)	0.04
Vitality	47.4 (14.26)	40.45 (8.3)	0.1	58.92 (10.7)	45.23 (9.04)	0.01
Social function	45.19 (14.91)	43.33 (10.2)	0.3	68.46 (12.01)	56.25 (10.45)	0.04
Emotional health	56.92 (14.65)	46.66 (11.69)	0.1	63.07 (9.69)	52.5 (8.21)	0.03
Role limitation due to mental health	41.63 (7.6)	36.07 (6.77)	0.1	66.48 (11.91)	51.36 (8.18)	0.01
Quality of life score	44.25 (7.5)	38.95 (8.34)	0.1	58.91 (6.93)	49.98 (6.31)	0.01

Data are means (SD), unless otherwise indicated. *P* values were calculated for the difference among groups using independent t test

Results

A total of 30 patients with DFU were included in the study and 24 participants completed the trial (ES, n=13; placebo, n=11). Two patients in the ES group and four patients in the placebo group left the study for personal reasons.

As given in Table 1, patients' baseline characteristics were not significantly different between ES and placebo groups ($P>0.05$).

MIR for the ES and placebo groups were 59.4% ± 10.2% and 27.07% ± 9.7%, respectively. MIR was significantly higher in the ES group than in the placebo group ($P=0.02$).

All the eight domains of the SF-36 are shown in Table 2. In the ES group, the results obtained for social function, emotional health, role limitation due to mental health, vitality, and bodily pain showed a significant increase after 12 sessions ($P<0.05$), whereas no significant improvement was seen in these variables in the placebo group ($P>0.05$).

At the first session, no significant difference was observed between the groups for all eight domains of the SF-36 ($P>0.05$). Whereas after 12 sessions of ES application, social function, emotional health, role limitation due to mental health, vitality, and general health were observed to be significantly higher than those in placebo group ($P<0.05$). Physical functioning, role limitation due to physical health, and bodily pain in the ES group were greater than the same values in the placebo group, but these increases were not significant ($P>0.05$). Overall, the score of QoL in the ES group showed significant improvement as compared with placebo group ($P<0.05$).

Discussion

The results showed that low intensity cathodal ES increased MIR in ischemic diabetic ulcers and caused improvement in the QoL of diabetic patients.

The results of the present study confirmed some findings of the previous studies for improving the healing rate of DFUs using different kinds of ES (9-13, 20). Lundeberg *et al.* (12) conducted a randomized trial involving 64 patients with chronic diabetic neuropathic foot ulcers. Wounds were randomized to receive either Pulsed Current (PC) together with standard care or standard care alone. After 12 weeks, there was a statistically significant positive effect based on the closure of 42% of the wounds in the active ES group compared to 15% of wound closure in the controls. Baker *et al.* (11) evaluated the effect of PC on wound healing of 80 individuals with diabetes and 114 open wounds. The authors showed that pulsed current combined with standard care enhanced the wound-healing rate by nearly 60% compared to control group wounds which were only treated through standard care. In another randomized, double-blind, placebo-controlled trial, Peters *et al.* (8) investigated the effect of HVPC as an adjunct to healing DFUs. The authors demonstrated that 65% of the wounds in the ES group closed, compared to 35% of wounds in the sham group. Lawson *et al.* (21) and Petrofsky *et al.* (9) reported that application of biphasic symmetric PC for four weeks induce promotion of wound healing in patients with DFU. Mohajeri and colleagues (16), too, indicated that 12 sessions of direct current applied to diabetic ulcers reduced the wound surface area to 31 percent as compared with the 10 percent in the placebo group.

The mechanisms by which ES increases the healing of chronic wound are not still well-understood, but in vitro and in vivo studies have suggested that ES especially direct current, based on galvanotaxis effect, may affect migration and proliferation of the cells such as fibroblasts, neutrophils, and keratinocytes and, therefore, promote the healing of chronic wound (22-24). In addition, it has been suggested the positive effects of ES for healing of chronic wound may be due to the increase in expression of angiogenic factors such as Vascular Endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF) in the wound site (17, 18, 25-27).

In the current study, we observed that ES significantly improved the QoL in the patients with DFU. Our results demonstrated that ES significantly improved mental and emotional aspects of patients according to SF-36 score, but no significant change was achieved in physical component in the experimental patients compared with that in the placebo group. Previous studies demonstrated that DFU has deleterious effects on patients' physical and psychosocial functioning and healing of these ulcers leads to improvement of patients' QoL (2, 28-30). Armstrong *et al.* (31) showed that healing of neuropathic foot ulcers by off-loading was associated with improvement of all SF-scales except bodily pain.

In the present study, social function, emotional health, role limitation due to mental health, vitality, general health, and overall QoL score increased significantly in the experimental group; whereas improvement of physical functioning, role limitation due to physical health, and bodily pain were not significant in the placebo group. It seems that improvement of QoL in ES group may be due to the positive psychological effects of ES on faster foot ulcer healing. Therapeutic interventions that result in more effective and rapid healing of DFUs could reduce the period of mobility restriction and patients' dependency, increased social interaction, improved wellbeing, improved self-confidence, and reduced depression (3, 29). Thus, it appears that ES with the parameters used in the current study, by promotion of the healing in DFUs, could affect the social function, mental, and emotional aspects, as well as general health of patients and improved the QoL.

Although the physical functioning score was higher in ES group, as compared with that in placebo group, this increase was not observed to be statistically significant. Both groups received standard dressing, so wound area reduction (with slower rate) was seen in placebo group, too. It is suggested that an existing foot ulcer has a negative influence on the physical aspects of participants' QoL (29). Perhaps the fear of re-opening the wound causes some avoidance behaviors in patients. It seems that after healing the wound, longer period of time should pass to reach the normal weight bearing and to overcome the limitations in daily living activities. This should be considered in future studies by investigating the kinetic and kinematic parameters of gait, foot pressure distribution, and some functional activities after foot ulcer healing in diabetic patients.

Conclusion

The results of the present study support the effectiveness of low intensity cathodal direct current in the treatment of DFUs. By promotion of wound healing, applied ES for 12 sessions could effectively increase the health-related QoL in patients with DFU.

Acknowledgments:
The authors thank the manager and personnel of Hajar Hospital and all the patients who participated in the study.

Conflict of interest:
None

Funding support:
The present project was supported by a grant from Medical Sciences of Tarbiat Modares University, Tehran, Iran.

Authors' contributions:

All authors made substantial contributions to conception, design, acquisition, analysis and interpretation of data.

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