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SHORT COMMUNICATION

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Effective treatment of symptomatic diabetic polyneuropathy by high-frequency external muscle stimulation

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Abstract *Aims/hypothesis:* Diabetic distal symmetrical sensory polyneuropathy (DSP) affects 20–30% of diabetic patients. Transcutaneous electrical nerve stimulation (TENS) and electrical spinal cord stimulation have been proposed as physical therapies. We performed a controlled, randomised pilot trial to compare the effects of high-frequency external muscle stimulation (HF) with those of TENS in patients with symptomatic DSP. *Methods:* Patients with type 2 diabetes and DSP (n=41) were randomised to receive treatment with TENS or HF using strata for non-painful (n=20) and painful sensory symptoms (n=21). Both lower extremities were treated for 30 min daily for three consecutive days. The patients' degree of symptoms and pain were graded daily on a scale of one to ten, before, during and 2 days after treatment termination. Responders were defined by the alleviation of one or more symptoms by at least three points. *Results:* The two treatment groups were similar in terms of baseline characteristics, such as age, duration of diabetes, neurological symptoms scores and neurological disability scores. The responder rate was significantly higher (p<0.05) in the HF group (80%, 16 out of 20) than in the TENS group (33%, seven out of 21). Subgroup analysis revealed that HF was more effective than TENS in relieving the symptoms of non-painful neuropathy (HF: 100%, seven out of seven; TENS: 44%, four out of nine; p<0.05) and painful neuropathy (HF: 69%, nine out of 13; TENS: 25%, three out of 12; p<0.05). The responders did not differ in terms of the reduction in mean symptom intensity during the trial. *Conclusions/interpretation:* This pilot study shows, for the first time, that HF can ameliorate the discomfort and pain associated with DSP, and suggests that HF is more effective than TENS. External muscle stimulation offers a new therapeutic option for DSP.

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Keywords Diabetes mellitus · Distal symmetrical sensory polyneuropathy · High-frequency external muscle stimulation · Transcutaneous electrical nerve stimulation

Abbreviations DSP: distal symmetrical sensory polyneuropathy · HF: high-frequency external muscle stimulation · TENS: transcutaneous electrical nerve stimulation · TSS: total symptom score

Introduction

Diabetic distal symmetrical sensory polyneuropathy (DSP) affects approximately 20–30% of the hospital-based type 2 diabetic population and 20% of community-based samples of diabetic patients [1, 2]. Neuropathic symptoms can be categorised as being positive or negative, based on spontaneous sensory symptoms or decreased responsiveness to stimuli, respectively [3]. There are numerous types of positive sensory symptoms, and it has been suggested that they should be divided into painful and non-painful categories [3]. Because the aetiology of DSP in humans is not well understood, symptomatic treatment using analgesics, tricyclic antidepressants and anticonvulsant drugs is often the only way of alleviating the discomfort and pain reported by these patients [2]. A recently published meta-analysis provided evidence that i. v. treatment with α-lipoic acid improves positive neuropathic symptoms and neuropathic deficits in DSP [4]. Transcutaneous electrical nerve stimulation (TENS) [5, 6], percutaneous electrical nerve stimulation [7], spinal cord stimulation [8], other physical therapies [11, 12] and acupuncture [13] have also successfully been used as non-pharmacological therapies, while electrical stimulation therapy through stocking electrodes was not effective [14].

We previously noticed an alleviation of neuropathic symptoms in patients treated with high-frequency external muscle stimulation (HF). Based on this finding, the aim of this randomised pilot study was to compare the effects of HF therapy with those of established TENS therapy in patients with DSP.

Subjects and methods

Subjects Patients who had type 1 or 2 diabetes and polyneuropathy, who were aged 18–80 years, and had HbA_1c levels <11% were enrolled in the present study. Patients taking medication that may influence neuropathic symptoms (such as α-lipoic acid, tricyclic antidepressants or anticonvulsants), and patients with ulcers, amputations caused by ischaemia, or cancer diseases were excluded. Forty-one adult diabetic patients were enrolled in this study; all participants gave their written informed consent. The study protocol was approved by the Ethical Review Board of the Heinrich-Heine-University Düsseldorf.

A detailed history of diabetes and a neurological examination of the lower extremities were performed to establish eligibility (Table 1). Classical symptoms and neurological deficiencies defined DSP. Scores for neurological symptoms or neurological impairment were used to assess the severity of DSP [15]. Participants were randomly assigned to the TENS or the HF treatment group using strata for patients with non-painful (paraesthesiae, numbness) and painful neuropathic symptoms (in addition to non-painful symptoms; burning, stabbing, shooting of an electrical nature).

Physical treatment procedure Each patient was treated for 30 min on three consecutive days. In the TENS treatment group the electrodes were placed on the lower extremities as described previously [4] (Fig. 1a). Transcutaneous electrotherapy was applied with the H-Wave device (Dumo 2.4; CEFAR Medical, Lund, Sweden), a portable, rechargeable unit that generates a biphasic exponentially decaying waveform with pulse widths of 4 ms, ≤35 mA, ≤35 V and 180 Hz. Intensity was adjusted according to the patient, and ranged from 20 to 30 mA.

Table 1 Baseline characteristics of 41 adults with diabetes who participated in the study

Characteristic	TENS treatment group (n=21)	HF treatment group (n=20)
Age (years)	57.8±12.5	64.2±12.7
Diabetes duration (years)	13.0±9.6	13.7±11.5
Type of diabetes (type 1/ type 2)	3/18	4/16
Sex (women/men)	11/10	8/12
Diabetes therapy (insulin/oral hypoglycaemic drugs)	18/3	17/3
BMI (kg/m^2)	28.1±5.8	29.5±5.9
Neurological symptoms score	6.6±1.3	7.1±1.3
Total symptom score	6.6±3.2	7.0±3.6
Neurological impairment score	5.5±3.2	7.4±1.6
HbA_1c (%)	9.3±1.6	9.3±2.4
Triglycerides (mmol/l)	3.0±4.3	1.9±1.3
Cholesterol (mmol/l)	6.0±2.0	5.6±1.0
HDL (mmol/l)	1.1±0.4	1.3±0.4
LDL (mmol/l)	3.7±1.2	3.7±0.9
GOT (U/l)	24.5±13.0	25.7±13.1
GPT (U/l)	27.8±15.4	25.7±13.4
Creatinine (mmol/l)	65.5±13.3	71.6±22.1
Urea (mmol/l)	6.0±1.9	6.8±2.0

Data are means±SD
GOT Glutamate–oxalate transaminase; *GPT* glutamate–pyruvate transaminase

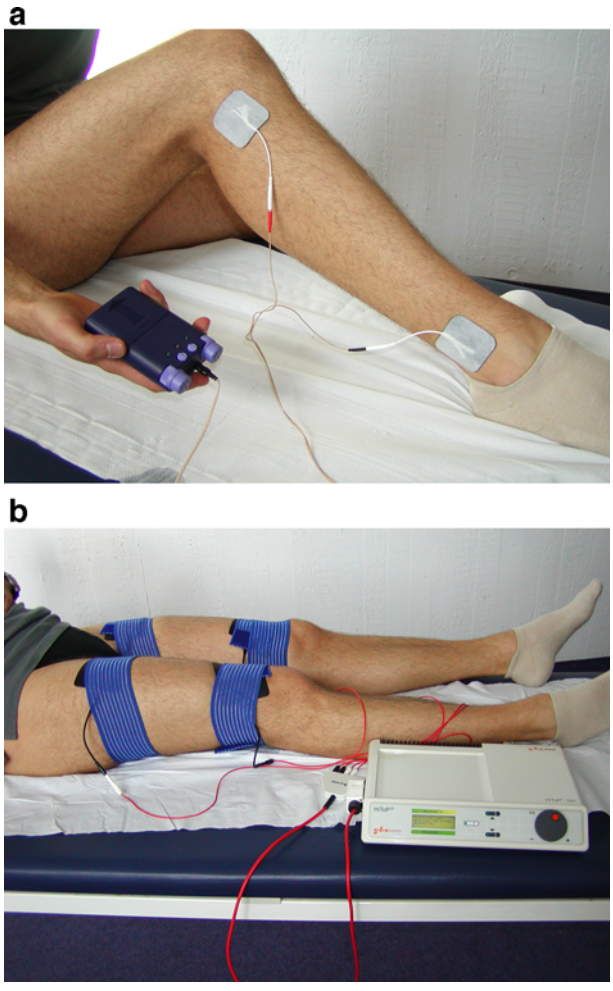


Fig. 1 Electrode placement in TENS (**a**) and HF (**b**) treatment

The electrodes for the HF therapy were placed on the femoral muscles (Fig. 1b). External muscle stimulation was performed using a non-portable 230-V power supply device (HiTop 181-H; gbo Medizintechnik, Rimbach, Germany) that generates pulse widths of ≤350 mA, ≤70 V. We used an initial frequency of 4,096 Hz, which was increased up to 32,768 Hz within 3 s; the maximum frequency was used for 3 s and then downmodulated from 32,768 to 4,096 Hz. For each patient, the intensity of the electrical stimulation was adjusted to a pleasant level that did not produce any pain or discomfortable paraesthesiae.

Grading of symptoms Patients were asked to record their baseline levels of the major symptoms—pain, numbness, numbness in painful areas, burning, paraesthesiae and dysaesthesia in the lower extremities—using separate visual linear 10-point scales, where 1=no symptom and 10=worst ever felt [16]. The questionnaires were completed by the

participants 1 day before the first treatment session, 1–2 h after the end of therapy on all three treatment days, and 2 days after therapy. An improvement of symptoms was defined as an improvement of three points or more for at least one symptom. The data were also analysed using the Total Symptom Score (TSS) [17].

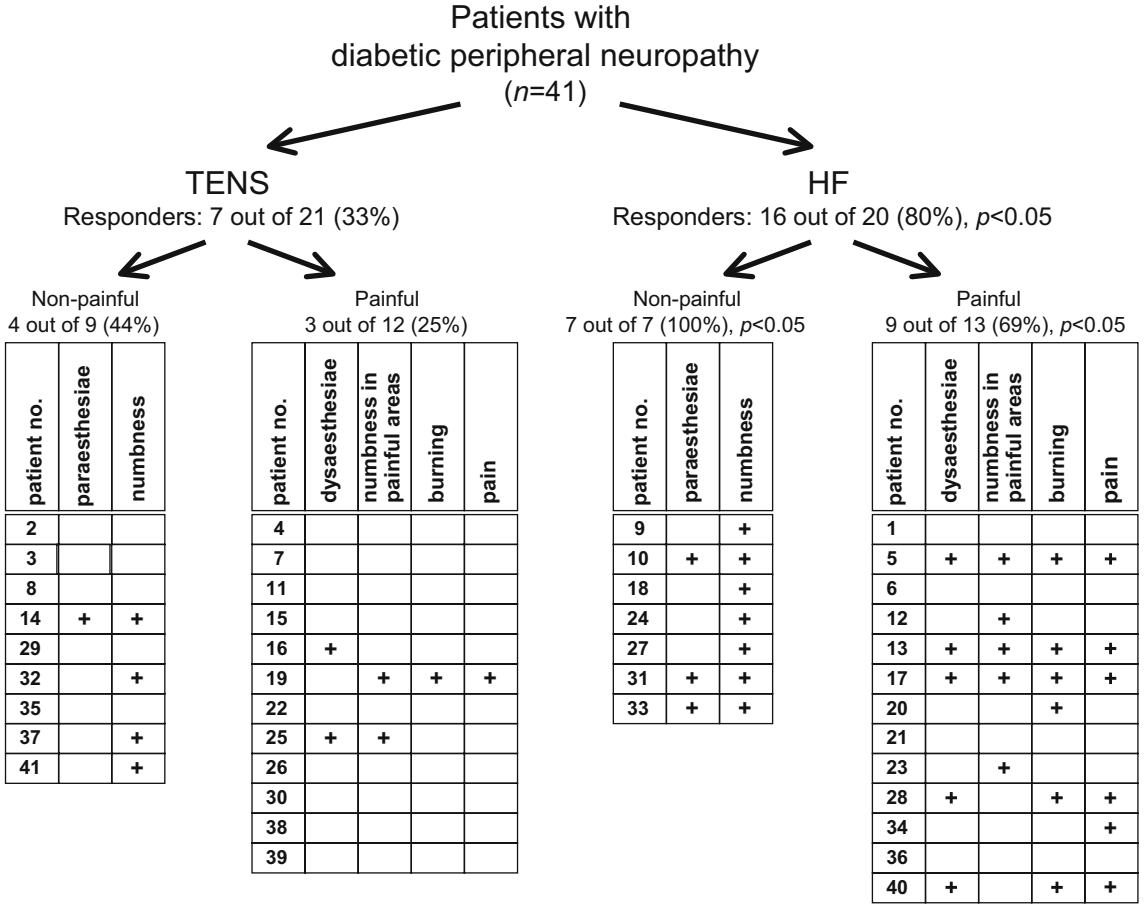
Statistical analyses All data are expressed as means±SD or as percentages. The analyses of responder data were performed using the chi square test. Changes in TSS were calculated by paired *t*-test (two-tailed). A *p* value less than 0.05 was considered statistically significant. Statistical analyses were performed using GraphPadPrism, Version 3.0 (GraphPad Software; San Diego, CA, USA).

Results

Patients were randomised to receive TENS (n=21) or HF (n=20). The demographic data, laboratory values and neurological symptoms and impairment scores at baseline were similar for the two treatment groups (Table 1). Both forms of electrical treatment were well tolerated, with no local or systemic side effects. Only one patient reported some muscular discomfort in his legs after the first HF treatment, which ceased within several hours. All 41 patients completed the study protocol.

Seven out of 21 patients (33%) in the TENS group and 16 out of 20 patients (80%) in the HF group reported an improvement of symptoms (p<0.05) (Fig. 2). Treatment with HF was more effective than TENS therapy in patients with non-painful DNP (HF: 100%, seven out of seven; TENS: 44%, four out of nine; p<0.05) and in patients with painful DNP (HF: 69%, nine out of 13; TENS: 25%, three out of 12; p<0.05) (Fig. 2). Both treatment modalities led to a significant decrease in TSS between baseline and the end of the observation period, although this reduction was more pronounced in the HF group (from 7.0±3.6 to 4.6±3.4, p<0.005) than in the TENS group (from 6.6±3.2 to 5.4±3.8, p<0.05).

Responders in both groups were analysed separately to compare the time courses for the improvement of symptoms with treatment (Fig. 3). The mean symptoms scores in responders decreased from 7.3±0.6 to 3.6±0.6 in the HF group and from 5.4±0.6 to 1.9±0.4 in the TENS group. An improvement of symptoms was reported immediately after the termination of the first treatment, with a further decrease in scores occurring during the subsequent days. A



patient no.	paraesthesiae	numbness
2		
3		
8		
14	+	+
29		
32		+
35		
37		+
41		+

patient no.	dysaesthesiae	numbness in painful areas	burning	pain
4				
7				
11				
15				
16	+			
19		+	+	+
22				
25	+	+		
26				
30				
38				
39				

patient no.	paraesthesiae	numbness
9		+
10	+	+
18		+
24		+
27		+
31	+	+
33	+	+

patient no.	dysaesthesiae	numbness in painful areas	burning	pain
1				
5	+	+	+	+
6				
12		+		
13	+	+	+	+
17	+	+	+	+
20			+	
21				
23		+		
28	+		+	+
34				+
36				
40	+		+	+

Fig. 2 Results of treatment with TENS versus HF for the complete groups and individual patients stratified into non-painful and painful groups. Responders were defined as patients who showed an improvement of three points or more for at least one symptom in the linear 10-point symptoms scales. Statistical differences were calculated using the chi square test. + An improvement of at least three points in the symptom scale

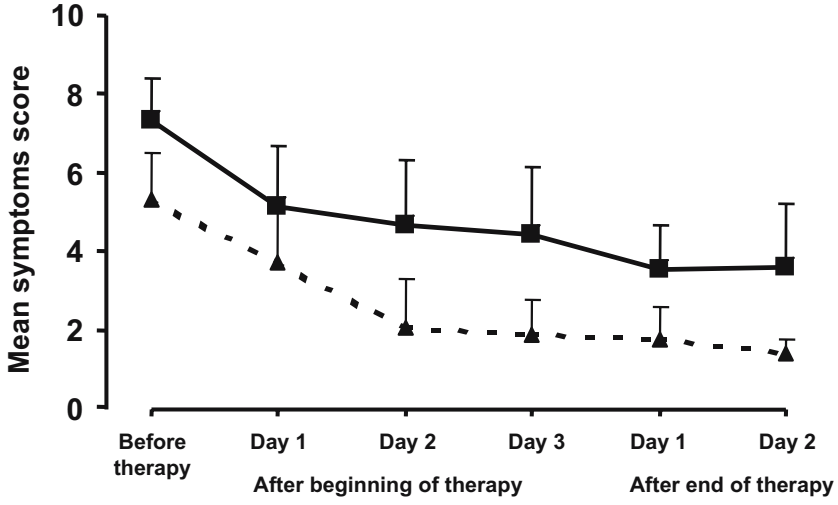


Fig. 3 Mean symptoms scores (+SD) of responders in the TENS (*black triangles*, *broken line*; n=7) and the HF groups (*black squares*, *solid line*; n=16)

reduction of symptoms was documented up to 2 days after the end of treatment. However, patients reported the recurrence of symptoms several days later, which was ameliorated by further electrotherapy (data not shown).

Discussion

In this prospective, randomised clinical pilot study we have shown, for the first time, that HF can reduce the pain and discomfort caused by DSP. This non-pharmacological form of treatment was well tolerated and might offer a new option for symptomatic relief.

Our finding that external muscle stimulation reduced neuropathic symptoms is in accordance with the clinical observation that neuropathic symptoms appear when people do not use their muscles during sleep, and disappear when they stand up or walk [18]. Treatment with TENS has previously been shown to be effective in the relief of pain and discomfort associated with DSP [5, 6]. In these studies a control group received sham treatment using placebo stimulators; however, use of this procedure does not exclude placebo effects. This problem was avoided in our study.

A special stimulation system (HiTop 181-H) was used for external muscle contraction. We applied 1-s frequencies of 4,096–32,768 Hz, introducing up to 5,000 mW into the muscles. High-frequency electrical spinal cord stimulation with implanted electrodes has previously been shown to be effective in the relief of chronic diabetic neuropathic pain [8] and several other chronic painful conditions, including back pain, phantom-limb pain, peripheral vascular disease and severe angina [19, 20]. Whereas this procedure is not free of risk and may give rise to life-threatening infection [21], the HF treatment used in our study is safe and may potentially be used for other chronic pain indications. The mechanisms that underlie the positive results associated with this therapeutic modality are not clear. It has been proposed that electrical stimulation activates the dorsal columns that inhibit the C fibres, thus interrupting/gating pain input [22]. Furthermore, short-term high-frequency electrical nerve stimulation decreases human motor cortex excitability [23]. Experiments indicate that electrical stimulation is followed by a decrease in the concentrations of the excitatory amino acids glutamate and aspartate in the dorsal horn, and that this effect is mediated by a GABAergic mechanism [24].

Microvascular changes, reduced blood flow, nerve oxygen tension [25, 26] and other vascular factors [27] contribute to the pathogenesis of diabetic neuropathy. Interestingly, electrical stimulation has been reported to improve microvascular blood flow in severe limb ischaemia [28], have effects on wound healing (indicating improved tissue circulation) [29, 30], and improve insulin resistance [31–34].

One of the limitations associated with our pilot study is its short duration, which might be responsible for the weak effect of TENS treatment. Long-term studies are needed to ascertain the cumulative effects of HF in diabetic patients. The patients' pain and discomfort was found to recur a few days after discontinuation of the therapy, implying that continuous treatment would be more beneficial. Limited experience with patients followed at our clinic suggests that treatment given weekly can reduce long-lasting neuropathic pain.

In summary, our study suggests that HF is a useful non-invasive, non-pharmacological treatment for the management of peripheral polyneuropathy in patients with diabetes.

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