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Transcutaneous Electric Nerve Stimulation on ischemic rest pain in inpatients: randomised trial

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SUMMARY

OBJECTIVE: To investigate the efficacy of a short-term application of Transcutaneous Electric Nerve Stimulation to relieve rest pain in patients with chronic limb-threatening ischemia.

METHODS: In patients ³18 years old, with chronic limb-threatening ischemia and rest pain ³3 in the Visual Analogue Scale, without diabetic neuropathy were randomly assigned to 1) Transcutaneous Electric Nerve Stimulation (100 Hz, 200 μs) or 2) sham intervention, both during one or two 20 min treatment sessions. The primary outcome was pain intensity, assessed by the visual analogue scale (0–10 cm) and described by the McGill Pain Questionnaire. We used a t-test for difference of means.

RESULTS: A total of 169 patients were assessed, 23 met the study criteria and were randomized. Thirty-four applications were performed in two days: in the 17 Transcutaneous Nerve Stimulation and 17 sham. The within-group analysis indicated a pain decrease in both groups (Transcutaneous Electric Nerve Stimulation, from 7–3.9 cm, p<0.0001, and sham from 5.8–3.2 cm, p<0.0001). No statistically significant difference was verified between-groups (p=0.5).

CONCLUSIONS: Both groups showed a decrease in rest pain of 54 and 55%, respectively. However, there was no difference between short-term high-frequency Transcutaneous Electric Nerve Stimulation and sham intervention to relieve ischemic rest pain in chronic limb-threatening ischemia patients.

KEYWORDS: Peripheral arterial disease. Ischemia. TENS. Randomized controlled trial. Pain.

INTRODUCTION

Rest pain in individuals with chronic limb-threatening ischemia (CLTI) is caused by a chronic ischemic state in severe stages of peripheral arterial disease and incidence is higher in those with risk factors for atherosclerosis[1,2]. High doses of opiates and non-steroidal antiinflammatory are prescribed for CLTI patients, but have sparse or insufficient results[3]. However, prolonged use of analgesic drugs is related with risks[4,5].

Transcutaneous electric nerve stimulation (TENS) is an inexpensive, non-pharmacological and non-invasive electrical stimulation delivered through electrodes placed in the skin[4,6]. TENS delivered at high frequency (HF) stimulates large diameter myelinated fibers (afferent Aβ). Low frequency (LF) TENS activates descending pain modulating mechanisms deriving from the brain stem and is not recommended for opioid tolerant individuals[7,8].

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Studies have shown that TENS reduces pain intensity in limb ischemia[9-13]. Yet, they investigated pain relief in acutely induced ischemia on healthy adults[10,14]. Some authors concluded that HF TENS may be more effective for people using opioids[7]. Cuschieri et al. showed analgesia with TENS in rest pain through continuous >24 h intervention[4]. Therefore, the present study sought to investigate pain relief of a short-term stimulation of HF TENS on rest pain.

METHODS

Trial design

Randomized single-blinded, controlled trial. Ethical approval was obtained from the Ethics Committee of Universidade Federal de Minas Gerais, CAAE# 12954313.8.0000.5149 and registered at Rebec, RBR – 8jg3bk.

Eligibility

Consecutive individuals with CLTI and rest pain ≥3 rated in the 0 to 10 cm visual analogue scale (VAS), Rutherford graded II and III, admitted to the Vascular Surgery Unit at Hospital Risoleta Tolentino Neves, were screened for eligibility. Content specialists with active registry at medical board performed evaluations and CLTI diagnosis, and confirmed at least with one objective additional test, ankle-brachial index (ABI), duplex ultrasound or angiography.

Participants had to be able to respond to the researcher and have a cognitive status, assessed by the Mini Mental State Examination (MMSE), of ≥23 for literates, ≥18 for illiterates[15]. We did not include those who had been previously treated with TENS, those with VAS <3 and/or diabetic neuropathic foot. Detailed flow of participants is depicted in the CONSORT[16], Figure 1.

Randomization

Participants were randomly assigned (random.org) into the intervention groups: TENS (TG) or sham (SG) in a 1:1 fashion. The allocation schedule was generated by an external researcher. Researchers involved with data collection were trained by the same personnel. In a visit to the hospital site, the same examiner could be involved with data collection in both groups, which depended on the randomization schedule and the number of available participants. An examiner knew which group the participant would be assigned to only after they signed consent form.

Intervention and blinding

Each intervention took 20 minutes[17], and participants were positioned in a supine position. A two-channels Neurodyn Portable TENS/FES (IBRAMED Ltda., São Paulo, Brazil) was calibrated before each session. Two carbon rubber and oval, 4 x 6.4 cm electrodes (ValuTrode®, Fallbrook, CA, USA) were applied to both sides of the tibial tuberosity in the painful lower limb, in L4 and L5 dermatomes to cover the calves. TENS parameters were 200 µs, 100 Hz, in a 'continuous' pulse, delivered as biphasic asymmetrical waveform[11]. Participants were not told which group they were assigned to. In the SG, the machine was turned on and an alternative channel used, but it did not allow current to be delivered to their skin. This way, application procedure was similar in both groups. The TENS unit was not visible to participants throughout the session. Individuals of both groups were told that 'TENS can be effective even in non-perceptive intensities'[11], and frequently asked whether the intensity faded during session[12]. If response was positive, intensity was increased and maintained at a strong but comfortable submotor level in the TG[17], while we mocked an increase in the SG.

Considering the non-cumulative effect of TENS, a second and independent 20 min application of the same intervention was performed in participants who, after 24 h, were still at the nursery room with no change in their group allocation. For ethical reasons, drug therapy routine was clinically assigned by medical doctors and not changed during the study.

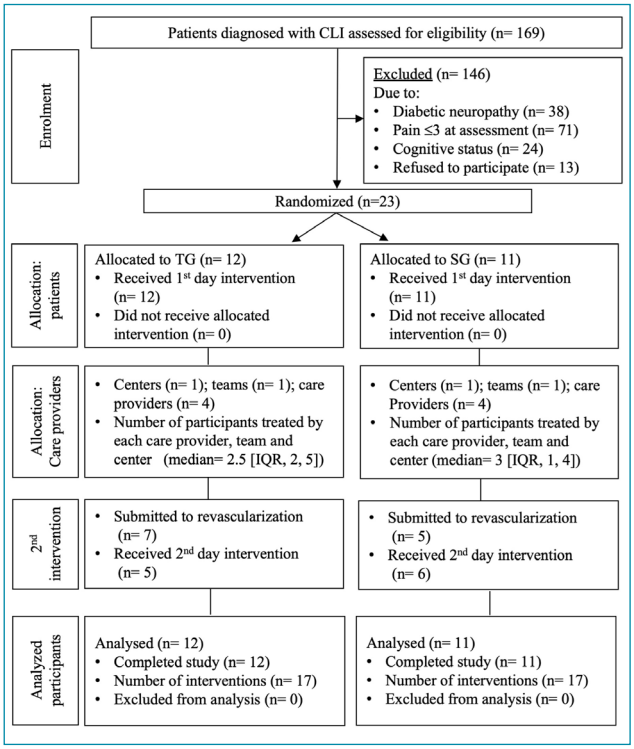

Figure 1. CONSORT flow diagram.

Pain description – experience

We assessed pain experience at the beginning of the study with the Brazilian version of the McGill Pain Questionnaire (MPQ)[18]. It consists of 68 adjectives distributed into five domains: sensorial, reactive, affective, evaluative, and miscellaneous[18]. To assess the number of words chosen (NWC), participants were encouraged to choose a single word from each category with a range from 0–20 possible words. Each word within these categories is assigned a scale value, which is intensity-dependent. The sensory pain-rating index (SPRI) is calculated based on the sum of scale value of each word chosen at the sensory category and ranges from 0–34. The reactive pain-rating index (RPRI) is the sum of rank values of all non-sensory categories and ranges from 0–34 points[18,19]. The total pain-rating index (TPRI) score is the sum of scale values of all categories, 0–68.

Demographic and clinical data

Demographic data were collected from medical records and included age, ABI, sex, comorbidities, presence of wound, medication in use, and duration of pain at the moment of hospital admission.

Primary outcome measure

The VAS was used to assess pain intensity[20]. Participants were encouraged to choose a value prior to and immediately after the application. They were explained that zero represents 'no pain' and 10, 'pain as bad as it could be'.

Sample size

Sample size was determined based on a previous study[10], which estimated a sample size of 17 participants in each group. The expected difference in VAS was 1.5 cm, or 30% improvement from baseline[21], considering a type 1 error of 0.05 and a type 2 error of 0.80.

Statistical analysis

Data were screened for normality with Shapiro-Wilk. Demographic characteristics expressed as means and standard deviation (SD). For the intragroup analysis, a paired t-test was used; independent sample t-test was adopted for the between-groups analysis. The significance level was set at p=0.05. The Levene's test for equality of variances was used with 2-tailed t-tests. An intention-to-treat approach was considered for data analysis with the last observation carried forward[22]. Subject was included in the analysis even when pain increased after intervention. The statistical analyses were performed with Stata/SE (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.).

RESULTS

A total of 169 individuals were screened for eligibility. Of them, 146 did not meet inclusion criteria or declined to participate. Then, 23 were randomized and completed the first intervention. Considering the second application, results shown in this section are for the analysis performed on the total number of interventions for each group, i.e., TG (17 interventions) and SG (17 interventions).

Participant characteristics and pain quality

There were no differences between groups regarding demographic characteristics (Table 1). Information on pain duration was found in the medical records of 18 participants. At the time of hospital admission, 27.8% were experiencing pain for less than seven days, 38.9% had it from eight to thirty days, and 33.3%, for more than 31 days. Both groups chose similar NWC, TPRI, SPRI, and RPRI scores (Table 1).

Table 1. Demographic and clinical characteristics at baseline. Data are expressed in mean (SD) or number of occurrence (%).

	Study Groups	
	TG (n=12)	SG (n=11)
Age, years old	62.9 (9.5)	65.6 (12.7)
Sex, female (%)	7 (58.3)	5 (45.5)
Current smoker (%)	6 (50)	5 (45.5)
Comorbidities		
Diabetes Mellitus (%)	5 (41.7)	4 (36.4)
SAH (%)	10 (83.3)	9 (81.8)
ABI	0.32 (0.29)	0.36 (0.27)
Open wound (%)	10 (83.3)	11 (100)
Medication in use		
Metamizole (Dypirone) (%)	12 (100)	9 (81.8)
Acetaminophene (Paracetamol) (%)	0 (0)	1 (9.1)
Opiates (%)	10 (83.3)	11 (100)
MMSE	23.6 (3.5)	23.1 (3)
McGill Pain Questionnaire Scores		
NWC	16.9 (2.9)	16.9 (2.8)
TPRI	38.8 (10.9)	41.1 (8.6)
SPRI	20.3 (4.9)	21.4 (5.6)
RPRI	18.5 (7)	19.7 (4.4)
VAS baseline	7 (1.9)	5.8 (1.4)

TG: TENS group; SG: sham group; SAH: systemic arterial hypertension; ABI: ankle-brachial index; MMSE: mini-mental state examination; NWC: number of words chosen; TPRI: total pain rating index; SPRI: sensory pain rating index; RPRI: reactive pain rating index; VAS: visual analogue scale score. *When differences were statistically significant at baseline.

Outcome measure

Prior to stimulation, the TG had a mean score of 7 cm (SD 1.9), whereas SG, of 5.8 cm (SD 1.4). Both showed similar baseline VAS, p=0.052 (Table 2).

The baseline VAS of both groups compared to its score after intervention showed they experienced a decrease in pain intensity. Despite the TG had a 54% and the SG a 55% decrease, no statistically significance was found between-groups, Table 2.

DISCUSSION

Short-term HF TENS at 100Hz did not provide greater pain relief in participants with rest pain when compared to a sham intervention. Ostelo et al. considered 30% the threshold of minimal clinically important difference in the VAS[22]. Both groups showed over 50% pain reduction after intervention.

Pain relief after sham intervention was demonstrated on several aspects of laboratory-induced ischemic pain and suggests involvement of affective mechanisms[10,12]. HF TENS efficacy has been reported in studies which used a tourniquet to induce ischemic pain[10,12]. However, induced ischemic models should be carefully extrapolated into CLTI chronic patients, given that induced ischemia elicits minimal tissue damage[10]. In our sample, 33.3% experienced rest pain for more than 31 days, different from acutely induced models. The MPQ scores confirm the difference in symptoms between our sample to those healthy individuals. Our participants had greater NWC, TPRI, SPRI, and RPRI scores than healthy individuals in induced ischemia studies, which indicates a more complex pain experience in our sample[9,12].

Peripheral nerve involvement, other than nociceptive C fibers, might corroborate to ischemic pain, which may be resistant to TENS. Chen & Johnson pointed that nerve fibers can experience refractory periods to electrical stimulation beyond 80 Hz of TENS stimulation, which might hinder transmission[10]. Seenan et al. demonstrated an increased walking distance with stimulation of 120Hz, but no reduction in pain intensity and quality[14]. However, our study shows a novel approach, as it included participants with rest pain.

Pain relief in rest pain was demonstrated by Cuschieri et al.[4] The average VAS score of our TG at baseline, i.e., 7 cm (SD 1.9), was analogous to their stimulated group, 72 mm, in a 100 mm scale. Our participants had similar CLTI staging compared to their study, as both included participants with very low ABI index[4]. In their report, pain relief was related to TENS intervention, despite analgesia in that group was only significantly greater than sham after 24h of continuous stimulation. However, our study found pain decrease after both TENS and sham stimulation; thus, we believe our short-term protocol is more feasible in the daily routine than their approach.

An important limitation of the present investigation is its single-blinded design. A triple-blind method should be the 'gold-standard'. Additionally, the TENS device did not have an amplitude display, so the intensity was individually set as a submotor level according to one's tolerance.

Despite this study's small sample size, we consider this a relevant contribution and alternative intervention to pharmacological resources and high opioid doses. However, further studies are required to investigate the effects of different parameters of high frequency (<80 Hz) of TENS stimulation in different aspects of pain, quality of life, and functionality in CLTI population.

CONCLUSIONS

This study showed a significant decrease in rest pain in inpatients diagnosed with CLTI in response to a short-term HF TENS and sham intervention of 54 and 55%, respectively. Despite HF TENS had no greater analgesic effect over sham, both therapies are safe and decreased rest pain.

AUTHORS' CONTRIBUTIONS

PEOG: Conceptualization, Data Curation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing. **MM:** Conceptualization, Writing – Review & Editing. **RLGF**: Conceptualization, Writing – Review & Editing. **TPN:** Conceptualization, Writing – Review & Editing. **CJM:** Conceptualization, Formal Analysis, Writing – Review & Editing. **LLC:** Conceptualization, Supervision, Formal Analysis, Writing – Original Draft, Writing – Review & Editing.

Table 2. Changes in rest pain intensity following interventions.

Study groups	Within-group change in VAS (95%CI)	p-value*	Between-groups change in VAS (95%CI)	p-value*
TENS	-3.1** (-4.6– -1.6)	<0.0001	0.5 (-2.1–1.1)	0.5
Sham	-2.6** (-3.3– -1.9)	<0.0001		

VAS: visual analogue scale; CI: confidence interval; TENS: Transcutaneous electric nerve stimulation. *t-test; **denotes statistically significant difference between pre and post intervention within-group. Significance was considered when p<0.05.

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ERRATUM

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Where it reads:
Jorge Machado

It should read:
Carla Jorge Machado

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