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Efficacy of the use of two simultaneously TENS devices for fibromyalgia pain

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Abstract:	BACKGROUND: Fibromyalgia is characterized by a range of symptoms that include muscle pain, fatigue and sleep disorders. Transcutaneous electrical nerve stimulation (TENS) is an established method for pain relief. The purpose of the study was to evaluate the effectiveness and safety of the use of two simultaneously new TENS devices for fibromyalgia pain. METHODS: After Ethics approval and informed consent, 39 patients were prospectively divided into three groups to evaluate TENS device, applied simultaneously in each patient: 1) at the lower back (perpendicular to the vertebrae canal, at the level of the 5th lumbar vertebrae), and 2) centrally above and below the space between the C7 and T1 spinous processes. The devices were applied during 20-min at 12-hour interval during 7 consecutive days. For the placebo group (PG), the devices did not transmitted electrical stimulus. The single-TENS group (STG) (n=13) had one active and one placebo TENS. The DTG applied both active TENS devices at the low back and cervical areas. Diclofenac was used as rescue analgesic. The efficacy measures were pain relief, reduction in use of daily analgesic tablets, quality of sleep, and fatigue. RESULTS: The evaluation within groups revealed that patients from DPG refereed no pain relief when compared to their previous VAS pain score (8-cm, $p>0.05$), while patients from the STG refereed improvement of 2.5 cm in the pain VAS (previous 8.5 cm compared to 6-cm after treatment) ($p<0.05$); and the DPG refereed daily maintained reduction of 4 cm in the VAS-pain (previous 8.5-cm to 4.3-cm) ($p<0.02$). Concurrent daily consumption of analgesic tablets was reduced in both STG ($p<0.05$) and DTG ($p<0.02$). Comparison among groups revealed that analgesia, as well as quality of sleep and disposition was: DTG > STG > PG ($p<0.05$). Participants subjectively found the active device useful. CONCLUSIONS: while the application of a single active TENS improved pain relief in fibromyalgia pain, pain and fatigue were further improved when two active devices were simultaneously applied at the low back and cervical area, with no side effects.
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Introduction

Fibromyalgia is a syndrome characterized by widespread musculoskeletal pain accompanied by tenderness. The pathogenesis involves a disturbance in pain processing and transmission by the central nervous system, leading to a general increase in pain perception with widespread hyperalgesia/allodynia to mechanical, thermal, electrical, and chemical stimuli and central nervous system abnormalities including central sensitisation as well as aberrant pain facilitation and inhibition (1-4). The American Pain Society considers Transcutaneous electrical nerve stimulation (TENS) a therapeutic modality with high scientific evidence[5] and there is sign to support its use in fibromyalgia pain (6-8). However, to date the use of only one site of peripheral nerve stimulation with TENS device has been considered. The purpose of the study was to evaluate the effectiveness and safety of the use of two simultaneously new TENS devices for fibromyalgia pain and status.

Methods

The Ethics Committee at the University of São Paulo's Teaching Hospital, Ribeirão Preto, approved the study protocol. After giving written informed consent, 39 patients suffering from fibromyalgia pain were randomized to one of three groups (n=13) and prospectively studied using a placebo-controlled design to examine analgesia and adverse effects. The diagnosis of fibromyalgia was based on the 1990 American College of Rheumatology classification criteria for fibromyalgia/fibromyalgia syndrome that was described as 2 components: (a) widespread pain, and (b) presence of 11 or more tender points (TP) among possible 18 sites (9). Patients were examined separately by two of the authors in order to avoid misdiagnosing (10). Al patients were taking 25-50 mg amitriptyline before bedtime as part of the protocol at least 3 weeks previously. Patients were assigned to treatments using a randomized number generator in a computer program.

The study was designed to have a power of 80% to detect a treatment difference of 1-day analgesia on a two-sided level of significance of α=0.05 assuming a standard deviation (SD) of 2 days, and a minimum number of 8 patients per group. Eligible patients were aged≥18 years, with a diagnosis of fibromyalgia. Subjects had to be willing and able (e.g. mental and physical condition) to participate in all aspects of the study, including use of medication, completion of subjective evaluations, attending the scheduled clinic visit and compliance with protocol requirements as evidenced by providing written, informed consent. Patients were excluded from the study for the following reasons: evidence of clinically unstable disease, psychiatric disease other than depression, refusal or known allergy to the devices used, and use of beta-blockers. The concept of a visual analog scale (VAS), which consisted of a 10 cm line with 0 equaling "no pain at all" and 10 equaling "the worst possible pain" was introduced. Regarding the assess outcomes, the use of validated and reliable instrument such as VAS for pain is the most commonly used assessment tools in the studies for fibromyalgia, and they are also widely used in the literature (11).

This prospective, double-blind randomized study evaluated the clinical utility of a new, very small and light, TENS device (TANYX®) in 39 patients suffering from fibromyalgia. TENS was performed with the following parameters: pulse shape was rectangular, Pulse width was 200μs, Frequency was 2- and 100- Hz, and intensity was 60 milliamperes. Two TENS device were applied simultaneously in each patient: 1) at the lower back (perpendicular to the vertebrae canal, at the level of the 5^{th} lumbar vertebrae), and 2) centrally above and below the space between the C7 and T1 spinous

processes, perpendicular to the spine. The two devices were applied during 20-min at 12-hour interval during 7 consecutive days (before bed-time and just after waking up in the morning). Patients were randomly divided into three groups: For the placebo group (PG), the two devices did not transmitted electrical stimulus, although they were externally similar to the active ones. The single-TENS group (STG) (n=13) had applied one active TENS device at the worst area of pain (low back or cervical), which produced a mixed (2- and 100-Hz) frequency of stimulation, and the placebo device at the less painful area. The third group (DTG) applied both active TENS devices at the low back and cervical areas. Diclofenac (50 mg) up to three times daily was used as rescue analgesic if necessary for pain control. The efficacy measures were pain relief evaluated on a VAS scale, reduction in use of daily analgesic tablets, quality of sleep and fatigue. Quality of sleep and fatigue were both defined as: 1) the same as previous to the 7-day treatment, 2) improved when compared prior to the 7-day treatment, 3) worsened when compared prior to the 7-day treatment.

Statistical analysis

The normality of the distributions was assessed using the Shapiro-Wilk's test. Groups were compared for demographic data (age, weight, and height) by one-way ANOVA. Incidence of adverse events, gender and site of primary disease were compared among groups by Chi-square analysis corrected for multiple comparisons. P was considered significant if <0.016. VAS scores; and the daily morphine consumption from day-zero to day-21 were compared among groups by two-way ANOVA for repeated measures (12). The statistical analysis compared among the six different groups on each day of the study. Tukey Honest analysis was applied to correct P values for multiple group comparisons. $P<0.05$ was considered significant. Data are expressed as mean±SD, otherwise stated.

Results

Patients were demographically similar. 36 patients completed the study. Three patients from the PG give up the study on the fourth day for absence of any pain relief, no sign of either fatigue or sleep pattern improvement. However, the minimum of 8 patients per group was maintained for statistical purposes. Upon fibromyalgia diagnosis, patients from the PG had 14 tender points among 18 possible sites, patients from the STG had 16 tender points and patients from DTG, 14 tender points ($p>0.05$). The musculoskeletal pain number of tender points did not improve during the 7-day evaluation ($p>0.05$), as concurrent miofascial pain was present in all patients. Depression was present in 6, 5 and 5 patients in the PG, STG and DTG, respectively ($p>0.05$), and also did not improve during the 7-day study.

The groups showed no differences regarding gender, weight, age and height (Table 1), or combination drug used before enrolment in the study. As part of the protocol, all patients were taking regularly 25-50 mg oral amitriptyline before bedtime. Before enrollment in the study groups, most patients were taking daily 5 mg cyclobenzaprine and 1 gr oral metamizol for pain control ($p>0.05$).

After applying the TENS devices, the evaluation within groups revealed that patients from PG refereed no pain relief when compared to their previous daily VAS pain score (8-cm, $p>0.05$), while patients from the STG refereed improvement of 2.5 cm in the pain VAS after the third day of TENS use (previous 8.5 cm compared to 6 cm after treatment) ($p<0.05$); and the DPG refereed daily maintained mean reduction of mean 4 cm in the VAS-pain after the third study day (previous 8.5-cm to 4.3-cm) ($p<0.02$, Figure 1; Table 2).

After the dual TENS devices application patients were free to take oral rescue diclofenac up to three times daily in order to keep pain VAS < than 4|10 cm, and their daily consumption is detailed in Figure 2. Concurrent daily consumption of analgesic tablets was reduced in both STG ($p<0.05$) and DTG ($p<0.02$) after the first day of the study.

Related to sleep pattern, in the PG, 4 of the patients referred worse sleep pattern. In the STG, 8 of the patients refereed improvement in sleep pattern, compared to 10 patients in the DTG ($p<0.05$). Comparison among groups revealed that fatigue was improved in 7 patients of the DTG, compared to 5 in the STG and none in the PG ($p<0.05$). In fact, 3 patients from the PG complained that the sensation of fatigue worsened during the study period. Concerning adverse effects, 2 patients from the STG got in

sleep after the device application, and complained of muscle sore due to more than 70-min active device application, which was subsequently improved by local hot application. Four patients in the PG and two in the STG referred gastric discomfort due to the oral diclofenac tablets ($p>0.05$). Individuals subjectively found the active device useful. No adverse effects were observed.

Discussion

In the present study we demonstrated that while the application of only one TENS device in the painful area resulted in improvement of pain (2.5 cm) improvement in the 10-cm VAS) and less daily analgesic consumption in accordance to others (5-8), the application of two simultaneously TENS devices resulted in reduction of 4-cm in the 10-cm VAS, and lesser rescue analgesic consumption compared to the group which used one device. TENS is an established method for pain relief, which does not involve the use of medication and can be advantageous, as adjuvant, for pain control in such circumstances (5-8). Patients suffering from fibromyalgia pain normally refer worst pain felt during bedtime, at night and before waking up in the morning, and pain is customarily widespread at the low back and cervical area, that was the main reasons the devices were applied either in the lumbar (7) or the cervical areas8. Another point was the prevalence of female in the study group, aged 27-60 year-old, in accordance to others (13).

All patients complained of chronic widespread musculoskeletal pain with no tissue inflammation or damage identified. While chronic widespread pain is the result of central sensitization of nociception, it seems to be somehow related to activation of a global stress response (14). Fibromyalgia presents hyper responsiveness of the central nervous system to mechanical hyperalgesia (15), and appears to reflect deficiencies in serotonergic and noradrenergic, but not opioidergic, transmission in the central nervous system. The heightened state of pain transmission may also be owing to increases in pronociceptive neurotransmitters such as glutamate and substance P (16). In some cases, psychological and clinical diagnoses are associated with A1AT polymorphisms (17).

With regard to TENS, it is used at varying frequencies, most commonly (i) a steady, high frequency between 50 and 120 Hz or (ii) bursts of a high frequency (HF) delivered at a low frequency (LF) between 1 and 4 Hz. Although not fully understood, it is thought that HF and LF TENS alleviate pain through somewhat different mechanisms of action. Both methods are thought to activate supraspinal and spinal mechanisms, which are involved in pain alleviation. Following LF TENS, increased levels of β-endorphin (19) and serotonin (20) were measured in the central nervous system. To activate the supraspinal inhibitory path ways, muscle contractions are required. In patients with FM, however, isometric muscle contractions increased pressure pain sensitivity, in contrast to healthy controls, where the pressure pain sensitivity decreased (21). HF TENS has resulted in increased levels of β-endorphin, encephalin, dynorphin (19) and γ-amino-butyric acid (22). Furthermore, when measured immediately

after HF TENS, pain thresholds in healthy female volunteers, but not in males, have been improved (23), so HF TENS might be an option for fibromyalgia patients. Nevertheless, our population was statistically similar related to gender, with only one male in STG and one in the DTG, what would not affect our final data evaluation.

Our patients who used daily two TENS devices for seven consecutive days displayed evident improvement of analgesia, improved fatigue and quality of sleep, probably due to a more intense peripheral action of both TENS applied, maybe through reduction of leukocyte migration and local action at peripheral opioids (24), decreasing local inflammatory reaction in the painful muscles where the TENS devices were located. Locally applied TENS could also act on sympathetic system. The results of the study suggested that the suppressive effects of LF on carrageenan-induced paw inflammation that were mediated by sympathetic post-ganglionic neurons, while the suppressive effects of HF were mediated by the sympatho-adrenal medullary axis (25). However, none of our patients were undertaking oral beta-blockers as part of the protocol, as analgesia could have been masked. We speculate that the two applied TENS devices at the painful muscle would result in more muscle contractions (21), decrease of trigger points, decreased inflammation and local sympathetic action apart from central one (25). One point to be considered was that mostly patients were taking oral 5 mg cyclobenzaprine prior to the study design. Analysis of cyclic alternating pattern sleep EEG revealed that significantly more subjects taking cyclobenzaprime had increased nights of restorative sleep in which was correlated to improvements in fatigue, and depression scores (26). In the present study, the 7-day study period did not improve the number of tender points, nor the degree of depression, probably due to the time of the study protocol. Side effects observed was correlated to the distraction of two patients who used the TENS device for a longer time (70-min), however showing only local muscle sore. The gastric upsetting was probably secondary to a higher consumption of oral diclofenac as pain rescue analgesic.

In conclusion, while the application of one active TENS device at either the lower back or cervical area improved pain relief in patients suffering from fibromyalgia pain, the pain and fatigue were further improved when two actives devices were simultaneously applied at the low back and cervical area, reflecting its usefulness as adjuvant for fibromyalgia pain.

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Table 1. Demographic data

	Time ofchronic pain complaint (years)	**Gender (f/m)**	**Weight* (kg)**	**Age* (years)**	**Height* (cm)**
PG	12±3	9/1	69±9	35±8	161±5
STG	10±5	12/1	72±7	32±8	160±7
DTG	12±6	13/0	68±8	30±12	162±5

P>0.05. *Data expressed as mean ± SDT. PG- placebo group; STG- single active TENS device group; DTG- double active TENS device group.

Table 2. Pain evaluation on days 1 and 7 of the study.

	VAS on day-1 (cm)*	**Daily anagesic consumption from day 3 to 7($n^{0.}$)****	**VAS on day-7 (cm)***
PG	8.2±2	3(3-3)	8±2
STG	8.5±1	2(1-2)	6±1
DTG	8.5±2	1(0-1)	4.3±2
P	>0.05	<0.05	>0.02

*Data expressed as Mean ± STD. ** Data expressed as median (25%-75% interval). PG- placebo group; STG- single active TENS device group; DTG- double active TENS device group. P refers to comparison between groups. VAS- visual pain analog scale (cm)

Figure

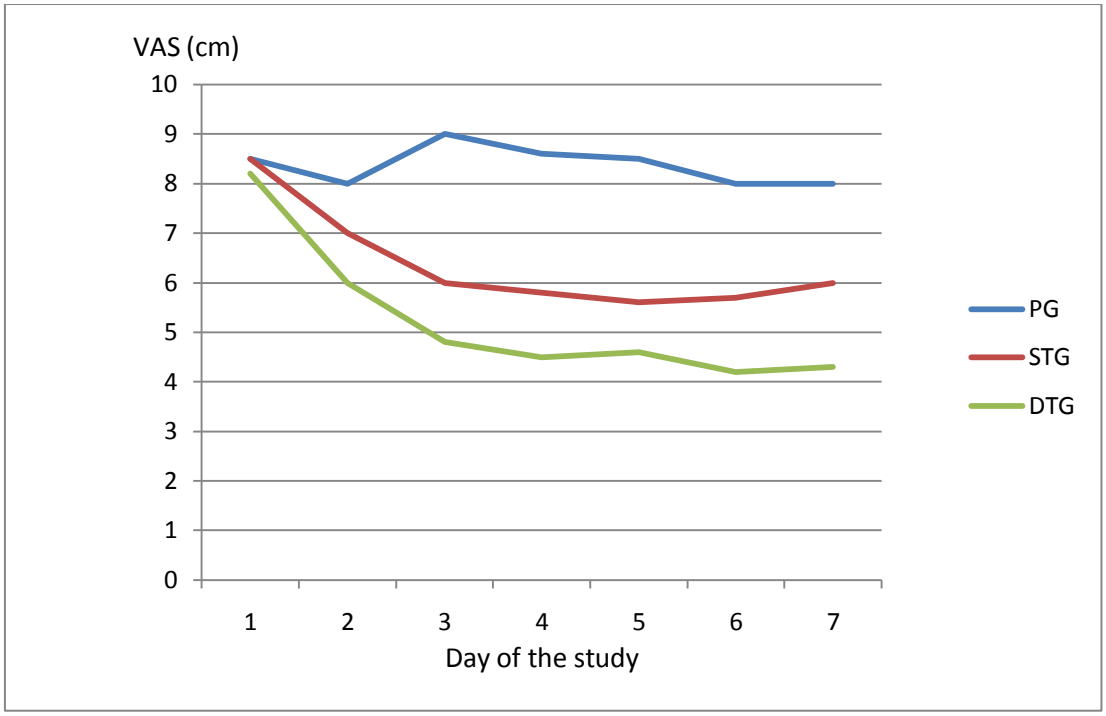

Figure 1. Mean daily VAS pain scores (cm) for the PG, STG and DTG. PG- placebo group; STG- single active TENS device group; DTG- double active TENS device group. After day-3, STD >PG ($p<0.05$) and DTG > PG ($p<0.02$).

Figure=2

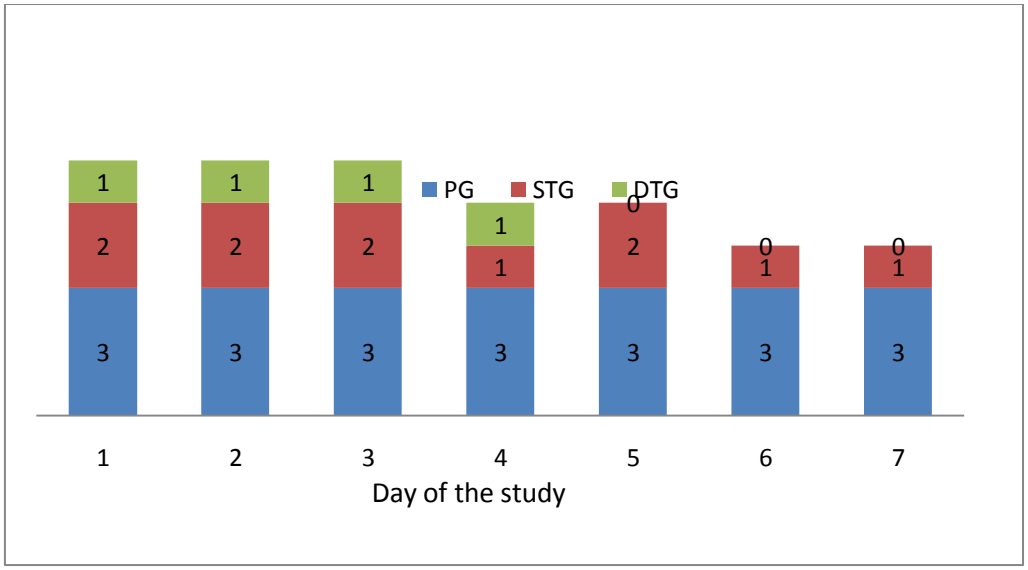

Figure 2. Number of oral diclofenac tablets taken per day for the PG, STG and DTG. PG- placebo group; STG- single active TENS device group; DTG- double active TENS device group. After day-1, STD >PG ($p<0.05$) and DTG > PG ($p<0.02$).