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Hormonal treatment isolated *versus* hormonal treatment associated with electrotherapy for pelvic pain control in deep endometriosis: Randomized clinical trial

Ticiana A.A. Mira[a], Daniela A. Yela[a], Sérgio Podgaec[b], Edmund C. Baracat[b], Cristina L. Benetti-Pinto[a,*]

[a] School of Medical Sciences, Department of Obstetrics and Gynecology, University of Campinas, Alexander Fleming, 101, Cidade Universitária, Campinas, SP, 13083-881, Brazil

[b] Medical School, Department of Obstetrics and Gynecology, University of São Paulo, Av. Dr. Enéas Carvalho de Aguiar, 255 - Cerqueira César, São Paulo, SP, 05403-000, Brazil

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ABSTRACT

Objective: The aim of the study was to evaluate the clinical effectiveness of complementary treatment using self-applied electrotherapy treatment for pain control over the standard hormonal treatment alone for deep infiltrative endometriosis (DIE).

Study design: Multicentre randomized clinical trial. We included a hundred-one participants with DIE in electrotherapy (n = 53) (hormonal treatment + electrotherapy) or control group (n = 48) (only hormonal treatment) by 8 weeks of follow-up. The primary measurement was chronic pelvic pain (CPP) using a visual analogue scale (VAS) and deep dyspareunia. The secondary outcomes were the quality of life by endometriosis health profile (EHP-30) and sexual function by female sexual function index (FSFI).

Results: CPP relief was observed only in the electrotherapy group (pre:7.11 ± 2.40, post:4.55 ± 3.08, $p < 0.001$). In terms of deep dyspareunia, improvements were observed for both groups (electrotherapy pre:2.02 ± 0.54–1.36 ± 0.96, $p < 0.001$; control pre:1.95 ± 0.86–1.68 ± 0.82, $p = 0.006$). Considering the secondary outcomes, a higher total score post-treatment for the EHP-30 was noted in both groups. Regarding sexual function, there was a statistically significant improvement in the FSFI score for the electrotherapy group ($p < 0.001$), with an increase in the scores for lubrication and pain domains ($p = 0.013$ and $p < 0.001$).

Conclusions: Electrotherapy treatment using transcutaneous electrical nerve stimulation proved to be a good complementary option for pain control, showing benefits in the reduction of CPP and deep dyspareunia and improving patient's quality of life and sexual function.

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Introduction

Endometriosis is a chronic disease in which women have pain symptoms, such as dysmenorrhea, chronic pelvic pain, and dyspareunia. [1] Although medical therapies are helpful for many women, they relieve symptoms in up to 50–80 % of the cases [2–5]. At least 20 % of patients still present residual symptoms. In these cases, complementary treatments may be considered. A recent systematic review revealed strategies such as acupuncture and the practice of exercises to control the symptoms, however only acupuncture was effective [6].

Studies using electrotherapeutic resources as complementary treatment for CPP not related to endometriosis showed an analgesic effect with low side effects, and benefits to some pelvic pain complaints related to women's health. [7–9] A randomized clinical trial has shown the efficacy in relieving pelvic pain symptoms using two different electrotherapeutic devices (acupuncture and self-applied electrotherapy) in women with DIE [10].

The aim of the present study was to evaluate the clinical effectiveness of complementary treatment using self-applied electrotherapy treatment for pain control over the standard hormonal treatment alone for endometriosis, describing its influence on the quality of life (QoL) and sexual function (SF) of women with DIE.

* Corresponding author.
E-mail addresses: ticiana.mira@gmail.com (T.A.A. Mira), yeladaniela12@gmail.com (D.A. Yela), sergiopodgaec@me.com (S. Podgaec), ecbaracat@gmail.com (E.C. Baracat), laguna.unicamp@gmail.com (C.L. Benetti-Pinto).

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Materials and methods

A multicenter randomized controlled trial study was approved by the research ethics committee from the Universities. The protocol was registered in the ClinicalTrials.gov (number NCT02769052) on May 10th, 2016. The participants were recruited from the Endometriosis Outpatients Clinic of centers from June 2016 to March 2018 and all of them signed an informed consent term. This study followed the CONSORT guidelines for randomized clinical trial.

Inclusion criteria: women at menacme, presenting DIE diagnosed by specialized transvaginal ultrasound or by magnetic resonance. All of them were using continuous hormonal treatment for at least 3 months and reported pelvic pain symptoms (CPP and/or deep dyspareunia). Exclusion criteria: pregnancy, pacemaker, decreased skin sensitivity, allergy to gel or electrode, epilepsy, cardiac arrhythmia, osteosynthesis in the application region, cancer, acute inflammatory pelvic disease, cognitive deficiency and difficulty to understand instructions and/or to use the instruments.

Participants were randomly placed into two groups: electrotherapy group (hormonal treatment plus self-applied electrotherapy) and control group (only hormonal treatment). These women were instructed not to stop drug treatment for endometriosis during the study. The randomization was carried out by groups of 20 cases by means of a lottery using sealed opaque envelopes. Each envelope contained the electrotherapy group (n = 10) or the control group (n = 10). Each time twenty patients were included; the lottery was restarted until the sample size was completed. The same researcher included and applied this randomized method in the two centers.

We describe in Table 1 the interventions applied in this study and primary and secondary outcomes measures. A secondary analysis was performed according to the same protocol when the control group, after the 8-weeks follow-up, used self-applied TENS.

Statistical analysis

Categorical variables and their comparison between groups were described by relative and absolute frequencies, by the chi-square and exact Fisher tests. Numeric variables were described in terms of mean, median, and standard deviation, performed by the Mann-Whitney test. Data analysis was intention-to-treat. Wilcoxon test was performed for comparison pre and post-treatment between the groups (initial protocol) and for secondary analysis for the control group. A p-value ≤ 0.05 was considered statistically significant. Statistical analysis was performed by the SAS System for Windows (Statistical Analysis System, version 9.2) and R for Windows (version 3.5.1).

For sample size calculation, to evaluate pelvic pain, 30 women (15 in each group) were required, considering the randomized controlled trial. [10] However, to address the secondary outcomes of SF and detect differences related to the SF for the total score of FSFI, we considered a difference between the mean equal to 5 points (alpha 0.05 and power of the test 0.80) according to previous studies [11,12]. However, the values for standard deviation (SD) in

Table 1
Detailed description of interventions applied and the primary and secondary outcomes measures.

INTERVENTIONS	
Electrotherapy group (self-applied TENS + hormonal treatment) The participants were treated with a self-applied transcutaneous electrical nerve stimulation device (TENS) (commercially available as Tanyx®). This device was registered in the National Agency of Sanitary Surveillance (ANVISA). - **Device parameters:** frequency: 85 Hz; pulse duration: 75 μs; intensity options: 10, 20, or 30 mA (instructions: the participant was instructed to choose a perception of the electrical stimulus that was "strong, but comfortable", always at the sensitive threshold). - **Technical specifications:** the device has an on/off button; a 3-volt lithium battery, lasting for 6 h of continuous application, with 46.5 mm diameter circular gel patch and 1.8 mm thickness; 7.0 ± 0.5 pH. This gel patch (contact with the skin), consisting of water, glycerol, allylamine, and potassium chloride, is applied to the contact metal bases only once and remains fixed until the battery is finished. The device is approximately 15 cm in size and has 10 cm distance between the centers of the electrodes. - **Application method:** the device was used in the parasacral region (S3-S4 position) twice a day, 20 min per application, for 8 weeks (Fig. 1). Each woman received written instructions and the physical therapist demonstrated its use step-by-step during the evaluation. The device was positioned and turned on so that the participant could have the sensation of the electrical stimulus and could answer her questions. - **Follow-up:** once a month consultation was scheduled for each patient to monitor the device usage. - **Symptoms notes:** they were instructed to take notes of their symptoms throughout the 8 weeks.	*Control group (hormonal treatment only)* The participants were followed-up while they were using a hormonal treatment for endometriosis. - **Follow-up:** the participants were also instructed to maintain hormonal treatment for endometriosis and no intervention was performed. - **Symptoms notes:** they would take notes about their symptoms throughout the 8 weeks. - **Additional method:** after the end of the follow-up period, women in this group were also invited to participate in the electrotherapy treatment for 8 weeks according to the same protocol used for the initial proposal (secondary analysis).
PRIMARY MEASURES - **Pelvic pain symptoms:** were evaluated before and after 8 weeks of treatment. CPP, dyschezia, dysuria, dysmenorrhea were evaluated by the Visual Analog Scale (VAS, 0–10 points); deep dyspareunia, using deep dyspareunia scale (DDS) (0–3 points: zero, no pain during intercourse until three for intense pain, which requires the interruption of intercourse). [10] We made a comparison between pelvic pain scores, pre and post 8 weeks of follow-up, by VAS and deep dyspareunia scale, and using a home pain diary.	
SECONDARY MEASURES - **Quality of life and sexual function:** we also accessed the Endometriosis health profile (EHP-30) and Female Sexual Function Index (FSFI) pre and post 8 weeks of treatment. EHP-30 consists of 53 questions: 30 in a core questionnaire and the 23 other questions, set up in a modular questionnaire, evaluating six domains, including work, children, intercourse, medical, treatment, and infertility. The lower the total score, the better the QoL. FSFI consists of 19 questions divided into six domains: desire, arousal, lubrication, orgasm, satisfaction, and pain. A lower value for the total score is associated with a worse SF. - **Symptoms notes:** the participants also took daily notes using a "pain diary". In these notes, all pelvic symptoms could be recorded daily (CPP, dyschezia, dysuria, pain during spotting - VAS), and pain during sexual intercourse (DDS). They also noted down any other medication ingested for pain. For the secondary analysis of the control group, the same scales were used.	

these studies have proven to be variable. We propose a new way of estimating it by estimating its weighted value [13]. This estimate was made by considering the maximum (max) FSFI value (36) minus the limit value between sexual dysfunction score (SDS) and normality (26.5) multiplied by this limit minus the minimum (min) value of the scale (2) divided by the maximum value minus the minimum value of the scale, resulting in an average of approximately 6.85 points as described by the formula below. Considering a two-sided test, we estimated a sample size of 30 individuals per group. The final sample size was 36 individuals per group, considering a drop-out rate of 20 %.

$$SD = \frac{(max - SDS) \times (SDS - min)}{max - min}$$

Results

A flow chart for randomized controlled trials is presented in Fig. 2. One hundred and thirty-eight women were assessed as eligible, but a hundred and one randomly participated in the follow-up. These women were allocated into: electrotherapy group (n = 53) and control group (n = 48).

Sociodemographic and clinical characteristics of the 101 participants are in Table 2. Mean age electrotherapy (n = 53) and control groups (n = 48) were 35.06 ± 6.17 and 37.21 ± 6.51 years old, respectively. The intercourse median frequency was once per week for both groups. From the onset time of symptoms to the diagnosis, it took from 3 to 5 years, on average. A history of at least one endometriosis surgery per women was reposted in both groups. Women were using medication for endometriosis for 29.53 ± 29.10 and 24.04 ± 20.87 months for the electrotherapy and control groups, respectively, being the most frequent progestin (84 % and 81 % for each group, respectively). The sociodemographic aspects related to age at onset of symptoms and diagnosis of endometriosis was statistically different (p = 0.015 and 0.027, respectively).

Pelvic pain evaluation, pre and post-treatment are described in Table 3. Chronic pelvic pain improved in the electrotherapy group (VAS decreased from 7.11 ± 2.40–4.55 ± 3.08, p < 0.001, 36 % decrease) but this was not observed in the control group (VAS from 7.33 ± 2.09–7.06 ± 2.33, p = 0.554, 3.68 % decrease). A reduction in the deep dyspareunia scale for the electrotherapy group (from 2.02 ± 0.54–1.36 ± 0.96, p < 0.001, a 32.67 % decrease) was observed and for control group, the difference was from 1.95 ± 0.86–1.68 ± 0.82, p = 0.006, 13.84 % decrease. The other pelvic pain complaints were related to as being mild or moderate, with values above 6 points in the VAS.

Fig. 1. Self-applied transcutaneous electrical nerve stimulation (TENS) (Tanyx® - Register in the ANVISA nº80542090001) positioned in the sacral region of the participant (Photo authorized by the participant).

Data from the pain diary showed a reduction in the number of days with pain, with difference between the first and eighth week in the electrotherapy (from 3.27 to 2.22, p = 0.028, 32.11 % decrease), but there was no difference for control group (from 4.55 to 4.07, p = 0.203, 10.54 % decrease). Considering the VAS applied to chronic pelvic pain, the reduction was observed from the 3rd week until the end of treatment in the electrotherapy group (Fig. 3). There was an expressive reduction in the average of CPP in the first week of treatment compared to the average in the evaluation (from 7.11 to 3.27) for the electrotherapy group. Over the 8 weeks of follow-up, the electrotherapy group took seven days of medication, in comparison to eighteen days in the control group (p = 0.005).

Quality of life (EHP-30) showed an improvement in all domains of the core questionnaire for electrotherapy group (reduction in the core score from 56.37 ± 20.59–41.40 ± 25.87, p < 0.001, 26.55 % decrease). In control group, statistical significances were observed for pain and, control and powerless domains, which also impacted the core questionnaire score (reduction from 49.85 ± 21.95–45.58 ± 23.35, p = 0.043, 8.56 % decrease). In modular questionnaire score, both groups showed a reduction (p < 0.001 for electrotherapy, p = 0.005 for control group). The total questionnaire score showed improvement for both groups, with no statistical significance for the pre and post intervention (p = 0.593) (Table 3).

There was an improvement in pain complaints during intercourse (score reduction from 2.02 ± 0.54–1.36 ± 0.96, p < 0.001 in the DDS) in electrotherapy group. A reduction was also observed in the EHP-30 intercourse domain score (from 61.13 ± 33.61–40.85 ± 35.02, <0.001). An improvement was observed in the deep dyspareunia scale in the control group (from 1.95 ± 0.86–1.68 ± 0.82, p = 0.006), but the EHP-30 intercourse domain showed no statistical reduction (48.75 ± 33.33–44.17 ± 31.26, p = 0.139) (Tables 3 and 4).

In the SF assessed by FSFI, the electrotherapy group demonstrated improvement in the lubrication domain (3.81 ± 1.30–4.11 ± 1.25, p = 0.013), pain during intercourse (2.60 ±a 0.98–3.50 ± 1.50, p < 0.001), and in total score (from 21.42 ± 5.04–23.58 ± 4.78, p = 0.001, 9.16 % increase), suggesting a general improvement in SF. In control group, the only statistical difference observed was in satisfaction domain (4.25 ± 1.40–3.85 ± 1.43, p = 0.014), demonstrating a decrease in satisfaction, besides FSFI score has not improved (from 20.93 ± 5.20–20.64 ± 5.54, p = 0.953). There was an improvement in the total score for the electrotherapy group for the pre and post intervention values (p = 0.011) (Table 3).

Secondarily, the aspects related to complaints of pain, QoL and SF of women in the control group who accepted to participate in the electrotherapy treatment for 8 weeks were analyzed. We observed that CPP improved after the use of electrotherapy in this group (p < 0.001). Similarly, all domains of the quality of life questionnaire showed improvement after analgesic resource, as well as in the lubrication domain of FSFI (Table 4).

Based on pain diary, some side effects observed were: six participants in complete amenorrhea reported spotting (16.2 %) in electrotherapy group and it was associated with mild pain (VAS: 3.33 ± 2.25) during the days of spotting. In the control group, this complaint was not reported. Therefore, no long-term side effects are expected and no participant contacted us reporting any complaints related to the use of the device.

Discussion

This clinical trial evaluated electrotherapy as a complementary treatment for DIE in comparison with a control group. Patients in

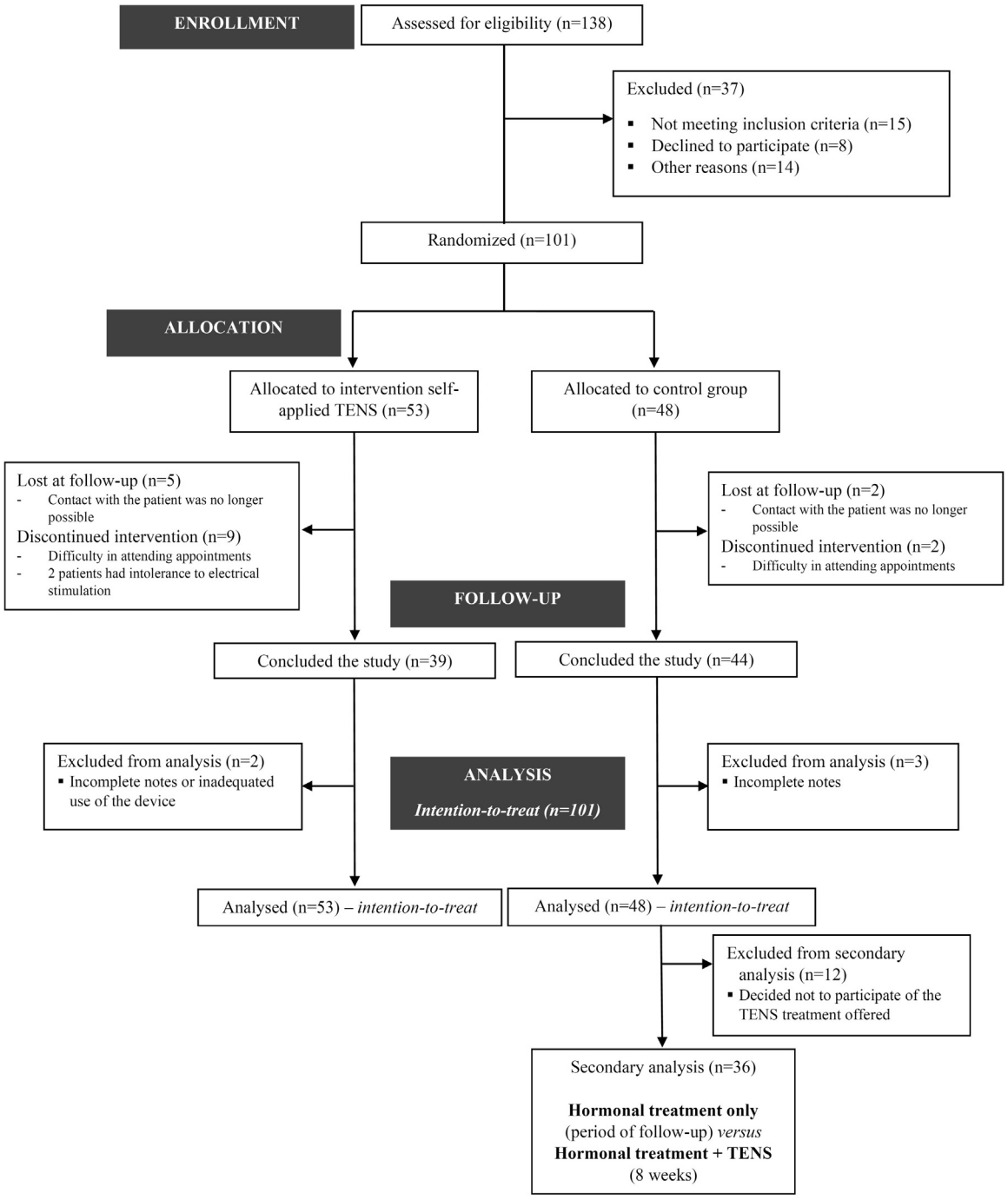

Fig. 2. The flow chart for Randomized Controlled Trials (RCT) showing the summary of participants of the clinical trial.

both groups had a diagnosis of deep endometriosis and they were using hormonal treatment. The eight-week follow-up showed that the use of self-applied transcutaneous electrical nerve stimulation (TENS) has benefits in the relief of CPP. This treatment also induced an improvement in the QoL and in SF.

Endometriosis can be considered a chronic disease, demanding pharmacological treatment for the relief of pain complaints, normally hormonal treatment. However, sometimes the pharmacological treatments are insufficient for pain control. [14] Our results showed that electrotherapy can be considered a complementary intervention option to relieve pelvic pain symptoms allied to medical treatment, improving the QoL.

Previous studies using electrotherapy demonstrated the benefits to relieve CPP not related to endometriosis. [8,9,15], To the best of our knowledge, possibly only our group has evaluated this resource for pelvic pain related to endometriosis [6]. We observe an improvement of CPP pre and post-treatment and from the 3rd week of the pain diary. This benefit is due to an electrical stimulus using the sensorial pathways to send impulses to the spinal cord in the ascending pathways, blocking the harmful visceral stimulus from endometriotic pelvic inflammatory lesions using high-frequency application (85 Hz). The high frequency is described in literature as any frequency above 70–100 Hz. Such a stimulus is thought to work in the Control Gate Theory [16]. But

Table 2
Main sociodemographic and clinical characteristics of women with deep endometriosis in the electrotherapy group (n = 53) and control group (n = 48).

Characteristics	Electrotherapy group (n = 53)		Control group (n = 48)		
	Mean ± SD	Median/min-max	Mean ± SD	Median/ min-max	p-value
Age (years)	35.06 ± 6.17	35.0	37.21 ± 6.51	37.0	0.082
Ethnicity	64.15(34)		60.42(29)		0.192
White	35.85(19)		39.58(19)		
Non-white					
Marital status (%)	79.25(42)		83.33(40)		0.600
With partner	20.75(11)		16.57(8)		
Without partner					
Body mass index (Kg/m^2)	26.49 ± 5.13	25.7	26.09 ± 3.72	25.9	1.000
Parity (number of children)	0.81 ± 1.05	0.0	0.98 ± 1.17	1.0	0.573
Parity (%)	49.06(26)		52.08(25)		0.460
0	26.42(14)		16.67(8)		
1	24.53(13)		31.25(15)		
≥2					
Number of intercourse (frequency per week)	1.57 ± 1.26	1.0	1.21 ± 1.20	1.0	0.073
Age at onset of symptoms (years)	21.48 ± 8.55	20.0	26.35 ± 10.28	26.5	**0.015**
Age at diagnosis of endometriosis (years)	28.36 ± 6.72	27.0	31.32 ± 6.84	31.0	**0.027**
Type of diagnosis (%)	43.40(23)		56.25(27)		0.102
Transvaginal ultrasound	15.09(8)		22.92(11)		
Magnetic resonance imaging	39.62(21)		20.83(10)		
Surgery	1.89(1)		0.0		
Biopsy					
Number of surgeries for Endometriosis	1.40 ± 1.90	1.0	0.88 ± 0.94	1.0	0.243
Time from the last surgery (months) [a]	56.8 ± 47.9	7–168	59.8 ± 49.2	7–156	0.779
Type of surgical procedure [a]	13.2 (9)		16.1 (11)		0.999
Laparotomy	23.5 (16)		29.4 (20)		
Videolaparoscopy	5.8 (4)		7.3 (5)		
No answer					
Time of use of the medication for endometriosis (months)	29.53 ± 29.10	18.0	24.04 ± 20.87	15.5	0.616
Type of medication (%)	84.91(45)		81.25(39)		0.891
Progestin	15.09(8)		18.75(9)		
Combined oral contraceptive (COC)					
Work position (%) [b]	51.28(20)		38.24(13)		0.411
Seated	41.03(16)		55.88(19)		
Standing	7.69(3)		5.88(2)		
Seated and standing					
Physical activity (%)	64.15(34)		75.00(36)		0.238
No	35.85(19)		25.00(12)		
Yes					

Fisher's test or χ^2 test for categorical variables comparison. Mann-Whitney for numerical variables comparison.
[a] Only those participants who have at least one surgery were considered in the analysis – Electrotherapy (n = 36) and control group (n = 29).
[b] Only those participants who were employed were considered in the analysis - Electrotherapy group (n = 39) and Control group (n = 34).

current studies show that the nociceptive control possibly happens even before it reaches the spinal cord [17]. There is an acute effect at the moment of application, extending to a cumulative effect, promoting pain pathway reorganization [18]. This effect can be seen in our study, in which the daily use of electrotherapy demonstrated pelvic pain relief.

Deep dyspareunia is a symptom associated to DIE. Rectovaginal endometriosis and lesions in uterosacral ligaments promote pain due to traction of inelastic tissue, making the uterus less mobile. [19] Surgery to remove the lesion is the option to treat this symptom, improving deep dyspareunia when evaluated 10–60 months after the procedure [20]. Hormonal treatment with progestin has also been shown to be appropriate. Hormonal therapy reduces pain during intercourse in two-thirds of women with rectovaginal lesions [21]. In this context, for those who do not respond, another treatment is required. Our study demonstrated improvement for dyspareunia using electrotherapy associated to hormonal treatment or using hormonal treatment exclusively. But the intervention using TENS decreased the intake of analgesic drugs, and electrotherapeutic treatment has fewer side effects than analgesic drugs [22,23].

CPP significantly jeopardizes the QoL of women with DIE, in addition to negatively affecting employment. [24,25] Chronic pain by itself, notwithstanding the cause, is a factor that negatively affects QoL [24,26], affecting psychological aspects and leading to depression and anxiety [27,28]. Considering this context, pain management is an important decision. Our results showed that pelvic pain relief in the electrotherapy group positively affected all domains of the EHP, demonstrating improvement in the control of pain, control and powerless, emotion, social support, self-image, work and treatment domains. This can also be observed when the control group, in a second moment, received the intervention.

Endometriosis affects sexual function. [12,29] One study presented the alarming data that 67 % of women with endometriosis have relationship problems resulting from the disease,29,31] implying in a divorce ratio of 7–19 % due to the incomprehension of the partner about the pelvic symptoms.29] Our study verified an improvement in the lubrication and pain (dyspareunia) domains and total score of the FSFI in electrotherapy group. The improvement was also observed in the intercourse domain in quality of life questionnaire. Possibly the disruption of the pain cycle (pain-fear-tension) contributed to sexual intercourse improvement. [27–31]. The same observations could be seen when we analyze the control group that was subsequently submitted to electrotherapeutic intervention.

The benefits could be seen better and in detail in the pain diary. Comparing the weeks, there was a statistically significant improvement from the 3rd week until the end of treatment with

Table 3
Comparison of treatment effects in the electrotherapy group (association with hormonal treatment) and control group (hormonal treatment only) on complaints of pelvic pain, quality of life (EHP-30) and sexual function (FSFI) in women with deep endometriosis.

	Electrotherapy group (n = 53)						Control group (n = 48)						
	Pretreatment		Post-treatment				Pretreatment		Post-treatment				
Pelvic Pain	Mean ± SD	Median	Mean ± SD	Median	Difference	p value [a]	Mean ± SD	Median	Mean ± SD	Median	Difference	p value [a]	p value of difference [b]
Chronic Pelvic Pain (VAS)	7.11 ± 2.40	8.0	4.55 ± 3.08	5.0	−2.55 ± 2.98	<**0.001**	7.33 ± 2.09	7.5	7.06 ± 2.33	7.5	−0.27 ± 2.18	0.554	<**0.001**
Deep dyspareunia (DDS)	2.02 ± 0.54	2.0	1.36 ± 0.96	2.0	−0.67 ± 0.98	<**0.001**	1.95 ± 0.86	2.0	1.68 ± 0.82	2.0	−0.27 ± 0.55	**0.006**	0.091
Dyschezia (VAS)	4.83 ± 4.09	5.5	3.04 ± 3.67	1.0	−1.79 ± 3.28	<**0.001**	3.75 ± 3.98	1.5	2.83 ± 3.55	0.0	−0.92 ± 2.65	**0.022**	0.761
Frequency of evacuation (per week)	5.17 ± 5.80	3.0	5.85 ± 6.05	4.0	0.67 ± 2.38	**0.030**	4.42 ± 3.46	3.0	4.35 ± 2.38	4.0	−0.06 ± 3.42	0.441	0.603
Dysuria (VAS)	1.79 ± 2.95	0.0	1.23 ± 2.41	0.0	−0.56 ± 2.13	**0.034**	1.25 ± 2.77	0.0	1.40 ± 2.84	0.0	0.15 ± 1.32	0.750	0.992
Pain during spotting (VAS)	2.29 ± 3.92	0.0	2.19 ± 3.67	0.0	−0.10 ± 2.35	0.867	2.31 ± 3.98	0.0	2.90 ± 4.05	0.0	0.58 ± 4.11	0.368	0.340
QUALITY OF LIFE													
Endometriosis Health Profile (EHP-30)													
Core questionnaire													
Pain domain	50.81 ± 27.11	54.55	37.95 ± 28.89	36.36	−12.86 ± 19.49	<**0.001**	47.96 ± 23.49	48.86	42.99 ± 23.23	43.18	−4.97 ± 18.86	**0.048**	0.290
Control and powerless domain	63.76 ± 26.12	66.67	41.27 ± 32.26	45.86	−22.48 ± 25.83	<**0.001**	59.11 ± 26.94	a	52.17 ± 28.05	54.17	−6.94 ± 18.22	**0.009**	0.087
Emotion domain	59.12 ± 23.94	62.50	44.10 ± 27.53	41.67	−15.02 ± 22.02	<**0.001**	54.34 ± 24.78	54.17	50.87 ± 27.56	54.17	−3.47 ± 18.60	0.205	0.199
Social support domain	58.02 ± 24.92	62.50	43.87 ± 30.70	37.50	−14.15 ± 27.60	<**0.001**	45.83 ± 25.96	46.88	39.32 ± 26.29	43.75	−6.51 ± 22.48	0.061	0.587
Self-image domain	50.16 ± 29.35	50.00	39.78 ± 30.99	33.33	−10.38 ± 25.26	**0.001**	42.01 ± 30.70	41.67	42.53 ± 31.43	50.00	0.52 ± 15.98	0.982	0.740
Core questionnaire score	56.37 ± 20.59	53.45	41.40 ± 25.87	41.67	−14.98 ± 19.65	<**0.001**	49.85 ± 21.95	48.77	45.58 ± 23.35	43.45	−4.28 ± 12.70	**0.043**	0.305
Modular questionnaire													
Work domain	23.96 ± 29.29	10.00	17.83 ± 23.13	0.00	−6.13 ± 21.07	**0.049**	20.52 ± 26.02	10.00	16.04 ± 23.25	0.00	−4.48 ± 16.38	0.057	0.834
Children domain	15.33 ± 31.07	0.00	13.44 ± 29.09	0.00	−1.89 ± 11.86	0.500	11.98 ± 23.20	0.00	9.38 ± 18.68	0.00	−2.60 ± 14.80	0.281	0.865
Intercourse domain	61.13 ± 33.61	70.00	40.85 ± 35.02	30.00	−20.28 ± 31.74	<**0.001**	48.75 ± 33.33	60.00	44.17 ± 31.26	45.00	−4.58 ± 23.13	0.139	0.667
Medical domain	17.22 ± 26.99	0.00	13.68 ± 21.27	0.00	−3.54 ± 25.55	0.429	15.23 ± 25.65	0.00	8.85 ± 19.12	0.00	−6.38 ± 31.36	0.087	0.103
Treatment domain	40.88 ± 28.88	41.67	28.30 ± 26.57	25.00	−12.58 ± 21.60	<**0.001**	28.65 ± 27.23	29.17	32.12 ± 29.32	29.17	3.47 ± 21.32	0.243	0.580
Infertility domain	30.90 ± 38.50	0.00	28.89 ± 36.01	0.00	−2.00 ± 22.56	0.560	20.44 ± 32.71	0.00	14.45 ± 27.90	0.00	−5.99 ± 24.49	0.144	**0.047**
Modular questionnaire score	31.57 ± 16.82	32.64	23.83 ± 17.40	22.71	−7.74 ± 13.35	<**0.001**	24.26 ± 14.51	22.85	20.83 ± 13.61	16.84	−3.43 ± 8.45	**0.006**	0.479
Total questionnaire score	43.97 ± 17.03	42.15	32.61 ± 20.38	32.66	−11.36 ± 15.48	<**0.001**	37.06 ± 16.03	36.03	33.21 ± 16.66	28.71	−3.85 ± 8.53	**0.005**	0.593
SEXUAL FUNCTION													
Female Sexual Function Index (FSFI)													
Desire	3.31 ± 1.30	3.00	3.40 ± 1.32	3.60	0.09 ± 0.68	0.403	2.91 ± 1.12	3.00	2.73 ± 1.09	2.40	−0.18 ± 1.03	0.372	**0.026**
Arousal	3.44 ± 1.32	3.60	3.74 ± 1.08	3.90	0.30 ± 1.34	0.156	3.21 ± 0.83	3.30	3.15 ± 1.12	3.30	−0.06 ± 1.16	0.560	**0.018**
Lubrication	3.81 ± 1.30	3.60	4.11 ± 1.25	4.20	0.29 ± 0.91	**0.013**	3.97 ± 1.25	3.90	4.16 ± 1.20	4.20	0.19 ± 1.09	0.278	0.867
Orgasm	4.12 ± 1.34	4.40	4.39 ± 1.12	4.40	0.28 ± 1.15	0.356	3.62 ± 1.44	4.00	3.70 ± 1.35	3.60	0.07 ± 1.15	0.592	**0.019**
Satisfaction	4.14 ± 1.35	4.40	4.44 ± 1.30	4.80	0.29 ± 1.15	0.390	4.25 ± 1.40	4.80	3.85 ± 1.43	4.00	−0.40 ± 0.91	**0.014**	**0.042**
Pain	2.60 ± 0.98	2.80	3.50 ± 1.50	3.60	0.90 ± 1.47	<**0.001**	2.96 ± 1.34	2.80	3.05 ± 1.29	3.20	0.10 ± 0.92	0.478	0.212
Total score	21.42 ± 5.04	21.30	23.58 ± 4.78	23.50	2.15 ± 4.52	**0.001**	20.93 ± 5.20	22.20	20.64 ± 5.54	20.70	−0.28 ± 3.65	0.953	**0.011**

[a] Wilcoxon test for comparison variables (pre and post-treatment). [b] Mann-Whitney test for comparison of the difference values between the groups. Intention to treat (ITT) analysis.
Legend: VAS (Visual Analog Scale): 0–10 points (zero: without pain to ten: intense pain) / DDS (Deep Dyspareunia Scale): 0–3 points (zero: without pain to three: intense pain).

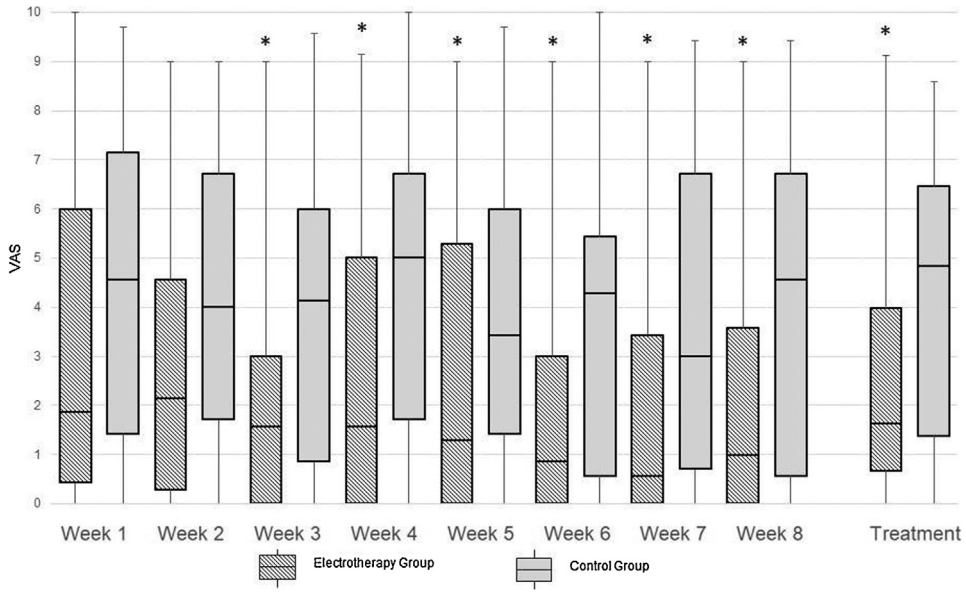

Fig. 3. Description of the distribution of VAS values based on annotations of daily pain control for electrotherapy and control groups throughout 8 weeks of treatment.

Table 4
Comparison of treatment effects in the control group in two moments: hormonal treatment only (period of follow-up) and hormonal treatment associated to electrotherapy treatment (period of treatment) on complaints of pelvic pain, the quality of life (EHP-30) and sexual function (FSFI) in women with deep endometriosis.

	CONTROL GROUP (n = 36)			
	Hormonal treatment only (period of follow-up – 8 weeks)		Hormonal treatment + TENS (period of treatment – 8 weeks)	
	Pre (t1)	Post (t2)	Post (t3)	
	Mean ± SD	Mean ± SD	Mean ± SD	*p-value*
PELVIC PAIN COMPLAINTS				
Chronic Pelvic Pain (VAS)	7.57 ± 1.43	7.14 ± 2.07	4.93 ± 2.73	<**0.001** [bc]
Deep dyspareunia (DDS)	2.20 ± 0.83	1.80 ± 0.77	1.40 ± 1.10	**0.004** [ab]
Dyschezia (VAS)	3.80 ± 3.97	2.50 ± 3.44	1.83 ± 2.72	**0.038** [ab]
Frequency of evacuation (per week)	4.90 ± 2.40	4.37 ± 2.34	5.87 ± 4.79	**0.001** [bc]
Dysuria (VAS)	1.60 ± 3.15	1.83 ± 3.22	1.43 ± 2.80	0.639
Pain during spotting (VAS)	2.17 ± 3.83	2.67 ± 3.96	1.73 ± 3.30	0.145
QUALITY OF LIFE				
Endometriosis Health Profile (EHP-30)				
Core questionnaire				
Pain domain	49.05 ± 24.07	42.36 ± 23.35	25.81 ± 31.40	<**0.001** [bc]
Control and powerless domain	60.65 ± 28.07	53.12 ± 28.41	25.81 ± 31.40	<**0.001** [abc]
Emotion domain	55.90 ± 25.11	53.24 ± 27.42	31.02 ± 29.42	<**0.001** [bc]
Social support domain	48.44 ± 26.49	43.75 ± 26.35	29.51 ± 31.22	**0.011** [bc]
Self-image domain	44.44 ± 31.31	45.14 ± 32.02	28.01 ± 30.93	**0.005** [bc]
Core questionnaire score	51.70 ± 22.88	47.52 ± 23.84	27.23 ± 26.85	<**0.001** [bc]
Modular questionnaire				
Work domain	21.25 ± 27.08	15.83 ± 24.36	10.69 ± 19.79	**0.003** [c]
Children domain	13.89 ± 25.14	10.42 ± 19.71	7.29 ± 18.99	0.142
Intercourse domain	48.19 ± 33.21	45.97 ± 31.16	28.61 ± 31.70	**0.007** [bc]
Medical domain	17.01 ± 27.78	10.24 ± 20.76	8.16 ± 20.58	**0.049** [c]
Treatment domain	34.72 ± 27.71	37.96 ± 30.04	20.83 ± 26.39	**0.005** [bc]
Infertility domain	20.49 ± 32.55	14.06 ± 26.02	8.16 ± 24.81	0.081
Modular questionnaire score	25.93 ± 14.07	22.42 ± 12.89	13.96 ± 16.18	<**0.001** [abc]
Total questionnaire score	38.81 ± 15.89	34.97 ± 16.16	20.59 ± 20.39	<**0.001** [abc]
SEXUAL FUNCTION				
Female Sexual Function Index (FSFI)				
Desire	2.72 ± 1.08	2.56 ± 1.00	3.06 ± 1.47	0.362
Arousal	2.91 ± 0.68	3.09 ± 1.13	3.36 ± 1.21	0.798
Lubrication	3.68 ± 1.12	4.25 ± 1.15	4.31 ± 1.26	**0.038** [ab]
Orgasm	4.56 ± 1.48	3.73 ± 1.37	3.77 ± 1.32	0.720
Satisfaction	4.08 ± 1.30	3.64 ± 1.44	4.32 ± 1.40	0.195
Pain	2.95 ± 1.25	3.09 ± 1.29	3.64 ± 1.41	0.085
Total score	19.89 ± 4.05	20.36 ± 4.91	22.46 ± 6.36	0.150

Friedman test for comparison of variables in three times. **t1 =** Evaluation (pre treatment); **t2 =** reevaluation of period of the hormonal treatment only (8 weeks) and beginning of the hormonal + TENS treatment period; **t3 =** reevaluation of the period of hormonal treatment + TENS (8 weeks). Wilcoxon test for comparison variables (pre and post-treatment) between two times → [a] t1 x t2; [b] t2 x t3; [c] t1 x t3 ($p < 0.05$).

the electrotherapy device. We believe the use of a pain diary can contribute towards a better understanding of symptom evolution in the course of the treatment for both the health professional and patient. In this context, the patient better comprehends the importance of treatment, as it favors the patient's visualization of the pain variation and thus the patient observes progress that contributes positively to her condition. This leads to more realistic pain perception and its progression during a follow-up or treatment period, since the pain reported can be skewed by a more recent intense pain memory.

Although we described the intention-to-treat analysis, the results from the per protocol analysis was performed and point in the same direction.

Despite the benefits showed, the main limitations are the short follow-up treatment time, considering the disease chronicity and the long-term electrotherapy treatment use is still unknown in this population. Strengths include the assessment of an electrotherapy protocol associated with hormonal treatment using a self-applied device, compared to a control group using hormonal treatment only. Besides that, it also includes the use of a pain diary, with a more rigid and reliable control for the use and effectiveness of our intervention. The results contributed to identifying the effectiveness of complementary treatment.

Conclusions

Electrotherapy treatment using transcutaneous electrical nerve stimulation proved to be a good option for endometriosis pain control, showing benefits in the reduction of chronic pelvic pain and deep dyspareunia and improving QoL and SF. Thus, this therapeutic tool can be considered a complementary treatment for DIE.

Declaration of Competing Interest

The authors report no declarations of interest.

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