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ARTICLE

An initial study on the effect of functional electrical stimulation in erectile dysfunction: a randomized controlled trial

Cristiane Carboni[1] · Alexandre Fornari[1] · Karoline C. Bragante[1] · Marcio A. Averbeck[1] · Patrícia Vianna da Rosa[1] · Rodrigo Della Mea Plentz[1]

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Abstract

Erectile dysfunction (ED) affects approximately 150 million men worldwide. Functional electrical stimulation (FES) therapy has shown a high regenerative capacity for smooth muscle cells and, therefore, is being increasingly adopted. FES can be a beneficial treatment option when the cause of ED is related to degeneration of cavernous smooth muscle. To evaluate the impact of FES on erectile function in men with erectile dysfunction. Twenty-two patients with ED participated in this randomized clinical trial. Participants were randomly assigned to two groups: intervention (IG) or control (CG). IG participants underwent FES therapy (50 Hz/500 μs) for a total of 4 weeks, divided into two weekly sessions lasting 15 min each, with intensity lower than the motor threshold. CG participants were treated with placebo FES and followed the same routine as the IG. Erectile function was assessed by the validated International Index of Erectile Function (IIEF-5) and Erection Hardness Score (EHS), applied before and after treatment, and quality of life, by the WHOQOL questionnaire. Statistically significant differences in IIEF-5 and EHS were found between the IG and CG after treatment ($p < 0.05$), as well as a within-group difference in the IG when comparing the post-treatment periods ($p < 0.0001$) The WHOQOL revealed a significant difference between CG and IG after treatment ($p < 0.05$), as well as a within-group difference in the IG after treatment ($p < 0.0001$), except in the Environment domain, in which there was no difference between the pre- and post-treatment periods (50.9 ± 2.8 pre vs. 52.3 ± 3.1 post). This trial showed that FES therapy may improve erectile function and quality of life in men with ED.

Introduction

Erectile dysfunction (ED) is defined as the persistent failure to achieve and sustain erections of sufficient rigidity for penetration during sexual intercourse [1]. The etiology of ED can be either psychogenic (such as anxiety or depression, which can potentially diminish the awareness of sensory experience) or organic (vasculogenic and neurological abnormalities, for example). Sexual dysfunction can affect patients' lives in a variety of ways, including disorders in interpersonal relationships, interference with sex life, problems with partners, and increased mental stress, making ED a major quality of life (QoL) issue [2].

Despite the availability of several pro-erectile drugs, there are many men who, for one reason or another, do not derive benefit from these agents. Indeed, up to 35% of men with ED do not respond to phosphodiesterase type 5 (PDE5) inhibitors [3], and discontinuation rates are reportedly high (35 to 45%) [4, 5]. The reasons for non-adherence to treatment include fear of possible side effects and high drug costs [6]. Consequently, there is an unmet need for the development of alternative, conservative approaches for ED management.

Physical therapy interventions offer noninvasive methods that are painless, inexpensive, and easy to perform. Studies [7, 8] have shown positive results for men who attended a pelvic-floor reeducation program for patients with ED. The understanding of possible conservative treatments for ED is connected to erection physiology. Even when dealing with diverse forms of ED, the major potential change can occur in the penile endothelium [9]. This is

✉ Cristiane Carboni
criscarboni@hotmail.com

[1] Department of Health Science and Rehabilitation, Federal University of Health Sciences of Porto Alegre–UFCSPA, Porto Alegre, Rio Grande do Sul, Brazil

important to highlight because the penile endothelium is the site of secretion of nitric oxide (NO), considered the main factor involved in immediate relaxation of smooth muscle cells of the penile blood vessels and corpus cavernosum. NO generated in the endothelium plays a relevant role in erection maintenance and in endothelial dysfunction, contributing to many subgroups of ED. Animal model studies have shown that functional electrical stimulation (FES) has a regenerative effect on the endothelium, with increased NO release [10, 11]. The regeneration of the cavernous smooth muscle prompted by FES should result in the spontaneous return of erectile capacity, if no other factors are involved in the etiology of ED [12]. Within this context, the aim of this study was to evaluate the effect of FES in the treatment of ED.

Materials and methods

This study was approved by the Ethics Committee in Research of the Universidade Federal de Ciências da Saúde de Porto Alegre, number 926.000. This study was a randomized controlled clinical trial (ClinicalTrials.gov identifier NCT02284659). We randomized 22 patients, aged 40 to 65 years, with known ED (defined as a score of less than 22 on the IIEF-5), who had been in a stable relationship for more than 6 months and not taking any ED medication. The exclusion criteria adopted were: neurogenic ED (due to spinal cord injury, Parkinson's disease, multiple sclerosis, prostatectomy); hypogonadism (total testosterone < 300 ng/dl); decompensated diabetes mellitus (fasting blood glucose > 200 mg/dl and/or glycated hemoglobin > 8%); decompensated systemic arterial hypertension (SBP > 160 and/or DBP > 100); morbid obesity; diagnosis of coronary heart disease and/or cerebrovascular disease; and inability to understand the study objectives/technique or to provide informed consent.

If patients were previously taking any commercially available drug or non-drug treatment for ED (e.g., injection therapy, topical applications, herbal, or alternative medicines, vacuum-assisted erection devices), such treatments should have been terminated at, or before, the screening visit and should not have been used at any time during the study until the final evaluation. Patients who were on PDE5 inhibitors were asked to complete a 4-week wash-out period before enrollment in the trial and not to use it until the last evaluation after finishing the treatment.

Randomization was carried out in two steps: generation of random numbers in each group, using the RANDOM subroutine of the PEPI software suite (computer programs for epidemiologists); and allocation concealment, which was ensured by placing numbers in letter-sized manila envelopes.

Participants were randomly assigned to two groups: intervention (IG) or control (CG). The intervention group received FES therapy (50 Hz/500 μs) for a total of 4 weeks, divided into two weekly sessions lasting 15 minutes each, with intensity set lower than the motor threshold that was assessed individually. Two self-adhesive electrodes measuring 3 cm each were used. One electrode was placed at the base of the penis, while the second was attached 2 cm below the first one. The control group was treated with placebo FES machine (the red light functioning but there was no power). Both groups attended sessions twice a week for a period of 4 weeks, for a total of 8 FES sessions. Erectile function was assessed by the validated International Index of Erectile Function (IIEF-5) and Erection Hardness Score (EHS) instruments. Quality of life (QoL) was assessed with the validated WHOQOL-BREF questionnaire. All of the questionnaires were applied before and immediately after the treatment. The instruments were completed by a blinded investigator, according to the protocol to which the patient had been randomized. Only the physiotherapist who applied the technique was aware of group allocation. Participants had no treatment costs.

Statistical analysis

Statistical analysis was performed in SPSS Version 22.0 (IBM, Chicago, IL, USA). Data are reported as mean ± SEM. The generalized estimating equations model was used to test for significant differences in different visits and time points, according to each treatment. Differences were declared significant if $p < 0.05$.

Results

During the study period, 22 patients with ED visited a private outpatient physical therapy service. All participants met the inclusion criteria and none were excluded. The 22 subjects completed the study as shown in the CONSORT flow diagram of patient randomization and analysis (Fig. 1).

Both groups showed a similar distribution of demographic variables at baseline (Table 1). Within-group analysis of results in the CG and collected through the EHS and IIEF-5 questionnaires, administered before and after treatment, showed no statistical difference (Table 2). Within-group assessment of the results in the intervention group, collected through the same instruments, demonstrated statistically significant differences ($p < 0.001$) (Fig. 2), as well as variation in pre- and post-treatment scores between the groups ($p < 0.05$) (Table 2), (Fig. 2).

Regarding the quality of life questionnaire (WHOQOL-BREF), CG participants exhibited statistically significant improvement in the psychological (47.3 ± 2.2 pre-post 50.4

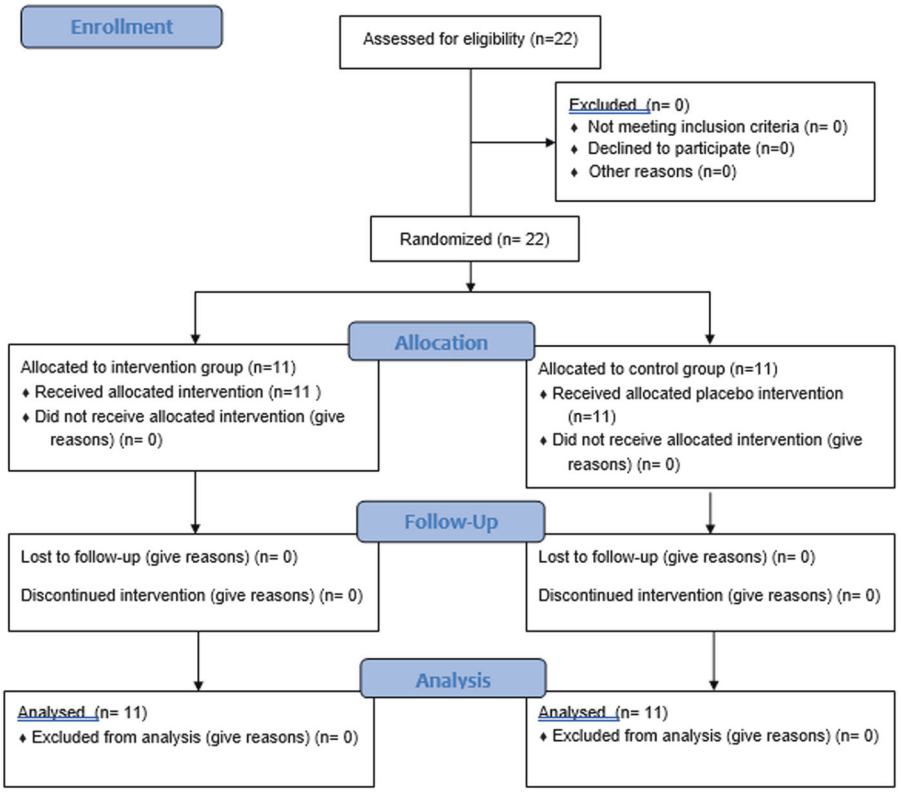

Fig. 1 CONSORT flow diagram of patient randomization and analysis

Table 1 Characteristics of the sample

Variable	Total sample	IG ($n = 11$)	CG ($n = 11$)	p
Age	58.5 ± 5.3	58.6 ± 5.3	58.4 ± 5.8	.940
Race				.534
White	19 (86.3)	10 (90.9)	9 (81.8)	
Black	3 (13.7)	1 (9.1)	2 (18.1)	
Scholarship	5 (4–8)	5 (4–8)	5 (4–8)	1.0
Smoker	12 (54.5)	5 (45.4)	7 (63.6)	.392
Alcoholic	5 (22.7)	3 (27.2)	2 (18.1)	.611

Table 2 Comparison between groups and intra groups regarding EHS and IIEF-5 questionnaire

	Placebo			Intervention		
Variable	Pre	Post	Diff	Pre	Post	Diff
EHS	1.64 ± 0.19	1.82 ± 0.17	.18	1.73 ± 0.13	2.82 ± 0.3*	1.1†
IIEF-5	11.4 ± 1.3	11.4 ± 1.4	0	11 ± 1.2	16 ± 1.7*	5†

Value are Mean ± SEM

Generalized Estimating Equations Model was used to test for significant differences at different visits and time points according to each treatment

EHS erection hardness score, *IIEF-5* International index of erectile function-5, *Diff* mean difference post-treatment

*$p < .0001$ from Pre in each questionnaire, †$p < 0.05$ Comparison between questionnaire changes

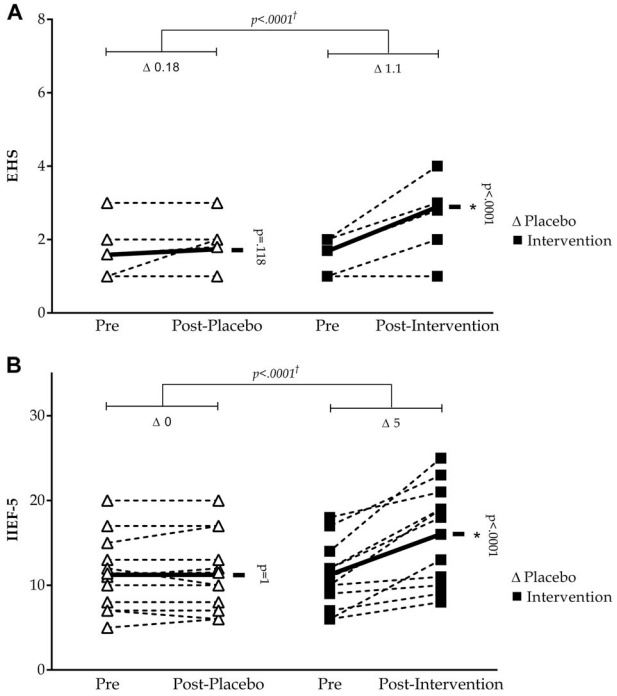

Fig. 2 Individual changes in the EHS score (**a**) and IIEF-5 score (**b**)

± 2, $p < 0.0001$*) and personal relationships (39.5 ± 3.5 pre-post 43.6 ± 4.5, $p < 0.0001$*) domains. Other domains showed no statistically significant difference.

Table 3 Comparison between groups and intra groups regarding WHOQOL-BREF questionnaire

Variable	Placebo			Intervention		
	Pre	Post	Diff	Pre	Post	Diff
WQ–PH	50 ± 2.1	50 ± 2.1	0	52.3 ± 3	67.7 ± 4.1*	15.4†
WQ–P	47.3 ± 2.2	50.4 ± 2*	3.1	47.3 ± 2	67.3 ± 2.9*	20†
WQ–SR	39.5 ± 3.5	43.6 ± 4.5*	4.1	41.8 ± 2.4	66.8 ± 4*	25†
WQ–E	50.9 ± 2.9	53.2 ± 3	2.3	50.9 ± 2.8	52.3 ± 3.1	1.4

Value are Mean ± SEM

Generalized Estimating Equations Model was used to test for significant differences at different visits and time points according to each treatment

WQ WHOQOL-BREF, *PH* physical health, *P* psychological, *SR* social relationships, *E* environment, *Different* mean difference Post-treatment

*$p < .0001$ from Pre in each treatment, †$p < 0.05$ Comparison between treatment changes

Within-group analysis of the IG showed significant differences in all areas, except the environment domain (50.9 ± 2.8 pre-post 52.3 ± 3.1). On between-group analysis of WHOQOL-bref domains, the only area in which no significant differences were observed was the environment domain (Table 3).

Discussion

The results of this trial showed two statistically significant improvements in the intervention group. First, according to IIEF-5 and EHS scores, there was a statistically significant difference in the erectile function in the relationship between the IG pre- and post-treatment with the CG ($p < 0.05$) (Table 2). Secondly, there was a statistically significant difference between the pre-treatment and post-treatment time points in the IG ($p < 0.0001$) (Table 2). In the WHOQOL-BREF questionnaire, only the environment domain showed no significance difference in the IG, while in the CG, there was no difference in any questionnaires. Individual analysis of each participant revealed a placebo effect in some of them, but the statistical analyses did not show any difference in final score.

Upon sexual stimulation, penile erection, occurring in response to the activation of pro-erectile autonomic pathways, is greatly dependent on adequate inflow of blood to the erectile tissue and requires coordinated arterial endothelium-dependent vasodilatation and sinusoidal endothelium-dependent cavernosal smooth muscle relaxation [13]. NO is the principal peripheral pro-erectile neurotransmitter, released both by parasympathetic-nitrergic autonomic nerves and by the sinusoidal endothelium to produce cyclic GMP (cGMP) and relax cavernosal smooth muscle, ultimately resulting in increased intracavernosal pressure [10]. Studies [10, 14] in animals support the view that FES causes NO and cGMP formation in the corpus cavernosum, as assessed by monitoring the simultaneous formation of nitrite (the spontaneous oxidation product of NO) and cGMP. This is one possible explanation for the positive results of the present study, in which both erection hardness and erectile function were evaluated. We intended to translate these principles to the bedside by applying them to real-world patients with ED. Electron microscopy studies have already shown that ED is often caused by cavernous smooth-muscle degeneration [15, 16]. In these patients, drugs, penile prosthetics, or the application of a vacuum device seemed to be the only treatment possible. Considering experimental studies on cavernous smooth-muscle cells [17], we now have the knowledge that smooth-muscle growth is easily inducible and that FES is an established method for muscle regeneration [2]. Therefore, FES should be considered as a treatment for ED.

In 1995, Stief et al. [12] conducted a similar study and found similar results in the intervention group, but as there was no control group, the placebo effect could not be evaluated. However, the aforementioned study found that some patients who had exhibited an insufficient response to vasoactive drugs started to respond after the intervention. Unfortunately, this possibility was not tested in our study. In 2000, Myung-cheol Gil et al. [18] reported a statistically significant improvement in erectile function, maintenance of erection, intercourse satisfaction, and overall satisfaction after FES treatment for ED.

ED is a complex and multidimensional condition, associated with psychological and relationship concerns, including decreased QoL and self-esteem and an increased incidence of depression and interpersonal relationship problems [19, 20] which demonstrates the importance of evaluating QoL in this group of patients. Laumann et al. [21] have noted that health status, stress, life satisfaction, and deterioration of general health and emotional functions are strongly correlated with sexual dysfunction. As in our study, they concluded that the social relationships and psychosocial well-being domains of QoL are particularly impaired in men with ED. Therefore, we believe that, by

restoring sexual function, one can also improve QoL levels. Although we had good QoL outcomes in the intervention group, the small number of sessions prevents a definitive conclusion; long-term results are needed before we can claim that our protocol restores sexuality-related QoL. It is hard to explain both lack of placebo effect in the CG and the good improvement in the QoL of the IG. Looking individually some of the control had a bit improvement but was not significant. And the few sessions that was done might gave a feeling of enthusiasm for the intervention. But this is just speculations. We would need a bigger study to have more conclusive data about the results.

Our findings suggest that FES for ED is feasible and has some beneficial effect on erectile capacity and QoL in our patients. One limitation of our study is the small sample size, although it was sufficient to show a clear statistical difference in terms of recovery of erectile function on comparison to the control group. Another limiting factor was the length of follow-up, which was insufficient to allow evaluation of long-term results. Further studies should be carried to corroborate our results, aiming to improve the methods of evaluation establishing the physiopathology pathways of the FES in the NO release, and finding selection criteria for patients suitable for this treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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