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ARTICLE

Transcutaneous functional electrical stimulation—a novel therapy for premature ejaculation: results of a proof of concept study

Arik Shechter[1,2] · E. C. Serefoglu[3] · Tal Gollan[4] · Shmuel Springer[5] · Gideon Meiry[4] · Boaz Appel[1] · Ilan Gruenwald[1]

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Abstract

Premature Ejaculation (PE) is a very common and disturbing sexual dysfunction in men. Currently available treatment modalities are associated with limited efficacy and low treatment adherence. In this prospective, single-blinded, self-controlled study, we evaluated the efficacy and safety of transcutaneous electrical stimulation (TES) for the treatment of (PE). We included 23 patients aged 20–60 (mean: 38.7) with lifelong PE. On the first visit, we delivered either TES or sham treatment to the perineum, based on the enrollment order. For stimulation, we used a commercial neuromuscular electrical stimulation device. The patients were invited for the second visit after at least 7 days for receiving the alternating treatment. During the treatment sessions, the patients were left alone in a privet silent room to masturbate and a stopwatch was used to measure their masturbation ejaculatory latency time (MELT). The patients also filled-out safety questionnaires after each visit and on each of the 3 following days. Of the 20 patients who completed the study, 17 (85%) experienced prolonged MELT under TES compared with the sham treatment. Mean MELT values increased 3.5-folds under TES ($p = 0.0009$). We demonstrated a significant increase in MELT in lifelong PE patients using TES. This therapeutic option may have the potential to become an on-demand treatment option for PE. Future studies with wireless devices are needed to confirm the efficacy and safety of this treatment concept during intercourse.

Introduction

Premature Ejaculation (PE) is a very common and disturbing sexual dysfunction in men. Twenty to thirty percent of sexually active men suffer from PE, according to type and to different definitions of professional associations [1–5]. PE is associated with detrimental psychological, physical, and social effects [6]. There is also a possible association between ED and PE [7]. Although this dysfunction has been widely investigated, its pathophysiology still remains unclear [8]. As for today, dapoxetine is the only oral compound, which has been specifically developed for the treatment of PE approved by the European Medical Agency and not by the US Food and Drug Administration [9–13]. The treatment of PE continues to be a major area of medical research.

Ejaculation is a complex reflex, which has two phases: emission and expulsion, both of which involve several pelvig-perineal anatomical structures [14]. After a sufficient erotic stimulus, a tight coordination of autonomic and somatic innervation is necessary for a normal antegrade ejaculation [15]. Emission is the advancement of semen into the posterior urethra, as a result of epithelial secretion and smooth muscle cell contraction around the epididymis and ductus deferens, pushing the sperm into the prostate and urethra [15]. All of the organs contributing to the emission phase are a densely innervated by the autonomic system, composed of both sympathetic and parasympathetic axons, which are mainly derived from

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✉ Arik Shechter
arikshec@gmail.com

1 Neurourology Unit, Rambam Healthcare Campus, Haifa, Israel

2 Department of Family Medicine, Ruth and Bruce Rappaport Faculty of Medicine, Technion Institute of Technology, Clalit Health Services, Haifa, Israel

3 Department of Urology, Biruni University School of Medicine, Istanbul, Turkey

4 Virility Medical Ltd., Nazareth, Israel

5 Physical Therapy Department, Faculty of Health Sciences Ariel University, Ariel, Israel

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the pelvic plexus [16]. Expulsion is a spinal cord reflex, which causes the ejection of sperm from the posterior urethra to the meatus [15]. During this phase, smooth muscle bundles contract in the bladder neck to prevent backflow of semen into the bladder, and the pelvic floor striated muscles (mainly bulbospongiosus and ischiocavernosus muscles), which play a major functional role and display significant rhythmic contractions to propel semen distally, throughout the bulbar and penile urethra towards the meatus [17, 18].

In 2017, Gruenwald et al. [19] proposed a new concept for treatment of PE based on the transient inhibition of the bulbospongiosus muscle contraction by neuromuscular transcutaneous electrical stimulation (TES). According to this new concept, TES delivered to the neuromuscular junction may keep the muscle ~80% contracted for several minutes, inhibiting its ability to display rhythmic contractions during the neural ejaculatory stimulus phase, either by keeping the muscle partially contracted and/or by driving it into fatigue. Therefore, the expected clinical outcome of this TES of bulbospongiosus muscle may be a delay in the ejaculatory latency time.

The objectives of this proof of concept study are to evaluate the feasibility and safety and feasibility of TES treatment applied to men with lifelong PE.

Methods

This study was approved by the institutional review board of the Rambam Medical Center, Haifa, Israel and was conducted at the Neuro-Urology unit between February and August 2017. Patients who met the International Society for Sexual Medicine (ISSM) definition for PE [20] were included in this study. This prospective, single blind, controlled study was designed such that each individual served as self-control to the treatment. Patients were screened according to the inclusion/exclusion criteria presented in Table 1, and eligible patients signed the study consent form after receiving a detailed explanation of the study goals and procedures, including potential side effects. Afterwards, they underwent a urogenital physical examination and their body mass index (BMI), blood pressure and heart rate were recorded. Perineal regions of the patients were inspected carefully and perineal skin-fold thickness was measured using a manual caliper.

TES device and configuration

All electrical stimulations were delivered using a battery powered commercial neuromuscular TES device (TensMed S82, ENRAF NONIUS, The Netherlands). Symmetrical rectangular biphasic waveform was applied with 300 µsec phase duration and frequency of 30 Hz. The stimulation intensity was limited to 25 mA max. TES was applied to the subjects' perineum during self-sexual stimulation, aiming at prolonging their masturbation ejaculatory latency time (MELT). Since there are no published data regarding the normal duration of MELT in normal sexually functioning males, we estimate that this measure will be more accurate than only the reported estimated latency time. Because the applied treatment is still an unknown modality with probably some need for an adaptation period, we assume that involvement of the partner in measurement of IELT could cause some difficulties. This measurement, in the clinical set-up, was considered as the individual baseline time to ejaculation and served to compare with results during the use of TES.

The TES device was used twice in two separate visits with at least a 7-day interval between them, to assure ejaculatory latency period recovery. In a random fashion, 1 day (not necessarily the first day) the TES device was activated during self-sexual stimulation (active treatment), whereas the patient masturbated while wearing the device without receiving any stimulation on the alternate day (sham treatment). Randomization of active and sham treatments was based on succeeding order of patient enrollment. Even numbered patients received TES during self-sexual stimulation on their first visiting day, whereas uneven numbered patients received TES on their second visiting day. Safety was monitored during every visit and patients were requested to report on any sensation especially if they feel any pain.

Table 1 Inclusion/Exclusion criteria

Inclusion criteria	Male, age range 18–60
	Generally healthy
	Clinical history of premature ejaculation according to ISSM definition
	Familiar with self-stimulation
	Ability to follow study instructions and complete study assessment tools
	Washout period of 2 weeks
Exclusion criteria	Any reported erectile difficulty
	History of cardiovascular disorders
	Any type of implanted pacemaker/defibrillator
	Hypertension
	Diabetes mellitus
	Local dermatological disease
	Local skin irritation/lesions
	Any neurological disorder
	Any psychiatric disease and/or psychiatric medications
	Any neoplastic disease in the past two years

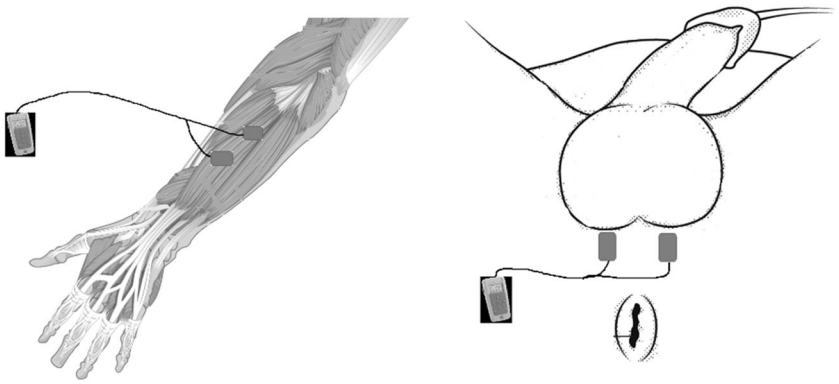

Fig. 1 Schematic electrode location over the forearm (left trace) and the perineum (right trace)

Stimulation phase I

In order to familiarize the patient with TES and to experience the sensation of muscle contractions upon stimulation (conditioning phase), we delivered TES to either left or right forearm via a pair of skin electrodes (EN-Trode, Ø 5 × 5 cm, The Netherlands). These were adhered (after hair trimming) to an area 5 cm distal to the elbow, on the area above the *extensor carpi ulnaris*, *extensor digitorum*, and *radialis* muscles (Fig. 1). Following this "conditioning phase", a new pair of skin electrodes (EN-Trode, Ø 3.0 cm, The Netherlands) were adhered to the patients' perineum, positioned as shown in Fig. 1.

During the conditioning (forearm stimulation) and study phase, initial stimulation intensity was 0 mA and was gradually increased by increments of 0.5 mA. The patients were asked to inform when they first feel any stimulation, and this intensity was marked as "intensity sensation" (IS). Following the identification of IS, we continued to increase the intensity and asked the patients to inform us when they feel any muscle contraction in the stimulated area. We named the stimulation intensity that generated perceived muscle contraction as "intensity muscle contraction" (IMC). In the perineal stimulation, this protocol was repeated twice, and the results from the two repeating measurements were averaged to give IS and IMC.

Stimulation phase III

Following determination of individual IMC while wearing the TES device, the patients were left alone in an isolated room and visual erotic stimulation was provided at their discretion for optimal sexual stimulation. The patients were requested to masturbate and measure their MELT using a calibrated stopwatch. They were requested to measure the interval time between full erection and ejaculation. To ensure their safety, patients were supplied with a handheld transceiver in case of immediate need to contact the investigator (physician) who was in an adjacent room. Based on enrollment order, the patients either received treatment with an inactive or active TES device at an intensity equal to their IMC on their first or on their second visiting days accordingly.

Patient discharge and follow-up

After finalizing the protocol at each visit, the investigator carefully examined the stimulated area for any abnormal skin signs. Thereafter, patients were asked about any disturbing sensations during the stimulation sessions, using the directed questions (Supplementary Table 1). At discharge from each of their two visits, patients were handed a 72-h follow-up self-report form that focused on possible study safety outcomes. The patient was instructed to answer at intervals of 24, 48, and 72 h from TES. (Supplementary Table 2).

Statistical analysis

Descriptive statistics were used to calculate continuous variables (mean and standard deviation), and percentages for discrete variables. MELT was compared between groups using a repeated measures ANOVA model, where MELT is modeled as a function of group (TES/self-control), study visit (1st/2nd), and sequence (TES first/control first) with the sequence nested within subject ID as the repeated measurement. Relationship between the patient parameters and MELT was evaluated as well by adding the parameters to the model as covariates. Statistical analyses were performed with SAS v9.4 (SAS institute, Cary, NC, USA) and a p-value of ≤0.05 was considered statistically significant.

Results

Twenty-three patients with a mean age of 38.7 (range 20–60) were initially included in the study. One patient withdrew due to personal reasons and two others were excluded due to having erectile difficulties. Twenty patients

completed the study and all underwent both sham and active TES treatments (Table 2).

During the active TES treatment mean MELT was significantly longer than the sham treatment (311.4 ± 237.14 s vs. 124.6 ± 107.02 s, $p = 0.0009$). This difference represents an averaged time-fold increase of 3.49 ± 3.12 in MELT. There was no difference in MELT whether a patient started the study with control or treatment (Supplementary Tables 3, 4).

Three (15%) patients did not show any benefit from treatment. When the findings of the responders' group (17/20 of patients) analyzed, the increase in MELT was more significant (325 ± 255 s vs. 93 ± 73 s, $p = 0.0009$).

The effect of several parameters on MELT was evaluated by adding the variables to the model as covariates. No significant relationship was found between MELT and each of age, BMI (Supplementary Table 5), blood pressure, heart rate, and perineal skin thickness (Supplementary Table 6).

Data from the satisfaction from treatment questionnaire showed that 75% of patients (15/20) were highly satisfied with the treatment and reported a much better sensation of ejaculation control. Thirteen patients (65%) reported that they would recommend this treatment to a friend. The main dissatisfaction related to the treatment was being connected to the TES device with wires and the uncomfortable clinical setting.

None of the patients reported any erectile difficulties with the TES treatment. No severe adverse effects were reported during the treatment or follow-up period. Three patients (15%) recorded unpleasant sensations during the treatment, which did not prevent them from continuing the stimulation. One patient (5%) felt a burning sensation during urination after the treatment, which disappeared after 24 h.

Table 2 Patients who completed the study (20 out of 23)

Patient number	Day 1 MELT (seconds)	Day 2 MELT (seconds)	Active/self-control
1	192	190	0.99
2	24	30	1.25
3	59	214	3.63
4	242	615	2.54
5	175	387	2.21
6	60	339	5.65
7	244	1038	4.25
8	41	104	2.54
9	25	35	1.4
10	140	359	2.56
11	351	315	0.9
12	345	194	0.56
13	48	241	5.02
14	60	496	8.27
15	38	540	14.21
16	89	165	1.85
17	53	138	2.6
18	166	451	2.72
19	33	116	3.52
20	83	261	3.14
Overall mean fold increase in MELT ($n = 20$)			3.49
Treatment responders: overall mean fold increase in MELT ($n = 17$)			3.96

Discussion

This study aims to investigate the feasibility and safety of a novel PE treatment modality. The results of this preliminary study support our hypothesis that on-demand application of TES onto the perineum may be a feasible, effective, and safe treatment option for PE [19]. By inhibiting the rhythmic contractions of the perineal muscles during sexual stimulation, TES treatment was able to increase MELT significantly, without any severe adverse effects related to the treatment.

There is an unmet need for the treatment of PE. A short acting selective serotonin reuptake inhibitor dapoxetine is currently the only approved medical treatment option for PE. Numerous clinical trials demonstrate that on-demand dapoxetine treatment is associated with a three–fourfold increase in baseline IELT [21]. The findings of our study demonstrate that TES treatment may also result in an average of 3.49-fold increase in MELT, which can be considered similar to the efficacy of dapoxetine treatment. In addition, the majority of the patients experienced a 1-min delay in MELT, similar to that considered as the minimally clinical important difference for IELT [22].

In many cases, sexual activities are unplanned and occasionally happen at the spur-of-the-moment [23]. It was shown that treatments that require anticipated planning of sexual activity of 30 min or longer, might affect the natural spontaneity of sex life and therefore may find little acceptance by the patient [24]. Dapoxetine should be used about 1 h prior to sexual activity and this may be the reason of the discontinuation to this treatment [11, 12]. However, TES treatment does not require such a long duration before coitus for its efficacy, which may increase patient adherence and satisfaction. Future studies are required to assess the patient compliance advantages of TES treatment.

We hypothesize that TES inhibits the natural rhythmic pelvic muscles contractions, which is necessary for the completion of the ejaculatory process [19]. This may prolong the time till these muscles reach their stimulatory threshold point for contraction that is built up during sexual stimulation (either penile stimulation or sexual excitement), thus prolonging MELT in PE patients. In the current study,

which is a proof of concept study, the main quantitative tool we had was the MELT. Since there are no published data on normal values of MELT, we had to rely on the basic results of MELT from these subjects who had reported PE on medical history as their main complaint. Our basic assumption was that MELT in PE patients correlates to their IELT. In clinical practice, the stopwatch measured IELT are known to be correlated with the reported IELT [25]. As involvement of the partner in this stage of the treatment was assumed as a complicated task and there are no known masturbatory measurement, we estimated the MELT as more accurate [26].

Our result indicated that 85% of patients improved their MELT with TES treatment. Yet, three subjects did not respond to treatment. We were not able to show the reason for the irresponsiveness of these three patients. Thus, future studies should investigate the characteristics of the PE patients that may benefit from TES treatment.

In the current study we used standard round electrodes (3-cm diameter) for the perineal stimulation. Electrode size, shape, and location are main factors for ensuring effective application of TES. Optimization of these parameters for perineal muscle stimulation may improve the TES treatment in PE. User acceptance to the stimulatory amplitude should also be better defined in order to improve patient compliance and satisfaction [27]. Custom-made electrodes, that will fit the anatomic dimensions of the pelvic floor and specifically to the bulbospongiosus muscle might stimulate more motor neurons, therefore might be more effective and may also enhance user comfortability. Future studies that will test and evaluate the effect of TES on PE with customized electrodes are warranted.

Moreover, several patients reported that they had difficulties with the stimulator wires. In order to further test the utility of this concept in real life setting, it is imperative to test human-factor parameters such as the ability to place the electrodes and to operate the system independently. In addition, the promising results of the present study should encourage the development of a stand-alone TES device for the treatment of PE.

The current protocol measured only the immediate effects of perineal TES on MELT; however, it may also have the long-term therapeutic effect. A recent study demonstrated that a 12-week pelvic floor muscle rehabilitation protocol consisted of physio-kinesiotherapy, electrostimulation, and biofeedback can improve ejaculatory latency time in patients with PE [28]. Therefore, it is possible that patients that will use perineal TES for a longer period of time, or routinely even without performing sexually, may further benefit from this treatment modality as it may have beneficial long-term therapeutic effects, and with time patients may enhance their performance independently.

Furthermore, it is well established that during the initial exposure to TES, a low level of stimulation should be applied in order to maximize user acceptance [29]. With prolonged use, stimulation intensity could be increased, and could potentially result in activation of deeper nerve branches leading to recruitment of additional motor units, and consequently maximizing the TES beneficial effects. The promising results of the present study should encourage future research that will test the effects of prolonged use of this concept including its lasting therapeutic effects.

This was a proof of concept study which has some limitations. A larger sample size of patient will be more accurate to define the effectiveness of this treatment modality. Therefore, we did not stratify the timing of appearance of PE nor did we use the expected tools when evaluating effect of treatment of PE. Moreover, our protocol tested the effect of perineal TES to treat PE in a laboratory setting and during self-stimulation. Clearly, masturbation is different than the experience of sexual intercourse and does not represent the accurate effect on men with PE during a sexual encounter, but this compromise allowed us to better evaluate the effect of TES on latency time of ejaculation.

Furthermore, although all subjects met the inclusion criteria and had a clinical history of lifelong PE, eight of these patients had a MELT greater than 2 min during sham treatment. This can be explained by the fact that MELT may be influenced by this clinical set-up, a situation that certainly opposes a sexual atmosphere and may somewhat delay ejaculation. It is probable that in some individuals, such a setup will not always mirror time to ejaculation during coitus. A study in the home setting with a steady partner using IELT and validated patient reported outcome measures is mandatory.

In this study, we demonstrated that TES to perineal muscles increased MELT 3.5-fold approximately, with no adverse effects related to the treatment. We can conclude that TES may have the potential to become an effective and safe on-demand treatment for delaying ejaculation in patients suffering from PE. Future studies with a wireless device, larger group of patients, with larger follow-up and with objective measurements are needed to prove this concept during intercourse.

Compliance with ethical standards

Conflict of interest AS is a consultant for Virility Medical Ltd, and received compensation. AS was also granted the option to purchase equity of Virility Medical Ltd. For conducting the study. SEC is a consultant for Virility Medical Ltd, and was granted the option to purchase equity of Virility Medical Ltd. TG is an employee of Virility Medical Ltd, and a shareholder. SS is a consultant and shareholder of Virility Medical Ltd. GM was an employee of Virility Medical Ltd during the time of the study, and was granted the option to purchase equity of Virility Medical Ltd. IG is a consultant for Virility Medical Ltd, and received compensation. IG was also granted the option to

purchase equity of Virility Medical Ltd for conducting the study. BA has no conflict of interest.

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