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ORIGINAL ARTICLE

A prospective randomized study to compare pelvic floor rehabilitation and dapoxetine for treatment of lifelong premature ejaculation

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Summary

Premature ejaculation (PE) is the most common male sexual disorder. We compared pelvic floor muscle rehabilitation to on-demand treatment with the selective serotonin reuptake inhibitor dapoxetine in 40 men with lifelong PE (baseline intra-vaginal ejaculatory latency time (IELT) ≤1 min). Subjects were randomized into the following two treatment groups: (1) PFM rehabilitation or (2) 30 or 60 mg of on-demand dapoxetine. Total treatment time for both groups was 12 weeks, at the end of which, IELT mean values were calculated to compare the effectiveness of the two different therapeutic approaches. At the end of treatment, 11 of the 19 patients (57%) treated with rehabilitation were able to control the ejaculation reflex, with a mean IELT of 126.6 sec (range: 123.6–152.4 sec). In the dapoxetine group, after 12 weeks of therapy, 5 of 8 (62.5%) patients in the 30 mg subgroup and five of seven (72%) in the 60 mg subgroup had an IELT >180 sec (mean: 178.2 and 202.8 sec, respectively). The results obtained in the group treated with pelvic floor rehabilitation are promising, and this treatment represents an important cost reduction if compared to dapoxetine on-demand treatment. The present study confirms the data that are previously available in the literature on the efficacy and safety of the new inhibitor of serotonin reuptake, dapoxetine, as well as proposes and evaluates a new type of physical treatment that may be a viable therapeutic option for treatment of PE.

Introduction

Premature ejaculation (PE) is the most common male sexual disorder and has a serious impact on the quality of life of both the patient and his partner (Althof, 2006; Carson & Gunn, 2006; Porst *et al.*, 2007). Over the years, the definition of PE has undergone several changes. Kinsey (1948) believed that PE is the norm in all mammals, including humans, while Kaplan (1974) considered PE to be a condition in which the subject lacks voluntary control over the muscles that regulate the ejaculation reflex. The PE definition recommended by the International Society for Sexual Medicine (ISSM) is 'a male sexual dysfunction characterized by ejaculation which always or nearly always occurs before or within about 1 min of vaginal penetration, and the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy' (McMahon *et al.*, 2008). The intra-vaginal ejaculatory latency time (IELT) is defined as the time from vaginal intromission to intra-vaginal ejaculation (Waldinger *et al.*, 2005), and this measurement is often used as a parameter to quantify the clinical response to therapy and as a standardized method to compare different treatments in clinical trials.

In the current prospective randomized study, men with lifelong PE underwent one of the following two treatments: (1) pelvic floor muscle (PFM) rehabilitation with modified techniques used to treat urinary and faecal incontinence (Hay-Smith *et al.*, 2007), including

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physiokinesitherapy, electro-stimulation and biofeedback; and (2) on-demand treatment with either 30 or 60 mg of the selective serotonin reuptake inhibitor (SSRI) dapoxetine (Pryor *et al.*, 2006).

The primary objective of our study was to compare the effectiveness of PFM rehabilitation with that of on-demand SSRI treatment by evaluating changes in the IELT after 12 weeks of therapy. In the first treatment group, we also evaluated the effectiveness of PFM rehabilitation for training the patient to recognize how and when to control the muscles involved in ejaculation control and for strengthening the muscles of the perineal floor. In the SSRI treatment group, our secondary objectives were to verify whether on-demand administration of dapoxetine is effective in delaying the time of ejaculation, as well as if the effect is dose-dependent.

Materials and methods

From July 2010 to August 2011, 40 male patients were enrolled in this study, after they were assessed and had signed an informed consent form. The study was conducted in accordance with the Declaration of Helsinki, and was approved by the local Medical Ethical Committee. The diagnosis of PE was made by applying the ISSM definition of PE. Each of the subjects had lifelong PE with a baseline IELT of ≤60 sec (mean: 43.2 sec, range: 24.6–58.8 sec). Each enrolled patient had to be in a stable relationship for at least 6 months and to engage in sexual intercourse once a week or more often. At the first visit, patients and partners were interviewed individually and each was requested to give an independent estimation of the IELT. Pre-treatment IELT was measured during a 4-week baseline period; patients were provided with a stopwatch and instructions on how to measure the IELT and were requested to experience coitus at least four times. Couples were instructed not to use condoms or topical anaesthetic cream, and not to pause during intercourse or have interrupted intromission. Furthermore, patients were instructed that if intercourse took place more than once in a single session, only the first intercourse was to be measured.

All patients reported that they suffered from lifelong PE and had tried different types of therapy (anaesthetic creams, tricyclic antidepressants and phosphodiesterase type 5 inhibitors) without a substantial response (no significant change in IELT). Patients were divided by a simple randomization (after a stratified randomization to control all the baseline covariates between the two study arms) into two treatment groups, either (1) PFM rehabilitation or (2) 30 or 60 mg of on-demand dapoxetine. To evaluate differences in the effectiveness of PFM rehabilitation vs. on-demand dapoxetine, we compared the mean IELT values of patients in the two groups after 12 weeks of treatment. The rehabilitation treatment group comprised 19 patients aged 19–48 years (mean age: 30 years) with a mean baseline IELT of 31.2 sec (range: 12.6–53.4 sec). The dapoxetine treatment group comprised 21 patients ages 23–51 years (mean age: 31 years) with a mean baseline IELT of 37.2 sec (range: 16.2–55.2 sec). None of the patients in either group had phimosis (six patients were circumcised), frenulum brevis, erectile dysfunction, or a history of chronic prostatitis. Before treatment commenced, all the patients underwent an andrological and urological screening that included the Meares–Stamey test to exclude the presence of bacterial prostatitis and a digital rectal examination.

The PFM rehabilitation protocol consisted of physiokinesitherapy to achieve a muscle contraction that allows patient to be aware of motor activity; electrical stimulation of the perineal floor to directly stimulate the pudendal nerve, resulting in stimulation of the pubo-rectalis muscle, which causes the urethral sphincter to contract; and biofeedback, in which the patient learns to control the muscle contractions of the perineal floor and the genito-urinary sphincter. Patients had three 60-min sessions each week, during which these three techniques were applied for 20 min each. The results were measured after the first 20 sessions (6 weeks) and then again at the end of therapy (12 weeks). Physiokinesitherapy and biofeedback were used to teach patients to recognize the muscular structures involved in pelvic floor contraction. Patients executed personalized physical exercises, during which they conducted isometric and isotonic contractions of the PFMs. During each session, after execution of physical exercises, patients underwent electrical stimulation to help strengthen the PFMs. A cylindrical anal probe was positioned in the anal canal. Contact between electrodes in the anal probe and the anterior portion of the sphincter system stimulated the pubovisceral muscles (puborectal and pubourethral); mild, painless electrical pulses were then sent to these muscles via the electrodes.

In the second treatment protocol, patients were randomly assigned to either the 30 mg or 60 mg dapoxetine subgroups. The drug was taken as required, 1–3 h before sexual intercourse. Six patients did not complete the study and were excluded (all patients resulted lost to follow-up). The remaining 15 patients (eight in the 30 mg subgroup and seven in the 60 mg subgroup) were treated for 12 weeks.

Statistical analysis was performed by using the computer statistical package SPSS/10.0 (SPSS, Chicago, IL, USA) and SAS/6.4 (SAS Institute Cary, NC, USA). A p-value less than 0.05 was considered statistically significant.

As the IELT in individual patients usually follows a skewed distribution, we calculated geometric mean IELTs

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instead of mean IELTs. The independent sample two-tailed t-test with associated 95% confidence intervals was used to compare the geometric mean IELTs. We compared the baseline characteristics of the two enrolled treatment groups to determine if there were any demographic differences that might influence outcomes.

Results

In the PFM rehabilitation group, at the end of 12 weeks of treatment, 11 of the 19 patients (57%) were able to control the ejaculation reflex, optimizing the latency time to ejaculation from the start of intra-vaginal intercourse (before therapy IELT was ≤60 sec). Five patients did not respond to treatment, whereas two patients had improved after the first 20 sessions and opted to drop out of the study. For the 11 patients who responded favourably to PFM rehabilitation, the results were maintained throughout the follow-up time (3 months after the end of 12 weeks of treatment). There were no reported side effects. At the first evaluation, after 6 weeks of rehabilitation, patients achieved a mean IELT of 114.6 ± 18.4 sec (range: 112.6–133 sec). At the end of week 12 of PFM rehabilitation, the mean IELT was 126.2 ± 37.2 sec (range: 114.6–151.2 sec).

In the SSRI study group, after 6 weeks of treatment with dapoxetine, the overall mean IELT had increased from <60 sec to 168.6 ± 42.6 sec (range: 145.2–187.8 sec). The IELTs for the 30 and 60 mg subgroups were 168.2 ± 36.6 sec (range: 133.2–205.2 sec) and 193.2 ± 43.8 sec (range: 151.2–234.6 sec), respectively. At the end of 12 weeks of therapy, five of eight patients (62.5%) in the 30 mg subgroup and five of seven patients (72%) in the 60 mg subgroup had IELTs of >180 sec. After 12 weeks of SSRI therapy, the overall mean IELT had increased from 37.2 to 199.14 ± 37.26 sec (range 160.92–238.32 sec) ($p < 0.001$) (Fig. 1). In the 30 and 60 mg subgroups separately, the mean IELTs increased from 31.21 to 168.62 ± 31.86 sec (range: 136.92–199.74 sec) ($p < 0.001$) and from 37.82 to 222.57 ± 54.71 sec (range: 173.43–280.28 sec) ($p < 0.001$), respectively (Fig. 2). As expected, the increase in IELTs disappeared with the cessation of SSRI therapy. Nausea, the most frequently reported adverse event, was reported by one of eight patients (12.5%) in the 30 mg subgroup and two of seven patients (28.5%) in the 60 mg subgroup. All three patients who reported nausea experienced it following their first dose of dapoxetine; over the course of the study, the nausea disappeared completely. Only one patient (from the 60 mg subgroup) complained of diarrhoea as a side effect. No severe adverse events were reported and none of the subjects discontinued the trial because of adverse events.

The results and *p* values are summarized in Table 1.

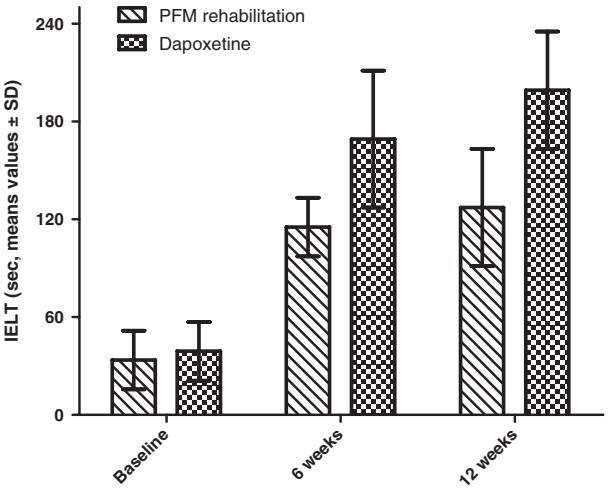

Figure 1 IELT mean values (sec) in the PFM rehabilitation and dapoxetine treatment groups: baseline, 31.2 and 37.2, respectively; after 6 weeks, 114.6 and 168.6, respectively; and after 12 weeks, 126.2 and 199.1, respectively. $p < 0.0001$ at the 12-week endpoint.

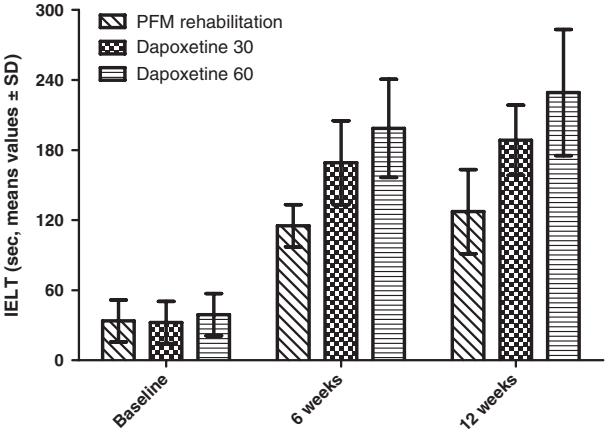

Figure 2 IELT mean values (sec) in the PFM rehabilitation and 30 mg and 60 mg dapoxetine treatment groups: baseline, 31.2; 31.2 and 37.8, respectively; after 6 weeks, 114.6, 168.2, 193.2, respectively; and after 12 weeks, 126.2, 168.6, and 222.5, respectively.

Discussion

Ejaculation is neuro-modulated by the spinal control centre, which coordinates sympathetic, parasympathetic and somatic activities, leading to emission and expulsion. The spinal control centre is influenced by the supra-spinal centres (McKenna, 1999), with the control mechanisms responsible for inhibition of ejaculation descending from the supraspinal level and involving a number of regulatory neurotransmitters. Of these, the most widely studied is 5-hydroxytryptamine (5-HT), or serotonin. At least

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Table 1 Mean IELTs in the PFM rehabilitation and SSRI groups after 12 weeks of treatment

Groups	Baseline IELT	IELT at Week 12 Endpoint	*p* values
PFM Rehabilitation	31.2 ± 18.6 seconds (range:12.79–53.52 seconds)	128.94 ± 37.44 seconds (range 115.14–152.46 seconds)	<0.0001
On-demand Dapoxetine (30 and 60 mg)	37.2 ± 18.3 seconds (range 16.26–55.22 seconds)	199.14 ± 37.26 seconds (range 160.92–238.32 seconds)	<0.0001
30 mg dapoxetine	31.21 ± 18.31 seconds (range 16.23–49.64 seconds)	168.62 ± 31.86 seconds (range 136.92–199.74 seconds)	<0.0001
60 mg dapoxetine	37.82 ± 18.02 seconds (range 17.42–55.82 seconds)	222.57 ± 54.71 seconds (range 173.43–280.28 seconds)	<0.0001

three serotonin receptor subtypes, 5-HT1a, 5-HT1b, and 5HT2c, play key roles in ejaculation; they are present in higher CNS centres, the spinal ejaculation centre, the vas deferens and the seminal vesicles (Kim & Paick, 2004; de Jong *et al.*, 2006). Activation of the 5-HT1a receptor has a proejaculatory effect, although activation of the 5-HT1b and 5-HT2c receptors is involved in delaying ejaculation (Giuliano & Clément, 2005). PE can be explained by three primary circumstances: inadequate serotonin activity at the central level, a hyposensitive 5-HT2c receptor, and hypersensitivity of the 5-HT1a autoreceptors (Waldinger, 2002).

The SSRIs block 5-HT transporter mechanisms, thus increasing 5-HT levels within the synapses and activating 5-HT1a and 5-HT1b receptors, with a consequent inhibition of serotonin release into the synapse site. This results in continuous, mild stimulation of all post-synaptic 5-HT receptors. After several days of SSRI treatment, the receptors become desensitized, reducing the inhibition of serotonin release. The overall result is increased serotonin release into the synaptic cleft and subsequent activation of 5-HT2C subtype receptors, which delays ejaculation (Giuliano & Clement, 2006).

The SSRIs are psychotropic medications that are usually used to treat mild depression, and one of the most common side effects is the onset of delayed ejaculation, creating a significant increase in the IELT of several minutes. Other side effects include dry mouth, drowsiness, nausea, and reduced libido, as well as erectile dysfunction (Montejo-González *et al.*, 1997; Montejo *et al.*, 2001). The need for an on-demand drug for PE treatment led to the development of dapoxetine for this specific use. Similar to other SSRIs, dapoxetine exerts its effects primarily through inhibition of the serotonin reuptake transporter, with minimal associated inhibitory activity at the norepinephrine and dopamine reuptake transporters (Gengo *et al.*, 2005). Unlike long-acting SSRIs, which are typically administered in a chronic (daily) fashion and may take days or weeks to reach steady-state plasma concentrations (Hiemke & Hartter, 2000), dapoxetine is a short-acting SSRI with peak plasma concentrations at 1.01 and 1.27 hours after administration, which may be better suited to on-demand treatment of PE (Modi *et al.*, 2006). In several studies dapoxetine has been shown to significantly increase the IELT compared to baseline measurements and placebo; IELTs of 1.66, 3.03 and 3.15 min were reported with placebo, 30 mg of dapoxetine, and 60 mg of dapoxetine, respectively, when the drug was taken 30–60 min before intercourse (Modi *et al.*, 2006). Dapoxetine was also shown to be effective from the first dose when taken 1–3 h before intercourse (Shabsigh *et al.*, 2008; Buvat *et al.*, 2009). In the present study, dapoxetine treatment was associated with a significant increase in IELT. Moreover, the IELT was greater in patients who took the higher dose of the drug. Once patients ceased taking dapoxetine as required, the increase in IELT disappeared.

The pelvic floor undoubtedly plays an important role in sexual function; evidence suggests active roles of the ischio- and bulbocavernous muscles and sphincters, with a significant increase in electromyographic (EMG) activity during the entire ejaculatory period (Colpi *et al.*, 1999). Shafik (2000) demonstrated rhythmic contractions of the external striated urethral sphincter during expulsion, which may act as a 'suction–ejection pump', sucking the seminal fluid into the posterior urethra while relaxed, and ejecting it into the bulbous urethra upon contraction.

The PFM rehabilitation protocol used in the present study addresses both these possibilities; physiokinesitherapy and electrostimulation are designed to improve the contractile strength of the perineal muscles, whereas biofeedback teaches the patient to recognize and contract the muscles to increase the closing strength of the urethral sphincter. Only a few studies have reported pelvic floor

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exercises as a possible treatment option for PE, and a protocol has not yet been standardized (Piediferro *et al.*, 2004). La Pera & Nicastro (1996) reported a study of 18 patients with PE; eleven subjects (61%) reported better control of the ejaculatory reflex after the first 20 sessions of PFM rehabilitation. After the end of treatment, 61% of patients learned to control the reflex and the results were maintained at follow-up (6–14 months). In our study we performed the same rehabilitation protocol and a similar percentage of treatment success was reported: eleven of nineteen patients (57%) were able to control the ejaculation reflex, optimizing the latency time to ejaculation from the start of intravaginal intercourse. Pelvic floor exercises for PE have been studied only minimally, and specific exercise protocols have not yet been established. The exercise instructions provided vary, and the type, amount of exercise, and whether the focus is on relaxation, strength, support, or control is still not clear. Therefore, further studies are necessary to validate the success and to completely explain the role of physical therapy interventions in ejaculatory disorders.

We want to underline that all patients suffered from lifelong PE and had not reported any significant improvements after other various therapeutic treatments, such as local anaesthetic cream, behavioural therapy (including the 'squeeze' and 'stop-and-start' techniques), and psychological treatment of various types. In the present study, pelvic floor exercises led to an improvement in body awareness in all of the enrolled subjects, which could help them to develop more self-confidence and a sense of control. In addition, active perineal muscle control could inhibit the ejaculation reflex through intentional relaxation of the bulbo- and ischiocavernous muscles, which are active during arousal. This is a learned technique that can be mastered using pelvic floor biofeedback. The outcome measures of the dapoxetine group were significantly improved compared to the PFM rehabilitation group; by 12 weeks, the dapoxetine groups had mean IELTs >180 sec, although the PFM group had a mean IELT of 128.9 sec and only one patient from the PFM group had an IELT >150 sec. Statistical analyses indicated that both doses of dapoxetine achieved significantly greater increases in mean IELT compared with PFM rehabilitation ($p < 0.001$ for both), and that 60 mg of dapoxetine was associated with a significantly greater increase in mean IELT compared to 30 mg of dapoxetine ($p = 0.006$) (Fig. 2). Many currently available treatment options for PE have limited long-term efficacy and undesirable sexual side effects. However, dapoxetine, a short-acting SSRI, that was developed to treat PE, is a good option for safe and effective treatment of PE. Treatment with on-demand dapoxetine lengthens the IELT with an associated significant improvement in the quality of the sex lives of patients with PE. In addition, the PFM rehabilitation protocol is easy to perform, has no side effects, and although not yet standardized, our results suggest that it can be included among the therapeutic options for patients with PE.

Limitations of our study include the small sample of patients enrolled, the number of patients who did not report for follow-up evaluations, the limited follow-up time and the lack of a self administered questionnaire such as PEDT. Therefore, further studies are needed to compare treatment of PE using physical therapy and SSRIs. Moreover, future studies should include another study group where patients initially undergo rehabilitation of the pelvic floor and are then treated with on-demand dapoxetine, to assess whether or not there are any additional benefits of this combined treatment.

Conclusions

The results obtained in the group treated with pelvic floor rehabilitation are promising. This treatment option represents an important cost reduction as compared with on-demand dapoxetine treatment, with a cost/benefit ratio that is certainly not negligible when considering the possibility of not being dependent on an on-demand drug treatment as with dapoxetine treatment. This study confirms the data in the literature regarding the efficacy and safety of dapoxetine, a new inhibitor of serotonin reuptake, as well as proposes a new type of physical treatment that may be a viable treatment option for PE.

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All of the authors contributed equally to design the research study, to the data analysis, and to the drafting of the manuscript.

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