Efficacy of Sildenafil Citrate (Viagra) in Men with Premature Ejaculation

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ABSTRACT

Objectives. Premature ejaculation (PE) is the most common ejaculatory dysfunction. We assessed the efficacy of sildenafil to increase the time to ejaculation, improve ejaculatory control, and decrease the postejaculatory erectile refractory time in men with PE.

Design and Methods. The main study was an 8-week, double-blind, placebo-controlled, parallel group study in men between 18 and 65 years of age with diagnosed PE. A substudy was also conducted using a subset of patients (two-way crossover, one center) before entry to the main study. The primary study measured intravaginal ejaculatory latency (IELT) and responses to the Index of Premature Ejaculation (IPE) questionnaire. The substudy measured vibrotactile stimulation ejaculatory latency time (VTS-ELT) and postejaculatory erectile refractory time. Differences between treatment groups were determined by ANCOVA at the 5% level of significance.

Results. The change in IELT (1.6 ± 6.08 vs. 0.6 ± 2.07 minutes) and VTS-ELT (2.9 ± 0.4 vs. 2.4 ± 0.4 minutes) were higher after taking sildenafil, compared with placebo, but did not reach statistical significance. However, patients who took sildenafil (vs. placebo) reported significantly ($P < 0.05$) increased ejaculatory control (1.8 ± 0.3 vs. 1.5 ± 0.3), increased ejaculatory confidence (2.2 ± 0.2 vs. 1.9 ± 0.2), and improved overall sexual satisfaction scores (3.1 ± 0.2 vs. 2.8 ± 02) on the IPE, and had a decreased postejaculatory erectile refractory time (3.2 ± 0.7 vs. 6.4 ± 0.7 minutes). The most common adverse events for sildenafil (vs. placebo) were headache (15% vs. 1%), flushing (15% vs. 0%), dyspepsia (5% vs. 1%), abnormal vision (5% vs. 0%), and rhinitis (5% vs. 0%).

Conclusions. Although IELT and VTS-ELT were not significantly improved, sildenafil increased confidence, the perception of ejaculatory control, and overall sexual satisfaction, and decreased the refractory time to achieve a second erection after ejaculation in men with PE.

Key Words. Premature Ejaculation; Rapid Ejaculation; Erectile Dysfunction; Sildenafil; Placebo-Controlled; Randomized

Introduction

Premature ejaculation (PE) is the most common male sexual disorder [1,2]. According to the DSM-IV, PE is defined as "persistent or recurrent ejaculation with minimal sexual stimulation, and before the subject wishes it" and is associated with "marked distress or interpersonal difficulty" [3]. The prevalence of PE in the United States is 21% among men aged 18–59 years [4], and ranges from 16% to 29% in men aged 40 years and older [5]. The prevalence among men in the United

Kingdom was estimated at 31% [6]. PE can be a lifelong condition or acquired and is associated with a significant negative impact on sexual relationships [7,8]. Treatment for PE includes topical creams and selective serotonin reuptake inhibitors (SSRIs), which are perhaps more effective than other remedies, such as the "pause/squeeze" technique [9]. A pooled meta-analysis of clinical studies indicated that paroxetine may be more effective than the other SSRIs [10]. However, a Food and Drug Administration (FDA)-approved treatment, specifically designed for PE, does not yet exist.

Sildenafil citrate (Viagra) is the most commonly prescribed therapy for the treatment of erectile dysfunction (ED) and has been prescribed to more than 20 million men in more than 110 countries [11]. Sildenafil may be a potential therapy for the treatment of PE. Normally, sexual arousal activates the nitric oxide/cyclic guanosine monophosphate (NO/cGMP) pathway, resulting in corporal smooth muscle relaxation, increased corporal blood flow, penile tumescence, and erection. Brain NO may be involved in regulating male sexual behavior [12–14]. NO precursors stimulate, and NO synthase (NOS) inhibitors reduce male reproductive behavior of rats, which may be mediated by dopamine release in the medial preoptic area of the brain [15]. Mice homozygous for eNOS gene deletion have similar mounting behavior as wild-type mice but have more frequent ejaculations requiring less stimulation than normal controls [16]. Conversely, NO donor drugs increase cGMP levels, potentiate vas deferens contractility induced by adrenergic stimulation, and decrease seminal vesicle contractility [17–20]. The walls of the vas deferens, seminal vesicles, ejaculatory ducts, and prostate are lined with smooth muscle cells, and NO may slow the ejaculatory process. Taken together, these results indicate that NO promotes erections and may inhibit seminal emission via smooth muscle relaxation, probably by decreasing sympathetic nervous system activity [21].

Sildenafil augments the activity of NO by inhibition of the cGMP hydrolyzing enzyme phosphodiesterase type 5 (PDE5). In uncontrolled studies in humans, sildenafil has been reported, as a treatment for PE, as monotherapy [22], or as combined therapy with paroxetine [23,24]. Although these studies suggest a potential role for sildenafil in the treatment of PE, they are limited by the lack of a placebo group, the estimation of baseline IELT by patient recall only, and the use of the Erectile Dysfunction Inventory of Treatment Satisfaction (EDITS) treatment response inventory, which is validated for ED but not for PE. The proposed mechanisms for the effect of sildenafil on ejaculatory latency include a central effect involving increased NO and reduced sympathetic tone, a peripheral effect with smooth muscle dilatation of the vas deferens and seminal vesicles, which may oppose sympathetic vasoconstriction and delay ejaculation, reduced performance anxiety due to better erections, and depression of the erectile threshold to a lower level of arousal so that increased levels of arousal are required to reach the ejaculation threshold.

In this double-blind placebo-controlled study, we investigated the effect of sildenafil on intravaginal (IELT) and vibrotactile stimulation ejaculatory latency time (VTS-ELT) in men with clinically diagnosed PE. We further assessed the impact of sildenafil on PE using an Index of Premature Ejaculation (IPE) questionnaire, and we assessed the effect of sildenafil on the postejaculatory erectile refractory time in a subset of patients.

Methods

Study Design

This was a multicenter, 8-week, double-blind, placebo-controlled, parallel group, flexible-dose study of sildenafil (50–100 mg, PRN) on IELT in patients with lifelong PE, which was determined by using the Diagnostic and Statistical Manual (DSM-IV) criteria [3] and an operational definition of PE: men who experience ejaculation within 2 minutes of vaginal penetration in ≥75% of sexual intercourse attempts. A second, two-way, randomized crossover study was performed on a subset of patients at one center before entering the main double-blind, placebo-controlled, parallel group study. In this subset study, a single dose of sildenafil (100 mg) or placebo was given 1 hour before VTS-ELT. Both studies, approved by an independent ethics committee and an institutional review board, were conducted in accord with the Declaration of Helsinki, and all patients provided informed consent.

Inclusion Criteria

Sildenafil naive men aged 18–65 years were included if they met the DSM-IV criteria for PE, which defines PE as "persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the subject wishes it." All patients had lifelong PE, i.e., since their first sexual experience, and had at least

6 months sexual contact with their current partner.

Patients were included if they had a score of ≥22 on the erectile function (EF) domain of the International Index of Erectile Function (IIEF) [25]. They were entered into a 4-week placebo run-in period, during which a diary of all sexual activity was kept. Subjects who reported at least one intercourse episode per week and IELT ≤2 minutes in 75% of intercourse attempts during the run-in period were enrolled and randomized to receive sildenafil or placebo for 8 weeks in the double-blind, placebo-controlled trial. Patients had to remain in a stable, single-partner relationship and have at least one sexual intercourse episode per week throughout the treatment period.

Exclusion Criteria

Patients were excluded if they always experienced ejaculation prior to penetration or had IELT ≥2 minutes in 75% of intercourse attempts. Patients were further excluded if they had a history of ED (score of <22 on EF domain of the IIEF) [25] or other ejaculatory dysfunctions. A score of <22 on the EF domain was selected as an exclusion criterion to limit the possibility of a response to sildenafil as a result of treating comorbid moderate to severe ED. Patients were also excluded if they used condoms or masturbated before sexual intercourse for purposes of decreasing penile sensitivity, or used any other treatment for PE, including sildenafil. Patients were excluded if they had a history of vascular disease including stroke, myocardial infarction, unstable angina, or life-threatening arrhythmias within the past 6 months, or were using organic nitrates or cytochrome P450 inhibitors.

Efficacy Assessments

The primary study outcome was patient-recorded change in mean IELT from baseline to end-of-treatment. The secondary study outcome was VTS-ELT, responses to the IPE questionnaire, and response to the Global Efficacy Question (GEQ), "Has the medication you have been taking improved your overall level of satisfaction during sexual intercourse?" IELT and VTS-ELT were recorded by the patient with a stopwatch. The IPE questionnaire was developed in consultation with external experts and is currently undergoing validation. Scores ranged from 1 (never/almost never) to 5 (always/almost always), with higher scores indicating a better response to treatment.

Statistics

This study was designed with 80% power to detect a difference from placebo of 2 minutes in the primary study outcome, assuming a standard deviation of 3.6 in 106 subjects at the 5% level of significance [26]. At least 118 subjects were required, to account for discontinuations, missing, or incomplete data. Differences between treatment groups were determined by ANCOVA using the SAS General Linear Model procedure. Multiple regression analysis was performed for mean I-ELT against sexual intercourse attempt number.

Safety

All observed and volunteered adverse events (AEs) were recorded for all patients who took at least 1 dose of study medication.

Results

Demographics

In total, 157 patients were enrolled and randomized to treatment. The treatment groups were well matched for age and weight and had a mean duration of PE of 22 years (range 1–50 years, Table 1). Of these, 144 patients (placebo = 71, sildenafil = 73) reported I-ELT, and 17 patients were recruited for the two-way crossover VTS-ELT study.

IELT and VTS-ELT and Postejaculatory Erectile Refractory Time

Baseline (mean ± SD) I-ELT for patients randomized to sildenafil or placebo was 0.96 ± 0.48 minutes and 1.04 ± 0.48 minutes, respectively (Figure 1A). At the end of treatment, I-ELT time increased to 2.60 ± 6.16 and 1.63 ± 2.16, respectively. This represents a mean change per patient of 1.6 4 ± 6.08 minutes for patients taking

Table 1 Characteristics of all patients enrolled

	Placebo N = 79	Sildenafil N = 78
Age (years)		
Mean ± SE	42.4 ± 1.3	43.3 ± 1.2
Race (n)		
White	72	72
Black	1	2
Asian	3	4
Other	3	0
Weight (kg)		
Mean ± SE	12.8 ± 1.6	15.9 ± 1.9
Duration of PE (years)		
Mean (range)	21.9 (1–45)	22.1 (1–50)

PE = premature ejaculation.

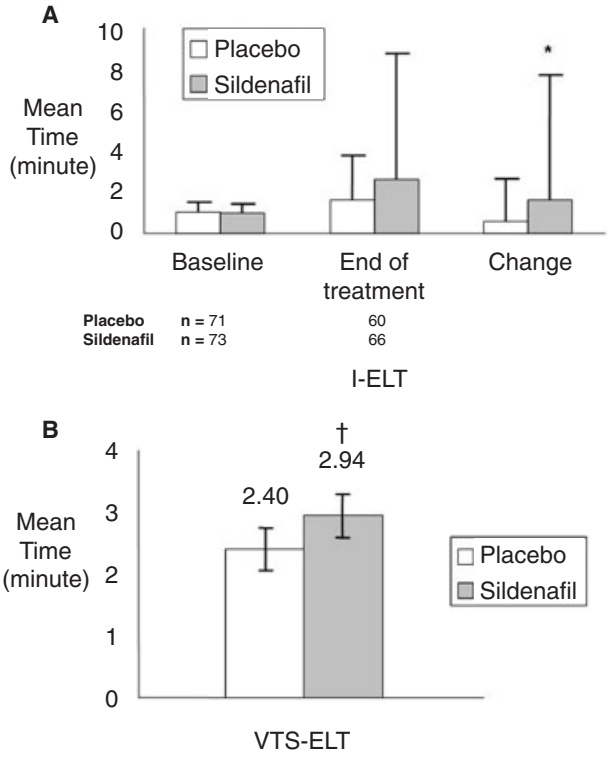

Figure 1 Sildenafil did not significantly increase intravaginal (IELT) or vibrotactile stimulated ejaculatory latency time (VTS-ELT). (A) Baseline (mean ± SD) IELT for patients randomized to sildenafil or placebo was 0.96 ± 0.48 minutes and 1.04 ± 0.48 minutes, respectively. At the end of treatment, IELT increased to 2.60 ± 6.16 and 1.63 ± 2.16 minutes, respectively. This represents a mean change per patient of 1.64 ± 6.08 minutes for patients taking sildenafil and 0.61 ± 2.07 minutes for patients taking placebo. (B) Baseline data were not collected in the two-way crossover trial because each subject was his own control. The mean VTS-ELT for sildenafil vs. placebo was 2.9 ± 0.4 vs. 2.4 ± 0.4 minutes. Data are mean ± SD. *$P = 0.3$ and †$P = 0.2$ vs. placebo.

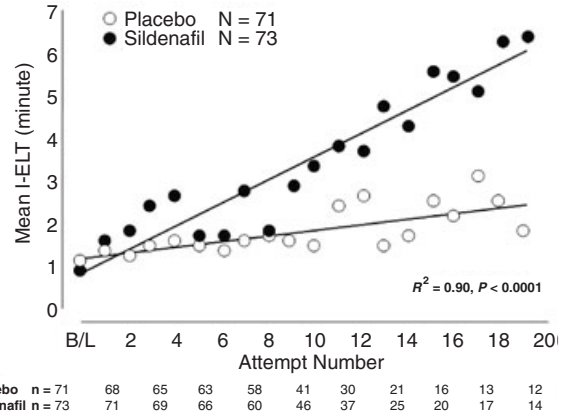

Figure 2 A trend existed between sildenafil use and duration of intravaginal ejaculatory latency time (IELT). Multiple regression analysis for treatment by attempt interaction revealed that a significant difference existed between the slopes of the lines for placebo and sildenafil ($R^2 = 0.90$, $P < 0.0001$). B/L = baseline. Data are the mean IELT duration in minutes for the indicated attempt number. Patients (sildenafil n = 73, placebo n = 71) reported at least one sexual attempt per week, and as many as 20 attempts (sildenafil n = 14, placebo n = 12) were made during the 8-week, double-blind, placebo-controlled study. IELT time between placebo and sildenafil was not statistically different at any individual attempt number: the 95% confidence intervals overlapped and are thus not shown for clarity.

sildenafil and 0.61 ± 2.07 minutes for patients taking placebo. However, the magnitude of the increase in IELT did not reach statistical significance ($P = 0.3$).

Baseline data were not collected in the two-way crossover trial because each subject was his own control. The mean VTS-ELT for sildenafil vs. placebo was nonsignificant (2.9 ± 0.4 vs. 2.4 ± 0.4 minutes, $P = 0.2$, Figure 1B). Multiple regression analysis ($R^2 = 0.90$) for treatment by attempt interaction revealed that a significant difference existed between the slopes of the lines for placebo and sildenafil ($P < 0.0001$, Figure 2).

Compared with placebo, sildenafil significantly ($P < 0.05$) decreased the postejaculatory erectile refractory time by half (3.2 ± 0.7 vs. 6.4 ± 0.7 minutes) in patients (n = 17) who achieved a second erection in response to audiovisual sexual stimulation and masturbation (Figure 3).

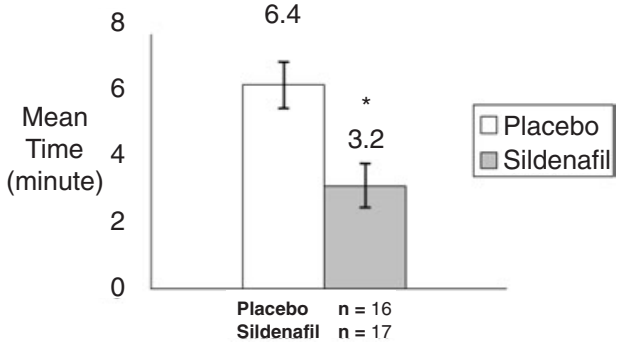

Figure 3 Sildenafil decreased the postejaculatory erectile refractory period. Following vibrotactile stimulated ejaculatory latency time, the time required to achieve a second erection (with masturbation and audiovisual sexual stimulation) was recorded to determine the postejaculatory erectile refractory period. Data were recorded during two clinic visits for each patient. Data are mean ± SE. *$P < 0.05$ vs. placebo.

Table 2 Index of premature ejaculation at end-of-treatment

	Placebo	Sildenafil
How willing were you to engage in foreplay?	3.87	3.93
How often have you limited the amount of foreplay you engage in?	4.04	4.2
How often did you ejaculate before you were ready?	2.36	2.72
How often did you have control over when you ejaculated?	1.45	1.83*
How confident were you with your control over ejaculation?	1.89	2.24*
How often were you able to maintain an erection to the point of ejaculation?	4.71	4.8
How satisfied were you with the quality of your orgasm?	2.87	2.92
How often was it satisfactory for you?	3.25	3.33
How satisfied were you with your sense of control over your ejaculation?	2.23	2.41
How satisfied were you with the time taken for you to ejaculate?	1.94	2.1
How satisfied do you think your partner was with the control of your ejaculation?	2.46	2.48
How satisfied have you been with your sexual relationship with your partner?	3.06	3.2
How satisfied have you been with your overall sex life?	2.8	3.1*
How much did you enjoy sexual intercourse?	2.7	2.62

Responses ranged from 1 (never/almost never) to 5 (always/almost always); higher scores indicate better treatment response. * $P < 0.05$ sildenafil vs. placebo.

IPE and GEQ Scores

The overall score on the IPE questionnaire was not statistically different between sildenafil and placebo. However, patients randomized to sildenafil reported significantly ($P < 0.05$) higher scores on the IPE for questions assessing ejaculatory control (1.8 ± 0.3 vs. 1.3 ± 0.1), ejaculatory confidence (2.2 ± 0.2 vs. 1.3 ± 0.1), and overall sexual satisfaction (3.1 ± 0.2 vs. 2.2 ± 0.1, Table 2).

The percentage of patients who responded "yes" on the GEQ, indicating that treatment improved their overall level of satisfaction during sexual intercourse, was threefold higher ($P < 0.001$) for patients who received sildenafil (48%) compared with the percentage of patients who received placebo (16%).

Safety

The most common treatment-emergent AEs (sildenafil vs. placebo, incidence >3%) were headache (15% vs. 1%), flushing (15% vs. 0%), dyspepsia (5% vs. 1%), abnormal vision (5% vs. 0%), and rhinitis (5% vs. 0%). All treatment-emergent AEs were considered mild to moderate in severity, and there were no reports of serious treatment emergent adverse events or discontinuations due to study.

Discussion

Currently, SSRIs such as paroxetine are used for the treatment of PE [10]. However, there are no FDA-approved therapies for the specific treatment of PE, and sildenafil is approved only for the treatment of ED. However, of the available oral PDE5 inhibitors for the treatment of ED, only sildenafil has been investigated for the treatment of PE. Although sildenafil significantly increased ejaculatory latency in rats [27,28], this study failed to demonstrate any significant impact of sildenafil after 8 weeks of treatment on either IELT or VTS-ELT in men with lifelong PE but did demonstrate significant improvements in perceived ejaculatory control, confidence, and sexual satisfaction. In addition, patients taking sildenafil reported decreased postejaculatory erectile refractory time. This finding is consistent with studies that show that sildenafil (vs. placebo) significantly decreased the postejaculatory latency time in rats (99 vs. 364 seconds, $P < 0.0001$) [27] and in healthy men (5.5 vs. 12.4 minutes, $P = 0.04$ [29] and 2.6 vs. 10.8 minutes, $P < 0.0001$) [30].

The literature contains several definitions of PE. However, a consensus definition for PE does not yet exist. Premature ejaculation is multidimensional and can be defined by quantitative measures of intercourse such as the IELT, the patient's assessment of his voluntary control over ejaculation, the extent of patient and partner sexual satisfaction, and the degree of resultant patient or partner bother or distress. These dimensions are not equally weighted and their importance varies between individual patients. Ejaculatory control is the most inconsistent dimension. Men with normal ejaculatory latency may paradoxically report a complete lack of ability to defer and therefore control ejaculation. The presenting symptom of PE and its main defining measure is brief ejaculatory latency. As such, the primary measure of treatment success is improvement over baseline IELT. Measures of control, satisfaction, and bother are of secondary importance but cannot be ignored in the overall evaluation of treatment efficacy.

Historically, attempts to explain the etiology of early ejaculation have included a diverse range of biogenic and psychological theories. Most of the proposed etiologies are not evidence-based and are speculative at best. The lack of an operationalized definition for PE and the presence of methodological problems related to the inadequate definitions used are a common flaw in the majority of these studies. Although empirical evidence suggesting a causal link between PE and any of the proposed causes is lacking, there is a limited amount of correlational evidence to suggest that lifelong PE may have a biogenic basis. As is the case with ED, long-standing lifelong PE may impose a significant psychological burden upon the sufferer. Lifelong PE can have a profound and long-lasting impact on self-confidence, relationships, sexual functioning, and the ability to relax during sexual intercourse [7].

The absence of a significant increase in IELT in this study suggests a lack of a direct effect of sildenafil upon the central or peripheral control of ejaculation. The improvements in ejaculatory control and confidence reported by patients may be related to improved erectile function and reduced performance anxiety. Sildenafil enhances erectile function with a lower level of sexual arousal. Thus, more time may elapse before a man reaches a level of arousal required for ejaculation. If this is the case, a long-term study of sildenafil may demonstrate further improvements in control and confidence sufficient to reverse any psychogenic component of lifelong PE, improve overall sexual functioning, and improve IELT.

Although only a small number of patients (sildenafil n = 14, placebo n = 12) reported at least 20 or more sexual intercourse attempts in the 8-week study, the trend toward increased IELT with increased sexual intercourse attempts observed in the regression analysis in this group is consistent with this hypothesis (Figure 2). However, the evidence to support a link between ejaculatory control and frequency of sexual activity is conflicting. Spiess reported that the frequency of sexual activity in men with rapid ejaculation is lower than age-matched controls with normal ejaculatory control, whereas Strassberg failed to demonstrate any relationship [31,32]. The observation that men with rapid ejaculation may develop a pattern of sexual avoidance may also explain this observed reduced frequency of sexual intercourse, indicating that the polarity of the relationship between rapid ejaculation and frequency of sexual activity remains undetermined [33].

A limitation to our study is that some of the patients enrolled may have had mild comorbid ED (EF domain score of the IIEF between 22 and 25, inclusive); men with a score <22 were excluded. However, of those randomized to placebo or sildenafil, only nine (12%) and 11 (15%) patients, respectively, had an EF domain score of between 22 and 25, inclusive.

Sildenafil has been a successful treatment option for ED, and successful treatment of ED is positively associated with increased confidence, self-esteem, and improved relationships [34–36]. However, because there are few randomized, double-blind, placebo-controlled studies on treatment options for PE, little is known about the effect of PE treatment on measures of quality of life. The reduction in postejaculatory refractory time and perceived improvements in ejaculatory control and confidence observed among men who received sildenafil in this study may lead to improved IELT in the longer term. Further studies are required for the evaluation of potential pharmacological therapies for the treatment of PE.

An international consultation of more than 200 multidisciplinary experts from 60 countries was assembled to establish specific objectives and scopes for various male and female sexual disorders [37]. The Committee Concerning the Disorders of Ejaculation/Orgasm in Men proposed a multivariate definition of PE: "premature ejaculation is persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration, and before the person wishes it, over which the sufferer has little or no voluntary control which causes the sufferer and/or his partner bother or distress." More research is needed for the proper management of PE in men [37].

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