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Efficacy of Sildenafil Citrate in Treatment of Primary Premature Ejaculation in Men

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ABSTRACT

Background: Primary premature ejaculation (PE) can be effectively treated with sildenafil citrate, according to recent research. This study evaluated sildenafil citrate efficacy in primary PE treatment, considering the female perspective.
Methods: Sixty sexually active men diagnosed with primary PE were split into two groups randomly and followed for 6 months. Group A received 50 mg of sildenafil citrate one hour before sexual activity in accordance with standard dosing guidelines (not fewer than once a week), while Group B received paroxetine 20 mg daily for six months. At baseline, 3 months, and 6 months following therapy, the intravaginal ejaculatory latency time (IELT), PE grade, intercourse satisfying score (ISS), intercourse frequency, and drug-associated side effects were noted.
Results: Both groups showed significant improvements in all measurements following 3 or 6 months of therapy, with no critical changes between two time points. However, sildenafil citrate was found to be significantly more effective than paroxetine in improving all parameters at both 3 and 6 months (P = 0.001).
Conclusion: Sildenafil citrate is a highly beneficial treatment for primary PE and is more effective than paroxetine.
Keywords: Premature ejaculation, Sildenafil citrate, Paroxitine.

INTRODUCTION

PE is a male sexual disorder characterized by persistent or recurrent ejaculation with minimal sexual stimulation, which can occur before, during, or shortly after penetration, and often leads to significant distress or interpersonal difficulty. With a prevalence of over 21%, affecting up to 75% of men at some point in their lives, the most prevalent male sexual condition is PE. This condition can have a significant impact on a man's life, causing reduced self-confidence, deteriorating relationships, and feelings of anxiety and depression. Furthermore, PE has been linked to female sexual dysfunction, indicating that it can also have negative effects on the partner's sexual health. Additionally, about 30% of men with PE may experience erectile dysfunction (ED), which can lead to early ejaculation without a firm erection. In a study involving 522 men with PE, 65.3% of patients were found to have ED as well [1].

Currently, drugs used for PE therapy can be categorized as either oral medications such as antidepressants, alpha-adrenoceptor blockers, and Chinese herbal medicines, or local drugs such as topical agents, intracavernosal injections, and local urethral medications. However, the use of some of these drugs can lead to unwanted side-effects. Antidepressants such as paroxetine, clomipramine, and ejaculation has been demonstrated to be delayed by sertraline effectively, but none of them have yet been approved by the FDA as PE drugs [2].

Recently, sildenafil citrate, cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 selective inhibitor and a first-line oral treatment for erectile dysfunction (ED), has been reported to have efficacy in treating associated PE in some studies [3].

However, some studies have focused on a combination of paroxetine and sildenafil citrate to treat PE, which makes it difficult to exclude the possibility of drug interactions. Additionally, the studies have only used male factors such as IELT, international index of erectile function (IIEF) intercourse satisfaction domain scores or PE grade to assess effectiveness, without considering female partner factors such as intercourse satisfaction score (ISS) [4].

In this prospective clinical study, we aimed to assess the effectiveness of sildenafil citrate as a standalone treatment for PE, while also comparing it with daily paroxetine. To achieve this, we included major parameters such as IELT, PE grade, male ISS, female ISS, and intercourse frequency per week.

PATIENTS AND METHODS

This prospective clinical study included 60 male patients with primary PE who visited the urological outpatient clinic at Benha University Hospitals from January 2022 to January 2023. Primary PE was characterized by ejaculation occurring before vaginal penetration or within 2 minutes after vaginal penetration. All patients were heterosexual and had maintained a stable sexual relationship with the same partner for more than 6 months.

All the patients were subjected to a detailed medical and sexual history, psychological profile and physical examination. PE grade, IIEF-5, IELT, ISS and intercourse frequency were recorded. They were also asked to have their sexual partners record their ISS. Only potent individuals with main PE (IIEF-5 > 21) were chosen for the trial.

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Exclusion criteria were secondary PE; significant psychiatric or psychological conditions, such as depression; ED; low libido; drugs alcohol, or substances abuse; organic diseases causing limitation in using SSRIs or sildenafil citrate; and use of different PE therapies within the last three months.

Men were randomly assigned into two therapy groups, with Group A receiving daily sildenafil citrate and Group B receiving daily paroxetine. Each group had thirty patients.

IELT refers to the delay between vaginal penetration and ejaculation. The duration was measured in minutes using a timer by the female companion. Each stopwatch was calibrated and delivered by the same manufacturer. No time was recorded whether ejaculation occurred prior to or during penile penetration into the vagina. Men having an average IELT score of fewer than two minutes participated in the trial during a six-month period [5].

Premature ejaculation grade:

By responding to the questions on the Center for Marital and Sexual Health's questionnaire on PE, patients assessed their ejaculatory dysfunction. This study comprised men having a mean PE score of 4 or above during the previous three months [6].

Intercourse satisfaction score:

Patients and their female companions assessed their ISS by responding to the question with reference to PE grade: 'How often in the last three months did you feel satisfied after having sex?'. The evaluation of the responses ranged from 0 to 8: 0 = almost never, 2 = sometimes, 4 = about half the time, 6 = most of the time, and 8 = almost always.

Intercourse frequency: To assess the frequency of sexual activity, the number of weekly vaginal encounters was employed. This study recruited males with a minimum intercourse frequency of 0.5 every three months for six months period.

Study protocol:

For 6 months, Group A patients got sildenafil citrate 50 mg one hour before sexual activity in accordance with standard dosing guidelines (not fewer than once a week). Group B patients received 20 mg of paroxetine daily for 6 months.

Six months of surveillance was conducted on the two groups. Prior to therapy and three and six months after treatment, patients and/or their sexual partners were instructed to report their IELT, PE grade, ISS, and intercourse frequency, as well as adverse drug effects.

Ethical considerations:

This trial was conducted in accordance with the Declaration of Helsinki. All participants signed an informed written consent form. The study was done after being approved by the Research Ethics committee, Faculty of Medicine, Benha University.

Statistical analysis

Statistical analysis was done by SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as range, mean and SD and compared between the two groups utilizing unpaired Student's t- test and Mann-Whitney test was used to compare samples which are not normally distributed. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test. A two tailed P value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics were shown in table 1.

Table 1: Baseline characteristics of patients with premature ejaculation (PE) according to treatment group

Variable	Group A (sildenafil citrate) (N= 30)	Group B (paroxetine) (N= 30)	*P-value*
Patient age (years) Mean ± SD	32.84 ± 5.50	32.13 ± 5.81	0.57
Range	20–45	20–50	
Mean ± SD Range Duration of PE (months)	33.18 ± 6.57 18–46 28.98 ± 18.76	33.07 ± 5.77 19–50 27.85 ± 18.30	0.93 0.89

Table 2 provides information on the patients' mean IELT, PE grade, ISS, ISS of their partners, and intercourse frequency at baseline, and at 3 and 6 months follow up in the two groups. Before treatment, there was no significant difference among the two groups in all the parameters. After 3- or 6-months therapy, Critical changes were observed between the two groups in all measurements. After three or six months of follow-up, the two groups demonstrated substantial differences in all indicators compared to pretreatment, except for intercourse frequency. Two groups had no substantial changes among and 6 months follow-up. Sildenafil citrate was more effective than paroxetine in terms of efficacy, with a downward trend. In general, sildenafil citrate and paroxetine were well tolerated.

Table 2: IELT, PE grade, ISS of patients and their sexual partners, and the frequency of intercourse at baseline, 3 and 6 months follow up

Variable	Group A (sildenafil citrate) (N= 30)	Group B (paroxetine) (N= 30)	*P*
IELT of patient (min) Baseline	1.08 ± 0.31	1.10 ± 0.35	0.73
3 months	6.18 ± 1.53	3.85 ± 1.18	0.001
6 months *P*	6.20 ± 1.75 0.001	3.89 ± 1.28 0.001	0.001
P (3 *vs* 6 months) PE grade of patient Baseline	0.87 5.55 ± 0.36	0.80 5.68 ± 0.47	0.80
3 months	1.57 ± 0.38	1.97 ± 0.43	0.001
6 months *P*	1.52 ± 0.46 0.001	1.88 ± 0.49 0.001	0.001
P (3 *vs* 6 months) ISS of patient Baseline	0.52 2.44 ± 0.91	0.33 2.52 ± 1.03	0.53
3 months	5.40 ± 1.31	4.60 ± 1.18	0.001
6 months *P*	5.60 ± 1.17 0.001	4.80 ± 1.35 0.001	0.001
P (3 *vs* 6 months) ISS of sexual partner Baseline	0.39 1.36 ± 0.90	0.44 1.37 ± 1.01	0.97
3 months	5.20 ± 1.40	4.17 ± 1.13	0.001
6 months *P*	5.36 ± 1.50 0.001	4.03 ± 0.97 0.001	0.001
P (3 *vs* 6 months)	0.56	0.52	
frequency of intercourse			
Baseline	0.87 ± 0.76	0.82 ± 0.89	0.86
3 months	2.35 ± 1.50	1.81 ± 0.99	0.001
6 months *P*	2.38 ± 1.30 0.001	1.85 ± 1.11 0.001	0.001
P (3 *vs* 6 months)	0.92	0.86	

Values shown as mean ± SD, Mann-Whitney test was used to compare normally distributed data, Friedman test was used to compare baseline, after 3 months, and after 6 months in each parameter when the data are abnormally distributed paired, unless we used post hoc.

Table 3 shows the adverse effects of the two drugs. Typical light or mild headache, nausea, nasal congestion and flushing were reported when using sildenafil citrate. Light dizziness, headache, nausea, fatigue and constipation occurred when using paroxetine. Most adverse effects disappeared over time.

Table 3: Adverse effects of sildenafil citrate and paroxetine

Drug	Headache	Nausea	Nasal congestion	Flushing	Dizziness	Fatigue	Constipation
Sildenafil citrate	6 (11.8)	3 (2.2)	5 (8.4)	4 (8.2)	0	0	0
Paroxetine	1 (3.1)	7 (9.0)	0	0	2 (3.1)	3 (4.0)	4 (5.6)
P	0.044	0.166	0.02	0.038	0.150	0.076	0.038

Values shown as n (%).

DISCUSSION

Historically, there was no commonly accepted definition of PE. There are several subjective and imprecise definitions. The best definition of IELT should include the male sexual pleasure amount, the female sexual satisfaction level, the ability to control ejaculation, the frequency with which the female sexual partner achieves orgasm, and mental and psychological components degree [7]. According to the study for describing PE for clinical investigations and the best criteria for detecting PE, our study recognized PE using IELT, patients ISS, PE grade, their sexual partners ISS, and sexual activity repetition [8]. Our goal was for this concept to be universally accepted. The Chinese Index of Premature Ejaculation (CIPE) has demonstrated the validity and logic of these particular PE assessment factors [9].

In a number of studies, IELT was employed to define PE; nevertheless, ejaculation within one minute or more of vaginal intromission was considered PE, excluding ejaculation anterior to vaginal intromission. This is insufficient, given the prevalence of this condition is higher among males who have never had a sexual relationship. Additionally, within two minutes of sexual vaginal penetration, we classified PE as IELT, as usual length of IELT in Chinese men is between two and six minutes. Additionally, a new proposal for the definition and diagnosis of erectile dysfunction made at the second symposium on sexual dysfunctions indicated that a man may be eligible for the diagnosis if his ejaculatory delay is less than two minutes [10].

ISS of patients and their spouses was not employed in research that used IELT, PE grade, or intercourse frequency to evaluate PE. In contrast to animals, one of the primary purposes of sexual activity in humans, aside from reproduction, is to make males and their sexual partners happy and comfortable. The ISS of patients and their partners was considered in our study in light of this [11].

We devised the trial to use sildenafil citrate alone and compare it with paroxetine to validate the effectiveness of sildenafil citrate in treating PE and to rule out the potential of any interaction between the two. The most successful treatment for PE up to this point has been thought to be paroxetine daily, and our study found that paroxetine was more beneficial than the baseline. However, when comparing sildenafil citrate with paroxetine, we found substantially critical improvements in all evaluated variables [2].

Our findings are consistent with a study by **Abdel-Hamid**, who demonstrated that sildenafil can dramatically raise IELT on its own. Additionally, sildenafil citrate had a considerably lower dropout rate than paroxetine, and the proportion of patients who wanted to continue treatment with the initial dosage was significantly higher, suggesting that sildenafil citrate is superior to paroxetine in treating PE [12].

Understanding of the NO-cGMP pathway in recent years provides potential explanations for how sildenafil citrate may treat PE. Research suggests that sildenafil citrate prevents the vas deferens from contracting, seminal vesicle, prostate, and urethra; induces peripheral analgesia; extends erections duration; and reduces central sympathetic output. Additionally, evidence from studies on knockout mice supports sildenafil citrate efficacy for treating PE. Mice that lacked the eNOS gene displayed a condition similar to PE, while those that lacked the heme oxygenase-2 gene showed a circumstance resembling prolonged ejaculation. There is evidence that NOS may be bound and inactivated by the carbon monoxide (CO) that is generated by HO-2. In males with PE, sildenafil citrate has been shown to improve confidence, the feeling of ejaculatory control, and overall sexual satisfaction while shortening the time needed to establish a second erection following ejaculation [13].

At present, further well-designed clinical and experimental trials are necessary to establish the precise processes by which sildenafil citrate cures PE because they are still unclear. However, sildenafil citrate has been extensively utilizing by ED patients around the world for about 25 years as the first oral drug licensed by the FDA for the condition [14]. Numerous studies have shown that when used as needed at a dose of 50 mg, sildenafil citrate is typically safe with some moderate side effects, including as a mild headache, nausea, nasal congestion, and flushing, which usually go away over time. In our study, sildenafil citrate had similar unfavorable effects in treating PE as it does in treating ED, and some patients experienced postural hypotension [14].

To obtain more accurate and scientific data, a prospective randomized clinical study was conducted, though there were limitations in the study design due to the constraints of clinical patients and funding. Placebo-controlled and double-blinded methods were not used in the study, but the findings can provide insights for future manufacturer-sponsored multicenter trials that employ

these methods to further research sildenafil citrate's possible effectiveness in treating PE. Furthermore, to validate the effectiveness of other PDE5 inhibitors like vardenafil and tadalafil in treating PE, more research is required. At the 7th Congress of the European Society for Sexual Medicine and the 2005 American Urological Association meetings, separate research on the possible effectiveness of vardenafil and tadalafil was discussed [15].

Recent information suggested that PDE5 inhibitors may be suitable for hypo-orgasmic cases, particularly in older patients or when PE coexists with ED. Combining psychosexual therapy techniques with PDE5 inhibitors may enhance long-term efficacy. On the other hand, young hyper-orgasmic forms patients may benefit more from the use of selective serotonin reuptake inhibitors [16].

To conclude, sildenafil citrate has demonstrated significant improvements in IELT, intercourse frequency, ISS, and a PE grade reduction with tolerable unfavorable reactions. Therefore, it is considered a safe and promising drug for treating PE. However, to further assess the effectiveness of selective PDE5-Is in PE therapy, a placebo-controlled large-scale double-blinded, multicenter trial involving a substantial patient's number is required.

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