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Can sildenafil treat primary premature ejaculation? A prospective clinical study

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Background: Recently, sildenafil has been demonstrated to be effective in treating premature ejaculation (PE). However, these studies ignored female factors and could not exclude the probability of drug interaction when combined with paroxetine. Therefore, the aim of this study was to evaluate the efficacy and safety of sildenafil alone in the treatment of primary PE, taking female factors into consideration.

Methods: One hundred and eighty potent men with primary PE were randomly divided into three groups and followed up for 6 months. Group A were treated with 50 mg sildenafil as needed, group B with 20 mg paroxetine daily and group C with squeeze technique daily. Intravaginal ejaculatory latency time (IELT), PE grade, intercourse satisfactory score (ISS), frequency of intercourse, and adverse effects of drugs were recorded before treatment, and 3 and 6 months after treatment.

Results: Compared with pretreatment, the three groups had significant differences in all the parameters after 3 or 6 months treatment, except the frequency of intercourse in Group C (all $P = 0.00$). However, there were no significant differences between 3 and 6 months. Compared with paroxetine and squeeze technique, after 3 or 6 months, sildenafil had significant differences in all the parameters (all $P = 0.00$). After 6 months, 1.7%, 18.3% and 36.7% patients in groups A, B and C, respectively, withdrew from the study and 86.7%, 60.0% and 45.0% patients, respectively, wanted to be treated further with the original administration, and this was statistically significant (both $P = 0.00$).

Conclusion: Sildenafil is very effective and safe to treat PE, and has much higher efficacy than paroxetine and squeeze technique.

Key words: premature ejaculation, paroxetine, sildenafil, therapy.

Introduction

Premature ejaculation (PE), also referred to as early or rapid ejaculation, is currently defined as persistent or recurrent ejaculation with minimal sexual stimulation before, upon, or shortly after penetration and before the person wishes. It is associated with marked distress or interpersonal difficulty.[1] With a prevalence of more than 21%,[2] and perhaps affecting as many as 75% of men at some point in their lives,[3] PE is regarded as the most common male sexual disorder.[2] It can impact on many aspects of a man's life, including reducing self-esteem, deteriorating relationships, and causing anxiety, embarrassment and depressed feelings.[4] Moreover, PE places a significant burden on the patient–partner relationship with evidence that there is a higher prevalence of female sexual dysfunction associated with PE.[5] About 30% of men with PE have co-occurring erectile dysfunction (ED), which typically results in early ejaculation without full erection.[6] Recently, 522 patients with PE were investigated and 65.3% patients were found to have ED.[7]

To date, drugs to treat PE have been divided into two categories: oral drugs such as antidepressants, alpha-adrenoceptor blocking agents and Chinese herbal medicines; and local remedies such as topical medicine, intracavernosal injection agents and local urethral drugs.[8] Although some of these drugs have some disturbing side-effects, daily use of them, particularly paroxetine, clomipramine and sertraline, have been demonstrated to effectively delay ejaculation. However, none of these drugs have been approved by the FDA as drugs for PE.[9]

Sildenafil, a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5, as a first line oral therapy for ED, has recently been reported to have efficacy on alleviating PE by a few studies.[10,11] However, these studies employed a combination of paroxetine and sildenafil to treat PE. Therefore, it is difficult to exclude a possibility of drug interactions. In addition, the authors only used male factors such as intravaginal ejaculatory latency time (IELT), PE grade, or international index of erectile function (IIEF) intercourse satisfaction domain scores as the parameters to evaluate the effectiveness, but did not take into account the factors of the female sexual partner, such intercourse satisfaction score (ISS).

Therefore, employing IELT, PE grade, male ISS, female ISS, and the times of intercourse per week as major parameters, we conducted this prospective clinical study to evaluate the efficacy of sildenafil alone and compared it with 20 mg paroxetine daily or squeeze technique daily in the treatment of PE.

Methods

Patients

From March 2001 to March 2004, 286 patients with primary PE who presented to the urological outpatient clinic in People's Hospital of Hainan Province were enrolled into this prospective clinical trial guided by St Peter's Center of Andrology. PE was defined as ejaculation before vaginal penetration or within 2 min after vaginal penetration. All patients were heterosexual and had had one stable sexual partner for more than 6 months.

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All the patients underwent a detailed medical and sexual history inquiry, physical examination (including Meares–Stamey test to exclude genital tract infection), and psychological profile. PE grade, IELT, IIEF-5, ISS and frequency of intercourse were recorded. Their sexual partners were also requested to record their ISS. For the purposes of the study, only potent patients (IIEF-5 >21) with primary PE were selected.

Study exclusion criteria were: secondary PE; erectile dysfunction (ED); low libido; major psychiatric or psychological illnesses including depression; alcohol, drugs or substances abuse; organic diseases causing limitation in using selective serotonin reuptake inhibitors or sildenafil; and use of other treatments for PE within the previous 3 months. Secondary PE was identified in 65 of 286 patients (25.4%), who were excluded from analysis. Of these 65 patients, 56 (86.2%) had chronic prostatitis. A further 41 patients (14.3%) who had accompanying ED were also excluded from this study, although they were considered for inclusion in another parallel study that was being performed to evaluate sildenafil in alleviating PE with and without ED.

Thus, 180 potent men with primary PE were enrolled in the study. The men were randomly divided into three treatment groups: Group A were treated with sildenafil as needed, Group B with paroxetine daily and Group C with squeeze technique daily. Each group had 60 patients.

Intravaginal ejaculatory latency time

Intravaginal ejaculatory latency time (IELT) is defined as the time that intercourse lasts from initiation of vaginal penetration to ejaculation.[12] It was measured by the female sexual partner using a stopwatch and expressed in minutes. All the stopwatches were calibrated and provided by the same company. If ejaculation occurred before or during penis penetration into the vagina, it was defined as 0 minute. Men whose mean IELT in the past 3 months was <2 min were enrolled in the study.

Premature ejaculation grade

According to the Center for Marital and Sexual Health questionnaire that dealt with PE,[13] patients graded their ejaculatory dysfunction by answering the question: 'How often did you ejaculate rapidly before vaginal penetration or within 2 min after vaginal penetration in the past 3 months?'. The answers were graded on a scale of 0–8: 0 = almost never, 2 = sometimes, 4 = about half the time, 6 = most of the time, and 8 = almost always. Men who graded their mean PE as 4 or greater in the past 3 months were enrolled in the study.

Intercourse satisfaction score

Referring to PE grade, patients and their sexual partners evaluated their ISS by answering the question: 'How often did you feel satisfaction about intercourse in the past 3 months?'. The answers were graded on a scale of 0–8: 0 = almost never, 2 = sometimes, 4 = about half the time, 6 = most of the time, and 8 = almost always.

Frequency of intercourse

The frequency of intercourse was the number of instances of vaginal intercourse per week. Men whose frequency of intercourse in the past 3 months reached 0.5 or more were enrolled in the study.

Study protocol

Patients in Group A received 50 mg sildenafil as needed an hour before intended intercourse according to the standard administration instructions (not less than one time per week). Patients in Group B received 20 mg paroxetine daily. Patients and their sexual partners in Group C were asked to use the classical squeeze technique daily. Patients and their sexual partners in Group C were shown how to employ the squeeze technique by the same specialist.

All groups were followed up for 6 months. Patients and/or their sexual partners were required to record their IELT, PE grade, ISS and frequency of intercourse, and adverse effects of drugs before treatment, and 3 and 6 months after treatment.

Statistical analysis

One way ANOVA test was used to compare data on the clinical details, IELT, PE grade, ISS and the frequency of intercourse in the three groups. Student's *t*-test was employed to compare data on PE grade, ISS and the frequency of intercourse between 3 and 6 month follow up. The chi-squared test was used to compare data on the adverse effect of sildenafil and paroxetine, and the rates of withdraw and willing to be treated further with original administration in the three groups. $P < 0.05$ was defined as statistically significant.

Results

Table 1 shows the clinical details of the three groups, including the age and age range of patients and their partners, and the duration of PE. There were no significant differences among the three groups.

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

Variable	Group A (sildenafil)	Group B (paroxetine)	Group C (squeeze)	*P*
Patient age (years)				
Mean ± SD	32.81 ± 5.50	32.11 ± 5.82	33.22 ± 6.45	0.59
Range	20–45	20–50	19–52	
Partner age (years)				
Mean ± SD	33.21 ± 6.58	33.08 ± 5.89	32.81 ± 6.22	0.94
Range	18–47	19–50	20–51	
Duration of PE (months)	28.89 ± 18.67	27.96 ± 18.25	29.09 ± 19.85	0.94

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)	Group B (paroxetine)	Group C (squeeze)	*P*
IELT of patient (min)				
Baseline	1.09 ± 0.32	1.11 ± 0.45	1.06 ± 0.36	0.84
3 months	6.19 ± 1.52	4.89 ± 1.25	2.76 ± 0.78	0.00
6 months	6.21 ± 1.86	4.93 ± 1.36	2.62 ± 0.69	0.00
P	0.00	0.00	0.00	
P (3 *vs* 6 months)	0.95	0.88	0.39	
PE grade of patient				
Baseline	5.58 ± 0.35	5.66 ± 0.48	5.62 ± 0.56	0.90
3 months	1.58 ± 0.39	1.98 ± 0.42	2.91 ± 0.66	0.00
6 months	1.53 ± 0.49	1.89 ± 0.47	2.89 ± 0.72	0.00
P	0.00	0.00	0.00	
P (3 *vs* 6 months)	0.54	0.31	0.90	
ISS of patient				
Baseline	2.42 ± 0.90	2.60 ± 1.02	2.56 ± 0.76	0.52
3 months	6.40 ± 1.30	5.60 ± 1.16	3.91 ± 1.38	0.00
6 months	6.60 ± 1.16	5.80 ± 1.36	4.00 ± 1.30	0.00
P	0.00	0.00	0.00	
P (3 *vs* 6 months)	0.38	0.43	0.76	
ISS of sexual partner				
Baseline	1.35 ± 0.90	1.36 ± 1.00	1.40 ± 0.98	0.96
3 months	5.30 ± 1.40	4.18 ± 1.14	2.80 ± 1.22	0.00
6 months	5.46 ± 1.50	4.04 ± 0.98	2.74 ± 1.30	0.00
P	0.00	0.00	0.00	
P (3 *vs* 6 months)	0.55	0.51	0.83	
Frequency of intercourse				
Baseline	0.86 ± 0.75	0.81 ± 0.88	0.89 ± 0.90	0.87
3 months	2.36 ± 1.50	1.80 ± 0.98	1.20 ± 1.40	0.00
6 months	2.39 ± 1.30	1.84 ± 1.10	1.26 ± 1.52	0.00
P	0.00	0.00	0.20	
P (3 *vs* 6 months)	0.91	0.85	0.85	

IELT, intravaginal ejaculatory latency time; ISS, intercourse satisfaction score; PE, premature ejaculation. Group A, 50 mg sildenafil as needed; Group B, 20 mg paroxetine daily; Group C, squeeze technique daily.
Values shown as mean ± SD.

Table 2 shows the mean IELT, PE grade, ISS of patients, ISS of their sexual partners, and the frequency of intercourse at baseline, and at 3 and 6 months follow up in the three groups. Before treatment, there was no significant difference among the three groups in all the parameters. After 3 or 6 months treatment, there were significant differences among the three groups in all the parameters (all $P = 0.00$). Compared with pretreatment, all the groups after 3 or 6 months follow-up had significant differences in all parameters (all $P = 0.00$), except the frequency of intercourse. All the groups had no statistical differences between 3 months and 6 months follow-up. In the term of efficacy, the descending trend was sildenafil > paroxetine > squeeze technique, and sildenafil was much better than paroxetine and squeeze technique (all $P = 0.00$).

In general, sildenafil and paroxetine were well tolerated. Anejaculation occurred in one patient in group A and one patient in group B, who withdrew from study after 1 months and 3 months, respectively. 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. Light dizziness, headache, nausea, fatigue and constipation occurred when using paroxetine. Most adverse effects disappeared over time.

After 6 months follow-up, one (1.67%), 11 (18.33%) and 22 (36.67%) patients in groups A, B and C, respectively, withdrew from the study because of no efficacy or adverse effects, and there was a significant difference among the three groups ($P = 0.00$). After 6 months study, 52 (86.67%), 26 (60.00%) and 16 (45.00%) patients in groups A, B and C, respectively, hoped to be treated further with the original administration, and there was a significant difference among the three groups ($P = 0.00$).

Discussion

To date, PE has not had a universally agreed definition. Many definitions are partial, subjective and non-specific. An ideal definition should consist of IELT, the ability to control ejaculation, the extent of male sexual satisfaction, the extent of female sexual satisfaction, the frequency of female sexual partner reaching orgasm and the extent of psychological and pathological factors.[14] So, according to the ideal criteria to define PE[14] and the report for defining PE for experimental and clinical investigations,[15] IELT, PE grade, ISS of patients, ISS of their sexual partners, and the frequency of intercourse were employed

Table 3 Adverse effects of sildenafil and paroxetine

Drug	Headache	Nausea	Nasal congestion	Flushing	Dizziness	Fatigue	Constipation
Sildenafil	7 (11.7)	2 (3.3)	5 (8.3)	5 (8.3)	0	0	0
Paroxetine	2 (3.3)	6 (10.0)	0	0	2 (3.3)	3 (5.0)	4 (6.7)
P	0.00	0.00					

Values shown as *n* (%).

in our study to describe PE. Our intention was that this definition could be clearer and widely accepted. The acceptability and reasonability of these selected parameters to assess PE have been supported recently by the Chinese Index of Premature Ejaculation (CIPE).[16]

In many reports, IELT was used to describe PE, but PE was defined as ejaculation within 1 or more than 1 minute of vaginal intromission, and did not include ejaculation before vaginal intromission. We think this is incomplete, because this condition is most common among young adults and men who lack sexual experience. In addition, we defined PE as IELT within 2 min of vaginal penetration, because the normal average IELT of Chinese men was 2–6 min.[8] Moreover, an updated proposal for PE definition and diagnosis provided after the second consultation on sexual dysfunctions[6] also defined that ejaculatory latency of 2 min or less may qualify a man for the diagnosis.

In many studies, IELT, PE grade and frequency of intercourse were used to evaluate PE, but ISS of patients and their sexual partners were not. Unlike in animals, one of the main aims of intercourse in humans, besides reproduction, is to make men and their sexual partners happy, satisfactory and comfortable and let both men and their sexual partners enjoy the happiness caused by orgasm. Therefore, ISS of patients and their sexual partners were taken into consideration in our study.

In order to avoid the possibility that there was interaction of sildenafil and paroxetine, we designed the study using sildenafil alone, and compared it with paroxetine and squeeze technique, as well as pretreatment, to confirm the efficacy of sildenafil in the treatment of PE. Paroxetine daily has been regarded as the most effective drugs to treat PE so far.[17,18] We also confirmed that paroxetine was much more effective when compared with baseline and squeeze technique. The squeeze technique has previously been thought to be a classically effective method, but it has recently been confirmed that it has little effect on PE,[18] which also is supported by our study, although the squeeze technique prolonged IELT significantly when compared with pretreatment.

Our results showed that compared with paroxetine, squeeze technique or pretreatment, sildenafil led to statistically significant improvement in all measured parameters. Our results are supported by Abdel-Hamid,[19] who demonstrated that sildenafil alone could prolong IELT significantly. Moreover, compared with paroxetine and squeeze technique, the dropout rate of sildenafil was significantly lower, and the percentage of hoping to be treated further with original administration was statistically significantly higher. All these results demonstrated that sildenafil was superior to paroxetine and squeeze technique in the treatment of PE. In this study all the patients only had PE alone, not accompanied by ED. In the other parallel study, we also confirmed that sildenafil could alleviate PE accompanied by ED and improve erectile function simultaneously. So, sildenafil is a promising agent to treat PE; in addition, it could be a case of 'two birds with one stone' if patients suffer from PE as well as ED.

With the increased understanding of the pathway of nitric oxide (NO)-cGMP, the possible mechanisms of sildenafil to treat PE could be explained:[20] inhibiting the contractile response of the vas deferens, seminal vesicle, prostate and urethra; inducing a state of peripheral analgesia; augmenting the total duration of erection; and lessening the central sympathetic output. Furthermore, there is evidence from knockout mice to explain the efficacy of sildenafil in the treatment of PE. Mice lacking the eNOS (nitric oxide synthase) gene developed a condition similar to PE; however, mice lacking heme oxygenase-2 (HO-2) developed a condition similar to delayed ejaculation. Some evidence indicates that carbon monoxide (CO) generated by HO-2 could bind and inactivate NOS.[20] In addition, sildenafil has been reported to increase confidence, the perception of ejaculatory control, and overall sexual satisfaction, and decrease the postorgasmic refractory time to achieve a second erection after ejaculation in men with PE.[21,22] To date, the mechanisms by which sildenafil treats PE are not clear, and well-designed clinical and experimental trials are needed to elucidate them.

Sildenafil, as the first oral drug approved by FDA to treat ED, has been used in millions of patients with ED around the world for nearly 8 years. All the reports demonstrate that sildenafil is very safe with some tolerable adverse effects using the dose 50 mg as needed, such as light or mild headache, nausea, nasal congestion and flushing, and these adverse effects will disappear with time. Sildenafil has similar adverse effects in the treatment of PE as it does in the treatment of ED.

In order to gain more scientific and exact data, we conducted a perspective randomized clinical trial. Certainly, owing to the limits of clinical patients and funds, there are some shortcomings in the design such as not employing perspective randomized, placebo-controlled, double-blinded clinical trial methods. However, this study can present clues for manufacturer-sponsored double-blinded, placebo-controlled, multicenter trials to further research the potential value of sildenafil in the treatment of PE. In addition, some study should be carried out to testify the efficacy of the other phosphodiesterase 5 inhibitors (PDE_5-Is) such as vardenafil and tadalafil in the treatment of PE. Recently, the potential usefulness of vardenafil and tadalafil were presented at the 7th Congress of the European Society for Sexual Medicine and 2005 American Urological Association meeting, respectively.[23,24] Interestingly, updated data suggest that PDE_5-Is should be employed in hypo-orgasmic forms, in old age or when PE is associated with ED, and therapeutic association with psychosexual therapy techniques might improve the efficacy, particularly in the long term, while selective serotonin reuptake inhibitors should be used in young patients with hyper-orgasmic forms.[25]

In summary, sildenafil can significantly increase IELT, ISS of patients and their sexual partners and the frequency of intercourse, and decrease PE grade with light or mild adverse effects. It is a very effective, promising and safe drug to treat PE. To determine whether selective PDE_5-Is will have a place in the treatment of PE, a manufacturer-sponsored, double-blinded, placebo-controlled, and multicenter trial with a large number of patients should be performed.

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