Combination of Sertraline and Sildenafil versus Sertraline Monotherapy in the Treatment of Acquired Premature Ejaculation without Concomitant Diseases

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Abstract

Objective: To determine the efficacy and safety of sertraline monotherapy and combination therapy with sertraline and sildenafil in the treatment of APE without concomitant diseases.

Methods: The study was conducted in 120 outpatients diagnosed with APE but without concomitant diseases. These patients were randomly divided into two groups: group A was treated with 50 mg sertraline daily; group B was treated with 50 mg sertraline daily and 50 mg sildenafil as needed. Assessment of the efficacy and safety of the two therapies was performed after 4 and 8 weeks. Patient or partner reports of Intravaginal Ejaculatory Latency Time (IELT), Premature Ejaculation Profile (PEP), Clinical Global Impression of Change (CGIC), and Treatment-Emergent Adverse Events (TEAEs) were assessed in this study. All the assessments were compared in the two groups after the treatment period. The efficacy was assessed by IELT, PEP and CGIC. On the other hand, safety was assessed by TEAEs.

Results: 112 participants completed the study voluntarily. The two groups were similar regarding demographics. At the end of study period, both groups had significant improvements in IELT and PEP measures compared with pretreatment (P<0.001). Compared with group A, group B had significantly greater values of IELT (7.20 ± 2.93 vs. 5.04 ± 2.79), PEP measures, and CGIC (subjects reporting at least 'better': 58.2% vs. 35.8%) (P<0.05 for all). Adverse effects including headache, flushing, etc. were found in both groups, and the total incidence was higher in group B than group A (31.7% vs. 23.3%, respectively), but the difference was not significant. All the adverse effects were mild and tolerated.

Conclusion: Both sertraline monotherapy and combination therapy with sildenafil and sertraline were efficacious and safe in the treatment of APE without concomitant diseases. The combination therapy had a higher efficacy than sertraline monotherapy without more adverse effects.

Keywords: Acquired premature ejaculation; Sertraline; Sildenafil; Treatment; Efficacy; Safety; Monotherapy; Combination therapy

Introduction

Premature Ejaculation (PE) is one of the most common sexual dysfunctions, affecting 20%-40% of sexually active men [1-3]. There were various definitions of PE by different professional organizations [4,5]. However, since the underlying physiopathology of PE was not well understood, there were no universally accepted definition of PE until the International Society for Sexual Medicine (ISSM) established the first evidence-based definition of lifelong PE in 2007 [6]. Subsequently, Waldinger et al. proposed a new classification for PE in 2008, which included four subtypes: lifelong PE (LPE), acquired PE (APE), natural variable PE (NVPE), and Premature-Like Ejaculatory Dysfunction (PLED) [7,8].

In recent years, although a lot of therapies have been proved to be efficacious in the treatment of PE, most research has focused on the treatment of LPE, or ignored the different types of PE [9,10]. There are few studies concerning the treatment of APE, although Serefoglu et al. revealed that APE was more severe than other subtypes [11]. To our knowledge, this is the first randomised trial to show sertraline monotherapy and a combination of sildenafil and sertraline in the treatment of APE in patients without concomitant diseases. Therefore, we conducted this clinical study to evaluate the efficacy of 50 mg sertraline daily and a combination of 50 mg sildenafil as needed and 50 mg sertraline daily in the treatment of APE in patients without concomitant diseases.

Methods

Subjects

Patients from outpatient clinics of the First Affiliated Hospital of Anhui Medical University in Hefei, Anhui, China who complained of APE but without concomitant diseases were recruited from May 2012 until April 2013. One hundred and twenty heterosexual consecutive men were enrolled in the study, as well as their partners. All patients were informed of the possible side-effects and provided informed consent before their participation in this study. Also, the study was approved by the local medical ethics committee. And it was registered in the Chinese Clinical Trial Registry.

APE was defined as IELT of less than 2 minutes, but with normal ejaculation experiences before, with onset either sudden or gradual.

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The dysfunction might be a result of urological dysfunction, thyroid dysfunction, psychological or relationship problems, and the patient's lack of the ability to delay ejaculation, as Waldinger et al. proposed [7]. In this study, only subjects with APE but without concomitant diseases were enrolled.

A thorough medical history was taken, and biochemical, haematological, and endocrine testing, and physical examination were performed for each patient. To be included in the study, other criteria needed to be met: (1) male patient aged ≥18 years; (2) in a heterosexual, stable, and monogamous sexual relationship with the same female partner for >6 months, and possible sexual attempts of once a week or more; (3) without any concomitant diseases, such as prostatic inflammation, Erectile Dysfunction (ED), psychological diseases, hypothyroidism, diabetes, etc. (4) with an International Index of Erectile Function-5 (IIEF-5) score ≥22, indicating normal erectile function; (5) without known hypersensitivity to Selective Serotonin Reuptake Inhibitors (SSRIs) or concomitant use of SSRIs, tricyclic antidepressants, or other medications during the study. Patients with previous therapies of PE, including psychological or medical, were excluded from the study. During the study, the patients were not allowed to use condoms, topical anaesthetic, or any behaviour therapy, such as the stop-start technique or the squeeze technique.

Study design and procedure

Patients were randomly divided into two groups according to the sequence of visit. The men in group A were treated with 50 mg sertraline daily at 16:00, and the subjects in group B were treated with sertraline 50 mg daily at 16:00 as well as 50 mg sildenafil 30 minutes before the desired sexual intercourse during an 8-week period. The previous self-estimated IELT and PEP at baseline of each group were recorded during a 2-week period before their participation in the study. The same outcomes were assessed for each participant after 4-week and 8-week periods of treatment, as well as the CGIC and adverse effects of the drugs. According to Kaufman et al., all efficacy analyses were conducted based on the Modified Intent-To-Treat (MITT) population. Patients who took one or more doses of study medication and answered the PEP and CGIC questions at baseline and at one or more sample times after baseline were included in calculating the MITT population [12].

Patient or partner reports of IELT, PEP, and CGIC were used to assess the efficacy of the two therapies and TEAEs were used to assess the safety in this study.

Main outcome measures

IELT: IELT was the interval between the start of vaginal intromission and the start of intravaginal ejaculation. And patient or partner reports of ejaculatory latency was used as a measure of IELT in this study, since studies have indicated that patient or partner self-report of ejaculatory latency correlate relatively well with objective stopwatch latency and might be useful as a proxy measure of IELT [13,14]. Furthermore, it was stipulated that only the first would be noted if intercourse occurred more than once in a single session.

PEP: PEP included perceived control over ejaculation, personal distress and interpersonal difficulty related to ejaculation, as well as satisfaction with sexual intercourse. Each measure was assessed on five-point scales. For perceived control over ejaculation and satisfaction with sexual intercourse, the scales ranged from 0=Very poor, 1=Poor, 2=Fair, 3=Good, and 4=Very good. For personal distress and interpersonal difficulty, the scales range from 0=Extreme, 1=Quite a bit, 2=Moderate, 3=A little bit, and 4=Not at all. The PEP index score was the mean of all four measures [15]. A composite Patient-Reported Outcome (PRO) definition of clinical benefit was defined as patients who reported at least a two-category increase in perceived control over ejaculation and at least a one-category increase in personal distress related to ejaculation from baseline to study endpoint [16,17].

CGIC: CGIC was a single-item measure assessed by asking patients about improvement or worsening of PE compared with the start of the study. It was evaluated on a seven-point scale: much worse, worse, slightly worse, no change, slightly better, better, or much better [18].

TEAEs: Safety of the two therapies was assessed by recording TEAEs, such as nausea, headache, dizziness, sexual desire difficulties, ED, flushing, etc., including the incidence, severity, type, etc.

Statistical analysis

Statistical analysis was performed using SPSS 13.0 software (SPSS Inc., Chicago, USA). For the quantitative data, results are expressed as mean ± Standard Deviation (SD) and a two-tailed unpaired Student t test was used. The comparison of proportions was performed by the chi-square test or Kruskal-Wallis Test. All statistical analysis was two-sided, and a P value of <0.05 was considered statistically significant.

Results

Subject disposition

A total of 168 patients were screened, and 120 patients meeting the criteria were randomised; 108 (90%) subjects receiving at least one dose of study drug were included in the MITT population, including 53 subjects treated with sertraline 50 mg daily and 55 subjects treated with sertraline 50 mg daily and 50 mg sildenafil as needed. One hundred and three patients successfully completed the 8-week treatment period (Figure 1). Among the 48 subjects who failed the screening, over half were related to ED or prostatitis. Nobody withdrew from this study due to the lack of efficacy and TEAEs. Baseline demographic information and clinical characteristics for the study population in the two groups are shown in Table 1. There were no significant differences in the demographic information and clinical characteristics at baseline.

![Figure 1: Subject distribution and completion information.](image-url)
Concerning on the effectiveness of the two therapies, our study showed that both groups had significant improvements in IELT and PEP measures compared with pretreatment (P<0.001). And group B had significantly greater values of IELT (7.20 ± 2.93 vs. 5.04 ± 2.79), PEP measures, and CGIIC compared to Group A (P<0.05 for all). With regard to the safe of treatments, adverse effects including headache, flushing, etc. were found in both groups, and the total incidence was higher in group B than group A (31.7% vs. 23.3%, respectively), but the difference was not significant.

IELT

The average self-estimated IELT is shown in Table 2. The mean ± SD self-estimated IELT values were 1.36 ± 0.53 and 1.47 ± 0.52 minutes in the sertraline group and combination treatment groups at baseline, respectively. After the 8-week treatment period, significant improvements in mean self-estimated IELT from 1.36 ± 0.53 to 7.20 ± 2.93 minutes in the combination group were observed (P<0.001 for both). In addition, the increases were significantly greater in self-estimated IELT in minutes in the combination group than in the sertraline group (P<0.01).

PEP measures

Table 2 also shows the significantly greater scores observed in all four PEP measures in both of the two groups after 8-week treatment (P<0.001 for all items). Also, the scores were significantly higher concerning personal distress related to ejaculation, satisfaction with intercourse, and interpersonal difficulty related to ejaculation in the combination treatment group than in the sertraline group (P<0.05). For perceived control over ejaculation, the mean score of the combination group (2.55 ± 0.60) was higher compared with the sertraline group (2.34 ± 0.71), but the difference was not significant. In addition, the PEP index score was significantly higher in the combination treatment group (2.49 ± 0.53) compared with the sertraline group (2.83 ± 0.47, P<0.01).

The percentage of subjects achieving one-category or greater improvement in perceived control over ejaculation, personal distress related to ejaculation, satisfaction with intercourse, and interpersonal difficulty related to ejaculation was 73.6%, 56.6%, 66.0%, and 52.8%, respectively, in the sertraline treatment group and 72.4%, 60.0%, 90.9%, and 63.6%, respectively in the combination treatment group (Table 2). The only significant difference between the two groups was observed in satisfaction with intercourse (P<0.01). All improvements in PEP measures are shown in Figure 2.
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Figure 2: Premature Ejaculation Profile (PEP) results. Percentages of subjects reporting “2=Fair”, “3=good” or “4=very good” to the item for (a) control over ejaculation and (b) satisfaction with sexual intercourse or “2=moderately,” “3=a little bit,” or “4= Not at all” in response to the item for (c) personal distress related to ejaculation (d) interpersonal difficulty related to ejaculation.

| Outcome measure | Sertraline (N=53) | Sertraline and sildenafil (N=55) | t/χ² | P* |
|-----------------|-------------------|----------------------------------|------|-----|
| Average IELT (Mean ± SD, minute) | | | | |
| baseline | 1.36 ± 0.53 | 1.47 ± 0.52 | 1.127 | 0.262 |
| endpoint | 5.04 ± 2.79 | 7.20 ± 2.93 | 3.919 | <0.001 |
| t | 10.236 | 14.203 | | |
| P* | <0.001 | <0.001 | | |
| Perceived control over ejaculation (Mean ± SD) | | | | |
| baseline | 1.34 ± 0.71 | 1.40 ± 0.60 | 0.481 | 0.632 |
| endpoint | 2.34 ± 0.71 | 2.55 ± 0.60 | 1.632 | 0.106 |
| t | 9.280 | 10.017 | | |
| P* | <0.001 | <0.001 | | |
| Achieved one category or greater improvement, N (%) | 39(73.6) | 40(72.4) | 0.010 | 1.000 |
| Personal distress related to ejaculation (Mean ± SD) | | | | |
| baseline | 1.66 ± 0.81 | 1.87 ± 0.66 | 1.242 | 0.217 |
| endpoint | 2.28 ± 0.72 | 2.58 ± 0.63 | 2.304 | 0.023 |
| t | 6.355 | 7.364 | | |
| P* | <0.001 | <0.001 | | |
At study end, a significantly greater percentage of subjects achieved the composite PRO-defined level of clinical benefit with the combination of sertraline and sildenafil (34.5%) versus sertraline monotherapy (15.1%, P<0.05). At the same time, the combination treatment group also achieved a significantly greater percentage of CGIC rating of at least ‘better’ (58.2%) versus the sertraline group (35.8%, P<0.05). The percentages of CGIC rating in the two groups are shown in Figure 3.

Safety

In general, TEAEs were reported by 23.3% in the sertraline group and 31.7% in the combination group. The adverse effects included nausea, headache, dizziness, flushing, ED, sexual desire difficulties, etc. There were no significant differences between the two groups concerning TEAEs (Table 3). On the other hand, all the adverse effects that occurred in this study were mild and tolerated, and gradually disappeared with continued treatment. Nobody in our study dropped out due to side-effects.

Discussion

Due to the absence of causal therapy for PE that target the aetiology, there are no US Food and Drug Administration (FDA) approved treatments for PE, and a lot of treatment options for PE have been used, consisting of behavioural therapies, psychotherapy, topical anaesthetic creams, oral pharmacotherapy, etc.

Among oral pharmacotherapies, SSRIs were considered as the first choice of treatment for PE [19]. Fluoxetine, sertraline, paroxetine, citalopram, etc. have been widely employed in clinical management of PE. Akgül et al. conducted a randomized controlled trial in 80 PE patients with sertraline 50 mg daily or citalopram. After 8 weeks,

Table 2: Outcomes at study endpoint in patients with combination therapy with sertraline and sildenafil versus sertraline monotherapy.

Table 3: Clinical Global Impression of Change (CGIC): Percentages of subjects reporting “no change”, “slightly better”, “better”, or “much better”.

Achieved one category or greater improvement, N (%) 30(56.6) 33(60.0) 0.128 0.845
Achieved one category or greater improvement, N (%) 35(66.0) 50(90.9) 9.962 0.002
Achieved one category or greater improvement, N (%) 28(52.8) 35(63.6) 1.297 0.329

Achieved composite PRO criteria for clinical benefit at end point, N (%) 8(15.1) 19(34.5) 5.446 0.026
Achieved a CGIC rating of at least “better” at end point, N (%) 19(35.8) 32(58.2) 5.401 0.020
The total duration of erection. Possible central mechanisms include: 1) contractile response of the vas deferens, seminal vesicles, and urethra; mechanisms. Possible peripheral mechanisms include: 1) decrease of the 5 inhibitor, has been suggested to be due to central and peripheral to those of previous studies in LPE. The efficacy of sildenafil, a PDE- inhibitors such as sildenafil also had efficacy in the treatment of PE. On the other hand, some research suggested that phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil also had efficacy in the treatment of PE [9,24-26]. Hosseini et al. chose 91 patients with PE who were given 20 mg fluoxetine daily or plus 50 mg sildenafil as needed [26]. IELT were significantly improved in patients treated with combination therapy of fluoxetine plus sildenafil compared with patients taking fluoxetine only. Wang et al. carried out a prospective clinical study in 180 patients with primary PE [9]. Compared with 20 mg paroxetine daily, the squeeze technique, and pretreatment, after 3 or 6 months, patients taking 50 mg sildenafil as needed had significant increases in IELT and intercourse satisfactory score. The results of our study indicated that compared with sertraline monotherapy, combined use of sertraline and sildenafil resulted in statistically significant increases in IELT and PEP measures of APE patients without concomitant diseases. These results are similar to those of previous studies in LPE. The efficacy of sildenafil, a PDE-5 inhibitor, has been suggested to be due to central and peripheral mechanisms. Possible peripheral mechanisms include: 1) decrease of the contractile response of the vas deferens, seminal vesicles, and urethra; alleviation of penile hypersensitivity by inducing peripheral analgesia via activation of the NO/cGMP signalling pathway; 3) prolongation of the total duration of erection. Possible central mechanisms include: 1) a potential role in the central nervous system NO/cGMP pathway in ejaculatory function; and 2) decrease of the central sympathetic output to the periphery [27].

Combined therapy of sertraline and sildenafil was demonstrated to be efficacious in the treatment of APE in patients without concomitant diseases in our study. However, it must be admitted that the use of SSRIs or PDE-5 inhibitors has some adverse effects, such as sexual desire difficulties, delayed ejaculation, anejaculation, absent or delayed orgasm, headache, nausea, dyspepsia, flushing, etc. [28,29]. In our study, some of the patients reported side-effects of nausea, dizziness, etc., and the incidence rate was higher in the combination treatment group than the monotherapy group. However, these side-effects were all mild and tolerated, and gradually disappeared with continued treatment. None of the patients in our study dropped out because of side-effects.

Some limitations and shortcomings of our study should be taken into consideration. Firstly, it was not a placebo-controlled study, so we could not eliminate the effect of placebo. Secondly, this study was a randomised, open-label trial. Although the selection of therapy for patients was randomised, a source of potential bias in the current trial was the lack of double blinding. Thirdly, we used PRO clinical benefit to assess the treatment outcomes which was defined as patients who reported at least a two-category increase in perceived control over ejaculation and at least a one-category increase in personal distress related to ejaculation. However, it was not validated by proper validation studies, Although McMahon et al. used the same approach [16,17]. Fourthly, we used patient or partner reports of IELT to assess mean IELT and not the geometric mean of IELT measured by a stopwatch, which might have had an effect on the results. Fifthly, we chose only subjects with APE but without concomitant diseases, and a further study to evaluate the efficacy and safety of these two therapies should be conducted in patients with comorbidities, since patients with APE are likely to have comorbidities. Besides, only 120 subjects were enrolled into our study and only followed up for 8 weeks, a larger patient sample, long-term follow-up and a placebo-controlled study in men with APE are needed to confirm our results.

Conclusions

Overall, both daily sertraline monotherapy and a combination of on-demand sildenafil and daily sertraline led to significant increases in IELT and PEP measures of APE in patients without concomitant diseases. Although some adverse side-effects were found, they were all tolerated, slight, and gradually disappeared with continued treatment. Both therapies were effective and safe, and the combination therapy had a much higher efficacy than sertraline monotherapy in the treatment of APE. To determine which therapy is the best one in the treatment of APE, a double-blind, placebo-controlled, and multicentre trial with a large number of patients should be performed in future.

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