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Comparison of the clinical efficacy and safety of the on-demand use of paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil in treatment of patients with premature ejaculation: A randomised placebo-controlled clinical trial

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Summary

The aim of the study was to compare the clinical efficacy and safety of the on-demand use of paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil in treatment of patients with premature ejaculation (PE). In a single-blind placebo-controlled clinical study, 150 PE patients without erectile dysfunction (ED) were included during the period of March 2015 to May 2016. Patients were randomly divided into five groups (30 patients each). On demand placebo, paroxetine (30 mg), dapoxetine (30 mg), sildenafil citrate (50 mg) and combined dapoxetine (30 mg) with sildenafil citrate (50 mg) were given for patients for 6 weeks in each group respectively. All patients were instructed to record intravaginal ejaculatory latency time (IELT) and evaluated with Premature Ejaculation Diagnostic Tool (PEDT) and the patient satisfaction score before and after treatment. The mean of IELT, satisfaction score and PEDT in all groups was significantly improved after treatment (p value = .001). Combined dapoxetine with sildenafil group had the best values of IELT, satisfaction scores and PEDT in comparison with other treatment groups (p value <.001). The combined dapoxetine with sildenafil therapy could significantly improve PE patients without ED as compared to paroxetine alone or dapoxetine alone or sildenafil alone with tolerated adverse effects.

KEYWORDS

premature ejaculation, dapoxetine, paroxetine, sildenafil

1 | INTRODUCTION

Premature ejaculation (PE) is the most prevalent sexual disorder in men. PE affects about 30% of the male population (Porst et al., 2007). PE exerts a psychological burden on men, their partners, the male/partner relationship and their overall relationship (Patrick et al., 2005; Rowland, Patrick, Rothman, & Gagnon, 2007). The aetiology of PE has been divided into psychogenic and biogenic factors (Waldinger, 2008). Psychogenic factors include anxiety or conditioning towards rapid ejaculation based on rushed early sexual experiences (Schapiro, 1943). Biogenic factors include hypersensitivity of glans penis (Xin, Choi, Rha, & Choi, 1997), genetic predisposition (Jern et al., 2009), disturbance in central serotonergic neurotransmission (Waldinger, Berendsen, Blok, Olivier, & Holstege, 1998), prostatitis (Screponi et al., 2001), thyroid disorders (Carani et al., 2005) and erectile dysfunction (Jannini, Lombardo, & Lenzi, 2005).

The recommended managements for PE include a behavioural/psychotherapy, a pharmacotherapy and combination of these

treatments. For the pharmacotherapy of PE, the main drugs are selective serotonin reuptake inhibitors (SSRIs) as dapoxetine or paroxetine and phosphodiesterase type-5 inhibitors (PDE5i) as sildenafil and vardenafil (Althof et al., 2014). According to the European Association of Urology guidelines, dapoxetine on demand therapy has been approved for PE in Europe (Hatzimouratidis et al., 2010). Dapoxetine can be effective for both lifelong and acquired PE (Yue, Dong, Hu, & Qu, 2015). However, a recent meta-analysis showed that IELT has been significantly improved with dapoxetine in PE patients but with modest efficacy (Castiglione et al., 2016). Also, the role of sildenafil in PE treatment has been shown in several studies (Gökçe, Halis, Demirtas, & Ekmekcioglu, 2011; Wang, Wang, Minhas, & Ralph, 2007). Therefore, in the current study, we aimed to compare the efficacy and safety of combined dapoxetine with sildenafil therapy for PE patients with paroxetine, dapoxetine and sildenafil alone.

This study was aimed at comparing the clinical efficacy and safety of the on-demand use of paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil in treatment of patients with PE.

2 | MATERIALS AND METHODS

A single-blind placebo-controlled clinical study was conducted on 150 male patients with PE. The patients were selected from those seeking medical advice at the outpatient clinics of Andrology at Sohag University Hospital, Sohag, Egypt, between March 2015 and May 2016. An informed consent was obtained by each patient after full explanation for the nature of the research. All patients were subjected to preliminary assessment including a detailed medical and sexual history, followed by general and genital examination.

Patients were considered to have PE if they fulfilled the criteria of the International Society for Sexual Medicine that defines PE as a male sexual dysfunction characterised by (i) ejaculation which always or nearly always occurs prior to or within 1 min of vaginal penetration, either present from the first sexual experience or following a new bothersome change in ejaculatory latency. (ii) Inability to delay ejaculation on all or nearly all vaginal penetrations. (iii) Negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy (Althof et al., 2014). Other patient inclusion criteria were age ≥20 years old, married and in a stable sexual relationship for at least 3 months before this study.

All patients were evaluated by the International Index of Erectile Function 5 item questionnaires to exclude those with erectile dysfunction (score ≥22) (Rosen, Smith, Lipsky, & Pena, 1999). In addition, patients with history suggestive of one of the following conditions were excluded: (i) diabetes mellitus (DM) (ii) advanced renal or hepatic diseases, (iii) chronic prostatitis, (iv) neurological diseases and (v) C.N.S. medications. Patients who had received medications for PE over the last 3 months prior to enrolment in the study were also excluded.

The sample size was assessed prospectively to provide a 95% power to detect a difference of 80-90s between mean IELT values, PEDT scores and satisfactions scores before and after treatment with an expected change in SD of =90 s, based on previous studies comparing results before and after treatment with different agents and with a significance levels of 0.05.

Patients were randomised equally divided into five groups (30 patients each). The distribution of the patients among the five groups was based on randomised coded cards, so the patients were unaware of the type of the drugs used. Group 1 was given placebo in form oral multivitamin tablet 1 hr before intercourse. Group 2 was given on-demand 30 mg paroxetine 4 hr before intercourse. Group 3 was given on-demand 30 mg dapoxetine 1–2 hr before intercourse. Group 4 was given on-demand 50 mg sildenafil citrate 1 hr before intercourse. Group 5 was given combined on-demand 30 mg dapoxetinewith 50 mg sildenafil citrate 1 hr before intercourse.

All treatments were administered for 6 weeks. All patients were instructed to do sexual intercourse 2–3 times per week.

All patients were evaluated before and after the treatment by Premature Ejaculation Diagnostic Tool (PEDT) (Symonds et al., 2007). The PEDT questionnaires include five questions about inability of ejaculation control, frequency of inability of ejaculation control, ejaculation with minimal simulation, feel of distress and interpersonal difficulty owing to PE. Response to each question is scored on a scale from 0 to 4. PEDT total score of ≥11 was used to define PE. All patients were instructed to record intravaginal ejaculatory latency time (IELT) using stopwatch before and at the end of treatment after full explanation about how to measure the ILET (starting from the time of intromission until ejaculation). Stopwatch was held by the female partner. All patients were asked to indicate their sexual satisfaction before and after treatment on a scale of 0–5 as proposed by Kim and Paick (1999), with 0 being extremely dissatisfied and 5 extremely satisfied. All patients were instructed to record any adverse effects after drug administration.

2.1 | Statistical analysis

Statistical analysis was carried out using Statistical Analysis Software version 16 (SAS Institute, Inc., Cary, NC, USA). Data were normally distributed as it was checked by Shapiro–Wilk test. Therefore, data were expressed as mean ± standard deviation and/or number (percentage) where appropriate. Comparisons of variables within each group before and after treatment were performed using paired *t*-test. One-way ANOVA test was used for comparison between the study groups after treatment. *p*-value of ≤.05 was considered statistically significant.

3 | RESULTS

The age of the included patients ($n = 150$) ranged from 24 to 48 years (34.1 ± 5.85), and the duration of marriage ranged from 2 to 13 years (6.85 ± 3.51). The duration of PE of all patients ranged from 2 to 12 years (5.46 ± 2.7) with the frequency of intercourse per week ranging from 1 to 4 acts per week (2.50 ± 0.7). Before treatment, the IELT (s) ranged from 25 to 60 s (38.9 ± 9.7), the satisfaction score ranged from 0 to 1 (0.95 ± 0.21) and PEDT ranged from 13 to 20 (17.12 ± 2.4). No statistically significant difference was found

TABLE 1 Patients' demographic data

	Placebo (n = 30)	Paroxetine 30 mg (n = 30)	Dapoxetine 30 mg (n = 30)	Sildenafil 50 mg (n = 30)	Dapoxetine 30 mg + Sildenafil 50 mg (n = 30)	p value
Age (years)	34.76 ± 5.8	33.36 ± 5.18	35.0 ± 6.36	32.80 ± 5.48	34.36 ± 6.38	.54
Duration of marriage (years)	7.13 ± 3.36	8.03 ± 4.6	7.08 ± 3.96	6.53 ± 3.35	6.8 ± 3.9	.83
Frequency of sexual intercourse/ week	2.56 ± 0.77	2.46 ± 0.62	2.56 ± 0.77	2.36 ± 0.61	2.56 ± 0.77	.76
PE duration	5.86 ± 3.03	4.53 ± 1.35	5.86 ± 3.22	5.46 ± 2.82	5.56 ± 3.04	.33
IELT before treatment (s)	40.33 ± 8.6	38.66 ± 9.9	38.86 ± 10.35	38.66 ± 9.9	38.33 ± 10.02	.94
Satisfaction score before treatment	0.93 ± 0.25	0.96 ± 0.18	0.96 ± 0.18	0.96 ± 0.18	0.93 ± 0.25	.92
PEDT before treatment	17.26 ± 2.62	17.5 ± 2.43	16.9 ± 2.29	17.33 ± 2.42	16.33 ± 2.28	.63

Data were expressed as mean ± standard deviation. ANOVA test was used for comparison between the study groups. PE, premature ejaculation; IELT, intravaginal ejaculatory latency time; PEDT, premature ejaculation diagnostic tool.

on comparing demographic data of the patients in the five treatment groups (p value >.05) as shown in Table 1.

The current study showed that the means of IELT in paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil groups were significantly higher after treatment (p value = .001). The means of IELT in the placebo group were insignificant after treatment (p value >.05) (Figure 1). The comparison of the means of IELT after treatment in different groups showed that the combined sildenafil with dapoxetine group had significantly higher ILET values than other groups (p value <.001) (Figure 1).

Also, the current study showed that the means of satisfaction score in paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil groups were significantly higher after treatment (p value = .001) (Figure 2). The comparison of the means of satisfaction score after treatment in different groups showed that the combined sildenafil with dapoxetine group had significantly higher satisfaction scores than other groups (p value <.001) (Figure 2).

In addition, the current study showed that the means of PEDT in paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil groups were significantly higher after treatment (p value = .001).

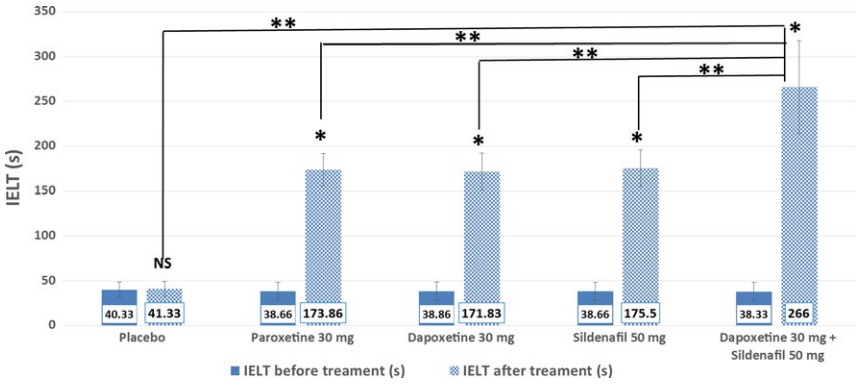

FIGURE 1 Comparison of IELT before and after treatment among study groups. Data were graphed using mean ± standard deviation of each group (n = 30). NS, nonsignificant p value using the paired t-test comparing before and after treatment. *p Value = .001 using the paired t-test comparing before and after treatment. **p Value <.001 using the one-way ANOVA test comparing all groups after treatment

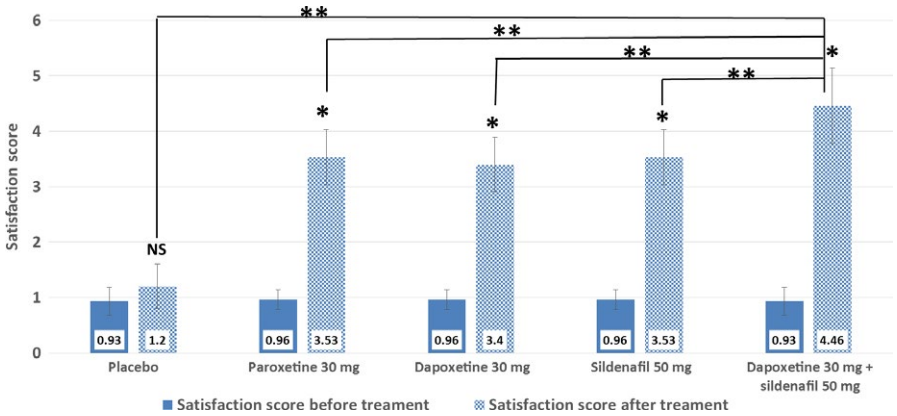

FIGURE 2 Comparison of satisfaction score before and after treatment among study groups. Data were graphed using mean ± standard deviation of each group (n = 30). NS, nonsignificant p value using the paired t-test comparing before and after treatment. *p Value = .001 using the paired t-test comparing before and after treatment. **p Value <.001 using the one-way ANOVA test comparing all groups after treatment

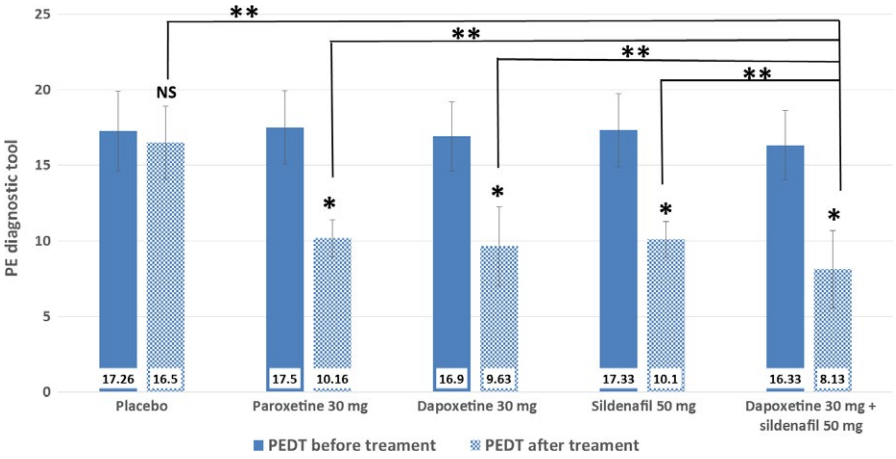

FIGURE 3 Comparison of Premature Ejaculation Diagnostic Tool before and after treatment among study groups. Data were graphed using mean ± standard deviation of each group (n = 30). NS, nonsignificant p value using the paired t-test comparing before and after treatment. *p Value = .001 using the paired t-test comparing before and after treatment. **p Value <.001 using the one-way ANOVA test comparing all groups after treatment

The means of PEDT in placebo group were insignificant after treatment (p value >.05) (Figure 3). The comparison of the means of PEDT after treatment in different groups showed that the combined sildenafil with dapoxetine group had significantly higher PEDT values than other groups (p value <.001) (Figure 3).

All treatments were well tolerated by all patients. The most adverse effects in different groups were constipation (placebo), sleep disturbance (paroxetine), nausea (dapoxetine), headache (sildenafil) and headache and nausea (combined dapoxetine with sildenafil). (Table 2).

4 | DISCUSSION

The recommended management of PE include behavioural/psychotherapy, drug therapy and/or combination of them. For PE drug therapy, SSRIs are still considered the gold standard treatment (Althof et al., 2014; Hisasue, 2016). This study aimed to compare the clinical efficacy and safety of the on-demand use of paroxetine, dapoxetine, sildenafil and combined dapoxetine with sildenafil in treatment of patients with PE. The current study shows that combined dapoxetine and sildenafil therapy for PE patients without ED could significantly increase the patients IELT and satisfaction score with decrease in PEDT as compared to paroxetine alone, dapoxetine alone or sildenafil alone. The better efficacy of the combined dapoxetine and sildenafil in the current study is supported by several studies. In a multicentre randomised controlled study, combined intake of dapoxetine and mirodenafil showed improvement of IELT, premature ejaculation profile and overall sexual act time, with similar adverse effects in comparison with dapoxetine only (Lee et al., 2013). Another study using the combination of fluoxetine and tadalafil showed a significant increased IELT in comparison with fluoxetine alone or tadalafil alone (Mattos, Marmo Lucon, & Srougi, 2008). These findings suggest that PDE5i could contribute to treatment of PE patients without ED.

In addition, analysis of the patients IELT, satisfactions score and PEDT in paroxetine alone, dapoxetine alone and sildenafil alone groups demonstrated their efficacy as a good option for PE therapy. Several studies in the literature support the different SSRI efficacy in the treatment of PE including paroxetine (Rivera, González, González, & Storme, 2005; Gameel et al., 2013; Simsek et al., 2014) and dapoxetine (Feige, Pinsky, & Hellstrom, 2011; Kaufman et al., 2009; McMahon, 2010; Pryor et al., 2006).

Dapoxetine has the advantage of being taken on demand due to rapid action in comparison with other SSRIs that should be taken daily

TABLE 2 Adverse effects among study groups during the treatment period

	Placebo (n = 30)	Paroxetine 30 mg (n = 30)	Dapoxetine 30 mg (n = 30)	Sildenafil 50 mg (n = 30)	Dapoxetine 30 mg + Sildenafil 50 mg (n = 30)
Headache	0	5 (16.7%)	2 (6.6%)	8 (26.6%)	10 (33.3%)
Flushing	0	0	0	5 (16.7%)	6 (20%)
Nasal congestion	0	0	0	7 (23.3%)	7 (23.3%)
Fatigue	0	2 (6.6%)	3 (10%)	5 (16.7%)	5 (16.7%)
Nausea	0	8 (26.6%)	8 (26.6%)	3 (10%)	10 (33.3%)
Vomiting	0	1 (3.3%)	0	1 (3.3%)	2 (6.6%)
Constipation	4 (13.3%)	0	0	0	0
Dizziness	0	5 (16.7%)	3 (10%)	2 (6.6%)	4 (13.3%)
Sleep disturbance	0	9 (30%)	4 (13.3%)	0	4 (13.3%)
Yawing	0	7 (23.3%)	5 (16.7%)	0	5 (16.7%)

Data were expressed as n (%).

(Hellstrom, 2009). Some PE patients prefer daily therapy to preserve their capabilities of initiating spontaneous sexual relations (Waldinger, Zwinderman, Olivier, & Schweitzer, 2007). Although daily dose of SSRIs has been shown to have better increase in IELT in comparison with on-demand dose, the on-demand dose can achieve satisfactory results in many patients (McMahon, 2016). A recent evidence-based review demonstrated the better efficacy and safety of the on-demand dapoxetine in PE treatment, improving not only the quality of life for patients but also their sexual partner (Russo et al., 2016). Also, dapoxetine could reduce PE associated with personal and interpersonal difficulties (Kaufman et al., 2009).

Although the combined dapoxetine with sildenafil showed better results in PE patients without ED in comparison with other groups in the current study, it has been suggested that administration of PDE5i alone or combined with SSRIs is better for patients having acquired PE secondary to ED (McMahon, 2016). Several studies showed the efficacy of PDE5i in the treatment of PE including sildenafil (Wang et al., 2007; Gökçe et al., 2011; Gameel et al., 2013).

Several mechanisms have been proposed for the role of PDE5i in PE therapy including central and peripheral actions (Aversa et al., 2011). PDE5i could act mainly as a relaxant for the smooth muscles of the vas deferens and seminal vesicle, prostate and urethra (Abdel-Hamid, 2004). Other possible actions include suppressing the central sympathetic tone, prolonging erection with improvement of the overall intercourse satisfaction (Aversa et al., 2011). Therefore, concomitant administration of dapoxetine and PDE5i in PE patients with ED is associated with better efficacy (McMahon et al., 2013).

The commonest adverse effects in the current study are associated with the combined dapoxetine and sildenafil group in the form of headache and nausea. This is consistent with the literature showing that dapoxetine is a well-tolerated treatment modality of PE (Yang et al., 2015). It has a better safety and compliance in comparison with other SSRIs. The most common side effects associated with dapoxetine include gastrointestinal upset (nausea, diarrhoea), dizziness and headache with rare serious side effects (Kaufman et al., 2009; Zhou & Li, 2015). Moreover, the combined intake of dapoxetine and sildenafil does not affect the pharmacokinetics of each other. The combined intake of dapoxetine (60 mg) and sildenafil (100 mg) did not show any significant clinical effects on dapoxetine pharmacokinetics. In the same context, dapoxetine did not change the sildenafil pharmacokinetics. These findings could show that this combination is well tolerated and support its use (Dresser, Desai, Gidwani, Seftel, & Modi, 2006). Also, a recent pharmacokinetic study demonstrated no clinically significant interactions between dapoxetine (60 mg) and udenafil (200 mg) (Kim et al., 2015).

Although dapoxetine has been considered as an approved treatment of PE, this does not imply that dapoxetine has a higher efficacy than other SSRIs, but this implies that dapoxetine has got a greater chance to be investigated in better designed clinical studies (Castiglione et al., 2016). In addition, the long-term effects of dapoxetine on reproductive functions should be cleared as some recent data demonstrated a negative impact on fertility (ElMazoudy, AbdelHameed, & ElMasry, 2015).

The current study has several limitations. The sample size was limited as several groups were recruited. In addition, the patients were not followed up after discontinuation of therapy in all groups. Also, a multivitamin tablet was used as a placebo because it is well established to be ineffective in treatment of PE, but it is better to use a tablet of starch as placebo. In addition, the PEDT questionnaire was translated into Arabic language for PE patient's evaluation; however, this Arabic version is not validated yet. A larger sample-sized study with long-term follow is recommended. Also, assessment of female satisfaction before and after treatment of males with PE should be included in further studies.

This study concluded that the combined dapoxetine and sildenafil therapy for PE patients without ED could increase the patients IELT and satisfaction score with decrease of PEDT as compared to paroxetine alone or dapoxetine alone or sildenafil alone.

CONFLICT OF INTEREST

There is no conflict of interest.

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