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Original Article

Comparative study of on-demand and daily use of sertraline in treatment of premature ejaculation: A randomized clinical trial

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KEYWORDS
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Abstract *Objective:* The intravaginal ejaculatory latency time (IELT) may increase less in on-demand compared to daily intake, but may fulfill a suitable treatment for specific patients. We decided to compare the efficacy and safety of on-demand and daily use of sertraline in order to find the most effective and least complicated method in treatment of premature ejaculation (PE).

Methods: This study was parallel or concurrent control randomized clinical trial. Two hundred and forty patients with PE diagnosed by urologist in the two groups of 120 from July 2017 to February 2019 enrolled in the study. In the first group, it is prescribed 50 mg sertraline each 12 h daily and the second group received 50 mg 4 h before coitus for 4 and 8 weeks. The IELT before treatment and during all coitus after treatment were recorded by the patient's wife with a stopwatch.

Results: Mean IELT before, 4 and 8 weeks after treatment in two groups were: On-demand group 101.62±65.44 s, 208.75±128.02 s and 265.87±145.70 s; daily use group 102.50±81.22 s, 276.87±181.08 s and 353.75±176.45 s, respectively. The ejaculation time increased significantly in both groups ($p<0.05$). However, increase in ejaculation time in daily use group was significantly higher than the on-demand group in 4 weeks ($p=0.036$), especially in 8 weeks ($p=0.009$). The percent of side effects in daily use group (26.7%) was higher than on-demand group (20%) ($p<0.05$). Drowsiness, diarrhea and vertigo were significantly higher in the daily use than on-demand ($p<0.05$).

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Conclusions: On-demand and daily use of sertraline are effective and usually have no serious complications, but the on-demand method is considerably more tolerable. In patients who did not tolerate to daily use of this drug, on-demand could be used as a salvage therapy.

1. Introduction

About one third of men suffer from premature ejaculation (PE). The most common type of sexual dysfunction in men is PE [1]. No standard time is defined for ejaculation. On the basis of the report of the second international society for sexual medicine (ISSM) for the definition of PE: (1) Lifelong PE is defined ejaculation that in all or most of time occurs in less than 1 min of vaginal penetration from the first sexual experience and acquired PE is a clinically notable and troublesome decrement in latency time, often to less than 3 min; (2) in all or nearly all vaginal penetrations, the patients have no ability to delay ejaculation; and (3) it leads to distress, bother, disappointment, behavioral disorders or the avoidance of confidence sexual relationship and other negative personal issue [2]. Men with acquired PE are older, and have cardiovascular disorders, comorbid illness and erectile dysfunction [3]. Shorter intravaginal ejaculatory latency time (IELT) causes more problems. Therefore, it is very important to diagnose and cure this problem [4].

In the past, PE treatment was limited to behavioral therapy that expanded into drug therapies over time due to knowledge about the role of serotonin in the central nervous system in controlling ejaculation [5]. In patients with PE, the dopamine pathway have a significant disorder especially in bilateral middle temporal gyrus, caudate, left orbitofrontal cortex and thalamus [6]. Kilinc et al. [7] had shown that physical activity increases serotonin level. They believed that men with physical activity at least 30 min per day had better IELT. Yildiz et al. [8] also believed that men with regular physical activity had longer ejaculation time. Nowadays there are several types of treatment for this problem, many of which are commercial drugs that are not confirmed by the World Health Organization and Ministry of Health. The drugs used for treatment of PE are divided into two groups including topical anesthetics and oral medications which are prescribed with regard to the patients' conditions [9]. Today, the most common drugs used to treat PE are selective serotonin reuptake inhibitors (SSRIs) including citalopram, flouxetine, sertraline, paroxetine and dapoxitene. Other drugs, such as tramadol and phosphodiestrase type 5 inhibitors (PDE5Is) and antidepressant are also used. PDE5Is are recommended in PE when accompanied with erectile dysfunction [10]. There is, however, no consensus and agreement on the type, dose, duration of treatment and side effects. Different results have been obtained from previous studies, and this is shown the importance of further investigations to achieve more definite and conclusive results [11].

The most side effects of these drugs are nausea, headache, anxiety, uneasiness, insomnia, and sexual dysfunction. The deprivation syndrome has also been described for SSRIs that might cause nausea, dizziness, anxiety, trembling, and heartbeat. The selective SSRIs are the inhibitors of liver cytochrome P450 enzymes and this leads to the increase in activities of other drugs including tricyclic antidepressants and warfarin [12].

Drugs are prescribed in two ways: Daily intake and on-demand. The IELT may increase less in on-demand compared to daily intake, but may fulfill a suitable treatment for specific patients. On-demand consumption of these drugs has been underestimated and limited studies have been carried out this therapeutic method [13]. On-demand dapoxetine have been introduced as drug of choice for treatment of PE but in clinical practice, drugs are chosen based on the availability of that drug in the country. Although dapoxetine is also found in Iran, due to its cost issue and limited distribution, the currently available drugs such as sertraline are commonly used. Therefore we decided to evaluate, outline and compare the efficacy and safety of two medicinal procedures of sertraline (on-demand and daily use) in order to find the most effective and least complicated method in treatment of PE.

2. Patients and methods

2.1. Study populations

This study was parallel or concurrent control randomized clinical trial without quasi drug group and blinding. The study population included 240 patients with PE (no advertisement/no incentive) who referred to Imam Reza hospital Tehran, Iran from July 2017 to February 2019. The sampling method was convenient. By reviewing the previous studies and using Altman's monogram, power 80% and standardized difference 80%, $\alpha=5\%$, 98 men were considered for each group. Also by using formula, $n=\frac{2\left(Z1-\frac{\alpha}{2}+Z1-\beta\right)^2\sigma^2}{d^2}$, $\sigma=2.52$, $\beta=20\%$, $\alpha=5\%$ and d=1, 99 participants were considered for each group. With dropout 20%, a total of 240 men were included for this study. During the study there was not dropout due to loss of follow-up and complication. Finally 240 patients completed the study and analyzed.

Patients were evaluated by an urologist and, if they had PE according to the definition of ISSM, they would be enrolled in the study. Randomization method in this research was simple randomization. Randomization unit was individual and patients' randomization was done by computerized random numbers. The starting point was completely random (selecting a number on the table with closed eyes) and the direction of movement in the table was selected to the

bottom. The patients were randomly assigned to one of the two study groups (each group consisted of 120 men) using the random numbers table and received the relevant intervention by urologist. Inclusion criteria were male with PE, possible at least once coitus a week and age between 20 and 65 years. Exclusion criteria were neurologic disorder, psychological disorder, age less than 20 and over 65 years, urinary and genital infection and history of pelvic surgery, diabetes, alcohol and drug abuse [Fig. 1].

2.2. Intervention groups

In the first group, it is prescribed 50 mg sertraline (Abidi-Tehran Pharmaceutical Company, Tehran, Iran) each 12 h daily and the second group received 50 mg 4 h before coitus for 8 weeks. Finally, the time of ejaculation before treatment (arithmetic mean time in at least three coitus) and during all coitus without condom after treatment were accurately measured and recorded by the patient's wife with a calibrated stopwatch. Patients are advised to record time from vaginal entrance to ejaculation. The participants took the normal life and recorded the information and presented the results to the clinic.

2.3. Main outcome measures

Main outcome measure used in this study was IELT and efficacy and side effects of sertraline for PE.

2.4. Statistical analyses

Data analyses were performed by SPSS statistical software version 24 (IBM Company, Chicago, USA). For qualitative variables, frequency and percent and for quantitative variables mean and standard deviations were calculated. The paired sample *t*-test was used for evaluation of IELT before, 4 and 8 weeks after treatment in each group and the Pearson correlation coefficient test was used for the evaluation of the IELT between two groups. Chi-square test was used to evaluate the side effects. A p-Value <0.05 was considered significance.

2.5. Ethical considerations

In all stages of the study, ethical issues of observation and the name and information of patients were kept confidential. Informed consents were obtained from all subjects. The ethics committee of Army University of Medical Sciences approved research project of this study (Reg No: IR.AJAUMS.REC.1396.111).

2.6. Clinical trial registrations

This study approved in Iranian Registry of Clinical Trials (IRCT ID: IRCT20180401039167N1).

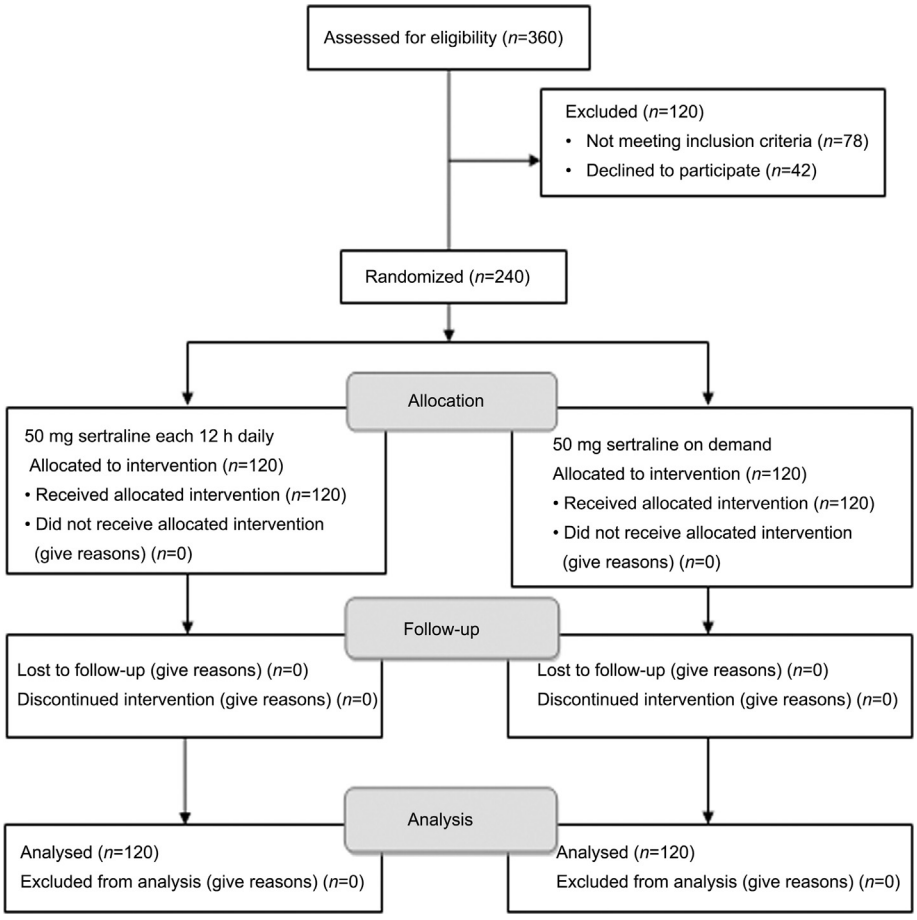

Figure 1 Flow diagram of the study.

3. Results

In this study, 240 patients with mean age of 36.5 years with SD of 11.41 years were studied. Mean age in daily use was 37.56±10.63 years and in on-demand group was 35.39±9.96 years. The mean age of the patients was match in two groups. Academic education in daily and on-demand group was 47.9% and 45.9%, respectively. The mean number of coitus per week in two groups was 1.64. All patients were matched for education level and coitus number. Eighty two and a half percent of daily use group and 81% in on-demand group were married. Mean IELT before, 4 and 8 weeks after treatment in two groups were: In on-demand group 101.62±65.44 s, 208.75±128.02 s and 265.87±145.70 s; in daily use group 102.50±81.22 s, 276.87±181.08 s and 353.75±176.45 s, respectively. Overall, the frequency of response to treatment in two groups was as follow: On-demand 82.5% and in daily use 91.8%. There was no significant difference between the two groups in the time of ejaculation before treatment ($p=0.954$). As it was seen, the ejaculation time increased significantly in both groups ($p<0.05$) (Table 1). However, increase in ejaculation time in daily use group was significantly higher than the on-demand group ($p=0.036$), especially 8 weeks after treatment ($p=0.009$) (Table 2). The percent of side effects in daily use group was higher than on-demand group. Frequency of side effects in two groups was: On-demand 20%, and each 12 h daily 26.7%. There was significant difference in drugs side effects between groups ($p<0.05$). The most common side effects were drowsiness and fatigue. Drowsiness, diarrhea and vertigo were significantly higher in the daily use than on- demand ($p<0.05$) (Table 3). It should be noted that none of the side effects of the drugs were severe that caused it to be discontinued.

4. Discussion

The IELT may increase less in on-demand compared to daily intake, but may fulfill a suitable treatment for specific patients [13]. On-demand consumption of these drugs has been underestimated and limited studies have been carried out this therapeutic method [14]. Therefore we decided to evaluate, outline and compare the efficacy and safety of two medicinal procedures of sertraline (on-demand and daily use) in order to find the most effective and least complicated method in treatment of PE.

In the current study the response rate to treatment in two groups was on-demand 82.5% and in daily use 91.8%. The ejaculation time increased significantly in both groups ($p<0.05$). However, increase in ejaculation time in daily use group was significantly higher than the on-demand group ($p=0.036$), especially 8 weeks after treatment ($p=0.009$).

Another finding of this study showed that the side effects in two groups were significantly different ($p<0.05$). The frequency of side effects in daily use group (26.7%) was higher than on-demand group (20.0%). The most common side effects were drowsiness and fatigue. Drowsiness, diarrhea and vertigo were significantly higher in the daily use than on-demand ($p<0.05$). Also, this study showed that none of the side effects of the drugs were severe that caused it to be discontinued.

Rezakhaniha and Siroosbakhat [15] studied the effect of citalopram in PE (63 patients received citalopram 40 mg in daily and 50 patients 20 mg on-demand). This study showed that both methods were effective but daily use has been more effective. The side effects were 15% in on-demand and 34% in daily. In our study, 240 patients were evaluated in two groups and the rate of side effects in on-demand and daily use was 20.0% and 26.7%, respectively.

In another study, 43 patients received flouxetine and 34 patients received citalopram daily for 4 weeks, both of which were effective in increasing the IELT. In this study, adverse effects were not studied [16]. However, in our study, 240 patients were studied for 8 weeks, and rate of side effect was also assessed in each group separately. In practice, the study of adverse effect is an important part of the evaluation of treatment for PE [17]. Dadfar and Baghinia [18] reported that citalopram can be used in

Table 1 Statistical analysis of both methods of sertraline in treatment of premature ejaculation*.

Method	Group	Ejaculation time, mean	Number	*p*-Value
On-demand[a]	Pair 1	Before treatment, t=101.62 s 4 weeks later, t=208.75	120	0.000
	Pair 2	Before treatment, t=101.62 s 8 weeks later, t=265.87 s	120	0.000
	Pair 3	4 weeks later, t=208.75 s 8 weeks later, t=265.87 s	120	0.000
Daily use[b]	Pair 1	Before treatment, t=102.50 s 4 weeks later, t=276.87 s	120	0.000
	Pair 2	Before treatment, t=102.50 s 8 weeks later, t=353.75 s	120	0.000
	Pair 3	4 weeks later, t=276.87 s 8 weeks later, t=353.75 s	120	0.000

*The ejaculation time increased significantly in both methods ($p<0.05$).
[a] Fifty mg sertraline 4 h before coitus.
[b] Fifty mg sertraline each 12 h daily.

Table 2 Comparison of ejaculation time before, 4 and 8 weeks after treatment in on-demand and daily use of sertraline.

Ejaculation time	Groups	Number	Mean, s	Standard Deviation, s	*p*-Value
Before treatment	On-demand	120	101.62	65.44	0.954*
	Daily use	120	102.50	81.22	
4 weeks later	On-demand	120	208.75	128.02	0.036†
	Daily use	120	276.87	181.08	
8 weeks later	On-demand	120	265.87	145.70	0.009†
	Daily use	120	353.75	176.45	

*There was no significant difference between the two groups in the time of ejaculation before treatment ($p=0.954$).
†The ejaculation time increased significantly in both groups ($p<0.05$). However, increase in ejaculation time in daily use was significantly higher than the on-demand ($p=0.036$), especially 8 weeks after treatment ($p=0.009$).

Table 3 Side effects in four groups.[a]

Side effects	On-demand	Each 12 h daily	*p*-Value
Insomnia	2	2	0.64
Drowsiness[b]	6	10	0.04
Dyspepsia	2	2	0.61
Diarrhea	—	3	0.05
nausea	2	2	0.61
Loss of appetite	1	1	0.72
Fatigue[b]	7	8	0.77
Headache	1	1	0.72
Vertigo	1	2	0.05
Anexity	1	1	0.72
Urinary retention	—	—	—
Loss of sexual desire	—	—	—

—, none.
[a] Number of patients.
[b] The most common side effects were drowsiness and fatigue. It should be noted that none of the side effects of the drugs were severe that caused it to be discontinued.

patients who did not respond to flouxetine as a salvage drug. According to their results, patients who do not respond well to a drug can use other drugs of SSRI.

Rezakhaniha and Khoshdel [19] in a study on 49 patients, confirmed that flouxetine was effective in increasing the IELT in both methods, daily and on-demand. The complication of daily intake was 44.9% and in on-demand 12.8%. However, in our research, adverse effects of sertraline in daily use and on demand were 26.7% and 20.0%, respectively. The cause of the higher incidence of side effects in daily use of flouxetine may be due to its active metabolite with the mean life of a few days, which is not seen in others. Sertraline, citalopram, and paroxetine do not make long-effect metabolites.

Sertraline is associated with a significantly higher rate of diarrhea than other SSRIs [20]. Our study showed that diarrhea was not observed in on-demand method but it was seen significantly in daily use (three patients).

Although on-demand dapoxetine have been introduced as drug of choice for treatment of PE that has short half life (1.5 h) and low bioavailability (42%), in clinical practice, drugs are chosen based on the availability of that drug in the country. In Iran, other SSRIs are available. Although dapoxetine is also found in Iran, due to its cost issue and limited distribution, the currently available drugs such as citalopram and flouxetine, sertraline and paroxetine are commonly used. These drugs are achieving maximal concentration in plasma (T_{max}) 4 h, 6—8 h, 4—6 h and 6—10 h, respectively [21]. With considering the T_{max} of these drugs, it seems that on-demand use of citalopram and sertraline may be more effective and safe in the treatment of PE than other SSRIs.

The limitations of our study were lack of consideration of extramarital and marital sexual behavior, body mass index, body fat percentage and PE diagnostic tool (PEDT). The duration of marriage and extramarital sexual behavior were not included because the participants were reluctant to response to the onset of coitus or extramarital and marital sexual behavior with respect to their privacy. Another limitation of the study was the use of arithmetic mean IELT. Waldinger and Schweitzer [22] have recommended the use of geometric method to avoid overestimation of treatment efficacy. Therefore, it is suggested that prospective studies be carried out with consideration of those.

5. Conclusion

According to the finding of this study, on-demand and daily use of sertraline are effective and usually have no serious complications, but the on-demand method is considerably more tolerable. In patients who did not tolerate to daily use of this drug, on-demand could be used as a salvage therapy.

Author contributions

Study concept and design: Bijan Rezakhaniha, Soheila Siroosbakht.
Data acquisition: Soheila Siroosbakht.
Data analysis: Soheila Siroosbakht.
Drafting of manuscript: Soheila Siroosbakht, Sadra Rezakhaniha.
Critical revision of the manuscript: Sadra Rezakhaniha.

Conflicts of interest

The authors declare no conflict of interest.

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References

[1] Symonds T, Roblin D, Hart K, Althof S. How does premature ejaculation impact a man s life? J Sex Marital Ther 2003;29:361—70.
[2] Serefoglu EC, McMahon CG, Waldinger MD, Althof SE, Shindel A, Adaikan G, et al. An evidence-based unified definition of lifelong and acquired premature ejaculation: report of the second international society for sexual medicine ad hoc committee for the definition of premature ejaculation. J Sex Med 2014;11:1423—41.
[3] McMahon CG, Porst H. Oral agents for the treatment of premature ejaculation: review of efficacy and safety in the context of the recent International Society for Sexual Medicine criteria for lifelong premature ejaculation. J Sex Med 2011;8:2707—25.
[4] Zargooshi J. Premature ejaculation: bother and intravaginal ejaculatory latency time in Iran. J Sex Med 2009;6:3478—89.
[5] Waldinger MD. Emerging drugs for premature ejaculation. Expert Opin Emerg Drugs 2006;11:99—109.
[6] Lu J, Zhang X, Wang H, Qing Z, Qing Z, Han P, et al. Short- and long-range synergism disorders in lifelong premature ejaculation evaluated using the functional connectivity density and network property. Neuroimage Clin 2018;21:607—15.
[7] Kilinc MF, Aydogmus Y, Yildiz Y, Doluoglu OG. Impact of physical activity on patient self-reported outcomes of lifelong premature ejaculation patients: results of a prospective, randomised, sham-controlled trial. Andrologia 2018;50: e12799. https://doi.org/10.1111/and.12799.
[8] Yildiz Y, Kilinc MF, Doluoglu OG. Is there any association between regular physical activity and ejaculation time? Urol J 2018;15:285—9.
[9] Kendirci M, Salem E, Hellstrom WJ. Dapoxetine, a novel selective serotonin transport inhibitor for the treatment of premature ejaculation. Ther Clin Risk Manag 2007;3:277—89.
[10] Safarinejad MR, Hosseini SY. Safety and efficacy of citalopram in the treatment of premature ejaculation: a double-blind placebo-controlled, fixed dose, randomized study. Int J Impot Res 2006;18:164—9.
[11] Hisasue S. The drug treatment of premature ejaculation. Transl Androl Urol 2016;5:482—6.
[12] Wang WF, Chang L, Minhas S, Ralph DJ. Selective serotonin reuptake inhibitors in the treatment of premature ejaculation. Chin Med J 2007;120:1000—6.
[13] Castiglione F, Albersen M, Hedlund P, Gratzke C, Salonia A, Giuliano F. Current pharmacological management of premature ejaculation: a systematic review and meta-analysis. Eur Urol 2016;69:904—16.
[14] Montejo AL, Montejo L, Baldwin DS. The impact of severe mental disorders and psychotropic medications on sexual health and its implications for clinical management. World Psychiatry 2018;17:3—11.
[15] Rezakhaniha B, Siroosbakhat S. Comparative study of therapeutic effects of two medicinal procedures of citalopram in premature ejaculation. Biosci Biotech Res Asia 2014;11: 953—8.
[16] Rezakhaniha B, Sirosbakht S. Efficacy of selective serotonin reuptake inhibitor (SSRI) in patient with premature ejaculation. IJRM 2010;8:55—9.
[17] Gur S, Sikka SC. The characterization, current medications, and promising therapeutics targets for premature ejaculation. Andrology 2015;3:424—42.
[18] Dadfar MR, Baghinia MR. Salvage use of citalopram for treatment of fluoxetine-resistant premature ejaculation in recently married men. A prospective clinical trial. Urol J 2010; 7:40—4.
[19] Rezakhaniha B, Khoshdel AR. Comparative study of therapeutic effects of two medicinal procedures of fluoxetine in premature ejaculation. JAUMS 2011;8:299—304.
[20] Abourehab MA, Ahmed OA, Balata GF, Almalki WH. Self-assembled biodegradable polymeric micelles to improve dapoxetine delivery across the blood-brain barrier. Int J Nanomed 2018;13:3679—87.
[21] Li J, Liu D, Wu J, Fan X, Dong Q. Dapoxetine for the treatment of premature ejaculation: a meta-analysis of randomized controlled trials with trial sequential analysis. Ann Saudi Med 2018;38:366—75.
[22] Waldinger MD, Schweitzer DH. Premature ejaculation and pharmaceutical company-based medicine: the dapoxetine case. J Sex Med 2008;5:966—97.