Tramadol Use in Premature Ejaculation: Daily Versus Sporadic Treatment

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ABSTRACT

Aim: Premature ejaculation (PME) is defined as ejaculation with the minimal sexual stimulation before, on or shortly after penetration and or before a person wishes it. It is a function of the time between intra-vaginal penetration and intra-vaginal ejaculation. Tramadol has shown efficacy in PME when used as sporadic basis. In this study, we compared the use of 100 mg of tramadol as sporadic treatment (administered 6-8 h before coitus) versus continued treatment with the objective of evaluating the therapeutic results of both modalities. We assumed our alternative hypothesis that they have similar effects. Materials and Methods: A prospective study was carried out on 60 patients divided into two groups of 30 patients each. Intra-vaginal ejaculation latency time (IELT) and coital frequency were measured both prior to and after the treatment. Group A received tramadol 100 mg daily for 4 weeks and on request (sporadically) for 4 weeks more. Group B was given placebo in the same manner. Results were statistically analyzed using the Student t-test. Results: Mean IELT prior to treatment was 59.2 s in Group A and 58.7 s in Group B. Mean pre-treatment coital frequency was 2.44 times/week for Group A and 2.13 times/week for Group B. Mean IELT was 202.5 s after continued tramadol treatment and 238.2 s after sporadic treatment in Group A. Mean IELT with daily placebo was 94.8 s and with sporadic placebo was 96.6 s. Coital frequency increased to 4.32 times/week with daily tramadol treatment and 4.86 times with sporadic treatment. Coital frequency increased to 2.88 times/week with daily placebo treatment and 3.23 times with sporadic treatment. Conclusions: The results of PME treatment with tramadol are similar with both continued and sporadic administration. The sex life of patients improved and they reported greater satisfaction with the sporadic treatment.

Key words: Intra-vaginal ejaculatory latency time, premature ejaculation, tramadol

INTRODUCTION

Premature ejaculation (PME) is one of the most common male sexual dysfunction. Prevalence PME has been estimated between 2% and 23%.[1,2] PME is markedly associated with poor satisfaction with sexual intercourse and high-levels of personal distress and interpersonal difficulty.[3] There are many definitions and guidelines of PME such as the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV-TR);[3] the International Consultation on Urological Disease;[4] and the American Urological Association guidelines.[5] All of these definitions include three main qualifications: Short time interval between penetration and ejaculation; little or no voluntary control of ejaculation; and negative consequences, like distress.[6]

The current definition of PME is based on intra-vaginal ejaculation latency time (IELT) which is measured as the time between intra-vaginal penetrations to intra-vaginal ejaculation by using stopwatch method.
Operation criteria provided by the American Psychiatric Association is the accepted guide. Diagnosis of this condition is made when: (a) There is a persistent problem of minimal sexual stimulation before or after ejaculation, (b) This problem causes anxiety in the patient that is not a side effect of any medication or substance, and (c) IELT is less than 1 min.\[4\]

There are several treatment options available for PME such as topical agents, creams, sprays, and systemic therapies. On-demand tramadol hydrochloride (HCl) has shown promise in the treatment of PME.\[7\] One small placebo-controlled study reported that tramadol HCl significantly increased IELT compared with placebo.\[8\] Tramadol HCl was initially developed in the 1970s and approved by the US Food and Drug Administration as an analgesic and has an excellent safety record established over >30 year of human use.\[9\]

The mechanism by which tramadol delays ejaculation has not been identified; numerous laboratory studies have shown that tramadol acts as a mild mu-opioid agonist, 5-hydroxytryptamine (5-HT2C) receptor antagonist, and a serotonin and norepinephrine modulator. It is possible that one or a combination of these effects leads to a delay in ejaculation.\[10\]

**AIM**

To compare the effect of daily and sporadic treatment of PME with tramadol.

**MATERIALS AND METHODS**

After obtaining approval of the local Ethics Committee, a clinical trial was carried out from March to July 2011 on out-patients from the psycho-sexual clinic, Department of Psychiatry at the Nehru Hospital, BRD Medical College, Gorakhpur, UP.

Patients who fit the following criteria were included in the study:

a. Male
b. 20-45 years of age
c. Healthy (not presenting with major physical illness such as type 2 diabetes mellitus, high blood pressure, sexually transmitted diseases, or psychiatric illnesses)
d. Not taking medication such as benzodiazepines, drugs to relieve anxiety, sleep-inducing drugs
e. In an emotionally stable relationship
f. Not using barrier contraception methods
g. Strict stopwatch use during coitus (patients were taught how to use stopwatch in their mobile phone).

All participants were informed and written consents were taken. All men were heterosexual; sexually active; in an ongoing, stable, sexual relationship for at least 3 months; and had no other sexual disorders, including erectile dysfunction (ED) as determined by the international index of erectile function questionnaire. Patients with chronic psychiatric or systemic diseases, such as diabetes mellitus; with hypertension; with alcohol or substance abuse; or who used any medications were excluded. Urinalysis and urine cultures were performed routinely to exclude urinary infections.

IELT, DSM-IV TR criteria, and the premature ejaculation diagnostic tool were used to assess PME before and after treatment. IELTs before and after treatment were calculated by using a partner-held stopwatch.

Patients who did not abide to strict stopwatch use during coitus, who changed their sexual partner or whose partner did not agree to participate in the study and patients who did not tolerate the side-effects of tramadol were excluded from the study. All patients signed letters of informed consent.

A total of 60 patients were randomly distributed into two groups (30 each). Group A patients were given 100 mg daily of tramadol for 4 weeks and then on request every 2 or 8 h before sexual contact for next 4 weeks. Group B patients were given a placebo tablet for 4 weeks then a placebo on request 2 or 8 h prior to sexual contact for next 4 weeks.

Subjects were instructed to take study medication 2-8 h before engaging in vaginal intercourse, with an interval between sexual intercourse events of at least 20 h to ensure wash-out of the drug and its effect. Female partners were instructed to time the IELT for each event by using the stopwatch (mobile phone stopwatch application) and recording the time in a study diary. Subjects were assessed after 4 and 8 weeks and their IELT, premature ejaculation profile (PEP) scores, vital signs, and Adverse Events were recorded. Patients were interrogated as to their coitus average/week and the degree of satisfaction in relation to medication administration (daily versus sporadic). Data were analyzed with descriptive tests and data inference analysis was obtained using the Student t-test.

**RESULTS**

The mean ages of the groups were similar: 37.5 year (range 28-45) and 38.3 year (range 28-45) in the tramadol, and placebo groups, respectively. The majority of the participants (90% (34 of 60)) were married.
The frequency of sexual intercourse and the characteristics of PE are shown in Table 1. The majority of the subjects (68.3% (41 of 60)) had life-long PE. 71.6% of the men reported ejaculation time as shortly after penetration, 18.3% men had ejaculation time at penetration, 3.3% men had ejaculation time with a very little stimulation, and 6.6% men had ejaculation time before penetration. 55% (33 of 60) men had sex frequency of 2-3 times/week (60% in tramadol group and 50% in placebo group).

The frequency of sexual intercourse and the characteristics of IELT after treatment are shown in Table 2. The mean IELT has increased to 202.5 s with the daily treatment and 238.2 s with sporadic treatment with tramadol ($P < 0.001$). Coital frequency has also increased from 2.44/week to 4.32/week and 4.86/week with daily and sporadic treatment, respectively. In the placebo group, mean IELT has increased 58.7 s to 94.8 s and 96.6 s with daily and sporadic treatment, respectively. Coital frequency has increased from 2.13/week to 2.88/week and 3.23/week with daily and sporadic treatment, respectively. It has been seen that sporadic treatment has produced slightly higher effects, although, it was not statistically significant in compare to daily treatment.

The overall AE rate was 9.8% (6.7%, and 12.4% for placebo and 100 mg tramadol respectively) ED occurred in 33.3% of men ($n = 1$). Vertigo was observed in 3.3% of patients ($n = 2$); dizziness, headache, drowsiness, and common cold were observed in 6.67% of patients ($n = 2$ each). There were no serious AEs.

### DISCUSSION

The results of this study demonstrate that tramadol is an effective treatment for PE, resulting in a significant prolongation of IELT that showed clinical improvements in satisfaction with sexual intercourse and control over ejaculation, and decreases in ejaculation-related personal distress and interpersonal difficulty. Tramadol was well tolerated; the overall AE rate was 6.7% for placebo and 12.4 for tramadol. Salem et al.,[8] previously examined the safety and efficacy of the same active ingredient present in tramadol (tramadol HCl) for the treatment of PE. Their AE rate in patients taking the study drug (13%) was similar to our study (12.4%).

Chronic use of serotonergic and selective serotonin reuptake inhibitor (SSRI) agents has shown effectiveness in delaying ejaculation. Today, they are the main treatment option available for the treatment of PME.[11] However, chronic use of SSRIs is associated with the serious AEs including psychiatric and neurologic consequences and unwanted sexual side effects; dose reduction or discontinuation is associated with the discontinuation syndrome.[11,12] On-demand use of SSRIs, including paroxetine, has shown some efficacy in treating PE.[12,14] One study, examines the effect of continued and sporadic use of paroxetine in the treatment of PME in similar manner as ours and found that both continued and on-demand use has similar effect with more patient satisfaction with sporadic treatment.[15] Dapoxetine, an on-demand short-acting SSRI, is the only currently approved oral treatment for PE. Dapoxetine has shown efficacy in PME when used as on-demand basis.[16,17]

However, very few studies on tramadol therapeutic efficacy comparing forms of administration (sporadic or continuous) have been published.[18] Bar-Or et al.[18] examined the effect of two doses of tramadol, 62 mg and 89 mg as sporadic use in a placebo-controlled study. Tramadol has shown significant improvement in IELT in both doses over placebo.[18] The present study shows that both types of treatment had the same

### Table 1: The frequency of sexual intercourse and the characteristics of premature ejaculation

| Category | Frequency of sexual intercourse/ characteristics of premature ejaculation | Tramadol group no. (%) | Placebo group no. (%) | Total no. (%) |
|----------|-------------------------------------------------|------------------------|----------------------|--------------|
| Frequency of intercourse | | | | |
| Daily | 3 (10.0) | 3 (10.0) | 6 (10.0) |
| 2-3 times/week | 18 (60.0) | 15 (50.0) | 33 (55.0) |
| 1 time/week | 6 (20.0) | 9 (30.0) | 15 (25.0) |
| 1-2 times/month | 3 (10.0) | 3 (10.0) | 6 (10.0) |
| Classification of premature ejaculation | | | | |
| Lifelong (primary) | 22 (73.3) | 19 (63.3) | 41 (68.3) |
| Acquired (secondary) | 8 (26.6) | 11 (36.6) | 19 (31.6) |
| Ejaculation time | | | | |
| With very little stimulation | 2 (06.6) | 0 (0.0) | 2 (03.3) |
| Before penetration | 1 (03.3) | 3 (10.0) | 4 (06.6) |
| At penetration | 5 (16.6) | 6 (20.0) | 11 (18.3) |
| Shortly after penetration | 22 (73.3) | 21 (70.0) | 43 (71.6) |

IELT – Intra-vaginal ejaculation latency time

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### Table 2: The frequency of sexual intercourse and the characteristics of IELT

| Category | IELT | Coital frequency |
|----------|------|-----------------|
|          | Range (s) | Mean | $P$ | Range (per week) | Mean | $P$ |
| Group A  | Before treatment | 9-244 | 59.2 | 0.25-7 | 2.44 |
|          | After treatment | 20-518 | 202.5 | 0.50-8 | 4.32 | 0.005 |
|          | Daily | 30-556 | 238.2 | 0.50-8 | 4.86 | 0.005 |
| Group B  | Before treatment | 8-236 | 58.7 | 0.25-7 | 2.13 |
|          | After treatment | 22-294 | 94.8 | 0.25-7 | 2.88 | 0.875 |
|          | Daily | 26-302 | 96.6 | 0.25-7 | 3.23 | 0.752 |

IELT – Intra-vaginal ejaculation latency time
results since IELT alterations were minimal. Although, abuse potential of tramadol is less but with continued treatment it has been reported. On-demand use of tramadol is better option considering its abuse potential. Besides this, considering the economical aspects, tramadol has greater advantage over other drugs used in the treatment of PME.

CONCLUSIONS

The results of the present study show a similar efficacy in the administration of tramadol on request and on a fixed schedule. It is worth noting that in relation to degree of satisfaction patients stated that they felt better with the on request administration. This is perhaps due to the fact that the results are the same with both types of administration but with the on request regimen there was a reduction in undesirable side-effects and there was also a lower monetary cost. Even though, 100 mg of tramadol has been reported to be well-tolerated in other studies, perhaps, it would be worthwhile to evaluate the results of administering a lower dosage. Another important point of the present study is that both an improvement in quality of sexual life of the patient and increase in coital frequency after tramadol administration were reflected. Recently, there have been many therapeutic options have been tried such as creams, sprays, and systemic therapies. Considering the cost factor tramadol could be a better option in mild to severe PME.

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