

The Effectiveness of Tramadol in Treatment of Premature Ejaculation on-Demand Basis

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ABSTRACT:

BACKGROUND:

Premature ejaculation (PE) is a worldwide problem. Selective serotonin reuptake inhibitors (SSRIs) are widely used "off label" as pharmacotherapeutic agents in the treatment of PE.

OBJECTIVE:

Assess the efficacy of Tramadol for on-demand treatment of PE.

PATIENTS AND METHODS:

During the period December 2008 through November 2009, 60 married men visited the surgical specialties hospital urology outpatient and consultancy clinics complaining of premature ejaculation were enrolled in this study. Intravaginal ejaculation latency time (IVELT) was used as an objective tool to assess the efficacy of the investigated treatment. Single-blind, placebo-controlled therapeutic trial was conducted on 60 patients with lifelong PE. PE was defined as IVELT of <2 minutes in at least 80% of intercourse episodes. The patients cohort was randomised into 2 equal sized groups. The intervention group (n=30) used 50 mg tablet of Tramadol hydrochloride, while the control group (n=30) used a placebo tablet for 8 weeks. Drugs were taken 1–2 hours before sexual activity, and sexual intercourse was required at least once per week. IVELT was timed by a stopwatch at each intercourse.

RESULTS:

The mean IVELT after tramadol and placebo significantly increased from 73.1 and 67.9 seconds to approximately 442.1 and 113.3 seconds, respectively ($P < 0.001$). Sexual satisfaction was used to assess the cut-off values of IVELT in defining the minimal and best clinical response to treatment. There was no withdrawal symptoms recorded following the use of tramadol or placebo, but more adverse events were associated with tramadol treatment

CONCLUSION:

Tramadol seems to provide significantly better results in terms of IVELT and intercourse satisfaction versus placebo. Further studies are required to draw final conclusions on the efficacy of this drug in premature ejaculation.

KEY WORDS: premature, ejaculation, tramadol.

INTRODUCTION:

PE is the commonest sexual problem in men affecting up to 75% of men at some point in their lives⁽¹⁾ and up to almost 40% of men experiencing the problem on a recurring basis^(2,3). The American Urological Association Guideline on Premature Ejaculation defines PE as "Ejaculation that occurs sooner than desired, either before or shortly after

penetration, causing distress to either one or both partners⁽⁴⁾". Both DSM-IV-R and ICD-10 definitions refer to three essential components for the diagnosis of PE: short ejaculatory latency, lack of control, and sexual dissatisfaction. The short ejaculatory latency is typically measured by intravaginal ejaculatory latency time (IVELT), defined as the time between vaginal intromission and ejaculation, averaged over a number of sexual encounters. Latencies of 2 minutes or less show minimal overlap with those of men without PE, which typically range from 2 to 10 minutes. Accordingly, any latency less than 2 minutes (Waldinger et al, 1998a; Rowland et al, 2000) suggests a possible PE diagnosis⁽⁵⁾. However,

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IVELT is generally considered the more reliable measure. PE, unlike erectile dysfunction (ED), affects men of all ages equally. However, both PE and ED coexist, and often PE can masquerade or be misdiagnosed as ED in many men. This is, in part, due to the lack of knowledge about PE, the absence of performing a careful history, and the non existence of diagnostic tools for PE⁽⁴⁾. PE has been classified as either primary (lifelong) that begins when a male first becomes sexually active or secondary (acquired), meaning that a male previously had an acceptable level of ejaculatory control and developed the condition later in life^(6,7).

A number of theories have been proposed regarding causes of PE; all suggest the cause to be either psychological "as anxiety, early sexual experience, etc" or biogenic "as penile hypersensitivity, hyper-excitability ejaculatory reflex, 5HT receptor dysfunction...etc". However; the most likely two causes are penile hypersensitivity, and 5hydroxytrptamien receptor sensitivity⁽⁸⁾. Waldinger and colleagues (1998a) hypothesized that lifelong PE in humans may be explained by hyposensitivity of the 5-HT_{2C} and/or hypersensitivity of the 5-HT_{1A} receptor⁽⁵⁾. Treatment with serotonin reuptake inhibitors (SSRIs) activates the 5-HT_{2C} receptor, adjusts the ejaculatory threshold set point, and delays ejaculation⁽⁸⁾.

The two corner stones of treatment are the psychological/behavioral treatment, and the pharmacologic treatment, the latter includes SSRIs, TCA, topical anesthetics, and most recently the use of PDE5 inhibitors like sildenafil citrate⁽⁸⁾. These drugs have been tried both on continuous daily doses and on-demand dosing.

Tramadol hydrochloride is a synthetic opioid analgesic that appears to have actions at m-opioid receptors as well as the noradrenergic and serotonergic systems^(9,10). It is used mostly to treat moderate to severe pain, however, it has been shown to be effective for alleviating symptoms of depression and anxiety because of this action on the noradrenergic and serotonergic systems^(11,12).

This combined effect of Tramadol on both serotonergic and noradrenergic systems and effect on alleviating symptoms of depression and anxiety may explain its effectiveness as a treatment for PE. This study aims to assess the efficacy of tramadol in treatment of PE on-demand basis.

PATIENTS AND METHOD:

Study design: Single blind Placebo controlled Clinical trial.

Study population: 60 Married men with a complaint of PE defined as an IVELT < 120 seconds.

Study period: The study subjects were treated for a total of 8 weeks and the study covered the period from December, 2008 to November, 2009.

Study sample: A systematic random sample of 60 married men with PE was recruited from patients consulting the outpatient clinic and referred to the urology consultancy clinic in surgical specialties hospital /medical city complex in Baghdad. Every 3rd PE patient seen and giving his consent to participate in the study was eligible for inclusion. Their ages ranged from 20 to 57 years with mean of 34 years \pm 7. 9 years (\pm -SD). The subjects were randomly allocated into 2 equal sized groups. One of the groups was treated with 50 mg tramadol hydrochloride on demand, while the other received a placebo drug and served as a control group. The drug/placebo was ingested 2 hours before the sexual act. A total of 6 patients declined from the study after its inception and were lost to follow up. A total of 28 subjects in the tramadol group and 26 in the placebo group were analyzed at the end of 8 weeks of follow up period.

All of the study participants were potent married men. None received other treatments of PE for at least four weeks before the start of the study. All patients had an active sexual life with score more than or equal to 22 on the erectile function domain of the International Index of the Erectile Function (IIEF)⁽¹³⁾. All patients had primary PE (lifelong PE since their first sexual experience).

IVELT with at least one intercourse episode per week, for all patients was <2 minutes in 80% of intercourse attempts in a 4 weeks test period prior to the start of treatment. This was an inclusion criterion for all patients in the study. The IVELT was time between the start of vaginal insertion and the start of intra-vaginal ejaculation.

Exclusion criteria included patients with erectile dysfunction according to the IIEF, an organic cause of PE, genital infection and neurological disorders, low libido, chronic depression, psychiatric or physical illness; alcohol, drugs, or substance abuse; organic illness causing limitation in SSRIs use; use of psychotropic and antidepressant medication; and serious relationship problems.

To be able to exclude organic sexual dysfunction, fasting blood glucose level, urine analysis, complete blood count, sex hormones (including prolactin) levels were measured. The patients had to be in a stable relationship with their wives for at least the previous 6 months, and possible sexual

intercourse equal or greater than one per week. Patients meeting study criteria had their medical and sexual histories and demographic information recorded.

All patients underwent preliminary assessment, including IVELT and IIEF. At the first visit, patients were interviewed and requested to an estimation of the IVELT. A stopwatch and instructions on how to measure the IVELT were then provided. Subjective estimation and question and questionnaire assessment of ejaculation latency may lead to a higher variability in clinical outcome measures⁽²⁰⁾; therefore, the most accurate method of determination of ejaculation latency is the use of stopwatch.

Couples were also instructed not to use condoms or topical anesthetic cream, not to pause during intercourse, or to have interrupted intromission and also not consume alcoholic drinks within 6 hours of sexual activity. Furthermore, they were requested not to increase their intercourse frequency, and if intercourse took place more than once in a single session, only the first intercourse was measured. Pretreatment frequency of sexual intercourse was the mean number of attempts per week during the previous 2 months.

Patients were given a diary to record frequency of coitus and adverse drug - related events. IVELT of each intercourse was reported by patients or partners. Patients were instructed to measure the IVELT by stopwatch from the start of penetration to the start of ejaculation by either the patient or the partner, a weekly mean estimate of IVELT, when available was recorded. The efficacy of treatment was assessed at the end of first week, fourth week during treatment and at the end of 8-weeks treatment period, using IVELT and adverse drug effects. Safety evaluation included monitoring of blood pressure, heart rate, and recording of nausea, vomiting, and other adverse events.

All patients were asked about their satisfaction with their control over ejaculation with treatment. The subjects were asked about satisfaction with their sexual act on drug with two questions “Are you satisfied with your control over ejaculation

with the treatment?”, and “Are you satisfied with your sexual act with the treatment?” Patients were also asked about their tolerance to the drug and if there were any side-effects. Intravaginal ejaculation latency time improvement, defined as the difference between IVELT at the end of treatment period and baseline with either drugs, was selected as the main outcome of interest in analysis.

Statistical analysis

Data were analyzed using SPSS13 (statistical package for social sciences) computer software. T-test (independent samples and paired), spearman rank linear correlation coefficient, and Wilcoxon signed rank test were used as appropriate. P value ≤ 0.05 was considered statistically significant.

RESULTS:

There is no significant difference between the tramadol and control groups in terms of mean age, duration of marriage, and mean baseline IVELT. (Table1). Both groups showed statistically significant increase in IVELT after 1,4 and 8 weeks of follow up. The magnitude of response was, however, different, the mean increase in IVELT at the end of 8 weeks was significantly higher in tramadol group (369 sec.) compared to placebo controls (45.4 sec.).The effect of the tramadol treatment was of higher clinical relevance compared to placebo group at the end of study, since the coefficient of effect size (Cohen's) was very high (15.1). In fact the effect size was very high as early as the first week of treatment (7.1) (Fig.1). The overall sexual satisfaction for both groups after treatment is demonstrated in fig. 2. The ROC test was used to set the optimum cutoff value for IVELT associated with minimum and best clinical response, and found to be 120 and 300 seconds respectively Fig.3. Tables 2 and 3 show the percentage of subjects with minimum and best clinical response in both groups at 1,4, and 8 weeks, which is significantly higher in tramadol group. Ten out of the whole study group experienced complications, 6 of them had nausea, 2 had vomiting, one had dizziness, and one had constipation.

Table 1: Mean age, duration of marriage, and baseline IVELT in both groups.

| | Placebo | Tramadol |
|----------------------------|---------------|--------------|
| Age (yr.) | | |
| No. | 26 | 28 |
| Mean | 34. 1(±7.4) | 33. 2(±8.8) |
| Baseline IVELT (sec) | | |
| No. | 26 | 28 |
| Mean | 67. 9 (±21.1) | 73. 1(±21.7) |
| Duration of marriage (yr.) | | |
| No. | 26 | 28 |
| Mean | 11.9(±3.2) | 12.2(±2.8) |

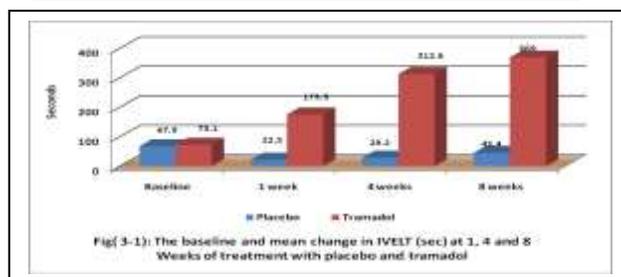


Figure 1: The baseline and mean change in IVELT (sec) at 1,4. and 8 weeks of treatment with placebo and tramadol.

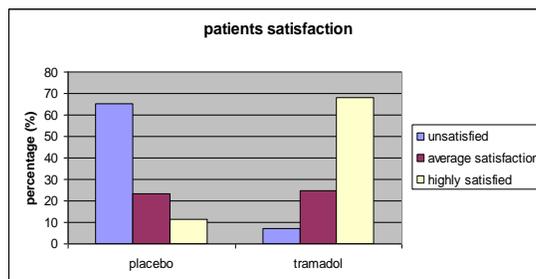


Figure 2: Percentage of sexual satisfaction reported by subjects at the end of 8 weeks treatment with placebo and tramadol.

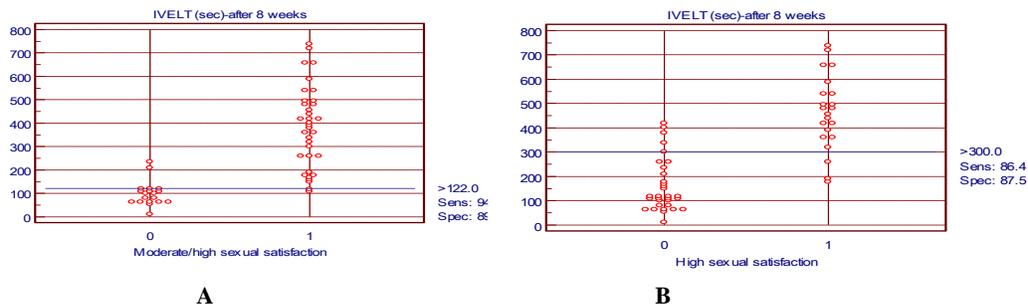


Figure 3: Optimum cutoff values of IVELT in seconds associated with (A) any grade of sexual satisfaction, and (B) high sexual satisfaction, at the end of treatment.

TREATMENT OF PREMATURE EJACULATION

Table 2: The rate of subjects achieving the minimal clinical response (IVELT>120 sec) after each week of follow up period in the two groups.

| Minimal clinical response (IVELT>120 sec) | | | | | | | | |
|---|--------|--------|--------|--------|--------|--------|--------|--------|
| weeks | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Placebo (n=26) | | | | | | | | |
| N | 2 | 3 | 5 | 5 | 8 | 7 | 8 | 9 |
| % | 7.7 | 11.5 | 19.2 | 19.2 | 30.8 | 26.9 | 30.8 | 34.6 |
| Tramadol (n=28) | | | | | | | | |
| N | 27 | 28 | 28 | 28 | 28 | 28 | 28 | 28 |
| % | 96.4 | 100 | 100 | 100 | 100 | 100 | 100 | 100 |
| P (Chi-square) | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

Table 3: The rate of subjects achieving the best clinical response (IVELT>300 sec) after each week of follow up period in the two treatment groups.

| Best clinical response (IVELT>300 sec) | | | | | | | | |
|--|-------|--------|--------|--------|--------|--------|--------|--------|
| weeks | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
| Placebo (n=26) | | | | | | | | |
| N | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Tramadol (n=28) | | | | | | | | |
| N | 9 | 13 | 18 | 22 | 23 | 23 | 23 | 24 |
| % | 32.1 | 46.4 | 64.3 | 78.6 | 82.1 | 82.1 | 82.1 | 85.7 |
| P (Chi-square) | 0.002 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 | <0.001 |

DISCUSSION:

The initial impetus behind current study was the observations of tramadol effect on sexual function in patients using this drug for analgesia. The fact that many of these patients had delayed ejaculation or anejaculation inspired the use of Tramadol empirically since the year 2000 in patients with PE. The second factor was the available data about serotonin syndrome with over dosage of Tramadol, or combination treatment with Tramadol and SSRIs⁽¹⁴⁾.

The current study demonstrates that Tramadol administered on-demand will prolong the ejaculation interval, the IVELT change after 1, 4 and 8 weeks of treatment was the main response parameter. In addition, the change in IVELT was matched with the degree of sexual satisfaction which is a subjective value to assess the effectiveness of tramadol in the treatment of premature ejaculation both subjectively and objectively. There was a significant increase in IVELT after 1, 4 and 8 weeks of treatment in Tramadol group, with a significantly higher magnitude of response compared to the control. The mean increase in IVELT at 1, 4 and 8 weeks was 175.5, 312.6 and 369 sec. respectively, which represented 3.4, 5.3, and 6 folds of the baseline IVELT. These results go hand in hand with the

experienced degree of sexual satisfaction reported by patients. While all patients were dissatisfied with their sexual life before treatment, after 8 weeks of treatment with tramadol only 2 patients (7.1%) were still unsatisfied and about two thirds (67.9%) of subjects reported high degree of satisfaction. In the control group, on the other hand, the rate of dissatisfied subjects was 65.4%, with only 11.5% reporting high degree of satisfaction. These findings were comparable to those reported by Safarinejad and Hosseini, 2006, who reported a rate of subjects with high satisfaction at 69% after 8 weeks of Tramadol treatment Vs 14% for placebo⁽¹⁵⁾. Safarinejad and Hosseini, 2006, published the first placebo controlled clinical trial on the use of on-demand 50 mg tramadol to treat PE, after 8 weeks of follow up the tramadol treatment group demonstrated a significantly higher improvement in IVELT compared to those receiving placebo. The mean increase in IVELT was 224 seconds in tramadol group compared to only 15 seconds in placebo group⁽¹⁵⁾. Salem et al, 2008 published a cross-over placebo-controlled clinical trial evaluating the on-demand use of tramadol treatment on PE, after 8 weeks of follow-up tramadol treatment significantly increased the IVELT by a mean of

372 second compared to 50 seconds only in the placebo group⁽¹⁶⁾. The present study provided another significant quantitative placebo controlled evidence for the effectiveness of tramadol on demand treatment in PE.

The Tramadol treatment effect was obviously more remarkable than that reported by Hellstrom et al, 2004, using Dapoxetine on-demand bases in a double-blind, placebo-controlled crossover phase II study. Dapoxetine on-demand treatment at a dose of 60mg was associated with a mean increase in IVELT of 56 seconds at the end of study period. Increasing the dose to 100 mg was associated with a further increase in IVELT of 20 seconds only⁽¹⁷⁾. In this study we were able also to define the minimal and best clinical response based on quantitative measurable criteria. Correlating the IVELT and sexual satisfaction at the end of follow up period aided by ROC analysis, we estimated the cut-off values of IVELT in seconds that define the minimal and best clinical response. It was found that subjects who reported any grade of sexual satisfaction had IVELT >122 seconds, while subjects who reported >300 seconds IVELT were highly satisfied and this was considered, therefore, the minimal value associated with best clinical response. These cut-off values are not much different from what is reported in literatures, since PE is diagnosed for IVELT<120 seconds⁽⁸⁾. Almost all tramadol treatment group (96.4%) attained the minimal clinical response as early as 1st week of treatment, while only 34.6% of placebo group attained this end point. None of placebo group attained the best clinical response, while a third of tramadol group reached this impressive clinical response as early as the first week of treatment, the majority (85.7%) reached this goal by the end of 8 weeks of treatment.

Although SSRIs are intended for use in the treatment of PE, they have pharmacokinetic profiles that would allow them to provide constant systemic concentration with long-term administration, it takes about 2–3 weeks to reach a maximum steady-state concentration in order to exhibit efficacy⁽¹⁸⁾. Therefore, SSRIs are commonly used in a daily dosing schedule⁽⁴⁾. In addition to the potentially desirable effect of delaying ejaculation, this dosing regimen for long-acting SSRIs is associated with a number of undesirable side effects, such as decreased libido, ED and non compliance of patients with daily regimen. Tramadol safety profile has been studied thoroughly in many clinical trials, such as

Cossmann et al, who found tramadol to be safe even in continuous dosing regimens⁽¹⁹⁾. The on-demand use of tramadol, as in this study, makes it even safer, for this reason, the reported side effects rate was very low, with most of the side effects being mild and self limiting.

CONCLUSION:

The present study showed that, on demand treatment with 50 mg tramadol led to a clinically relevant and statistically significant ejaculation delay. Tramadol seems to be a useful and well-tolerated oral treatment of PE on as-needed basis.

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