BIOSCIENCES BIOTECHNOLOGY RESEARCH ASIA, August 2014. Vol. **11**(2), 953-958

Comparative Study of Therapeutic Effects of Two Medicinal Procedures of Citalopram in Premature Ejaculation

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doi: http://dx.doi.org/10.13005/bbra/1365

(Received: 30 April 2014; accepted: 10 June 2014)

Premature ejaculation is the most common type of sexual dysfunction in men younger than 40 years. The optimal medical treatment for premature ejaculation has not been established in previous studies, but single dosing prior to sexual relations can work for some males, while in others, achieving a blood level through daily use of the medication may be necessary, as in the treatment of clinical depression. Obviously, if single dosing is successful, therapy is simpler and is associated with fewer adverse effects. Therefore, this may be the preferred initial therapy. Hence in this study, two therapeutic protocols of citalopram including as needed and twice a day were compared. This study was an un-blind randomized clinical trial. The patients aged older than 18 years with premature ejaculation were evaluated by urologist and after the disease was established and the questionnaire was fulfilled they were enrolled into the study. The patients were randomly assigned to receive either twice a day 20 mg citalopram or 20 mg four hours before coitus. The mean ejaculation time in two groups of PRN and BD was significantly differed in fourth week ($P < 0.05$) with 286.9±252.6 and 269.51±350.21 seconds, respectively, but apposite of BD group (485.±519.93 seconds), the patients in PRN group (288.53±267.27 seconds) showed no significant difference ($P > 0.05$), and however the baseline and fourth week measurement were alike between two groups; but in eighth week after treatment there was a significant difference between two groups ($P < 0.05$). Totally, it may be concluded that citalopram with every dose is effective in the treatment of premature ejaculation. However the BD regimen is more effective.

Key words: Premature ejaculation, Citalopram, Impotency, Clinical trial, Sexual dysfunction.

Premature ejaculation is the most common type of sexual dysfunction in men younger than 40 years[1-4]. Most professionals who treat premature ejaculation define this condition as the occurrence of ejaculation prior to the desires of both sexual partners. This broad definition thus avoids specifying a precise duration for sexual relations and reaching a climax, which is variable and depends on many factors specific to the individuals engaging in intimate relations.

Because many females are unable to reach climax at all with vaginal intercourse (no matter how prolonged), this situation may actually represent delayed orgasm in the female partner rather than premature ejaculation in the male; the problem can be either or both, depending on the point of view. This highlights the importance of obtaining a thorough sexual history from the patient (and preferably from the couple)[2,3].

The criteria for premature ejaculation stated in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, text revision (DSM-IV-TR) is as follows: (1) persistent and

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recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration before the person wishes it; (2) marked distress or interpersonal difficulty; and (3) not exclusively due to direct effects[1].

The human sexual response can be divided into 3 phases: desire (libido), excitement (arousal), and orgasm. The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) classifies sexual disorders into 4 categories: (1) primary, (2) general medical condition–related, (3) substance-induced, and (4) not otherwise specified. Each of the 4 DSM-IV categories has disorders in all 3 sexual phases (1).

Premature ejaculation is stressful and cause of bad marital relationships and decreased quality of life[3, 4]. It may be primary or secondary. Primary premature ejaculation applies to individuals who have had the condition since they became capable of functioning sexually (ie, postpuberty). Secondary premature ejaculation means that the condition began in an individual who previously experienced an acceptable level of ejaculatory control, and, for unknown reasons, he began experiencing premature ejaculation later in life. Secondary premature ejaculation does not relate to a general medical disorder and is usually not related to substance inducement, although, rarely, hyperexcitability might relate to a psychotropic drug and resolves when the drug is withdrawn. Premature ejaculation fits best into the category of "not otherwise specified" because the cause is unknown, although psychological factors are suggested in most cases[5-8].

Medical treatment for premature ejaculation (rapid ejaculation) includes several options. Any serious primary medical condition (eg, angina) should be treated; for the purpose of the following discussion, the male is assumed to be healthy and premature ejaculation is assumed to be his only problem [9-11].

No drug is approved by the FDA for the treatment of premature ejaculation (rapid ejaculation). However, numerous studies have shown that selective serotonin reuptake inhibitors (SSRIs) and drugs with SSRI-like side effects are safe and effective to treat this condition, and many physicians use these agents for this purpose. SSRIs have been the most successful agents in delaying the too-rapid response in men who experience premature ejaculation. Desensitizing creams containing local anesthetic agents can also be useful in some men with premature ejaculation[12]. These agents are not approved by the FDA specifically for this use, but they are believed to be of at least some efficacy and are a minimal-risk option for patients. SSRIs have a high toxic-to-therapeutic ratio, and fatalities are uncommon with pure SSRI overdoses. Commonly prescribed SSRIs include sertraline (Zoloft), fluoxetine (Prozac), paroxetine (Paxil), citalopram (Celexa) and fluvoxamine (Luvox). Potent SSRI used to treat premature ejaculation. Improvement may not be evident until at least 3 wk following initiation of treatment. If no benefit (with respect to premature ejaculation) after 6 wk or if adverse effects become troublesome, discontinue in favor of alternative treatment[12].

The optimal medical treatment for premature ejaculation has not been established in previous studies[13-20], but single dosing prior to sexual relations can work for some males, while in others, achieving a blood level through daily use of the medication may be necessary, as in the treatment of clinical depression. Obviously, if single dosing is successful, therapy is simpler and is associated with fewer adverse effects. Therefore, this may be the preferred initial therapy[13]. Hence in this study, two therapeutic protocols of citalopram including as needed and twice a day were compared. Because it is possible that a patient has no response to twice a day regimen; but the dose of four hours before coitus is effective in him.

METHODS AND MATERIALS

This was an un-blind randomized clinical trial. The inclusion criteria were the patients aged more than 18 years and premature ejaculation that were evaluated by urologist and after the disease was established (mean time in three coituses according to measurement by patient's parent) and the questionnaire was fulfilled they were enrolled into the study. The exclusion criteria were drug hypersensitivity and lack of satisfaction to participate in the study. The sampling was convenient and then simple random allocation. The patients were randomly assigned to receive either twice a day 20 mg citalopram or 20 mg four hours before coitus. The demographic variables, response initiation, mean before and after Intravaginal

Ejaculation Latency Time (IELT), risk factors, background diseases, and lab tests were recorded. The questionnaire was filled by urologist and measuring the IELT was learned to the patient. The time between penile insertion and ejaculation was measured by the partner with a timer and recorded as seconds. The times were for before-treatment, 4 weeks, and 8 weeks after treatment.

All the patients were signed informed consent form. Finally the data from 113 patients (50 PRN and 63 BD) with mean (±standard deviation) age of 36.32 ± 8.81 years and 34±11.57 years in PRN and BD groups respectively were analyzed using SPSS (version 13.0) software [Statistical Procedures for Social Sciences; Chicago, Illinois, USA]. Differences were tested by Exact Fisher, Independent-Sample-T and Chi-Square tests and were considered statistically significant at P values less than 0.05.

RESULTS

The mean age of the patients was alike between two groups (P > 0.05) (Table 1 and 2). 42.9% in PRN group and 35.5% in BD group had academic education (P > 0.05). 81.6% in PRN group and 52.4% in BD group were married (P > 0.05).

The mean ejaculation time in two groups of PRN and BD were 2.17 ± 0.76 and 1.55 ± 0.84 times, respectively. The mean ejaculation time in two groups of PRN and BD was significantly differed in fourth week (P < 0.05) with 286.9±252.6 and 269.51±350.21 seconds, respectively, but apposite of BD group (485.±519.93 seconds), the patients in PRN group (288.53±267.27 seconds) showed no significant difference (P > 0.05), and however the baseline and fourth week measurement were alike between two groups; but in eighth week after treatment there was a significant difference between two groups (P < 0.05) (Table 3). The contributing and risk factors and drug side effects were alike between two groups (Tables 4 and 5) and therefore the matching between two groups was considered. The most common complication in both groups was sedation with 52.94% in PRN and 50% in BD group.

Table 1. Mean age in two groups

Group	Count	Minimum	Maximum	Mean	Standard Deviation
PRN	50	19	60	36.32	8.81
BD	63	21	72	34	11.57

Table 2. Age groups in two groups

Group	PRN	BD
< 20	1 (2%)	—-
20-30	12 (24%)	34 (54%)
31-40	19 (38%)	16 (25.4%)
41-50	15 (30%)	6 (9.5%)
51-60	3 (6%)	4 (6.3%)
> 60	—-	3 (4.8%)

DISCUSSION

The optimal medical treatment for premature ejaculation has not been established, but single dosing prior to sexual relations can work for some males, while in others, achieving a blood level through daily use of the medication may be necessary, as in the treatment of clinical depression. Obviously, if single dosing is successful, therapy

Table 3. Intravaginal Ejaculation Latency Time in two groups

Group	PRN(Mean ± SD, Sec)	BD(Mean ± SD, Sec)	P Value
Before treatment	(9.6-300) 94.39±74.38	(19.8-420) 86.33±70.81	0.559
4th after treatment	(15-1500) 286.9±252.6*	(30-2400) 269.51±350.21*	0.787
8th after treatment	(30-1500) 288.53±267.27***	(60-2400) 485.±519.93**	0.028

* Significant difference with P value 0.0001
** Significant difference with P value 0.007
*** No significant difference with P value 0.058

is simpler and is associated with fewer adverse effects. Therefore, this may be the preferred initial therapy. Hence in this study, two therapeutic protocols of citalopram including as needed and twice a day were compared. The cause of study on citalopram was its effects on resistant cases.

Our result showed that both regimens were effective but citalopram with BD use is more effective than PRN protocol (especially in eighth week after treatment) and has no major side effects which no patient need to treatment discontinuation.

Kendirci et al, in a review article, reported that paroxetine is the most potent SSRI for premature ejaculation and BD regimen is better than PRN one as well as our study (14). Another study by Atmaca et al was performed . The study was consisted of 26 married patients diagnosed with premature ejaculation according to Diagnostic and Statistical Manual of Mental Disorders Third Revised Version (DSM-III-R). The patients were randomly assigned to two groups, citalopram (group I) and placebo (group II), each consisting of 13 patients. The effects of drug on the ejaculatory function were assessed by the intravaginal ejaculation latency time. Additionally, all patients were screened by using Clinical Global Impression-Improvement Scale (CGI-I) and Yonsei Sexual Function Inventory-II (YSFI-II). The increase in the intravaginal ejaculation latency time in the citalopram group was statistically significant than that of placebo group. In addition, with respect to the subscales of the YSFI-II scale, similar overall significant improvements were seen in the patients given citalopram compared to those given placebo. Of group I patients, five (38.5%) were considered as 'very much improved' and four (30.8%) 'much improved' by CGI-I and only one of group II patients (7.7%) showed 'much improved'. We had no drug DC similar to their study and also in our study the drug side effects were compared between two groups (15).

The efficacy of two treatments was assessed every 2 weeks during treatment, at the end of study and in 3- and 6-month follow-up after cessation of treatment, using responses to IIEF, IVELT evaluation, mean intercourse satisfaction domain, mean weekly coitus episodes and adverse drug effects in a study by Safarinejad et al. The trial was completed by 51 (88%) men. Analysis revealed a difference in the evolution of IVELT delay over time ($P < 0.001$). The IVELT after citalopram and placebo gradually increased from 32 and 28 s to approximately 268 and 38 s, respectively. The mean weekly intercourse episodes increased from pretreatment values of 1.3 and 1.2 to 2.4 and 1.4, for citalopram and placebo, respectively ($P < 0.05$). Baseline mean intercourse satisfaction domain values of IIEF 10 and 11 reached to 16 and 10 at 12-week treatment in groups 1 and 2, respectively ($P < 0.05$). Mean IVELT in group 1 was 210 and 198 s at 3- and 6-month follow-up, while in group 2 it was 27 and 25 s ($P < 0.001$), respectively. At 3- and six-month intercourse satisfaction domain values of IIEF were 15 and 14 in group 1 and 10 and 10 ($P < 0.05$) in group 2, respectively. Group 1 patients reported a significantly higher number of intercourse episodes per week ($P < 0.05$). Mean number of adverse events was 12 for citalopram

Table 4. Risk and contributing factors in two groups

Risk and contributing factors	PRN	BD	P Value
Psychiatric Disorder	28.6	35.3	0.443
Erectile Dysfunction	43.1	14.3	0.0001
Metabolic Disorder	2	1.6	1.000
Cardiovascular Disorder	2	1.6	1.000
Hypertension	—-	3.2	0.501
Hypertriglyceridemia	7.8	3.2	0.405
Diabetes mellitus	3.9	6.3	0.690
Neurological Disorder	3.9	—-	0.198
Pelvic surgery	2	—-	0.447
Smoking	25.5	22.2	0.683
Positive Drug History	15.7	9.5	0.319
Opium use	—-	7.9	0.064

Table 5. Drug side effects in two groups

Side Effect	Dyspepsia	Sedation	Fatigue	Anxiety	Vertigo	Nausea	Headache	Insomnia	P Value
PRN	—	9 (52.94%)	2 (11.76%)	1 (5.88%)	2 (11.76%)	—	2 (11.76%)	1 (5.88%)	17
BD	1 (10%)	5 (50%)	1 (10%)	1 (10%)	1 (10%)	1 (10%)	—	—	10
P Value	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

and 4 for placebo ($P < 0.05$). In conclusion, these results indicate that citalopram has significantly better results in terms of IVELT and intercourse satisfaction versus placebo (16). However we had no placebo, but we obtained similar results.

In a review article by Wang et al it is mentioned that Many kinds of SSRIs, such as fluoxetine, sertraline, paroxetine and citalopram, have widely been employed to treat PE. However, their effects are moderate and there is no a universal agreement about the kind, dose, protocol and duration. Dapoxetine, as the first prescription treatment of PE, may change this bottle-neck situation. SSRIs are suggested to be used in young men with lifelong PE, and acquired PE when etiological factors are removed but PE still exists. Phosphodiesterase 5 inhibitors (PDE(5)-Is) are suggested to be employed alone or combined with SSRIs when SSRIs fail to treat PE or sexual dysfunction associated with SSRIs occurs. The protocol of taking drugs on demand based on taking them daily for a suitable period is proposed to be chosen firstly. The possible mechanisms include increasing serotonergic neurotransmission and activating 5-hydroxytryptamine 2C (5-HT(2C)) receptors, then switching the ejaculatory threshold to a higher level, decreasing the penile sensitivity and their own effect of antidepression (17). This review article showed the need to studies such as ours. Also Moreland et al reported that Trials evaluating the ejaculation-delaying ability of SSRIs demonstrated that paroxetine, fluoxetine, sertraline, and citalopram produce a statistically significant increase in the ejaculation latency time compared with placebo (18). This matter is similar to our finding.

Another study was performed by Rezakhaniha et al. The procedure of that study was based on non stochastic clinical test without quasi drug group and a comparison from therapeutic effect and symptoms of two medicinal procedures of fluoxetine 4 hours before coitus and each 12 hours in premature ejaculation treatment in 88 patients refer to 501 hospital and private clinic. Patient were divided into two groups in peradventure manner. In first group, it is prescribed 20mg of fluoxetine daily 4 hours before coitus in 39 patients and in 2nd groups group, it is prescribed 20mg of fluoxetine each 12 hours before coitus in 49 patients. Finally it was analyzed data in SPSS software. The average of ejaculation duration in fluoxetine group 4 hours after coitus before treatment was 139.97 Sec. that after 4 weeks of hospitalization reached to 225.25 and p.v:0.0000 and after 8 weeks to 261.153 Sec. and p.v:0.0000 and in compare with ejaculation duration between 4th and 8th weeks it gained p.v:0.003. The average of ejaculation duration in fluoxetine group 12 hours after coitus before treatment was 107.04 Sec. that after 4 weeks of hospitalization reached to 294.08 and p.v:0.0000 and after 8 weeks to 324.08 Sec. and p.v:0.0000 and in compare with ejaculation duration between 4th and 8th weeks it gained p.v:0.029. In comparing ejaculation duration between 2 groups' fluoxetine 4 hours before coitus (t=225.25) and each 12 hours (t=294.08) in 4th week after treatment it gained p.v:0.03. In comparing ejaculation duration between 2 groups' fluoxetine 4 hours before coitus (t=261.153) and each 12 hours (t=324.08) in 8th week after treatment it gained p.v:0.0000. Symptom measure in fluoxetine group 4 hours before coitus 12.8% and symptom measure in fluoxetine group 12 hours before coitus 44.9 and p.v:0.001 (19). In our study in a opposite manner the frequency of side effects was less in BD group. The lower rate of side effects in BD regimen may be more time to accommodate and the higher rate in PRN may be due to idiosyncratic reactions to drug.

In a prospective clinical trial, citalopram hydrobromide was used as a salvage agent in 16 newly married men with premature ejaculation who experienced a history of unsuccessful treatment with fluoxetine hydrochloride. Intravaginal ejaculation latency time (IVELT) was recorded by a stopwatch before and after the treatment, and a 5-stage visual scale was designed and used to compare patients' sexual satisfaction levels during the 1-month treatment period. The IVELT and sexual satisfaction levels both significantly improved after citalopram prescription. The mean measured IVELT was 0.388 +/- 0.212 minutes before the treatment, which increased to 4.313 +/- 2.886 minutes after the treatment. The reported drug untoward effects were mild. Citalopram was ineffective only in 1 patient, which was discontinued after 4 weeks (20). Our sample volume and duration of follow up (8 weeks) were more.

Totally, it may be concluded that citalopram

with every dose is effective in the treatment of premature ejaculation. However the BD regimen is more effective. Finally assessment of other SSRIs is recommended. Also the evaluation of contributing factors for therapeutic response is recommended especially with exclusion of confounding factors such as patients with background disease.

ACKNOWLEDGEMENTS

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