Basrah Journal Of Surgery

Bas J Surg, March, 13, 2007

CLOMIPRAMINE AS DAILY DOSE IN THE TREATMENT OF PATIENTS WITH PREMATURE EJACULATION: PROSPECTIVE PLACEBO-CONTROLLED STUDY

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Abstract

This is prospective study to assess the use of clomipramine as daily dose to improve premature ejaculation when on demand dose fail to achieve it. The study included 38 men with premature ejaculation who fail to response to clomipramine as on demand treatment were divided into two groups: group A used a daily dose of 10 mg clomipramine in 1st 3weeks increased to 25 mg in the next 3 weeks and group B used placebo for the same period. The patients were asked to determined the intravaginal ejaculation latency time (IELT) and any unpleasant symptoms. The subjects were contacted every 3 weeks to assess the improvement, satisfaction and presence or absence of side effects. We found a significant dose dependant increase in the mean IELT in group A from 47.7 ± 21.2 sec to 76.5 ± 33.9 sec with 10 mg of clomipramine and to 143.1 ± 53.9 sec with 25 mg while in group B the increase was from 45.5±10 sec to 51.2 ± 15.2 sec after 3 weeks and to 55.4 ± 14.9 sec after 6 weeks. The IELT in group A was statistically significantly ($p < 0.05$) longer than that in group B. The patients' sexual satisfaction rates were statistically significant ($p < 0.05$) after treatment with clomipramine and placebo which were 54% and 21% respectively. The side effects in both groups were mild. We conclude that a daily dose of clomipramine is effective treatment for patients with premature ejaculation to improve their IELT with high patients' satisfaction and accepted side effects.

Introduction

Premature ejaculation (PE) is a common sexual problem, associated with significant adverse effects on the sexual and overall quality of life of affected men[1-3]. The etiology of this condition is unclear. Psychological and organic mechanisms have been suggested as causative factors and the etiology is probably multifactorial and complicated by poor consensus of definition among physicians and therapists[4,5]. Despite the difficulties with published definitions of premature ejaculation, different definitions have been used on the basis of partner satisfaction, male voluntary control, duration of ejaculatory latency and number of intravaginal thrusts to describe premature ejaculation[6]. Some define PE as failure to control ejaculation before their partners reach orgasm in at least half of attempts at sexual intercourse[7]. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) defines premature ejaculation as "the persistent or recurrent ejaculation with minimal sexual stimulation before, or shortly after penetration, and before the person wishes"[8].Varying incidence rates have been estimated from different populations, systematic review of 28 studies suggested an incidence of 15%[9]. Ejaculation is affected by numerous mechanisms, among these; the most accepted and may be the most important one is central serotonin level. Elevated

central serotonin level results in ejaculation delay. Therefore, tri-cyclic anti depressants (clomipramine) and selective serotonin reuptake inhibitors (SSRIs: fluoxetine, sertraline, paroxetine) have emerged as safe and effective new treatments. Besides serotonin reuptake inhibition, clomipramine also inhibits the reuptake of nor-adrenaline[10]. Ejaculation is determined by the complex interplay of local and distal influences, although ejaculation is a spinal sympathetic reflex generated in the lumbosacral spinal cord, it is influenced by genital sensory input and by tonic descending inhibitory serotonergic control from the nucleus paragigantocellularis (nPGi). The nPGi receives modulatory influences from the medial preoptic area and paraventricular nucleus of the hypothalamus[11]. Behavioral therapies, such as the "squeeze" and "stop–start" techniques and psychotherapy, have been the mainstay of PE management for many years. There are no pharmacotherapies specifically licens-ed for the treatment of PE, but a number of agents have been used "off label" to treat the condition[1]. The potential of antidepressants to treat PE was first suggested by Ahlenius et al. in 1979[12].

Aim of this study was to assess the efficacy of clomipramin as daily treatment in patients with premature ejaculation PE who did not respond to on demand scheme of treatment with clomipramin in comparison with control.

Patients and methods

This is a prospective study that included 38 men with premature ejaculation who did not respond to on demand dose of clomipramine, assessed from February 2004 to August 2006.

Intravaginal ejaculation latency time (IELT) is defined as the time between the start of vaginal intromission and ejaculation[3]. It is commonly accepted that a normal ILET should not be < 2min[7].

The inclusion criteria were age 18-50 years, a regular sexual life, and those seeking medical help spontaneously, only patients who were living in a stable relationship with possible sexual intercourse equal or greater than two per week and who did not respond to clomipramine as on demand treatment were included. Exclusion criteria were the presence of an organic cause for PE (anatomical abnormality, genital infection, depression and neurological disorder), history of erectile dysfunction (ED), detectable risk factors for ED (alcohol or substance abuse, diabetes mellitus, hypertension, etc.)[7].

Patients were randomly assigned into 2 groups: group A (19 patient) received clomipramine for 6-week period (10 mg clomipramine in 1st 3 week period titrated to 25 mg) and group B (19 patients) received placebo for the same period.

The patients were asked to determine their IELT by stopwatch, and the average time for 3 consecutive episodes of intercourse reported by the patients was recorded. The patients were not permitted to use condoms or topical anaesthetics during the study and no psychotherapeutic interventions were made. Subjects visited the clinic every 3 weeks for interview and physical examination. They completed questionnaires about their ILET, side effects and assessing other sexual aspects including desire, erection and satisfaction.

Paired T test was used to analyze the results and a P value of <0.05 was considered significant.

Results

Only 27 patients out of 38 completed the study (13 in group 1 and 14 in group 2). Nine of them were lost to follow up and two did not follow the instructions.

Mean patient age, age of wives and duration of marriage plus or minus standard deviation were 33.2±8.4, 28.8±6.7 and 5.1±3.5 years, respectively in group 1 and 31.4±9.8, 27.8±8.1 and 5.9±3.3 years, respectively in group 2.

Intravaginal ejaculation latency time IELT before treatment was 47.7±21.2 seconds in group 1 and 45.4±10 seconds in group 2.

IELT increased to 76±33.9 seconds in the treatment group and 51.2±15.2 seconds in the placebo group after 3 weeks of treatment. This difference was statistically significant in the treatment group ($p < 0.05$) but not in the control group ($p > 0.05$), it further increased to 143.1±53.9 seconds in the treatment group and 55.4±14.9 seconds in the placebo group after 6 weeks of treatment. This difference was statistically significant in the both groups ($p < 0.05$). However, significant difference was found between clomipramine and placebo groups ($p < 0.05$).

The side effects (table I) in group 1 were found in 38% after 3 weeks of treatment and it was similar after 6 weeks when the dose was increased. The most common side effects were dry mouth 15%, decreased libido 7.7%, insomnia 7.7% and drowsiness 7.7%, while in group 2 it was 14% including insomnia 7% and headache 7%. The incidence of side effects with clomipramine was significantly higher ($p < 0.05$) compared to that of placebo.

Patients' sexual satisfaction rates (table II) after treatment with clomipramine and placebo were 54% and 21% respectively. Differences among these drugs in satisfaction rates were statistically significant ($p < 0.05$).

Discussion

In this prospective placebo controlled study, we assess the efficacy of clomipramine when used in a daily dose of 25mg for patients with premature ejaculation who did not respond to it as demanding dose (25 mg 6-24 hr before intercourse) and their IELT were still < 2 min. The idea was that chronic administration with 25 mg may be an effective modality of treatment[13,14]. In a placebo controlled, double-blind study Girgis et al showed that clomipramine was effective in the treatment of premature ejaculation[15]. They reported anticholinergic side effects, loss of libido and genital anesthesia related to the dose of the drug and this is agreed by others[13-16].This drug must be administered on a chronic daily basis to achieve optimal response, on-demand administration being unpredictable and limited by significantly reduced efficacy and a delayed time of onset of clinical effect from time of administration[17].The pharmacokinetic profiles of existing selective serotonin reuptake inhibitors (SSRIs) include prolonged time to reach maximum serum concentration (T_{max}) and consequently a relatively long onset of action that need accumulation with daily dosing, this may be associated with an increased incidence of adverse effects including hypoactive sexual desire and erectile dysfunction compared to on demand dosing[17,18].

This study shows that clomipramine is effective in the treatment of premature ejaculation as daily dose when on need dose fail to achieve satisfaction and increase in IELT, although the questions were when should stop the medication, what is the optimum dose and what is the next for those who not respond should be answered. Because long-term follow-up of the patients could not be achieved we have insufficient information on whether the symptom reappears after the drug is discontinued.

Although the incidence of side effects with clomipramine was significantly higher ($p < 0.05$) compared to that of placebo, they were mild in effect as no patient withdrew from the study due to side effects, no hemodynamic

abnormalities, no loss of libido or change in potency and frequency of intercourse were observed .Furthermore, when the dose increased from 10mg to 25mg there was no significant increase in the side effects which might be attributed to the a small dose used compared to that applied in the treatment of depression and due to gradual increase of the dose itself. While patients' satisfaction in clomipramine group was significantly higher than placebo group ($p < 0.05$) we should remember that subjective estimation and questionnaire assessments of ejaculation and satisfaction may lead to a higher variability in clinical outcome measures[6].

There are several considerations in ensuring that an accurate evaluation and diagnosis of PE is performed. Of primary importance is the differentiation of PE from other sexual dysfunctions. For instance, it is common for patients with erectile dysfunction (ED) to present with the chief complaint of PE when the actual problem is the patient's haste to achieve orgasm before the failure of an erection. In these cases, successful treatment for ED may often resolve the problem.

Many obstacles are found in the management of premature ejaculation. The lack of universally accepted criteria for diagnosis of the condition, making patients identification difficult. Another limitation is the absence of a clear clinical definition and lack of normative data on ejaculatory latency time that limits the physician's capacity to evaluate and compare therapeutic strategies. There is also, the embarrassment of the patient to discuss the condition with their physician and the loss of continuous and regular medical visits because of patients not considering premature ejaculation is a distressing illness. In addition to variability in clinical outcome measures that yield from subjective estimation and assessments. Lastly the amount and nature of the sexual stimulation which may affect IELT directly (the presence or absence of foreplay) are difficult to be assess because what can be consider as excessive for one might elicit little excitement in another[17].

Advances in neurobiological research are providing insights into the mechanisms by which serotonergic agents affect the ejaculatory process and these advances give hope that therapies more specific for PE can be developed in the future and depart from the psychosexual model of treatment previously regarded as the cornerstone of treatment[18].

We can conclude that daily dose of clomipramine is an effective treatment for patients with premature ejaculation when on demand treatment failed to improve their IELT with accepted side effects. Increasing the sample size would, in our conviction, shed more light on the subjects and further strengthen the validity of our results.

Table I . Side-effects with clomipramine and placebo

side effects	clomipramine	placebo
dry mouth	2	0
Dizziness	0	0
Drowsiness	1	0
Headache	0	1
Insomnia	1	1
Fatigue	0	0
palpitations	0	0
Nausea	0	0
Reduced libido	1	0
Reduced potency	0	0
No. of patients (%)	5 (38%)	2(14%)

Table II . Sexual satisfaction rates of the patients

	Satisfied No.(%)	Moderate No.(%)	Dissatisfied No.(%)
Baseline	0	0	27 (100)
Placebo	3 (21)	4 (29)	7 (50)
Clomipramine	7 (54)	3 (23)	3 (23)

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