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ALTUĞ TUNCEL

YILMAZ ASLAN

M. MURAD BAŞAR

ALİ ATAN

TÜBİTAK

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E-mail: medsci@tubitak.gov.tr

Efficacy of Clomipramine, Sertraline and Terazosin Treatments in Premature Ejaculation

Altuğ TUNCEL[1]
Yılmaz ASLAN[1]
M. Murad BAŞAR[2]
Ali ATAN[1]

Aim: To compare the efficacy of oral clomipramine, sertraline and terazosin to placebo in premature ejaculation.

Materials and Methods: A total of 90 patients aged from 20 to 58 years were enrolled in this study. Patients were randomized into 4 groups. Group 1 (n: 22) took placebo and served as controls. Group 2 (n: 23) patients took 25 mg clomipramine HCl nightly; Group 3 (n: 20)

50 mg sertraline nightly; and Group 4 (n: 25) 5 mg terazosin nightly. The medications were used for two months. After 8 sexual attempts, the patients' clinical responses were assessed using the patient self-description method. Clinical responses were classified as "no change", "improvement" and "under control". Success was described as improvement + under control.

Results: Success rates were 36.3% in Group 1, 91.3% in Group 2, 90% in Group 3 and 76% in Group 4. Although the efficacy of each medical treatment was superior to placebo (P = 0.001), no significant difference in efficacy was found between the medical treatment groups (P = 0.537).

Conclusions: Clomipramine, sertraline and terazosin are more efficient than placebo. No significant difference was observed in terms of efficacy among these three medical treatments.

Key Words: Premature ejaculation, treatment, antidepressant, alpha blocker

[1] Third Department of Urology, Ministry of Health, Ankara Numune Research and Training Hospital, Ankara - TURKEY

[2] Department of Urology, Faculty of Medicine, Kırıkkale University, Kırıkkale - TURKEY

Prematür Ejakülasyonda Klomipramin, Sertralin ve Terazosin Tedavilerinin Etkinliği

Amaç: Prematür ejakülasyonda klomipramin, sertralin ve terazosin etkinliğini plasebo ile karşılaştırmak.

Yöntem ve Gereç: Yaşları 20 ile 98 arasında olan 90 hasta çalışmaya alındı. Hastalar randomize olarak 4 gruba ayrıldılar. Grup 1'deki 22 hastaya placebo verildi. Grup 2, 23 hastadan oluşuyordu ve her gece 25mg Klomipramin aldı. Grup 3'teki 20 hasta her gece 50mg Sertralin kullandı. Grup 4'teki 25 hasta ise her gece 5mg Terazosin kullandı. Her tedavi iki ay süre ile kullanıldı. Sekiz kez cinsel ilişki sonrasında hastaların klinik yanıtı kendi kendine tanımlama yöntemi ile yapıldı. Klinik yanıtlar "yanıt yok", "gelişme var" ve "kontrol altında" şeklinde sınıflandı. Tedavi başarısı ise gelişme var ve kontrol altında yanıtlarının toplamı olarak tanımlandı.

Bulgular: Başarı oranları Grup 1'de % 36.3, Grup 2'de % 91.3, Grup 3'de % 90, Grup 4'te ise % 76 idi. Her bir medikal tedavi plasebo'ya üstünlük göstermesine rağmen (P = 0.001), her bir medikal tedavinin etkinliği arasında fark bulunmadı (P = 0.537).

Sonuç: Klomipramin, Sertralin ve Terazosin plasebo'dan daha etkili idi. Üç medikal tedavi arasında etkinlik yönünden farklılık gözlenmedi.

Anahtar Sözcükler: Prematür ejakülasyon, tedavi, antidepresan, alfa blokör.

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Correspondence

Altuğ TUNCEL
Third Department of Urology
Ministry of Health
Ankara Numune Research and Training Hospital
06120 Ankara - TURKEY

E-mail: tuncelaltug@yahoo.com

Introduction

Premature ejaculation (PE) is a very common sexual dysfunction in the male population, affecting 30% to 40% of sexually active men in an age-dependent manner (1). This condition may be normal and temporary in adolescents, inexperienced men and in men who have abstained from sex for a long time. Although the exact etiology of PE is not well-understood, it is well known that ejaculation latency is precisely affected by psychological, cognitive and somatic factors (2).

Numerous drugs and various techniques have been used to treat this sexual dysfunction with varying degrees of success. Behavior therapy and psychological

counseling are the initial approach. However, these techniques require the active participation of both partners, and some cultural and socioeconomic groups do not participate in the therapies. Hence, some pharmacological agents such as tricyclic antidepressants, selective serotonin re-uptake inhibitors (SSRIs), topical anesthetic agents, and sildenafil citrate are recommended in the treatment of PE (3,4).

Ejaculation is mediated partly through a neural reflex stimulated by sensory input to the penis and terminating in smooth and striated muscle contractions that produce seminal emission and ejaculation (1,2). Since emission and ejaculation in normal men are mainly under the control of the sympathetic nervous system, sympatholytic agents have been used in the treatment of PE (5,6).

In the present study, we prospectively compared the efficacies of clomipramine, sertraline and terazosin with that of placebo in PE treatment.

Materials and Methods

Ninety patients 20 to 58 years old complaining of PE presented to our outpatient clinic. The study was a single blinded study. PE was defined according to the International Classification of Diseases of the World Health Organization-Version 10 as the inability to control ejaculation sufficiently for both partners to enjoy sexual interaction (7). All men were either married or had been in a stable relationship with a female sexual partner for at least 12 months.

Duration of PE in the patients ranged from 9 to 72 months (mean: 33.4 ± 18.6) and indicated the length of time that the patients considered PE as an important sexual problem.

All the patients underwent preliminary assessment including a medical and sexual history, self-administration of the first five questions of the International Index of Erectile Function (IIEF) questionnaire (8), and physical examination. Routine urine analysis, urine culture and prostate fluid examination were performed to exclude genital tract infection.

Study exclusion criteria were erectile dysfunction according to the first five questions of the IIEF (score <21), alcohol and drug abuse, mental retardation, low libido, orthostatic hypotension, thyroid disease, previous use of any drugs for PE, recent history of myocardial infarction, uncontrolled diabetes mellitus, previous history of major depression including other psychiatric or psychological illness, previous history of organic illness causing limitations in selective SSRIs use, and presence of organic disorders such as prostatitis or genital tract infection.

The 90 patients were randomized into four groups. Group 1 (n: 22) took placebo and served as controls. Group 2 (n: 23) patients took one tablet of 25 mg clomipramine HCl (Anafranil®, Geigy Inc.) (tricyclic antidepressant) nightly; Group 3 (n: 20) one capsule of 50 mg sertraline (Lustral®, Pfizer Inc.) (SSRI) nightly; and Group 4 (n: 25) one tablet of 5 mg terazosin (Hytrin®, Abbott Inc.) (alpha-1 blocker) nightly. The medications were used in all patients for two months. All patients provided informed consent.

After eight sexual attempts, the patients' clinical responses were assessed based on the patient self-description method. Their clinical responses were classified as "*no change*", "*improvement*" and "*under control*". Under control was defined as ejaculation delayed until desired by the patient and improvement was defined as an increase in ejaculation time compared to pre-treatment time. Success was described as *improvement* + *under control*. Side effects were recorded.

Statistical Analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) for Windows 8.0 software. The difference in age among the groups was calculated using one-way ANOVA test. Subsequently, the effectiveness and side effects of the treatment alternatives were compared using Pearson correlation test. A p value of less than 0.05 was considered significant.

Results

Mean age of patients was 37.6 ± 8.1 years. The median age in Groups 1, 2, 3 and 4 were 34.9 ± 9.0, 36.2 ± 7.4, 36.9 ± 6.9 and 41.8 ± 7.6 years, respectively (one-way ANOVA test, P = 0.018).

Improvement and under control ratios in each group are given in Table 1. Success rates were 36.3% in Group 1 (8/22), 91.3% in Group 2 (21/23), 90% in Group 3 (18/20) and 76% in Group 4 (19/25). Although medical treatment efficacies were superior to placebo (Pearson χ_2

Table 1. Treatment results.

	TREATMENT RESULTS			
GROUPS	No change n (%)	Improvement n (%)	Under control n (%)	TOTAL n (%)
Group 1 (Placebo)	14 (63.7)	5 (22.7)	3 (13.6)	22 (100)
Group 2 (Clomipramine)	2 (8.7)	10 (43.5)	11 (47.8)	23 (100)
Group 3 (Sertraline)	2 (10.0)	7 (35.0)	11 (55.0)	20 (100)
Group 4 (Terazosin)	6 (24.0)	9 (36.0)	10 (40.0)	25 (100)

= 23.075, P = 0.001), no significant difference was found in terms of efficacy between the medical treatment groups (Pearson χ_2=3.123, P = 0.537).

None of the antidepressants had clinically relevant effects on sexual desire, arousal, erectile function or penile rigidity. The side effects are given in Table 2. Headache, hypotension, ejaculation disorder and drowsiness were the major side effects observed in our patients. There were statistically significant differences between the active treatment groups and the placebo group with respect to these side effects (Pearson χ_2 = 22.971, P = 0.028). However, there were no significant differences in terms of the side effects between the medical treatment groups (Pearson χ_2 = 10.959, P = 0.204).

Discussion

There is no consensus about the definition of PE. Depending on the study, any ejaculation occurring within 1 to 7 minutes has been considered as premature (9-11). Others specify the number of penile thrusts, considering 8 to 15 thrusts as a criterion for PE (12). These cut-off points mentioned above for ejaculation time and thrust number were not derived from objective measurements but were subjectively chosen by the different authors. The absence of a clear, popular and widely accepted definition of PE allows a "patient-dependent" definition and a "patient-decided" diagnosis (13). Stopwatch is an objective method introduced in 1983 for measuring the outcome of the treatment results in PE. Although this method has been widely accepted to define PE and treatment response (14), in our country, the patients can not regularly use this method because it requires active involvement between patients and their partners. Hence, we preferred using the patient self-description method for assessing the treatment success.

Neurologically, the ejaculatory process is under the control of the central and peripheral nervous systems. The anterior hypothalamus is the probable region of central control of ejaculation. Within the central nervous system, serotonin seems to be an inhibitory agent on

Table 2. Side effects.

SIDE EFFECTS	Group 1(Placebo) (n = 22)	Group 2 (Clomipramine) (n = 23)	Group 3 (Sertraline) (n = 20)	Group 4 (Terazosin) (n = 25)
Headache	2	8	5	5
Hypotension	-	1	-	3
Drowsiness	-	2	3	-
Ejaculation disorder	-	-	-	2
TOTAL	2/22 (9.1%)	11/23 (47.8%)	8/20 (40%)	10/25 (4%)

ejaculatory function (15). A study by Lorrain et al. (16) suggested that the observed increase in extracellular serotoninergic system (5-HT) in both the anterior lateral hypothalamus and medial preoptic area of male rats following ejaculation may suppress subsequent ejaculation and is responsible for the ejaculatory refractory period. Different 5-HT receptor subtypes have an impact on sexual function. Animal and human psychopharmacological studies showed that PE is related to decreased central serotonergic neurotransmission, 5-HT_{2C} receptor hyposensitivity and/or 5-HT_{1A} receptor hypersensitivity. Treatment should provide 5-HT_{2C} receptor stimulation and/or 5-HT_{1A} inhibition (3,17). Also, Berendsen and Broekkamp (18) reported that activation of 5-HT_{1A} receptors in male rats with a selective agonist shortens the ejaculatory latency time. 5-HT_{2C} receptor stimulating with antidepressants exerted an ejaculation delay.

The medial preoptic area in the rostral hypothalamus and nucleus paragigantocellularis in the ventral medulla are suggested to have important roles in the process leading toward ejaculation. Electrical stimulation of the medial preoptic area promotes ejaculation. Ejaculation is tonically inhibited by serotonergic pathways descending from the nucleus paragigantocellularis to the lumbosacral motor nuclei. Disinhibition of the nucleus paragigantocellularis is supposed to lead to ejaculation (3,19).

The tricyclic antidepressant clomipramine has been shown to be effective in treating PE with different doses in several studies. Possible mechanisms for action of clomipramine include inhibition of the ejaculatory reflex, diminished psychologic arousal and anxiolytic effect (15). In a study by Kim et al. (20), clomipramine was shown to have the strongest inhibitory effect compared to the other SSRIs such as fluoxetine, sertraline, and paroxetine on hypogastric nerve stimulation-induced seminal vesicle pressure. Segraves and associates (21) showed a dose-dependent increase in intravaginal ejaculatory latency time (IELT), which was superior in the clomipramine group compared to placebo group. A study by Haensel and co-workers (22) reported that "on demand" clomipramine taken 12 to 24 hours before sexual activity was more effective than placebo.

The SSRIs enhance 5-HT neurotransmission and activate 5-HT receptors by blocking presynaptic and somatodendritic 5-HT re-uptake transporter receptors (23). SSRIs have been shown to delay ejaculation in several placebo-controlled randomized studies. In one study, sertraline treatment produced significant improvements relative to placebo in time to ejaculation and number of successful attempts at intercourse (24). Balbay et al. (25) reported that 68.7% of the patients who used 50 mg sertraline had improved ejaculatory control at the end of the second week. Another study (26) showed that the mean IELT was significantly improved after four weeks of sertraline treatment when compared to placebo.

In the present study, clomipramine and sertraline resulted in improved ejaculatory control in comparison to placebo. Nevertheless, we did not find a significant difference in effectiveness between clomipramine and sertraline. Clomipramine and sertraline are safe treatment options in rejection of or in conjunction with psychological treatment for PE. Comparison between the two types of antidepressants showed the higher efficacy of clomipramine, although it had more side effects (27). This is not found in our study. The most common side effects of clomipramine and sertraline are drowsiness, dry mouth, dizziness, dyspepsia, anejaculation, reduced libido, constipation and fatigue (22,26,27). In the present study, we did not detect any serious side effects in relation to either clomipramine or sertraline usage. The two types of medical agents were well tolerated by our patients and none of these side effects (hypotension, headache and drowsiness) was severe enough to stop the treatment.

In morphological and psychological experimental studies, it has been shown that the noradrenergic system, through ascending pathway to the brain and descending pathways to the spinal cord, and alpha-1 adrenoreceptors may regulate sexual function (1,3). Many studies have been conducted to identify alpha-1 adrenoreceptors mediating contraction in male accessory sex organs. Alpha-1 adrenoreceptors have been demonstrated in rat vas deferens and prostate (28,29). It is also known that alpha-1 adrenoreceptors play a role in the contraction of the seminal vesicle induced by catecholamines (30). The emission phase is regulated by the adrenergic system and by the release of norepinephrine. Alpha-receptor activation in the vas deferens, epididymis, prostate, and seminal vesicles facilitates copulation, emission and ejaculation. Blockage of the sympathetic ganglia by ganglionic blockers can lead to ejaculatory failure due to

inhibition of contractions of the seminal vesicle, ampulla and ductus deferens (13). Kim and co-workers (20) observed that alpha-adrenergic blockers inhibited both intraluminal seminal vesicle and vas deferens pressure responses in a concentration-dependent manner.

Alpha blockers seem to be the most suitable medical treatment option in PE based on ejaculation physiology in patients with lower urinary tract symptoms. Cavallini (5) reported that efficacies of the alpha-blocker agents such as alfuzosin and terazosin were 50% in PE unresponsive to psychological approach. Another study (6) showed that sympatholytic agents inhibited the contractile response of rat seminal vesicle to electrical nerve stimulation in an animal study. Furthermore, this study strongly suggested clinical usage of alpha-blockers because of their comparable potency with different agents.

In the present study, terazosin was found to be more effective than placebo (76% vs 36.3%). Nevertheless, no significant differences in efficacy were determined among the three drugs. Side effects of alpha-blockers are impeded orgasm, dry mouth, nasal congestion, drowsiness and fatigue. However, these have been rarely observed in therapeutic doses. The other important side effect of alpha-blockers is impaired ejaculation or retrograde ejaculation. However, with the exception of tamsulosin, no cases of abnormal ejaculation have been reported with alpha-blockers (31). In our study, no significant difference was found in terms of the side effects between terazosin and the other antidepressant drugs. Hypotension, headache and ejaculation disorder were the most common side effects related to terazosin usage. No side effects of terazosin causing treatment cessation were observed in the patients.

In conclusion, clomipramine, sertraline and terazosin are more efficient than placebo in PE treatment. These three treatment modalities demonstrated equal efficacy with the same rates of side effects and each of them was well tolerated by our patients. Each medical agent mentioned above can be used with the same efficacy and side effects, and can be chosen according to individual preference.

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