ELSEVIER

EFFICACY OF SILDENAFIL AS ADJUVANT THERAPY TO SELECTIVE SEROTONIN REUPTAKE INHIBITOR IN ALLEVIATING PREMATURE EJACULATION

JUZA CHEN, NICOLA J. MABJEESH, HAIM MATZKIN, AND ALEXANDER GREENSTEIN

ABSTRACT

Objectives. To evaluate the efficacy of sildenafil and selective serotonin reuptake inhibitor in alleviating premature ejaculation (PE) in patients in whom other treatments had failed.

Methods. Healthy men evaluated for primary PE graded their ejaculation on a scale of 0 to 8 (0 = almost never, 8 = almost always). The intravaginal ejaculatory latency time (IVELT) was graded on a scale of 0 to 3 (0 = longer than 5 minutes, 3 = shorter than 1 minute). The 138 men who scored their PE as 4 or greater and IVELT as 2 or greater comprised the study group. Psychological and behavioral counseling was provided during the study. PE was graded using the same scales 3 months after the initiation of each treatment. Topical 5% lidocaine ointment comprised the initial treatment: dissatisfied patients (PE grade 4 or greater, IVELT 2 or greater), took one tablet of paroxetine 20 mg for 30 days and then one tablet 7 hours before intercourse. Sildenafil was added to the treatment of patients dissatisfied with paroxetine alone.

Results. The mean initial PE grade was 5.67 ± 0.13 and that for IVELT was 2.9 ± 0.19 for all participants (mean age 28.7 years). Thirty-eight reported improvement (PE grade 2.0 ± 0.8, $P < 0.01$; IVELT 0.13 ± 0.34, $P < 0.001$) after local lidocaine application. Of the 100 treated with paroxetine, 42 reported improvement (PE grade 2.5 ± 0.1, $P < 0.01$; IVELT 0.28 ± 0.46, $P < 0.001$), and 56 of the remaining 58 who were treated with a combination of paroxetine and sildenafil reported improvement (PE grade 1.78 ± 0.23, $P < 0.001$; IVELT 0.16 ± 0.37, $P < 0.001$). Two patients remained dissatisfied with all treatment modalities.

Conclusions. Sildenafil combined with paroxetine and psychological and behavioral counseling alleviated PE in patients in whom other treatments failed. UROLOGY **61:** 197–200, 2003. © 2003, Elsevier Science Inc.

Ejaculation is an important element of male sexuality and has a major impact on the quality of life for most men. Premature ejaculation (PE) may be defined as inadequate ejaculatory control and a problem that affects the sexual satisfaction of both partners. PE is the most common type of male sexual dysfunction, with an estimated incidence of 30%.[1] The goal of any type of therapy for PE is to increase patient control over the timing of his ejaculation. The present study was designed to evaluate the efficacy of sildenafil as adjuvant therapy in alleviating PE.

From the Department of Urology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Reprint requests: Alexander Greenstein, M.D., Department of Urology, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 64239, Israel

Submitted: May 13, 2002, accepted (with revisions): August 12, 2002

MATERIAL AND METHODS

POPULATION

Men with primary PE treated at the erectile dysfunction clinic of the Tel Aviv Sourasky Medical Center participated in this prospective study. A total of 178 men underwent a detailed medical and sexual history, physical examination, psychological profile, and self-grading of their PE and intravaginal ejaculatory latency time (IVELT). Those with a medical history of chronic illness or concomitant medication or with erectile dysfunction were excluded, leaving 138 apparently healthy men who comprised the study group.

PE GRADING

Patients graded their ejaculatory dysfunction by answering the question: "How often did you ejaculate prematurely during intercourse during the past 3 months?" This question is the one in the Center for Marital and Sexual Health questionnaire that deals with PE.[2] The answers were graded on a scale of 0 to 8 (0 = almost never, 2 = sometimes, 4 = about one half the time, 6 = most of the time, and 8 = almost always). This question was professionally translated into Hebrew and validated in both healthy men and patients with PE. Men who graded their PE as 4 or greater were enrolled in the study.

0090-4295/03/$30.00
PII S0090-4295(02)02075-7

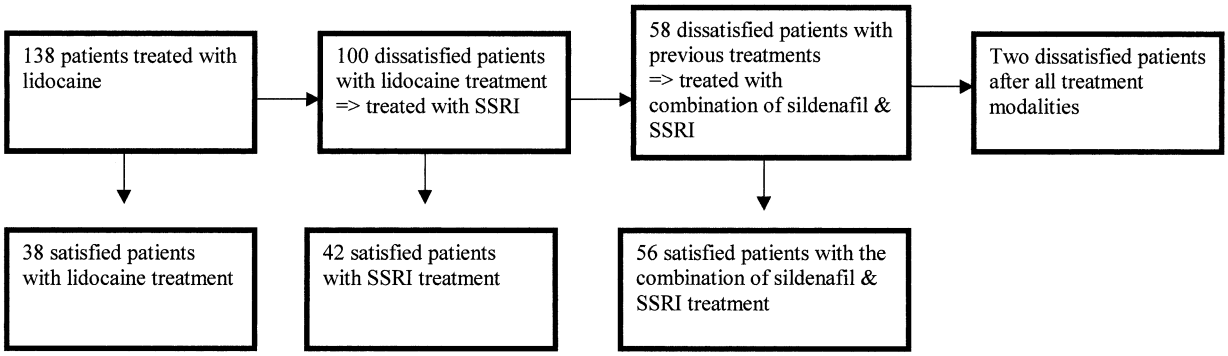

FIGURE 1. *Distribution of patients in each treatment group.*

Intravaginal Ejaculatory Latency Time

Patients graded their IVELT on a scale of 0 to 3 (0 = longer than 5 minutes, 1 = between 3 and 5 minutes, 2 = between 1 and 3 minutes, and 3 = less than 1 minute). Those with IVELT scores of 2 or greater were enrolled in the study.

Study Protocol

Psychological and behavioral counseling was provided during the study to all the study participants. This included guidance in systemic relaxation techniques and sexual stimulation without the demand for erection, ejaculation, or vaginal penetration. The initial treatment consisted of topical lidocaine ointment (5%) applied 20 minutes before intercourse. Patients who remained dissatisfied with this treatment (PE grade 4 or greater after 3 months) were given a 30-day course of a selective serotonin reuptake inhibitor (SSRI) consisting of one tablet of paroxetine 20 mg in the morning with food. After having completed this course, these patients were instructed to take one tablet 7 hours before intercourse. Sildenafil was added to the regimen of patients who were not satisfied with SSRI treatment alone (PE grade 4 or greater after 3 months). They were instructed to take one tablet of paroxetine 20 mg 7 hours before intercourse and one tablet of sildenafil 1 hour before sexual activity, 2 to 3 hours after a meal. The initial sildenafil dose in all patients was 25 mg and was increased to 50 and 100 mg until a satisfactory duration of erection was maintained, not exceeding more than one tablet per day.

The patients graded their PE and IVELT before treatment initiation and 3 months after having tried each treatment modality.

Statistical Analysis

The data were analyzed separately for successful treatment (satisfied patients) and unsuccessful treatment (dissatisfied patients) using one-way analysis of variance and analysis of variance with repeated measures. The Wilcoxon nonparametric statistic was used for the analysis of IVELT data. Spearman's rank correlation was used to analyze the PE and IVELT correlations.

RESULTS

Of 178 eligible men treated in our erectile dysfunction clinic, 138 men (mean age 28.7 years, range 18 to 35) met the entry criteria and were enrolled in the study. The mean (± SE) PE grade of the group was 5.67 ± 0.13, and the mean IVELT was 2.9 ± 0.19. Thirty-eight patients reported improvement in the severity of PE (to grade 2.0 ± 0.8, $P < 0.01$) and IVELT (to 0.13 ± 0.34, $P < 0.001$) after 3 months of local lidocaine application, leaving 100 patients who switched to the SSRI treatment. Forty-two patients (42%) treated with the SSRI alone reported improvement in the severity of PE (to grade 2.5 ± 0.1, $P < 0.01$) and IVELT (to 0.28 ± 0.46, $P < 0.001$). The remaining 58 patients in the study group who were not satisfied with the SSRI treatment were treated with a combination of paroxetine and sildenafil. Fifty-six (97%) of these 58 reported improvement in the severity of PE (to grade 1.78 ± 0.23, $P < 0.001$) and IVELT (to 0.16 ± 0.37, $P < 0.001$). Only 2 of the 138 study patients were not satisfied with the improvement of their PE with any of the three treatment modalities. Thus, 98% of the patients treated for PE were satisfied (PE grade less than 4) with our treatment protocol. The number of patients in each treatment group is presented in Figure 1. The mean ± SE values of the PE and IVELT grades before and after each treatment modality of satisfied patients are presented in Table I. The same parameters for PE and IVELT for the dissatisfied patients are presented in Table II. No correlation was demonstrated between the grade of PE or IVELT before treatment initiation and the extent of improvement, between the treatment modality and the extent of improvement, or between the PE and IVELT grades ($r = -0.02$).

COMMENT

Widely different definitions have been used to describe PE.[3] Among them are the inability to delay ejaculation sufficiently to enjoy intercourse, persistent or recurrent occurrence of ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it, and ejaculation too early for achieving satisfaction on the part of the female partner. In addition, "time," measured in minutes, such as the inability

TABLE I. *PE and IVELT grades of satisfied patients*

Treatment	Patients (n)	Before Treatment	After Treatment
Lidocaine	38		
PE		5.67 ± 0.13	2.0 ± 0.8*
IVELT		2.9 ± 0.19	0.13 ± 0.34†
SSRI	42		
PE		5.7 ± 0.14	2.5 ± 0.1*
IVELT		3.0 ± 0.2	0.26 ± 0.46†
Sildenafil and SSRI	56		
PE		5.68 ± 0.12	1.78 ± 0.23†
IVELT		2.8 ± 0.22	0.16 ± 0.37†

KEY: *PE = premature ejaculation; IVELT = intravaginal ejaculatory latency time; SSRI = selective serotonin reuptake inhibitor.*
*P *<0.01.*
†P *<0.001.*

TABLE II. *PE and IVELT grades of dissatisfied patients*

Treatment	Patients (n)	Before Treatment	After Treatment
Lidocaine	100		
PE		5.67 ± 0.13	5.71 ± 0.11
IVELT		2.9 ± 0.19	2.83 ± 0.38
SSRI	58		
PE		5.71 ± 0.11	5.69 ± 0.14
IVELT		2.83 ± 0.38	2.80 ± 0.38
Sildenafil and SSRI	2		
PE		5.69 ± 0.14	5.80 ± 0.23
IVELT		2.80 ± 0.38	2.92 ± 0.4

Abbreviations as in Table I.

to control the IVELT (ie, from initiation of vaginal penetration to ejaculation) or an IVELT of less than 1 minute, has been used, as was counting the number of penile thrusts until the occurrence of ejaculation.[3] Regardless of what terminology is chosen, PE clearly hampers the sexual satisfaction of both the affected man and his partner, often causing marked distress and interpersonal problems.

Among our patient population, we found the patient's perception of the frequency of the occurrence of PE to be more convenient for the patient than a precise measurement using the stopwatch technique of IVELT. Therefore, we chose to use a modification of question 8 of the Center for Marital and Sexual Health ejaculatory function questionnaire, requiring the answer to one question "How often did you ejaculate prematurely during intercourse during the past 3 months?"[2] In addition, we used the patient's assessment of the IVELT on a scale of less than 1 minute to more than 5 minutes.

PE has traditionally been considered to have a psychological basis, and individual, conjoint, and group psychological and behavioral techniques such as "start-stop," "squeeze technique," progressive sensate focus, biofeedback, masturbation, and "quit vagina" with the female astride have been practiced with varying degrees of success.[4] $Alpha_1$-blocking agents were found to be effective in patients who did not respond to these psychological approaches.[5] Penile hypersensitivity was proposed as an organic basis of PE,[6] and this led to the introduction of local anesthetics (prilocaine-lidocaine)[7] or SS-cream (extracts of nine natural products) applied to the glans penis before intercourse.[8] In recent years, the SSRI antidepressants were demonstrated to be effective in alleviating PE, with paroxetine inducing the strongest delay in ejaculation compared with baseline values.[9]

Our study design was that of an escalating approach to treatment. Only patients who were not satisfied with one treatment modality were offered another one, with psychological and behavioral counseling the only common denominator for all study participants. On the basis of the report by McMahon and Touma,[10] paroxetine was first ingested on a daily basis for a period of 1 month, after which it was used "on demand." However, in the current study, we found this approach to be effective in only 40% of our patients.

We demonstrated that sildenafil combined with paroxetine led to a statistically significant improvement in the PE of patients for whom treatment with paroxetine alone failed in both the PE grades and the IVELT scores. The PE grade after sildenafil combined with paroxetine treatment was better than the one after lidocaine application or paroxetine treatment alone (1.78 ± 0.23, 2.0 ± 0.8, and 2.5 ± 0.1, respectively).

Our results are supported by those reported by Abdel-Hamid *et al.*,[11] who demonstrated that patients treated with sildenafil alone reported having a prolonged IVELT. Even though our patients had good quality erections when recruited to the study, some of these satisfied patients who used the combination of sildenafil and SSRI stated that they had even better erections with this treatment. Because sildenafil seems to be effective in alleviating psychogenic erectile dysfunction, it is reasonable to consider that this drug could be effective in the treatment of primary PE, which may also be associated with similar causes. The ejaculation latency time has been reported by Balon[12] to be dependent on the erection time, and, by improving erection quality, it follows that sildenafil may have a beneficial effect on PE.

The central effect of sildenafil through nitric oxide on the ejaculation reflex could be another possible mechanism of its action on PE. Phosphodies-

terase enzymes have been found in the rat brain, and nitric oxide, the intracellular messenger of sildenafil, was reported to perform numerous physiologic functions, one of which is neural communication in the brain.[13] It has been suggested that nitric oxide activity in the medial preoptic area tonically inhibits ejaculation by decreasing sympathetic tone.[14]

Some restrictions of our study need to be addressed. First, it was not a placebo-controlled study, but rather an open-label investigation. Nine months elapsed since study enrollment for the 58 patients treated with combined sildenafil and paroxetine. It is possible that their PE could have improved after 9 months of psychological and behavioral counseling, regardless of any additional pharmacologic treatment. The long-term effects of each treatment and dropout rates are not available in our study, because satisfied patients were referred back to their community physician. Despite the statistically significant improvement in both parameters, no correlation between the PE and IVELT grades was demonstrated. This finding can be attributed to the difference in the scales of the two measurements: the PE grade used a scale of 0 to 8 and the IVELT scale was restricted to 0 to 3.

According to the findings of Abdel-Hamid *et al.*,[11] the improvement observed in our patients using combined sildenafil and paroxetine could be attributed entirely to sildenafil alone. Additional research into the role of sildenafil alone and in combination with other medications in the treatment of primary PE is recommended.

CONCLUSIONS

Sildenafil in combination with SSRI and with psychological and behavioral counseling has a major impact on patients with primary PE. The use of this combination alleviated PE in patients in whom previous treatments had failed.

ACKNOWLEDGMENT. To Pearl Lilos, B.Sc., from the Statistical Laboratory, School of Mathematics, Tel Aviv University for the statistical analysis and to Esther Eshkol, M.A., for editorial assistance in preparing this manuscript.

REFERENCES

1. Read S, King M, and Watson J: Sexual dysfunction in primary medical care: prevalence, characteristics and detection by the general practitioner. J Public Health Med **19:** 387–391, 1997.

2. Glick HA, McCarron TJ, Althof SE, *et al:* Construction of scales for the Center for Marital and Sexual Health (CMASH) sexual functioning questionnaire. J Sex Marital Ther **23:** 103–117, 1997.

3. Rowland DL, Cooper SE, and Schneider M: Defining premature ejaculation for experimental and clinical investigations. Arch Sex Behav **30:** 235–253, 2001.

4. Vale J: Ejaculatory dysfunction. BJU Int **83:** 557–563, 1999.

5. Cavallini G: Alpha-1 blockade pharmacotherapy in primitive psychogenic premature ejaculation resistant to psychotherapy. Eur Urol **28:** 126–130, 1995.

6. Xin ZC, Chung WS, Choi YD, *et al:* Penile sensitivity in patients with primary premature ejaculation. J Urol **156:** 979–981, 1996.

7. Berkovitch M, Keresteci AG, and Koren G: Efficacy of prilocaine-lidocaine cream in the treatment of premature ejaculation. J Urol **154:** 1360–1361, 1995.

8. Choi HK, Jung GW, Moon KH, *et al:* Clinical study of SS-cream in patients with lifelong premature ejaculation. Urology **55:** 257–261, 2000.

9. Waldinger MD, Hengeveld MW, Zwinderman AH, *et al:* Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. J Clin Psychopharmacol **18:** 274–281, 1998.

10. McMahon CG, and Touma K: Treatment of premature ejaculation with paroxetine hydrochloride. Int J Impot Res **11:** 241–245, 1999.

11. Abdel-Hamid IA, El Naggar EA, and El Gilany AH: Assessment of as needed use of pharmacotherapy and the pause-squeeze technique in premature ejaculation. Int J Impot Res **13:** 41–45, 2001.

12. Balon R: Antidepressants in the treatment of premature ejaculation. J Sex Marital Ther **22:** 85–96, 1996.

13. Kotera J, Fujishige K, and Omori K: Immunohistochemical localization of cGMP-binding cGMP-specific phosphodiesterase (PDE5) in rat tissues. J Histochem Cytochem **48:** 685–693, 2000.

14. Pfaus JG: Neurobiology of sexual behavior. Curr Opin Neurobiol **9:** 751–758, 1999.