Silodosin Has Nocebo Effect on Sexual Adverse Effects: A Randomized Controlled Trial

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ABSTRACT

Objective: Nocebo effect is known in patients refered to side effects of drugs that cause more side effects than expected. Side effects on sexual function have been reported in about 60% of patients using silodosin. To investigate whether there was nocebo effect of silodosin in the side effects on sexual function.

Materials and Methods: Between May 2014 and March 2017, 129 moderate-to-severe LUTS patients were included in the study. For the patients, PSA (ng/mL), prostate volume (cc), uroflowmetry test IIEF-15 and IPSS questionnaires were filled at the time of before and after treatment. Patients were divided into two groups, referred to as side effects that was mentioned and not mentioned. After 3 months control, all patients were asked whether they had sexual side effects. It was analyzed whether there was significantly differences between two groups.

Results: The groups were compared in terms of the frequency of androgenic side effects, low semen volume was 40.9% in Group 1 and 22.2% in Group 2 (p=0.04). Anejaculation rates were 6% and 4%, respectively (p=0.12); loss of libido and erectile dysfunction were observed in one patient in both groups (p=0.42). There was no statistically significant difference between the groups for anejaculation, decreased libido and erectile dysfunction. 9 patients (7%) who left medication due to side effects were excluded from the study.

Conclusion: In patients, mentioned about the sexual side effects, low semen volume was seen more frequantly, but anejaculation, decreased libido and erectile dysfunction were same. Therefore, be informed about the side effects before treatment is a matter of debate.

Keywords: Nocebo effect, silodosin, urology

Introduction

Sexual function is a condition in which couples expect each other in an interrelated fashion, and it has an important influence on enjoyment [1]. Benign prostatic hyperplasia (BPH) is most commonly associated with lower urinary tract symptoms (LUTS) and sexual dysfunction in the elderly. Numerous large-scale studies have demonstrated that sexual dysfunctions such as erectile dysfunction (ED), ejaculatory disorders (EjD), and decreased libido are associated with moderate-to-severe LUTS [2, 3].

Alpha-blockers are the first-line option for the treatment of LUTS [4]. Among them, silodosin has shown high affinity and selectivity for α-1A adrenergic receptors, which are more intense in the prostate stromal smooth muscle cells than in the other cells [5]. Treating sexual dysfunction associated with treatment of LUTS is expected. Compared with other alpha-blockers, treatment with silodosin results in the loss of ejaculation, which frequently leads to treatment discontinuation [6].

The beneficial and harmful non-specific effects associated with a drug treatment are termed the placebo and nocebo effects, respectively [7]. Because of ethical concerns, the nocebo effects have not been studied as extensively as the placebo effects [8].

In this study, we examined the occurrence of a nocebo effect linked to sexual side effects observed in patients treated with silodosin.

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Materials and Methods

We enrolled previously untreated patients with moderate-to-severe LUTS (n=129) in the study between May 2014 and March 2017. We determined prostate specific antigen (PSA) levels (ng/mL) and prostate volume (cc), and performed uroflowmetry. At the initiation of the study, the patients completed the international prostate symptom score (IPSS) and international erectile function index (IIEF-15) questionnaires. The inclusion criteria for this study were as follows: i) IPSS >7 (moderate-to-severe LUTS); ii) uroflowmeter maximal flow rate (Qmax) <15 mL/s; iii) PSA level <4 ng/mL; iv) no suspicion of cancer based on rectal examination; v) regular sexual activity for the past six months (IIEF score>25); and vi) no history of previous treatment for LUTS, prostate surgery, ureteral catheterization, diabetes, or neurogenic bladder.

All patients were randomly divided into two groups, and they were treated with silodosin 8 mg/day for three months. Patients in Group 1 were informed that although silodosin is an effective therapeutic agent for the treatment of LUTS, it might cause side effects such as low semen volume, anejaculation, loss of libido, and ED. Patients in Group 2 were also informed regarding the effectiveness of the drug; however, they were not informed about the sexual side effects associated with this treatment.

After three months, we questioned all patients individually regarding the occurrence of side effects during treatment with silodosin. The patient-reported outcomes were recorded. In addition, each patient completed the IIEF-15 questionnaire prior to and after each visit to investigate the patient's sexual desire and libido, orgasmic situation, and sexual satisfaction.

The local ethics committee approved the study. Written informed consent form was obtained from all participants.

Statistical Analysis

The Statistical Package for the Social Sciences v.15.0 (SPSS Inc.; Chicago, IL, USA) software was used for statistical analysis. Statistical analysis was conducted using the Mann-Whitney U test to examine differences between the groups. A p<0.05 denoted statistical significance.

Results

Of the 129 patients included, 9 (7%) patients discontinued the treatment due to anejaculation (6 and 3 patients in Groups 1 and 2, respectively). The mean age of patients was 63.2±4.4 years (range: 53-76 years). No significant differences were observed between the groups in terms of mean age (p=0.84), PSA level (p=0.77), prostate volume (p=0.52), Qmax values (p=0.44), libido scores (p=0.45), orgasmic scores (p=0.62), and average sexual satisfaction scores (p=0.85) using the IIEF-15 and IPSS questionnaires (Table 1).

After three months of treatment, the incidence of sexual side effects was compared between the groups. In Groups 1 and 2, the incidence of low semen volume was 40.9% and 22.2%, respectively (p=0.04). The anejaculation rates in the entire study population (including patients who discontinued treatment) were 22.7% and 14.3%, respectively (p=0.12). No statistically significant difference was observed between the groups in terms of decreased libido (p=0.52) and ED (p=0.94). Among other known side effects of silodosin, dizziness was found to be significantly higher in Group 1 than in Group 2 (p=0.037). None of the other side effects showed statistically significant differences between the groups (p>0.05).

In addition, the scores of libido, orgasmic situation, and sexual satisfaction before and after treatment were compared between the two groups using the IIEF-15 questionnaire, which revealed no statistically significant differences (p>0.05). However, statistically significant differences between before and after treatment were recorded both groups using the IPSS scores (p=0.008) and Qmax values (p=0.002).

Discussion

LUTS/BPH and sexual dysfunctions (decreased libido, ED, and EjD) are interrelated commonly reported in older males [9]. Risk factors of ED are common among patients with LUTS [10]. In the literature, a pathophysiological link between LUTS/BPO and sexual dysfunction (particularly ED) has been suggested [11].

Alpha-1A adrenergic receptors are largely distributed in the bladder neck, urethra, prostate, seminal vesicles, and vas deferens [12]. Previously, it was considered that bladder neck relaxation and low semen volume are responsible for the development of EjD. However, recent evidence has shown that tamsulosin acts on the seminal vesicle and vas deferens through a peripheral effect and on the dopaminergic and serotonergic

Table 1. Comparison of the parameters and side effects between the groups

	Group 1 (66 patients)		Group 2 (63 patients)		
Parameters	Before	After	Before	After	p*
Age average (years)	63.8	-	62.6	-	0.84
PSA value (ng/mL)	1.74	-	1.65	-	0.77
Prostate volume (cc)	54	-	58	-	0.52
IPSS score	18.2	11.4	17.4	11.1	0.81
IIEF score (1-5th and 15th questions)	28.2	28.5	28.5	28.1	0.87
Libido score (11-12th questions**)	8.2	8.4	8.5	8.6	0.45
Orgasmic score (9-10th questions**)	8.8	8.9	9.1	9	0.62
Sexual satisfaction (6-8th questions**)	13.8	14	13.7	13.8	0.85
Q max value (cc/s)	11.3	17.4	10.2	16.8	0.44
Side effect ratios and percentages of the groups					
Low semen volume n,%	27 (40,9)		14 (22,2)		0,04*
Anejaculation n,%	15 (22,7)		9 (14,3)		0,12
Erectile dysfunction n,%	2 (3)		2 (3,2)		0,94
Nasal congestion n,%	6 (9,1)		5 (7,9)		0,62
Diarrhea n,%	2 (3)		2 (3,2)		0,94
Dry mouth n,%	3 (4,5)		2 (3,2)		0,73
Dizziness n,%	12 (18,2)		3 (4,8)		0,037*
Allergic reaction n,%	0		0		-
Decreased libido n,%	2 (3)		1 (1,6)		0,52
Fainting n,%	0		0		-

PSA: Prostate specific antigen; IPSS: International prostate symptom score; IIEF: International erectile function index; Qmax: Uroflowmetric maximum flow rate

*Statistically significant when p<0.05

**The questions of the IIEF-15 questionnaire, 6-8th for sexual satisfaction, 9-10th for orgasm, and 11-12th for libido.

receptors through a central effect, which disrupts the ejaculatory function [11, 13].

Studies have reported that silodosin is the most uroselective and effective agent for ejaculation [5, 6, 11, 13]. It is thought that the effect of silodosin on dry ejaculation is largely due to a peripheral effect rather than the central nervous system [14].

Under normal conditions, in males, orgasm is in the same time as ejaculation. Orgasm occurs through the processing of sensorial stimulation of the pudendal nerve by the brain during events in the ejaculatory process [15]. In the case of EjD, it has been suggested that sensorial stimulation of the pudendal nerve originates from urethral bulb muscle contraction caused by silodosin, thus allowing the orgasmic feeling in the absence of ejaculation [14].

Some mechanisms that may be associated with the development of the nocebo effect have been proposed, including a conditioning process in which the patient learns from previous experiences, associating somatic symptoms with drug intake; psychological features such as anxiety, depression, and a tendency for somatization and situational and contextual factors [16]. Recent experimental evidence has suggested that negative verbal instincts cause anticipatory anxiety regarding increasing of approaching pain. This verbalized anxiety facilitates the transmission of pain through the activation of cholecystokinin [17].

This study analyzed real-life data to assess the relationship between the nocebo effect and sexual dysfunction in sexually active males treated with silodosin (8 mg/day) for three months. At the end of the treatment period, the incidence of low semen volume was 40.9% and 22.2% in Groups 1 and 2, respectively (p=0.04). These results confirm that the nocebo effect frequently occurs in clinical practice. The findings of this study are consistent with those of a previous study that showed significantly higher rates of sexual dysfunction among patients who are aware of potential side effects than in those who are blinded to the potential side effects [18]. Interestingly, a higher incidence of dizziness was also observed in Group 1; however, this was probably coincidental because of the limited number of patients included in the study.

In this study, only nine (7%) patients discontinued the treatment due to anejaculation. Chapple et al. [6] have reported that only 1.3% of males discontinued treatment with silodosin due to EjD, indicating that although the occurrence of anejaculation is common, the degree of discomfort is relatively low. In this study, the low discontinuation rate associated with EjD may be attributed to the high efficacy of silodosin for the treatment of LUTS, as has been demonstrated in previous studies [19].

There are a few limitations of this study. First, the relatively small sample size may have affected the power of this study. Second, analysis of semen could have been conducted prior to and after drug meetings, instead of assessing patient-reported outcomes. Third, this was not a double-blinded study.

In conclusion, the nocebo effect occurs in patients informed of the potential side effects of silodosin, with frequently reported low semen volume and anejaculation, decreased libido, and ED. Therefore, further research is warranted to investigate the importance of informing patients regarding the potential side effects prior to treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ataturk University.

Informed Consent: Written informed consent was received from all patients who participated in this study.

Peer-review: Externally peer-reviewed.

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