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ORIGINAL ARTICLE

Efficacy and safety of combined therapy with tamsulosin and tolterodine in female patients with a maximal flow rate less than 12 ml/s

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Abstract
Introduction and hypothesis We assessed the effect of tamsulosin HCl (0.2 mg) with or without tolterodine extended release (2 mg) on female patients with a maximal flow rate (Qmax) less than 12 ml/s who were suspected of having functional bladder outlet obstruction.
Methods From January 2007 to December 2008, 250 patients with a Qmax less than 12 ml/s were selected for this study. Initial drop-out rates in groups I (15.2%) and II (40.0%) are significantly different: 19 of 125 patients in groups I and 50 of 125 patients in group II failed to complete the 12-week clinical trial. The patients were treated with tamsulosin alone (0.2 mg/day; group I, $n=106$) or with tamsulosin combined with tolterodine (2 mg/day; group II, $n=75$). The effectiveness of these medications was assessed at baseline and after 12 weeks of treatment on the basis of the International Prostate Symptom Score (IPSS) and other measures including the Qmax and the postvoid residual urine volume.
Results The total IPSS, the voiding symptom score, the Qmax, and the residual urine volume were significantly improved from baseline after 12 weeks of treatment ($p<0.05$) in both groups, whereas the storage symptom score significantly improved only in group II ($p<0.05$). After 12 weeks of treatment, there were no significant differences in subjective symptom scores or objective uroflowmetric parameters between the two groups, except for storage symptoms (group I, 4.3±1.6 vs group II, 3.8±0.9) and postvoid residual urine (group I, 31.8±22.4 vs group II, 56.1±29.7), which was not considered to be clinically meaningful.
Conclusion Combination therapy with tamsulosin and tolterodine improved the subjective symptoms and uroflowmetric measures of female patients with a maximal flow rate of less than 12 ml/s. Women with a slight degree of storage symptoms will not be benefitted by prescribing anticholinergics.

Keywords Lower urinary tract · Symptom · α-Blocker · Cholinergic antagonist · Bladder outlet obstruction

Introduction

Effective voiding may be altered as the result of impaired detrusor contractility, dysfunction of bladder neck opening, or anatomical obstruction [1]. As in males, female bladder outlet obstruction (BOO) may have anatomical or functional causes. In men, α-blocker therapy is an established treatment for BOO that is related to benign prostatic enlargement; yet little is known about the effect of α-blocker therapy in women. The use of α-blockers has been reported in women with obstructed urine flow [2–4]. Athanasopoulas et al. reported that alfuzosin significantly improved the urodynamic parameters and alleviated the bothersome symptoms of patients with BOO [4].

BOO is often overlooked when diagnosing female lower urinary tract symptoms. Although BOO in women has traditionally been considered to be uncommon, recent studies have shown that it is an underdiagnosed cause of female lower urinary tract symptoms [1]. Some reports have shown that the real incidence of voiding difficulty in women is between 6.5% and 24% [5]. Diagnosing BOO in

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women is still controversial, however. Obstruction is characterized by a decreased flow rate and a high detrusor pressure, both of which are due to increased bladder outlet resistance. Groutz et al. defined urethral obstruction as a persistent low free maximal flow rate (Qmax) of less than 12 ml/s combined with high detrusor pressure at a maximum flow greater than 20 cmH_2O [6].

However, it is well known that BOO can cause irritative and obstructive symptoms. BOO in women can present in various ways. The typical complaints of slow urinary flow and difficulty emptying the bladder are not the only symptoms and can coexist with other presenting symptoms such as irritative voiding complaints secondary to BOO [7]. It would therefore be logical to expect that combination therapy with an α-blocker plus an anticholinergic drug would significantly alleviate lower urinary tract symptoms in these patients. A concern over such combination therapy is based on the theoretical danger of aggravating the obstructive symptoms and possible acute urinary retention. However, little research has been conducted on the efficacy and safety of combined therapy with α-blockers and anticholinergics in female patients with a low Qmax who are suspected of having functional BOO. Therefore, we assessed the effectiveness of administering tamsulosin HCl (0.2 mg) with or without tolterodine extended release (2 mg) in female patients with a Qmax than 12 ml/s.

Materials and methods

Subjects and study design

In this prospective study that was conducted from January 2007 to December 2008, 250 patients who predominantly presented with lower urinary tract symptoms, an International Prostate Symptom Score (IPSS) of more than 8 and a maximal flow rate of less than 12 ml/s, were selected as subjects. All patients underwent urological evaluation before treatment including a medical history, physical and neurologic examinations, urine analysis, urine culture, urethrocystoscopy, and calibration of urethral diameter to exclude anatomical BOO. Patients were randomly assigned to treatment with tamsulosin alone (0.2 mg/day, group I) or tamsulosin combined with tolterodine extended release (2 mg/day, group II) once daily. The subjects were instructed to take their medications in the evening approximately 30 min after dinner. The medication period was 12 weeks. All participants provided written informed consent with data collection and received approval from the local ethics committee and the institutional review board. The study procedures complied with the guidelines provided by the Declaration of Helsinki.

Exclusion criteria

Patients were excluded from the analysis according to the following criteria: a peak urinary flow rate less than 5 ml/s, residual urine over 100 ml/s, a history of recurrent urinary tract infections, and other urologic diseases or drug treatments that could affect bladder function or cause lower urinary tract symptoms. Patients who had received an α-blocker or anticholinergics during the 3 months before random assignment were excluded from the study. Those patients with contraindications to the use of α-adrenergic receptor antagonists or anticholinergic agents were excluded. Patients who had any possible causes of neurogenic bladder or significant pelvic organ prolapse (stage III or IV, POPQ) were also excluded.

Efficacy assessment

The effectiveness of these medications was assessed at baseline and after 12 weeks of treatment on the basis of the IPSS and other measures including the maximal urinary flow rate (Qmax) and the postvoid residual urine volume. The primary endpoint was the change from baseline in the IPSS and quality of life (QoL) score. IPSS was analyzed in terms of the total index and the storage and voiding symptom subscales. The secondary endpoint was the change from baseline in Qmax and postvoid residual urine volume.

Safety and tolerability assessment

Safety assessments at week 12 included Qmax on free uroflowmetry, postvoid residual urine volume assessment by ultrasound, changes in physical and vital signs, and any other adverse events. Reports of adverse events and withdrawals were evaluated with special attention to voiding difficulties.

Statistical analyses

SPSS (version 17 for Windows; SPSS Inc., Chicago, IL) was used for the statistical analyses. The data were expressed as means±standard deviations and were analyzed by two-sided Student's *t* tests or the Mann–Whitney test. Numerical data for the baseline state of patients and their posttreatment outcome were compared by using the chi-square test or Fisher exact test. The analysis of covariance was used to compare response to treatment between the two groups after adjustment for pretreatment value. P values<0.05 were deemed to be statistically significant. A sample size of 250 was predicted for a two-tailed α level of 0.05 with 80% power to detect a meaningful difference between the two groups in the change from baseline at 12 weeks.

Results

The mean patient age was comparable in the two groups (52.3±5.3 years in group I and 53.7±10.8 years in group II; $p>0.05$). The baseline characteristics of the two study groups are shown in Table 1. There were no statistical differences between the two groups. As shown in Table 2, the patients' chief complaints of lower urinary tract symptoms were not only voiding symptoms but also storage symptoms of nocturia (50.8%), frequency (47.5%), and urgency (33.1%).

Of the 250 patients with a Qmax less than 12 ml/s who met the inclusion criteria and were enrolled in this study, 181 women completed the study and 69 failed to do so with a drop-out rate of 27.6%. Drop-out rates in groups I (15.2%) and II (40.0%) are significantly different: 19 of 125 patients in groups I and 50 of 125 patients in group II failed to complete the 12-week clinical trial. In group I ($n=106$), the total IPSS, the voiding symptom score, Qmax, and residual urine volume significantly improved from baseline after 12 weeks of treatment ($p<0.05$; Table 3). In group II ($n=75$), the storage symptom score as well as the voiding symptom score and uroflowmetric parameters significantly improved from baseline after treatment ($p<0.05$; Table 3).

In group I, the patients' storage symptoms were not significantly relieved by treatment with tamsulosin monotherapy. After 12 weeks of treatment, there were no significant differences in subjective symptom scores or objective uroflowmetric parameters between the two groups except for storage symptoms (group I, 4.3±1.6 vs group II, 3.8±0.9) and postvoid residual urine (group I, 31.8±22.4 vs group II, 56.1±29.7). Storage symptoms improved significantly more after combination therapy than after tamsulosin monotherapy ($p<0.05$; Table 3). By contrast, postvoid residual urine increased compared with that in the monotherapy group ($p<0.05$; Table 3), but this difference was not considered to be clinically meaningful.

Statistical analysis revealed a significant improvement in the QoL score from baseline in both groups, with no significant difference between the two groups (Table 3). In the tamsulosin treatment group, the pretreatment QoL score was 4.1±0.4, whereas the posttreatment score was 3.1±0.2. In the combination group, the QoL scores before and after treatment were 4.2±0.3 and 2.9±0.2, respectively.

Four patients in group I and two patients in group II stopped taking tamsulosin because of orthostatic hypotension. In group ll, eight patients stopped their medication because of dry mouth, and five patients stopped their medication because of constipation. The overall incidence of adverse events was 8.4% in group I and 29% in group II, which was significantly different ($p<0.05$). The major adverse events in group II were dry mouth (10.7%) and constipation (6.7%). No incidence of acute urinary retention and no serious adverse events were reported in either group. The details of the adverse events in the two groups are shown in Table 4.

Table 1 Comparison of baseline characteristics between the groups

Patients' characteristics	Group I ($n=106$)	Group II ($n=75$)
Age (years)	52.2±5.3	53.7±10.8
Duration of symptoms (months)	20.1±14.3	26.9±21.5
Menopausal state, *n* (%)	38 (35.8)	28 (37.3)
Hormonal replacement therapy	4 (3.7)	2 (2.5)
Hysterectomy, *n* (%)	11 (10.3)	8 (10.6)
Additional disease, *n* (%)	44 (41.5)	25 (33.3)
Hypertension	18 (16.9)	9 (12.0)
Diabetes mellitus	8 (7.5)	5 (6.6)
Cardiovascular disease	8 (7.5)	6 (8.0)
Others	10 (9.4)	5 (6.6)
IPSS total	14.5±3.4	14.1±4.9
Voiding symptoms	9.7±3.1	9.1±3.7
Storage symptoms	4.8±0.9	5.0±1.6
QoL	4.1±0.4	4.2±0.3
Maximal flow rate (ml/s)	10.1±2.3	9.9±2.1
Residual urine (ml)	61.5±32.8	53.7±31.4

Group I: tamsulosin group (treatment with tamsulosin only); group II: combination group (treatment with tamsulosin plus tolterodine)

IPSS International Prostate Symptom Score, *QoL* quality of life

Table 2 The patients' chief complaints

Symptom	No. of patients (%)
Slow stream	132 (72.9)
Sense of incomplete voiding	125 (69.0)
Straining while voiding	121 (66.8)
Hesitancy	76 (41.9)
Nocturia	92 (50.8)
Frequency	86 (47.5)
Urgency	60 (33.1)

Discussion

Combined therapy with tamsulosin and tolterodine significantly improved both voiding symptoms and subjective storage symptoms in female patients with a low maximal flow rate of less than 12 ml/s. Furthermore, combined therapy significantly improved the Qmax and did not induce acute urinary retention except for a minimal impact on postvoid residual urine that was not considered to be clinically meaningful.

Table 3 Comparison of clinical parameters between baseline and after 12 weeks of treatment

	Group I		Group II		*p* value[a]
	Baseline	12 weeks	Baseline	12 weeks	
Initial drop-out rate (%)[b]	19/125 (15.2)		50/125 (40.0)		0.001
IPSS total	14.5±3.4	10.1±4.1*	14.1±4.9	10.6±4.1*	0.434
Voiding symptoms	9.7±3.1	6.3±2.6*	9.1±3.7	7.1±2.9*	0.122
Storage symptoms	4.8±0.9	4.3±1.6	5.0±1.6	3.8±0.9*	0.027
QoL	4.1±0.4	3.1±0.2*	4.2±0.3	2.9±0.2*	0.163
Maximal flow rate (ml/s)	10.1±4.3	13.2±3.9*	9.9±4.1	13.0±4.9*	0.549
Residual urine (ml)	61.5±32.8	31.8±22.4*	53.7±31.4	56.1±29.7	0.013

Group I: tamsulosin group (treatment with tamsulosin only); group II: combination group (treatment with tamsulosin plus tolterodine)

IPSS International Prostate Symptom Score, *QoL* quality of life

[a] The *p* value for the treatment difference between the two groups based on an analysis of covariance model

[b] The number of subjects that could not complete the study at the initial period after randomization

*$p<0.05$, compared based on a paired *t* test comparing baseline with 12-week values

The real prevalence of BOO in women is still not well known and is likely to be underestimated [8]. Recent reports have suggested that BOO is an underdiagnosed cause of female lower urinary tract symptoms with a prevalence of up to 29% in women who have undergone urodynamic study [5]. Urodynamic study currently remains the gold standard for assessing the presence of BOO by measuring Qmax and detrusor pressure at Qmax [1]. During urodynamic study, an obstruction is highly suspected when the study results show a low urine flow rate despite a detrusor contraction of adequate power [9, 10]. Axelord and Blaivas defined BOO as a sustained PdetQmax ≥20 cmH_2O combined with a Qmax ≤12 ml/s [11]. Blaivas and Groutz suggested the usefulness of the free flow rate, and they reported that BOO can be diagnosed if the free flow Qmax is ≤12 ml/s with normal detrusor power [12].

Table 4 The adverse reactions caused by treatment

Adverse events	No. of events (%)	
	Group I	Group II
Orthostatic hypotension	4 (3.7)	2 (2.7)
Incontinence	2 (1.9)	0 (0)
Lethargy	3 (2.8)	2 (2.7)
Dry mouth	–	8 (10.7)
Constipation	–	5 (6.7)
Headache	–	3 (4)
Dry eye	–	2 (2.7)
Total	9 (8.4)	22 (29)

Group I: tamsulosin group (treatment with tamsulosin only), group II: combination group (treatment with tamsulosin plus tolterodine)

However, it is difficult to diagnose BOO on the basis of urodynamic criteria only, because for women there are no cut off values for the urodynamic parameters that can be used to characterize obstruction [1]. Even though men and women share a common micturition character, the definitions that are used to describe BOO in men do not apply to women [4]. Some women habitually void urine by abdominal straining. The voiding pressures used to define obstruction in women are different from those in men because the normal voiding pressure is significantly lower in women than in men [1]. However, abnormal uroflowmetry has been used as a surrogate marker for voiding dysfunction [13]. Some authors have suggested that an abnormal flow rate of ≤15 ml/s can be used to reliably predict the patients who are more likely to have voiding disturbance [14]. In the present study, considering the invasiveness of urodynamic study and on the basis of a clinical diagnosis of suspected BOO, we included patients with a low maximal flow rate of less than 12 ml/s on free uroflowmetry.

Alpha-blocker therapy is an established treatment for BOO related to benign prostatic enlargement in men. However, little is known about the effect of α-blocker drugs in women. The use of α-blockers in women with obstructed urine flow has been reported [2–4]. Kessler et al. examined the effect of terazosin on functional BOO in women and concluded that terazosin had a significant symptomatic and urodynamic effect in two thirds of patients [3]. Athanasopoulos et al. reported that alfuzosin significantly improved urodynamic parameters and alleviated the bothersome symptoms of patients with BOO [4]. In the present study, we also observed a significant improvement in uroflowmetric parameters (Qmax, postvoid residual urine) and subjective symptom scores after tamsulosin treatment in patients with a low urine flow rate.

Women have fewer reported classic obstructive symptoms such as poor flow, hesitancy, and stranguria than do men because they void in private and have little opportunity to compare voiding patterns with others [15]. Female patients with BOO are often missed in the initial evaluation in clinics because their symptoms of voiding dysfunction are usually mixed [16]. Women with BOO most commonly present with urinary frequency, urgency, and urge incontinence as well as obstructive symptoms. Irritative lower urinary tract symptoms can be the result of detrusor instability associated with outlet obstruction [17]. In the present study, most of the patients included in the study had mixed symptoms including the storage symptoms of nocturia (50.8%), frequency (47.5%), and urgency (33.1%). Therefore, it would be logical to expect that combination therapy with an α-blocker plus an anticholinergic would significantly alleviate the lower urinary tract symptoms of such patients. Concerns related to combination therapy are based on the possibility of aggravating the obstructive symptoms and causing acute urinary retention. However, we found no significant deterioration of the uroflowmetric parameters or the subjective symptom score. As is well known, urodynamic study is extremely invasive and costly. Furthermore, it is not practical to evaluate every patient with urodynamic studies to diagnose female BOO if they have voiding symptoms and a low flow rate on free uroflowmetry. In the present study, the patient's storage symptoms were not significantly relieved by treatment with tamsulosin monotherapy. After combination therapy, however, the women's storage symptoms improved to a significantly greater degree than with tamsulosin monotherapy, but the combination therapy did not attenuate their voiding symptoms. Our results indicate that the patients included in this study benefited from the combination therapy with tamsulosin and tolterodine in terms of their storage symptoms. However, the rate of some of the adverse events was higher in the combination group (22/75) than in the tamsulosin monotherapy group (9/106).

This preliminary study had some limitations. For instance, the number of patients included in the study was very small. In addition, our study did not have a placebo control group. Thus, considering the low number of female patients with functional BOO, a multicenter, double-blind, placebo-controlled trial would be ideal to further determine the efficacy and safety of administering a combined α-blocker and anticholinergic treatment to these patients. And we could not evaluate exactly the reason of drop-out from this study. In this study subjects, they had such a high drop-out rate as 27.6% and there was significant difference between the numbers of drop-out in group I (15.2%) and group II (40%). The 50 women constituting 40% of the original attendees in goup II who failed to complete this study cannot be ignored. It is supposed that women assigned to group II did not suffer from storage symptoms severe enough to tolerate pharmacologic effects of anticholinergics, tolterodine. Considering the possible harmful effects of anticholinergics, women with slight degree of storage symptoms, which is equivalent to less than 5.0 in IPSS, will not be benefited by prescribing anticholinergics. In summary, combination therapy with tamsulosin and tolterodine improved subjective lower urinary tract symptoms and uroflowmetric measures in female patients with a low maximal flow rate of less than 12 ml/s.

Conflicts of interest None.

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