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The Efficacy of Additive Tolterodine Extended Release for 1-Year in Older Men With Storage Symptoms and Clinical Benign Proastatic Hyperplasia

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Aim: To determine the efficacy of toterodine extended release (ER) treatment for 1 year in older men with benign prostatic hyperplasia (BPH) and storage symptoms treated with alpha-blockers and/or 5-alpha-reductase inhibitors (5ARI). **Methods:** Men aged over 70 years with BPH/bladder outlet obstruction (BOO) and clinical storage symptoms were randomly treated with or without tolterodine ER in combination with alpha-blockers and/or 5ARI for 12 months. Among them, 50 patients (group 1) received additive tolterodine extended release (ER) 4 mg q.d., another 87 patients (group 2) did not. All patients had a baseline and 12th month post-treatment evaluation, which comprised of uroflowmetry, post-void residual (PVR) volume, International Prostate Symptom Score (IPSS), and quality of life index (QoL-I), transrectal ultrasound of the prostate and serum prostate specific antigen. **Results:** One hundred thirty-seven of 153 enrolled patients with a mean age of 74.9 years completed the study. Treatment benefit demonstrated in both groups included deceased total, voiding and storage IPSS scores, increased peak urinary flow rate and deceased QoL-I. Intergroup difference was only observed on the storage domain of IPSS score ($P = 0.012$). The mean PVR after treatment did not significantly differ between two groups. Two patients of group 1 and three of group 2 developed acute urinary retention. Among group 1, six patients discontinued tolterodine ER for intolerable dry mouth; among group 2, three patients reported dizziness. **Conclusions:** This longer comparative study indicated that additive treatment with tolterodine ER in older men with BPH/BOO and significant storage symptoms is a beneficial and safe therapeutic option. *Neurourol. Urodyn. 30:568–571, 2011.* © 2011 Wiley-Liss, Inc.

Key words: antimuscarinics; overactive bladder symptoms; prostate

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common condition among elderly men, occurring in up to 70% of men older than 60 years.[1] BPH associated bladder outlet obstruction (BOO) classically results in voiding symptoms including weak stream, intermittency, hesitancy, straining, or terminal dribbling and postmicturition symptoms such as feeling of incomplete emptying and postmicturition dribble.[2] However, up to half of patients suffered from storage symptoms based on a multicenter population-based study.[3] Storage symptoms are thought to be more bothersome in men than other lower urinary tract symptoms.[4]

Previous studies have shown that the gold standard of treatment of BPH is transurethral resection of the prostate (TURP). However, in most current practice patterns, uroselective alpha-1-adrenoreceptor antagonists (alpha-blocker), are often the choice of the initial therapy for symptomatic BPH. The 5-alpha-reductase inhibitors (5ARI) inhibit the conversion of testosterone to the potent androgen 5 alpha-dihydrotestosterone, which lead to decrease in 5 alpha-dihydrotestosterone and to induce prostatic epithelial apoptosis, atrophy, and reduction of size.[5] However, the mechanisms of alpha-blocker and 5ARI are unlikely to attenuate derusor overactivity (DO) and related storage symptoms.[6,7]

In urodynamic evaluation, storage symptoms are attributed to DO, which might arise secondary to BOO from BPH in men. However, the incidence is comparable between men and women, which implied that the pathophysiology of overactive bladder (OAB) might not only refer to obstruction. In addition, a proportion of men with OAB have no BOO, and about 30% of men with both OAB and BOO still have OAB symptoms after TURP.[8]

In general, storage symptoms are managed with anticholinergic drugs, because detrusor contractions are mediated by cholinergic muscarinic receptor stimulation. Although these agents are clinically effective, the higher rate of adverse effects from widespread antimuscarinic blockade (e.g., dry mouth, constipation, esophageal reflux) might complicate treatment. Recent investigators have demonstrated that several types of antimuscarinic agents are effective and safe for men with BPH and storage symptoms, which do not response to alpha blockade therapy.[9,10] However, the observation period is short and the mean age of these patients are less than 70 years old. Thus we assessed the efficacy and safety of adding an tolterodine extended release (ER) in these men with urodynamic proven BOO and OAB under combined therapy of an alpha-blocker and/or 5ARI by a observation study of an elder cohort in a 12-month duration.

Conflicts of interest: none

Chris Winters led the review process.

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METHODS

Male patients who were 70 years or older, with an IPSS score >8 and a storage subscore >5, quality of life index (QoL-I) score>3, total prostate volume (TPV) >20 ml, maximum flow rate (Q_{max}) <15 ml/sec, and with urodynamic confirmed BPH/BOO were enrolled.

Patients were assigned to receive additive tolterodine ER therapy or not by simple randomization at enrollment. They received an alpha-blocker (doxazosin extended release 4 mg q.d.) and/or 5ARI (dutasteride 0.5 mg q.d.) for BPH/BOO with or without adding an tolterodine ER 4 mg q.d. Patients with a TPV of more than 30 ml were treated with 5ARI and alpha-blocker. Patients with a TPV less than 30 ml were treated with alpha-blocker alone. None of the patients received 5ARI alone.

BPH was also evaluated by transrectal ultrasound of the prostate for TPV and transitional zone index (TZI). Prostate specific antigen (PSA) level was also evaluated in each patient. Prostate biopsy was performed to exclude prostate cancer if the PSA level was greater than 4 ng/ml. Exclusion criteria included abnormal digital rectal examination, previous medical therapy or surgery for BPH, previous or current pharmacological therapy including an alpha-blocker, finasteride or antimuscarinic agents, urinary tract infection, indwelling urethral catheter and previous urinary retention or PVR > 250 ml. Men with history of malignancy of genitourinary tract, neurological diseases (stroke, diabetes, multiple sclerosis, Parkinson's disease), symptomatic congestive heart failure, and chronic kidney disease were excluded.

This study has been approved by the Institution Review Board and Ethics Committee of this hospital. Informed consent was obtained from all participants before clinical data collected. During the initial screening visit a urological history was taken and the men had a thorough physical examination. All men had video-urodynamics, uroflowmetry, PVR measurement and completed the IPSS-voiding, IPSS-storage and IPSS-total at baseline. The objective parameters and IPSS scores were also completed by all patients after 12 months.

The efficacy at primary end-point of this study was assessed by the improvement of IPSS subscores (voiding and storage IPSS) at 12 months compared to the baseline values. A successful outcome was considered if a reduction of IPSS score by 25% was achieved at 12 months. The safety profile was assessed via patients' self-reported adverse events, and drop-out rate due to adverse events during the study period.

Results were assessed statistically using a commercially available data analysis package. End point values after 12 months of treatment were compared to baseline values using the Student *t*-test. The values are expressed as the mean ± standard deviation, with $P < 0.05$ considered to indicate significant differences.

RESULTS

A total of 153 patients aged 70 years or older were prospectively enrolled at baseline. However, 16 patients did not continue treatment for 12 months due to personal reasons or discontent with long-term medical treatment, leaving 137 men in the final statistical analysis. A total of 50 men received tolterodine ER plus alpha-blocker and/or 5ARI (group 1, mean age 73.6 ± 2.3 years); 87 men received alpha-blocker and/or 5ARI only (group 2, mean age 77.2 ± 3.7 years). Among them, 24 patients (48%) in group 1 and 47 (54%) in group 2 had urodynamic DO at baseline. No significant difference in urodynamic DO was noted between the two groups.

The mean IPSS-voiding, IPSS-storage, IPSS-total, and QoL-I scores improved similarly in both groups by 12 months follow-up (Table I). The patients in group 1 experienced a better reduction of IPSS-storage symptoms (4.26 vs. 1.42, $P < 0.001$). However, the change of PVR in group 1 after intervention did not significantly differ from group 2 (15.2 vs. 8.9 ml, $P = 0.690$). The mean serum PSA and TPV as well as TZI were reduced in the both groups. Patients receiving additive tolterodine ER also demonstrated a significant improvement in Q_{max} (11.1 ± 5.34 vs. 9.03 ± 4.27 ml/sec, $P < 0.05$) as well those in the non-additive treatment group (11.3 ± 5.16 vs. 8.7 ± 4.04 ml/sec, $P < 0.05$). The incidence of acute urinary retention requiring catheterization was similar in both groups, 2 (4%) in group 1 and 3 (3.5%) in group 2. The differences of the improvements on abovementioned domains were not statistically significant between two groups as the Table II shows.

TABLE I. The Changes of IPSS, Uroflow, and Prostate Volume Parameters From Baseline to 12th Month

	Baseline	12th month	*P*-Value
Patients with additive tolterodine ER			
IPSS (voiding)	8.50 ± 6.81	2.88 ± 3.43	<0.001
IPSS (storage)	9.44 ± 3.01	5.18 ± 2.62	<0.001
IPSS (total)	18.1 ± 8.30	8.06 ± 4.54	<0.001
QoL	4.06 ± 1.17	2.22 ± 0.97	<0.001
Q_{max} (ml/sec)	9.03 ± 4.27	11.1 ± 5.34	0.012
Voided vol. (ml)	134 ± 117	150 ± 103	0.239
PVR (ml)	75.2 ± 84.9	66.7 ± 56.0	0.174
TPV (ml)	49.2 ± 26.3	39.7 ± 15.3	0.001
TZI	0.46 ± 0.13	0.44 ± 0.11	0.039
PSA (ng/ml)	3.44 ± 1.55	2.00 ± 1.67	<0.001
Patients without additive tolterodine ER			
IPSS (voiding)	9.83 ± 5.66	4.78 ± 4.54	<0.001
IPSS (storage)	8.34 ± 2.51	6.92 ± 2.06	<0.001
IPSS (total)	18.2 ± 6.59	11.7 ± 5.61	<0.001
QoL	3.92 ± 1.18	2.46 ± 0.83	<0.001
Q_{max} (ml/sec)	8.70 ± 4.04	11.3 ± 5.16	<0.001
Voided vol. (ml)	162 ± 120	190 ± 113	0.037
PVR (ml)	81.6 ± 87.6	72.7 ± 65.3	0.381
TPV (ml)	53.3 ± 22.1	44.2 ± 21.5	<0.001
TZI	0.47 ± 0.15	0.43 ± 0.13	0.001
PSA (ng/ml)	3.90 ± 2.06	2.93 ± 3.53	0.013

Data are expressed as mean ± standard deviation.
IPSS, International Prostate Symptom Score. Voiding symptoms: incomplete emptying, straining, intermitency, and weak stream. Storage symptoms: frequency, urgency, and nocturia. QoL, quality of life index; Q_{max}, maximum flow rate; PVR, postvoid residual; TPV, total prostate volume; TZI, transition zone index; PSA, prostate specific antigen.

TABLE II. The Changes of IPSS, Uroflow, and Prostate Volume Parameters From Baseline to 12th Month Between Patients With and Without Additive Tolterodine ER

Change	With tolterodine ER	Without tolterodine ER	*P*-Value
ΔIPSS (voiding)	4.62	5.05	0.726
ΔIPSS (storage)	4.26	1.42	**<0.001**
ΔIPSS (total)	8.88	6.47	0.116
ΔQoL	1.62	1.46	0.551
ΔQ_{max} (ml/sec)	1.64	2.60	0.275
ΔVoided vol. (ml)	14.0	27.7	0.483
ΔPVR (ml)	15.2	8.90	0.690
ΔTPV (ml)	9.53	9.13	0.877
ΔTZI	0.03	0.04	0.671
ΔPSA (ng/ml)	1.43	0.97	0.434

IPSS, International Prostate Symptom Score; QoL, quality of life index; Q_{max}, maximum flow rate; PVR, postvoid residual; TPV, total prostate volume; TZI, transition zone index; PSA, prostate specific antigen.

Regarding the adverse effects, intolerable dry mouth was reported in 7 (14%) and 5 (5.7%), blurred vision in 2 (4%) and 4 (4.6%), increased severity of constipation in 4 (8%) and 2 (2.3%); and dizziness in 3 (6%) and 3 (3.4%) patients of the groups 1 and 2, respectively. Among group 1, six patients discontinued tolterodine ER for intolerable dry mouth. There was no significant difference of adverse events between two groups except dry mouth, which occurred significantly greater in group 1.

DISCUSSION

BPH/BOO and lower urinary tract symptoms (LUTS) are common generally associated with aging. Though voiding symptoms are more common, the storage symptoms are usually more bothersome and significantly affect the quality of life. DO, a urodynamic finding characterized by involuntary detrusor contractions during the bladder storage phase, is thought to be the main etiology of storage symptoms. DO is not uncommon in subjects of BPH/BOO and the probability increased with ageing.[11] Unfortunately, DO might persist after TURP and lead to unsatisfactory surgical outcomes,[8,12] which implied that another unclear mechanisms associated with urothelium and bladder neck might play roles in storage symptoms of patients with BPH/BOO.[12]

Antimuscarinic agents are usually effective for treatment of OAB, which suggests that muscarinic receptors are involved in the pathogenesis of LUTS. In addition to blockade of muscarinic receptors on the detrusor to decrease bladder contraction by interrupting parasympathetic impulses, local inhibitory effect on receptors located on the urothelium have been also demonstrated by intravesical administration of antimuscarinic agents.[13] In contrast to women with OAB as well as DO, the use of antimuscarinic agents in men with BPH/BOO and OAB are not common. For instance, antimuscarinic agents have historically been contraindicated in patients with LUTS associated with BPH because of concerns for developing acute urinary retention especially in older men, who have a decreased detrusor contractility.

In a recent large scale retrospective study, Morant et al.[14] found that only 6–7% of men with storage LUTS received antimuscarinics. In terms of the guideline established by American Urological Association (AUA) or European Association of Urology (EAU), antimuscarinic agents are not recommended for men with BPH. Athanasopoulos et al. reported the first randomized controlled trial to evaluate the effect of tolterodine combined with tamsulosin on quality of life in patients with BOO and concomitant DO. In this prospective study, the men treated with a combination therapy enjoyed a significant reduction in maximum detrusor pressure during micturition (Q_{max}), a significant increase in bladder capacity, lower maximum unstable contraction pressure, and higher volume at first unstable contraction. They concluded that combination therapy of muscarinic antagonist and alpha-blocker is effective and safe for male with BOO and DO.[15]

Recently, Abrams et al. conducted a multicenter, multinational, double-blind study with a larger case number to evaluate the safety of tolterodine versus placebo in men with OAB and BOO. A total of 221 men were randomized to tolterodine ($n = 149$) versus placebo ($n = 72$) after excluding those who have PVR of 40% or more of maximum cystometric capacity or had prior prostate or bladder surgery. They were followed for 3 months with urodynamics and for adverse events. Based on their findings, the improvements from baseline in Q_{max} and detrusor pressure at Q_{max} for both groups were statistically equivalent.[16] Kaplan et al. also reported the TIMES (Tolterodine and Tamsulosin In Men with LUTS Including OAB: Evaluation of Efficacy and Safety) study and demonstrated that men with BPH and OAB showed significant improvements in LUTS with tolterodine ER plus tamsulosin, compared with placebo or tolterodine ER or tamsulosin alone. In contrast to the study published by Abrams et al.[16] In this well-designed randomized controlled study, the investigators excluded the subjects who had a PVR >200 ml or $Q_{max} < 5$ ml/sec.[10]

In another study conducted by Lee et al.[17] who also attempted to assess the efficacy of combined treatment with doxazosin and tolterodine for men with BOO and OAB, the exclusion criteria is PVR >150 ml. Kaplan et al.[18] have reported a study, which evaluated and followed 43 men for 6 months, found that tolterodine ER is efficacious in treating men with BPH and OAB symptoms, which did not respond to alpha-blockers. In their study, they excluded the subjects of low Q_{max} as 4 ml/sec.[18] Taken together, no clinical parameter obtained by uroflowmetry or urodynamics could contraindicate the use of muscarinic receptor antagonist in these patients is established by a consensus.

The results of this study are consistent with previous studies in men with BPH and OAB symptoms. The additive tolterodine to an alpha-blocker and/or a 5ARI for elderly patients with BPH/BOO and OAB, is well tolerated and more efficacious in improving storage symptoms. On the other hand, the present study presents a longer investigation period with a significant patient number, though a shortcoming was the lack of randomization in study design. Besides, the mean age of these observed patients is higher than abovementioned studies. Our data support the interpretation by Malone-Lee et al.[19] who concluded that tolterodine is safe in the treatment for older patients.

The incidence of adverse events including dry mouth or urinary retention in our present study is similar to other previous studies. Combination antimuscarinic and alpha-blocker therapy and/or 5ARI for BPH/BOO and OAB in elderly men does not significantly increase the incidence of urinary retention nor increased PVR. This study supported that combined therapy with alpha-blocker and anticholinergics may be more beneficial than monotherapy for LUTS.[20]

The unique aspect of this study is the older age in patient population, who are more likely to be bothered by storage symptoms. The results of this study revealed that additive antimuscarinics is effective and safe in reducing the storage symptoms in older patients with BPH/BOO.

CONCLUSIONS

The observational study of an older cohort with a longer treatment period and the results suggest that additive tolterodine ER is an effective and well tolerated treatment for older men with storage symptoms secondary to BPH/BOO. A well-designed, prospective randomized, controlled study is warranted to increase the level of evidence.

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