

# Efficacy and safety of low-dose anticholinergics to treat men with lower urinary tract symptoms with overactive bladder: a retrospective study based on real life practice

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**Purpose:** To investigate whether combination treatment using an  $\alpha$ -blocker and 2 mg of tolterodine could improve the International Prostate Symptom Score (IPSS) as much as  $\alpha$ -blocker and 4 mg of tolterodine without voiding difficulties in real life practice.

**Methods:** We retrospectively recruited patients who were treated at four urology clinics between January 2006 and May 2008. A total of 1,094 men with lower urinary tract symptoms/overactive bladder (LUTS/OAB) were assigned to one of three groups: an  $\alpha$ -blocker only group (group I, n=152), an  $\alpha$ -blocker plus tolterodine 2 mg group (group II, n=520), and an  $\alpha$ -blocker plus tolterodine 4 mg group (group III, n=574). Eligible patients were 50 years or older men who had a total IPSS of 8 or higher and a IPSS storage subscore of 5 or higher and were followed up for 12 weeks.

**Results:** The total IPSS score and quality of life scores were significantly improved at week 12 in groups II and III. The incidence of acute urinary retention was similar between both combination treatment groups, but the incidence of voiding difficulty was much lower in group II (2.1%) than group III (10.8%) tolterodine.

**Conclusions:** Our results suggest that treatment of LUTS/OAB patients with an  $\alpha$ -blocker plus tolterodine 2 mg is as effective as  $\alpha$ -blocker plus tolterodine 4 mg, and the incidence of voiding difficulty was in the low-dose anticholinergic is lower. These results indicate that dose strength should be decided on a case-by-case basis to balance the efficacy and safety.

**Keywords:** Lower urinary tract symptoms, Adrenergic alpha-antagonist, Overactive urinary bladder, Cholinergic antagonists

## INTRODUCTION

Lower urinary tract symptoms (LUTS) and overactive bladder (OAB) are highly prevalent in the adult population, and the prevalence increases along with age [1,2]. OAB, which is defined by urgency, frequency, and nocturia, with or without incontinence, affects 15.6% of men aged 40 years and older in

European countries [3]. Storage/OAB symptoms are bothersome to patients, interfere with daily activities, and have a negative impact on patients' quality of life (QoL) [4].

Generally, women patients who complain of OAB are treated with anticholinergics as a first-line drug [5]. However, in male OAB patients, muscarinic receptor antagonists are not widely used because of the risk of urinary retention.

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Recently, several randomized trials have revealed that muscarinic receptor antagonists are effective and safe to be used in male OAB patients [6-8].

Despite these reports, however, physicians have been reluctant to use muscarinic receptor antagonists in real life practice, mainly because they often encounter patients who experience mild to moderate voiding difficulty after treatment with  $\alpha$ -blockers and anticholinergics.

Herein, we investigated whether combination treatment using an  $\alpha$ -blocker and 2 mg of tolterodine improved the storage subscore of the international prostate symptom score as much as a combination of  $\alpha$ -blocker and 4 mg of tolterodine without voiding difficulty in men with LUTS/OAB symptoms in a clinical setting.

## MATERIALS AND METHODS

### 1. Patients

Patients were retrospectively recruited from those who were treated at four urology clinics in Korea between January 2006 and May 2008. A total of 1,094 men with benign prostatic hyperplasia (BPH) and OAB were included in this study.

Eligible patients were men who were 50 years or older, had an International Prostate Symptom Score (IPSS) of 8 or higher and an IPSS storage subscore of 5 or higher, and were followed up for 12 weeks with the same drugs.

The exclusion criteria were as follows: men with clinically significant bladder outlet obstruction (BOO; defined as a post-voided residual volume (PVR) >200 mL and a maximal urinary flow rate <5 mL/sec), serum prostate-specific antigen (PSA) of more than 10 ng/mL with risk of prostate cancer, history of some neurologic condition affecting bladder function (e.g., multiple sclerosis, spinal cord injury, Parkinson's disease), prostate cancer, prior surgery of the prostate or bladder, acute urinary retention (AUR) requiring catheterization, BOO due to causes other than BPH, history of treatment with a drug affecting voiding function such as an  $\alpha$ -blocker within 2 weeks, anticholinergics within 1 month, or a 5 $\alpha$  reductase inhibitor within 3 months. Of patients who were prescribed tolterodine 2 mg at baseline, 141 patients were also excluded as the dose was increased to 4 mg during the 12-week period of treatment because of no improvement in storage symptoms. The Institutional Review Board of our institution approved this study.

### 2. Study design

All subjects were divided into three groups according to the physician's preference: an  $\alpha$ -blocker group (group I, n=152),

an  $\alpha$ -blocker plus tolterodine 2 mg group (group II, n=520), and an  $\alpha$ -blocker plus tolterodine 4 mg group (group III, n=574). Four urologists treated their patients based on the personal preferences. When subjects experienced grade 3 urgency (voiding cannot be delayed for more than 15 minutes, proposed by De Wachter and Wyndaele [9]) at least once a day through 3 days of voiding diary, we subscribed combination drugs ( $\alpha$ -blocker plus tolterodine). Of these, subjects who had less than 100 mL of PVR were assigned to group III, subjects with greater than 100 mL of PVR in group II. The remaining subjects formed group I.

Serum PSA levels, maximal flow rate (Q<sub>max</sub>) according to uroflowmetry (Uroflow 1000, Medtronic, Minneapolis, MN, USA) PVR (BladderScan BVI 3000, Verathon Inc., Bothell, WA, USA), and prostate volume (Pro Focus Ultra View type 2202, BK Medical Aps, Peabody, MA, USA) at baseline were evaluated in all patients.

Total IPSS score and QoL score were assessed at baseline and at week 12, and are reported as changes from baseline values. Patients were asked about adverse events at every visit, and all adverse events were recorded. Voiding difficulty was defined as an adverse event if the subject complained of new bladder emptying symptoms after 2 weeks of receiving the study medications.

### 3. Statistical analysis

Based on the characteristics of the data, mean  $\pm$  standard deviations were calculated. The paired *t*-test was used to compare data before and after the 12-week treatment for each group. One-way analysis of variance was used to compare data among the three groups. When significance was detected, Scheffé's test was used to ascertain intergroup significance. Values of *P*=0.05 were considered significant.

## RESULTS

Patients demographic and baseline clinical characteristics are summarized in Table 1. The mean subject age was 65.1 years old (range, 40 to 75 years). There were no significant differences in age, prostate volume, PSA levels, or the mean Q<sub>max</sub> among the three groups.

The total IPSS score, IPSS voiding & storage subscores, and QoL score were significantly improved at week 12 after therapy compared to baseline in all three groups (Fig. 1). IPSS subscores for storage symptom and urgency were only significantly improved in the combination therapy groups even though group III was more effective in terms of urgency compared to group II (Figs. 1, 2). However, there was no sig-

nificant difference in the change in IPSS storage subscores and QoL between groups II and III (Fig. 2).

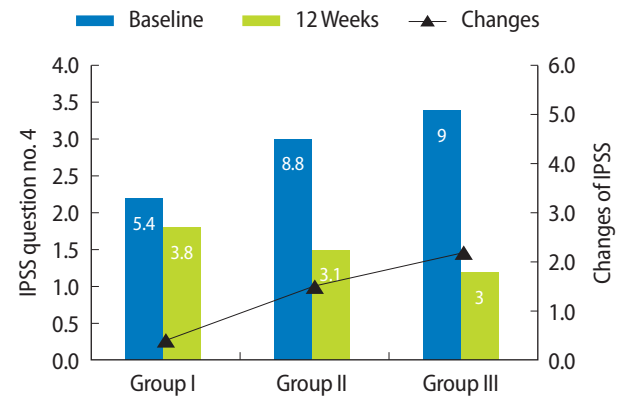
Patients in the combination therapy groups experienced

**Table 1.** Subject characteristics of the  $\alpha$ -blocker-only group and the two combination therapy groups

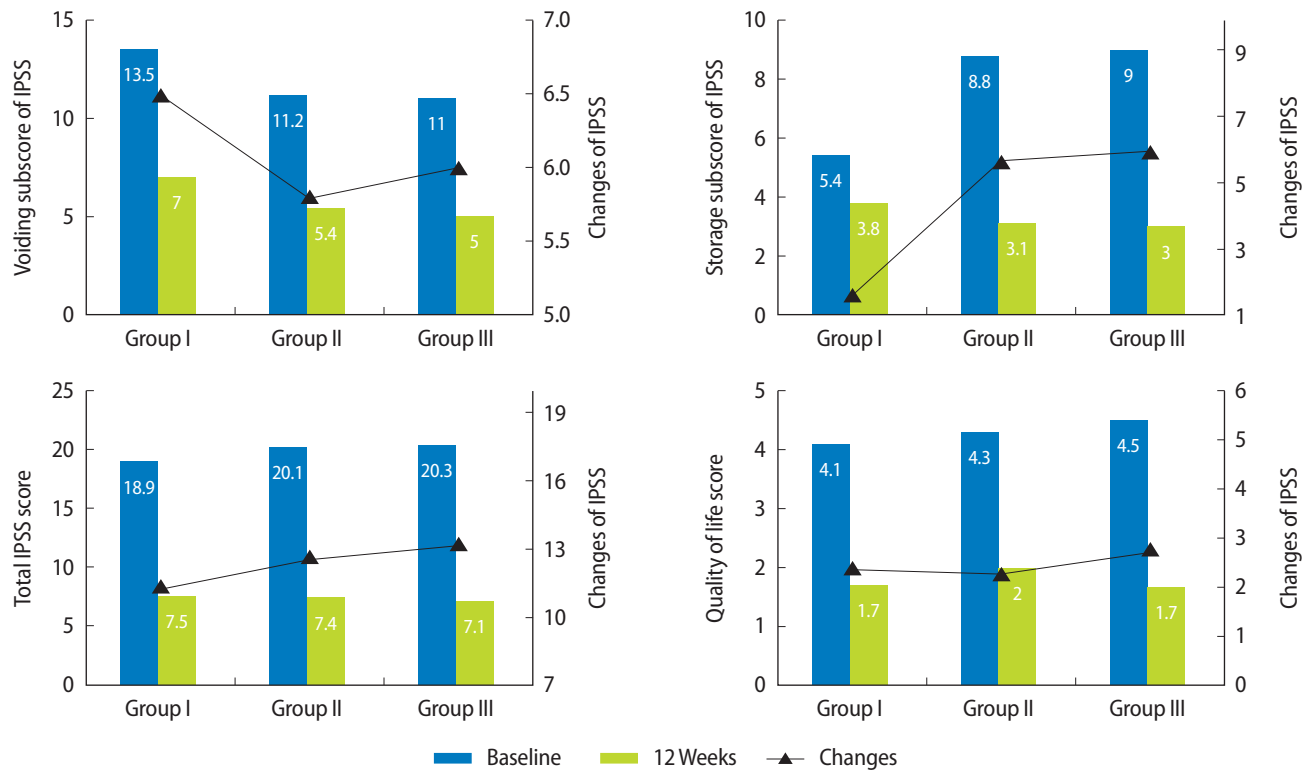
Characteristic	$\alpha$ -blocker	$\alpha$ -blocker+ tolterodine SR 2 mg	$\alpha$ -blocker+ tolterodine SR 4 mg	P-value*
No. of patients	152	520	574	
Age (yr)	63 $\pm$ 3.4	66 $\pm$ 4.3	65 $\pm$ 3.7	0.57
Prostate volume <sup>a)</sup> (g)	29.4 $\pm$ 12.4	30.8 $\pm$ 18.3	30.9 $\pm$ 17.3	0.76
PSA (ng/mL)	1.89 $\pm$ 1.3	1.88 $\pm$ 0.7	1.92 $\pm$ 1.0	0.19
Qmax <sup>b)</sup> (mL/sec)	9.6 $\pm$ 2.6	10.3 $\pm$ 5.4	10.1 $\pm$ 4.6	0.24
Total IPSS score	18.9 $\pm$ 7.7	20.1 $\pm$ 9.3	20.3 $\pm$ 9.2	0.05
Voiding subscore	13.5 $\pm$ 4.5	11.2 $\pm$ 5.1	11.0 $\pm$ 5.2	0.12
Storage subscore	5.4 $\pm$ 3.0	8.8 $\pm$ 3.7	9.3 $\pm$ 4.1	0.01
Q #1 frequency	1.9 $\pm$ 1.3	3.4 $\pm$ 1.3	3.6 $\pm$ 1.3	0.03
Q #4 urgency	1.5 $\pm$ 1.4	3.0 $\pm$ 1.5	2.7 $\pm$ 1.6	0.01
Q #7 nocturia	1.0 $\pm$ 1.0	2.9 $\pm$ 0.7	3.0 $\pm$ 0.8	0.02
Quality of life	4.1 $\pm$ 1.0	4.3 $\pm$ 1.1	4.5 $\pm$ 1.3	0.56

Values are presented as mean  $\pm$  standard deviation. PSA, prostate-specific antigen; Qmax, maximal urine flow. <sup>a)</sup>Measured by transrectal ultrasound. <sup>b)</sup>Measured by uroflowmetry. \*P<0.05 among the three groups by analysis of variance, no statistical difference between the tolterodine 2 mg and 4 mg combination therapy groups.

symptoms such as dry mouth and voiding difficulty. More group III patients complained of adverse events than those in group II. However, the incidence of AUR was not significantly different among the three groups (Table 2).



**Fig. 2.** Comparison of International Prostate Symptom Score (IPSS) scores on urgency according to treatment regimen. All subjects were assigned to one of three groups: an  $\alpha$ -blocker group (group I), an  $\alpha$ -blocker plus tolterodine 2 mg group (group II), and an  $\alpha$ -blocker plus tolterodine 4 mg group (group III). Significant difference between baseline results and those measured at 12 weeks. There were no significant change in the urgency score between baseline and 12 weeks between groups II and III (P=0.09).



**Fig. 1.** Comparison of the efficacy of the three regimens. All subjects were assigned to one of three groups: an  $\alpha$ -blocker group (group I), an  $\alpha$ -blocker plus tolterodine 2 mg group (group II), and an  $\alpha$ -blocker plus tolterodine 4 mg group (group III). All groups showed a significant difference in baseline scores and scores at 12 weeks. IPSS, International Prostate Symptom Score.

**Table 2.** No. of patients that experienced adverse events according to treatment group

	No. of $\alpha$ -blocker	No. of $\alpha$ -blocker+ tolterodine SR 2 mg	No. of $\alpha$ -blocker+ tolterodine SR 4 mg
Dizziness	3 (0.2)	4 (0.7)	6 (1.8)
Dry mouth	0 (0)	13 (2.5)	52 (9.0)
Voiding difficulty	0 (0)	11 (2.1)	62 (10.8)
AUR	1 (0.6)	2 (0.3)	3 (0.5)

Values are presented as number (%).  
AUR, acute urinary retention.

## DISCUSSION

The combination therapy with 2 mg of tolterodine and an  $\alpha$ -blocker was effective and had a lower rate of adverse events than the one combining 4 mg tolterodine and an  $\alpha$ -blocker. Therefore, the combination therapy with 2 mg of tolterodine is reasonable for patients with LUTS and mild to moderate voiding urgency.

Alpha-1-adrenergic antagonists are widely used to treat LUTS because of their rapid effects and safety. In patients with LUTS accompanied by OAB, however, monotherapy with an  $\alpha$ -blocker is not effective [10].

Therefore, it would be logical to assume that adding an anticholinergic would be helpful for the management of these symptoms. However, anticholinergics decrease bladder contractility by blocking acetylcholine binding at muscarinic receptors in the bladder. These effects do not inhibit overactive detrusor contraction. However, they may theoretically exacerbate voiding symptoms, residual urine volume or, even worse, provoke AUR.

Abrams et al. [6] randomly treated 221 men with urodynamically verified (BOO) with oral tolterodine 2 mg for 12 weeks. Changes from baseline urodynamics in the patients treated with tolterodine were statistically equivalent to those who received a placebo. The median increase in PVR was significantly greater in the tolterodine group (25 mL) than the placebo group (0 mL). AUR was reported in one patient in each group.

Kaplan et al. [11] treated 39 men who did not respond to  $\alpha$ -blocker therapy for 5.7 months with tolterodine 4 mg monotherapy for 6 months. They concluded that monotherapy with 4 mg of tolterodine induced a significant increase in the Qmax of patients and decreased PVR, in contrast to the results reported by Abrams et al. [6].

These contradicting safety findings indicate that large, placebo-controlled studies in men with OAB symptoms and other LUTS are needed to confirm the efficacy and safety of

anticholinergics.

In a meta-analysis of randomized controlled trials which used anticholinergics to treat OAB, most anticholinergics were safe and effective except oxybutynin which significantly increased the risk of AUR compared with placebo [12].

Despite the evidence that anticholinergics can safely and effectively treat OAB symptoms in men, only 40% of men with OAB symptoms who received drug treatment were prescribed anticholinergics [13]. Recent studies suggest that a combination of antimuscarinic and  $\alpha$ 1-receptor antagonist may more effectively reduce male LUTS than the use of  $\alpha$ 1-receptor antagonists alone.

Athanasopoulos et al. [8] used a combination of tamsulosin 0.2 mg and tolterodine 2 mg to treat 50 patients with BOO and detrusor overactivity, and reported improvement in QoL and bladder volume. Furthermore, no AUR occurred in any of the patients.

A few randomized controlled trials have demonstrated that anticholinergics are a safe option in patients with mild to moderate risk of BOO [7,14,15].

However, previous studies of the safety of medications focused on the rate of urinary retention or increased residual volume rather than voiding difficulty as a subjective symptom after treatment. Based on our clinical experience, however, patients who take anticholinergics may complain of voiding difficulty without urinary retention or increased residual volume. In this study, only 5 subjects who were treated with combination therapies complained of AUR during the study period. However, 14.6 times more subjects ( $n=73$ ) complained of voiding difficulty in combination therapy groups. These showed the high prevalence of voiding difficulty compared to previous studies [7,14,15]. This could be attributed to the fact that we included mild to moderate symptoms of voiding difficulty. Actually, AUR frequently occurs in subjects with severe voiding difficulty. Although it may not be considered as a serious issue to many other investigators, we believe that subjective symptoms should not be neglected.

Because we think previous studies did not well reflect real life practice in respect of safety of regimen, in this study, we investigated the optimal combination dose of anticholinergics and  $\alpha$ -blocker to minimize urinary or nonurinary side effects and maintain the efficacy of the combination therapy. We found that 2 mg of tolterodine and an  $\alpha$ -blocker regimen was effective in patients with OAB and resulted in much less voiding difficulty and dry mouth symptoms than combination therapy with tolterodine 4 mg. Therefore, we suggest that a combination therapy of an  $\alpha$ -blocker and tolterodine 2 mg is a feasible regimen in male patients with mild-to-moderate

OAB and patients who present severe storage symptoms and want to minimize dry mouth symptom and voiding difficulty.

There were some limitations in this study. First, our analysis was based on the results of an open-label, retrospective, observational study without a placebo control, which limits interpretation of the data. However, the study included a large number of subjects, which allowed analysis of multiple subgroups. Furthermore, as patients were treated and data were recorded under real-life conditions, the findings are likely to be applicable in clinical practice.

A second limitation of this study was that the follow-up period was relatively short compared to other studies. However, we believe that a period of 12 weeks is reasonable to evaluate the efficacy and safety of a drug regimen.

In conclusion, our results suggest that treatment of LUTS/OAB patients with an  $\alpha$ -blocker plus tolterodine 2 mg resulted in less side effects and was as effective as treatment of LUTS/OAB patients with an  $\alpha$ -blocker and tolterodine 4 mg. However, the combination of tolterodine 4 mg with an  $\alpha$ -blocker resulted in greater improvement in urgency symptoms than other regimens evaluated in this study. Therefore, we suggest that the combination therapy for the treatment of LUTS/OAB be customized each patient.

## CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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