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COMPARISON OF THE EFFICACY AND SAFETY OF TOLTERODINE SR 2MG AND 4MG COMBINED WITH DOXAZOSIN IN MEN WITH LOWER URINARY TRACT SYMPTOMS AND OVERACTIVE BLADDER: A PROSPECTIVE, RANDOMIZED CONTROLLED TRIAL

Hypothesis / aims of study
Recently, studies revealed that antimuscarinic was effective, safe and well tolerated for residual storage symptoms suggestive of overactive bladder (OAB) in men receiving α-blocker treatment for lower urinary tract symptoms (LUTS). In real clinical situation, some patients complain hesitancy and voiding difficulty after addition of standard dose antimuscarinic and want to stop antimuscarinic. Therefore, some clinicians prefer to use lower doses antimuscarinic in male patients. It is not certain whether the same doses of antimuscarinic used for the treatment of OAB men without bladder outlet obstruction (BOO) are also necessary for men with both BOO and OAB. Further research is necessary to determine the optimal dosage of antimuscarinic in patients with BOO. This study was designed to investigate the optimal doses of tolterodine SR in combination with doxazosin in men with lower urinary tract symptoms and overactive bladder based on efficacy, safety, and tolerability.

Study design, materials and methods
This was a 12-week, randomized controlled study conducted in single center in Korea. Men aged >50 years with LUTS and residual OAB symptoms despite treatment with α-blocker for 4 weeks were eligible for inclusion in the study. Inclusion criteria were total international prostate symptom score (IPSS) of ≥12, IPSS quality of life (QoL) score of ≥3, urinary frequency (≥8/24 hrs), and urgency (≥2 times/24 hrs). Patients were randomly assigned to tolterodine SR 2 mg plus doxazosin 4mg or tolterodine SR 4 mg plus doxazosin 4mg, once a day for 12-week. At 12-week after medication, all patients completed the IPSS, 3-day bladder diary, patient perception of bladder condition (PPBC), OAB questionnaire (OAB-q), global assessment of treatment benefit, satisfaction, and willingness to continue (BSW), maximum flow rate (Qmax), and postvoid residual (PVR). The primary outcome was the 12-week changes in IPSS total scores. Secondary outcomes included the 12-week changes in the IPSS sub-scores and bother score, bladder diary parameters (urgency, frequency, nocturia, urgency urinary incontinence (UUI)), PPBC, OAB-q, BSW, and adverse events (AEs).
Sample size calculations were taken from previous data comparing α-blocker plus antimuscarinic. To detect a difference in reduction of the same magnitude or greater 4 points IPSS total score at the 5% statistical significance level and with 80% power, a minimum total sample size of 86 patients was required. We recruited 98 patients to allow for a 15% dropout rate. The primary and secondary endpoints were analyzed using the ITT. In the ITT population for missing data, the Last Observation Carried Forward (LOCF) method was applied. Comparisons of continuous variables between the treatment groups were performed by two-sample t-test or Mann-Whitney test. Changes of ordinal variables between the treatment groups was compared by analysis using GEE (Generalized Estimating Equation). Change of continuous variable, and ordinal variable within treatment group was performed with paired t-test or Wilcoxon's signed rank test, and GEE, respectively.

Results
A total of 98 patients enrolled in this study and 95 patients were randomized. Of these, 79 completed the study. Baseline clinical characteristics including age, IPSS, and bladder diary parameters were comparable between the two groups.
Primary endpoint: IPSS total score was significantly decreased in both groups from baseline to 12 weeks treatment. There was no significant difference in change of IPSS between treatment groups at 12-week (table).
Secondary endpoints: IPSS storage, voiding, and bother score were significantly decreased within treatment group after 12-week, respectively. There were no significant differences between treatment groups in changes in scores for IPSS storage, voiding, and bother score. Urinary frequency, nocturia episodes were significantly decreased both treatment groups after 12-week, respectively. However, urgency, UUI episodes were significantly decreased in tolterodine 4mg group after 12-week. There were no significant differences of changes between two treatment groups, including the number of urgency, frequency, nocturia, and UUI episodes. Improvement in PPBC ratings was reported by 44.2% of subjects (19 of 43) in tolterodine SR 2mg group and 43.2% (19 of 44) in tolterodine SR 4mg group without statistical significance (p=0.436). There were no significant differences between the groups in changes in scores for OAB-q and patient reporting treatment benefit and satisfaction (p>0.05).
Safety and tolerability assessments: Treatment-emergent AEs were reported by 51.2% of subjects(22 of 43) in tolterodine SR 2mg group and by 52.3 % (23 of 44) in tolterodine SR 4mg group. The most common AE in both treatment groups was dry mouth. Other AEs were comparable in both treatment groups. In tolterodine SR 4mg group, PVR was significantly increased after 12-week compared with tolterodine SR 2mg group. However, there was no significant or clinically meaningful changes in Qmax were observed for either group. One patient in tolterodine SR 2mg group, one patient in tolterodine SR 4mg group was discontinued because of voding difficulty. There was no patient with AUR and catheterization in the two treatment groups.

Interpretation of results
Tolterodine SR 2mg plus doxazosin was noninferior to tolterodine SR 4mg plus doxazosin for the improvement of IPSS, OAB symptoms, bladder diary parameters, PPBC, and patient reporting treatment benefit, satisfaction.

Concluding message

In patients with residual OAB symptoms after α-blocker treatment for LUTS, add-on of tolterodine SR 2mg is effective for the improvement of OAB symptoms. Lower dose of antimuscarinic is recommended as starting dose for the relief of residual OAB symptoms in men with LUTS.

Table. Comparison of changes between treatment groups from baseline to end of treatment

Variables	Tolterodien SR 2 mg + doxazosin 4mg (n=43)		Tolterodine SR 4 mg + doxazosin 4mg (n=44)		p-value†
	Baseline	12-week	Baseline	12-week	
IPSS, mean±SD					
Total	19.3±5.5	13.8±6.9*	20.6±6.7	14.3±6.1*	0.5310
Storage	9.2±2.4	6.2±3.2*	9.9±2.4	6.8±2.5*	0.8573
Voiding	10.1±4.5	7.6±4.9*	10.8±5.5	7.6±4.2*	0.3832
QoL	4.3±0.8	3.6±1.4*	4.3±0.8	3.7±1.0*	0.9228
Bladder diary, mean±SD					
Urgency	7.2±3.2	5.8±4.7	8.2±4.5	6.0±4.2*	0.3792
Frequency	10.8±2.1	9.5±2.8*	11.6±3.4	10.0±2.4*	0.4981
Nocturia	1.9±0.9	1.5±0.9*	1.8±1.1	1.4±1.0*	0.8067
UUI	1.6±1.1	0.9±1.2	3.9±8.6	0.0±0.0*	0.3013
Benefit, n (%)		n=42		n=44	> 0.05
Much benefit		10 (23.8)		13 (29.5)	
Little benefit		31 (74.8)		30 (68.2)	
No benefit		1 (2.4)		1 (2.3)	
Satisfaction, n (%)					> 0.05
Very satisfied		11 (26.3)		8 (18.2)	
A little satisfied		25 (59.5)		30 (68.2)	
A little dissatisfied		3 (7.1)		3 (6.8)	
Very dissatisfied		3 (7.1)		3 (6.8)	
PVR (mL), mean±SD	30.9±29.0	31.5±26.1	17.9±20.0	69.8±136.2*	0.0254
Qmax (mL/s), mean±SD	14.9±8.3	14.3±8.0	14.8±6.3	15.3±7.5	0.4213

*p<0.05 comparison between baseline and 12-week within group

† between groups

Disclosures

Funding: This study was funded by Pfizer. **Clinical Trial:** Yes **Registration Number:** NCT00922506 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** Institutional Review Board of Samsung Medical Center (2008-08-092) **Helsinki:** Yes **Informed Consent:** Yes