

CHANGES IN OVERACTIVE BLADDER SYMPTOMS AFTER WITHDRAWAL OF SOLIFENACIN FOLLOWING INITIAL 12-WEEK COMBINATION THERAPY WITH TAMSULOSIN: A MULTICENTER PROSPECTIVE STUDY IN MEN WITH BENIGN PROSTATIC HYPERPLASIA AND COEXISTING OVERACTIVE BLADDER

Hypothesis / aims of study

Recent studies suggest that the combination of an alpha blocker and antimuscarinic agent for treatment of bladder outlet obstruction (BOO) with concomitant overactive bladder (OAB) seems promising. The existing data show that this combination therapy effectively improves patient quality of life, and the previously held perception that use of antimuscarinic agents in the setting of BOO should be contraindicated was shown to be unfounded [1,2]. However, there is no true consensus or guideline regarding antimuscarinic therapy in the management of benign prostatic hyperplasia (BPH)-related storage symptoms, and there remain many unanswered questions such as which between initial combination therapy and antimuscarinic add-on therapy after alpha blocker monotherapy should we choose? To our knowledge, there has been no published study about the treatment strategy consisting of initial combination therapy followed by withdrawal of antimuscarinics in men with both BPH and OAB.

In this multicenter prospective study, we investigated the changes in OAB symptoms after the discontinuation of solifenacin following initial 12-week combination therapy with tamsulosin in BPH patients with coexisting OAB. The predictors associated with resuming of solifenacin medication were also assessed.

Study design, materials and methods

Patients were recruited at 4 urologic clinics. A total of 82 men who met research criteria for both BPH and OAB were enrolled. Eligible patients were men 45 years or older with a total International Prostate Symptom Score (IPSS) of 8 or higher, a total overactive bladder symptoms score (OABSS) of 3 or higher and a score of 3rd item (urgency) of the OABSS [3] of at least 2, and findings suggestive of BPH on transrectal ultrasonography. Those with postvoid residual urine (PVR) more than 100ml, or maximum flow rate less than 8ml/s were excluded.

All patients enrolled in this study were treated with 0.2mg (the usual therapeutic dose recommended in Asia) of tamsulosin plus 5mg of solifenacin once a day. After 12 weeks of initial combination therapy, all patients switched to tamsulosin monotherapy for 4 weeks with solifenacin discontinued. Study subjects completed OABSS, the patient perception of bladder condition (PPBC), and IPSS, including the quality of life (QOL) score at weeks 4, 12, and 16 as well as at baseline. They were also requested to fill up three-day frequency-volume charts at baseline and prior to each visit at weeks 4, 12, and 16. And uroflowmetry with measurement of PVR was performed at each study visit.

For the assessment of efficacy of combination therapy for OAB, changes in the OABSS, PPBC, and storage symptom score of IPSS from baseline were evaluated at week 12. Variables of the frequency-volume charts including total micturitions per 24hours, micturitions per night, and functional bladder capacity were also analyzed in available patients. To investigate the changes in OAB symptoms after withdrawal of solifenacin following 12-week combination therapy, we compared OAB-related parameters between weeks 12 and 16. At week 16, the patients' intention of resuming administration of solifenacin was asked, and the predictors associated with re-treatment with solifenacin were assessed.

All adverse events were recorded to examine the safety of the treatment.

Results

43 (52.4%) of 82 patients completed the 16-week study. 39 (47.6%) discontinued study. 6 (7.3%) dropped out due to lack of efficacy and 13 (15.9%) due to adverse events. 18 patients were lost to follow up. Total OABSS, PPBC, and storage symptom score of IPSS were improved significantly from 8.25±2.27, 4.29±0.94, and 9.39±2.45 at baseline to 3.42±1.92, 2.31±1.21, and 4.53±2.63 at week 12, respectively ($p<0.01$ for all). Total micturitions per 24 hours, micturitions per night, and functional bladder capacity were also improved significantly after 12-week treatment ($p<0.01$ for all). After discontinuation of solifenacin, total OABSS, PPBC, and storage symptom score of IPSS at week 16 were still lower than those at baseline ($p<0.01$ for all). However, compared with week 12, all these questionnaire scores for OAB at week 16 were higher significantly ($p<0.01$ for all). QOL score was also increased significantly after withdrawal of solifenacin. 21 (48.8%) of 43 patients who had completed the 16-week study wanted to resume administration of solifenacin. Logistic regression analysis revealed diabetes, storage symptom score of IPSS and QOL score at baseline were positively associated with resuming of solifenacin medication at week 16.

78 subjects were included in safety analysis. Adverse events developed in 39 (50.0%) patients and 13 patients discontinued treatment because of adverse events. The most frequent adverse event, dry mouth was reported in 32 (41.0%). In 4 (5.1%) patients, increased voiding difficulties or significantly increased PVR was reported. However, there was no case of acute urinary retention. After initial 12-week combination therapy, mean maximum flow rate was increased significantly compared with baseline (14.59ml/s vs 12.23ml/s, $p<0.01$) and voiding symptom score of IPSS was also improved ($p<0.01$). After withdrawal of solifenacin, all parameters related to voiding were improved compared with week 12.

Interpretation of results

The results of our study showed again that the combination of an alpha blocker and antimuscarinic agent is effective for treating men with BPH and coexisting OAB. After withdrawal of solifenacin following initial combination therapy, OAB symptoms were worsen. Although tamsulosin monotherapy induced more improvement of voiding symptoms than combination therapy, the QOL

was deteriorated significantly after discontinuation of solifenacin. These results support that patient QOL is mainly affected by the symptoms of OAB.

In terms of serious adverse events or aggravation of voiding symptoms including acute urinary retention, the combination therapy was safe. However, high incidence of other adverse events such as dry mouth and constipation due to solifenacin increased the dropout rate.

Concluding message

The co-administration of solifenacin with tamsulosin was effective to improve lower urinary tract symptoms due to BPH and OAB. After discontinuation of solifenacin following initial combination therapy, OAB symptoms were aggravated, and QOL was deteriorated. About half of patients who had completed the study sought re-treatment with solifenacin. Diabetes, storage symptom score of IPSS and QOL score at baseline were positively associated with resuming of solifenacin medication.

References

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<i>Is this a clinical trial?</i>	Yes
<i>Is this study registered in a public clinical trials registry?</i>	No
<i>Is this a Randomised Controlled Trial (RCT)?</i>	No
<i>What were the subjects in the study?</i>	HUMAN
<i>Was this study approved by an ethics committee?</i>	Yes
<i>Specify Name of Ethics Committee</i>	IRB of Clinical Research Institute of Kangwon National University Hospital
<i>Was the Declaration of Helsinki followed?</i>	Yes
<i>Was informed consent obtained from the patients?</i>	Yes