

COMBINATION OF SOLIFENACIN WITH TAMSULOSIN BUT NOT TAMSULOSIN AFFECTS MORPHOMETRIC AND FUNCTIONAL PARAMETERS OF THE PROSTATE IN PATIENTS WITH BENIGN PROSTATE ENLARGEMENT (BPE) AND OVERACTIVE BLADDER (OAB). RESULTS FROM A RANDOMIZED PILOT STUDY.

Hypothesis / aims of study

Lower urinary tracts symptoms (LUTS), benign prostatic enlargement (BPE) and overactive bladder (OAB) are interrelated, but the extent of their interrelation and the underlying pathophysiologic mechanisms have not been fully elucidated. Approximately 50% of patients with BPE present with OAB symptoms and demonstrable detrusor overactivity urodynamically, while 30% of men with bladder outlet obstruction (BOO) will have persistent OAB symptoms post-prostatectomy (3). However, the frequency of LUTS and OAB in women is comparable to men. Such data suggest that, further to the acknowledged development of OAB as a result of detrusor hypertrophy to overcome the infravesical obstruction in men with BOO, additional mechanisms may be involved in the pathogenesis of OAB in men with BPE. Nevertheless, co-administration of alpha-blockers with antimuscarinics is now a recommended treatment option in such cases. Interestingly, all five muscarinic receptors subtypes have been detected in the prostate, but their role in BPE-OAB is also unclear.

We, thus, aimed to explore a potential effect of antimuscarinics on morphometric and functional parameters of the prostate in patients with BPE-OAB.

Study design, materials and methods

In this longitudinal, prospective, active comparator controlled study we randomized treatment-naïve men above 50 years of age, with BPE, who presented with predominately storage LUTS as defined by IPSS (storage subscore \geq voiding subscore and score ≥ 3 in the urgency question). Study participants should have prostate volume >30 ml, maximum flow rate (Q_{max}) ≥ 10 ml/s, post-void residual (PVR) <100 ml, PSA ≤ 10 ng/ml and at least 3 urgency episodes per 24h in a 3-day bladder diary. Patients with neurogenic bladder or a history of urinary tract malignancy were excluded. Patients with positive DRE as well as PSA values 4-10ng/dl were included only after negative prostate biopsy. All subjects were randomized in 1:1 fashion into two groups to receive either Tamsulosin 0.4mg monotherapy (Group 1) or combination Tamsulosin 0.4mg & Solifenacin 5mg (Group 2). The Institutional Review Board and the University Ethics Committee approved the study and all patients gave written informed consent.

All recruited patients filled questionnaires (IPSS, OABq, IIEF), had transrectal and transabdominal ultrasonography (prostate and adenoma volume, PVR, detected vessel surface), had a free flow test and underwent a pressure-flow study and basic biochemistry tests together with PSA and Testosterone levels both at baseline and at 6 months, in order to assess the effects of treatment on clinical and morphometric parameters. Interim follow-up tests included the IPSS, OABq, free flow and transabdominal ultrasound at 4 and 12 weeks. At the 4-week follow-up, solifenacin dose could be titrated to 10mg depending on clinical efficacy. The Good Urodynamic Practice and the Standardization of bladder ultrasonography were followed as per ICS protocols (1), (2).

The paired t-test and Mann-Whitney test were used for intra- and intergroup variability of examined parameters. An analysis of covariance (ANCOVA) was used to adjust for pretreatment differences. Extreme outliers (>4 stds) were removed from the analysis. The statistical software SPSS 21.0 (Armonk, NY: IBM Corp).

Results

Eighty patients were recruited of whom 68 fulfilled the inclusion criteria and were allocated to the two study groups. Sixty-three patients completed the study (Group 1 n=31, Group 2 n=32). Three patients were lost to follow up and 2 withdrawn due to pharmacotherapy related adverse events.

At baseline, both groups were comparable for age (mean 69.1 \pm 8.4 vs. 67.9 \pm 9.4 years), body mass index (28.3 \pm 2.4 vs. 28.7 \pm 2.8), total IPSS (20.1 \pm 4.0 vs. 20.3 \pm 4.4), micturition frequency (9.74 \pm 2.36 vs. 9.75 \pm 2.49), prostate volume (47.9 \pm 13.8 vs. 51.3 \pm 19.6), Q_{max} (11.88 \pm 4.42 vs. 13.9 \pm 5.95) and PVR. At end of treatment, both groups improved in total IPSS (p=0.001). Group 1 showed greater improvement in voiding subscore (5.8 vs. 6.4, p=0.01) while Group 2 in storage score (5.9 vs. 5.2, p=0.024). In both groups the OABq and quality of life scores improved, but without statistical significance between the groups.

The Q_{max} improved in both groups (13.4 \pm 4.6 vs. 13.3 \pm 6.9). The PVR was increased in group 2 (+34.79%) as opposed to a decrease in group 1 (-17.05%) (p=0.001). Cystometric capacity improved in combination treatment only (p=0.013). The improvement in Bladder outlet obstruction index was comparable between the 2 groups (p=0.042 vs p=0.011). The Bladder contractility Index was unaffected in monotherapy group but it was reduced by 13.2% in the combination group.

Based on the ANCOVA models, total prostate volume increased by a mean 9.02% in monotherapy group as opposed to an 8.98% decrease in combination therapy group (p<0.001). Such changes were also reflected in adenoma volume (Group 1: +18.16% vs Group 2: -13.53%, p<0.001) and in detected vessel surface size (Group 1: +91.14% vs. Group 2: -14.08%, p=0.0005). PSA was increased in both groups (Group 1: +22.72% vs. Group 2: +12.30%, p=0.654). There was no difference in testosterone levels between the two study groups.

Adverse events were more common in the combination therapy group with dry mouth affecting 11 patients and constipation 10 patients. However, the two withdrawals were from Tamsulosin monotherapy group, one due to increased daytime dizziness and the other due to cardiovascular collapse attributed to postural hypotension.

Interpretation of results

This is the first study, to our knowledge, to show that anticholinergics affect morphometric parameters of the human prostate. Despite the restricted sample size, the duration of the study is longer than most of the studies using combination therapy, which usually last 8-12 weeks. Combination therapy was associated with reductions of total prostate volume, adenoma volume and

prostate vascular surface as opposed to tamsulosin monotherapy which could not reverse increases in prostate volume and prostatic vascularity. In accord with the literature, both the monotherapy and combination therapy had beneficial effects on OAB symptoms, as demonstrated by significant improvements in questionnaire scores in both groups. Urodynamic results are also in accordance with well-known multicenter randomized studies, where cystometric capacity and PVR are increased in combination therapy while maximum flow is improved in monotherapy. A smaller PSA rise noted in the combination group might be another indication of anticholinergic effect on the secretory mechanisms of human prostate, despite the lack of statistical significance.

Concluding message

Results of this pilot study suggest that combination of solifenacin with tamsulosin affect morphometric properties of the human prostate with a decrease in total prostate and adenoma volume as well as vascularity contrary to the effect of tamsulosin monotherapy. Results need to be confirmed in larger studies, while mechanistic studies could clarify whether these reflect a molecular effect of anticholinergics on the prostate, in parallel with their expected bladder effect.

References

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Disclosures

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2. Institutional Review Board/Scientific Committee, Ippokration Hospital, Thessaloniki, Greece **Helsinki:** Yes **Informed Consent:** Yes