

## Role of Anticholinergic Drugs in Patients with Benign Prostatic Hyperplasia Symptoms

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### ABSTRACT:

#### BACKGROUND:

We determined the efficacy and safety of combination therapy of  $\alpha$ -blockers and anticholinergic drugs in patients with benign prostatic hyperplasia complain mainly of storage symptoms.

#### OBJECTIVE:

Study has been design to assess the efficacy and safety of combined treatment with oxybutynin plus tamsulosin in patients with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH).

#### PATIENTS AND METHODS:

Prospective randomized controlled study of patients with moderate to severe lower urinary tract symptoms. Eligible patients were men 40 years and older with a total IPSS of 12 or higher; An IPSS quality-of-life (QOL) item score of 3 or higher. Additional inclusion criteria were micturition frequency ( $\geq 8$  micturitions per 24 hours) and urgency (micturitions with urgency rating  $> 3$  per 24 hours) for 3 or more months. Men with clinically significant bladder outlet obstruction, or serum prostate-specific antigen of more than 4 ng/mL with risk of prostate cancer were excluded.

#### RESULTS:

A total of 24(80%) patients receiving oxybutynin plus tamsulosin (Group3) reported treatment benefit by week 12 compared with 13(46.4%) patients receiving placebo (Group1) ( $P=0.02$ ), 16 (53.4%) patients receiving tamsulosin(Group2) ( $P=0.45$  vs. placebo), there is statistically significant difference between group 3 and group 2 with the p value 0.04. Patients receiving oxybutynin plus tamsulosin compared with placebo experienced significant reductions in urgency urinary incontinence, Urgency episodes, micturitions per 24 hours, and micturitions per night. Group3 Patients demonstrated significant improvements on the total International Prostate Symptom Score ( $-7.22$  vs.  $-3.46$  in G1,  $P=.003$ ) and QOL item ( $-2.21$  vs  $-1.17$ , In G1  $P=.003$ ). The incidence of acute urinary retention requiring catheterization was low in group3, the incidence was only 1 patient 3.3%; 3 patients(10.3%) in group1, while in tamsulosin group there was no patient complain of acute urinary retention 0% .

#### CONCLUSION:

These results suggest that treatment with oxybutynin plus tamsulosin provides benefit for men with moderate to severe LUTS and BPH.

**KEYWORDS:** Anticholinergic, symptoms,(BPH), bladder.

### INTRODUCTION:

Benign prostatic hyperplasia is a common condition among elderly men, occurring in up to 70% of men older than 60 years<sup>(1)</sup>. Symptomatic BPH is thought to be due to bladder out flow obstruction and is often referred to as lower urinary tract symptoms suggestive of bladder outlet obstruction<sup>(2)</sup>. Urinary symptoms, especially storage/filling symptoms, are bothersome to the patient, interfere with daily life activities and have a negative impact on quality of life<sup>(3,4)</sup>. Storage symptoms are mainly attributable to detrusor instability, Which is thought to occur in up

to 40% to 60% of patients with benign prostatic obstruction or bladder outlet obstruction. Although the conditions of LUTS, BPH and over active bladder (OAB) are clearly causally related, The extent to which they are and the nature the mechanisms linking them are ill-understood. OAB might arise secondarily to bladder outlet obstruction (BOO) through the mechanism of detrusor instability, although alternative mechanisms in the cause of this condition seem likely, As the incidence of LUTS and OAB in elderly women nearly matches that of men proportion although they have no BOO in most of cases<sup>(5,6)</sup>, and 30% of men with both OAB and BOO continue to have symptoms despite correcting the BOO<sup>(7)</sup>. Depending on results of many studies that shows some men enrolled in OAB studies do not respond to antimuscarinic agents, and some men

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enrolled in BPH studies do not respond to  $\alpha$ -receptor antagonist<sup>(8,9)</sup>, hence, the idea arose of treating these patients with anticholinergic drugs, alone or in combination with  $\alpha$ 1-receptor antagonists. Based on the physiology of  $\alpha$ -adrenergic and muscarinic receptors, the inhibition of each one would be expected to be more beneficial than that of either alone because they would work on two components of detrusor function. The main concern with this approach is that, is it safe to use an anticholinergic in a man with possible BOO? There seems to be little guidance for the practicing urologist, despite the common occurrence of both LUTS/BPH symptoms and OAB symptoms in the same individual. This study has been design to address this approach and to assess the efficacy and safety of combined treatment with oxybutynin\_plus tamsulosin in patients with LUTS and BPH.

**PATIENTS AND METHODS:**

Prospective randomized controlled study of patients with moderate to severe lower urinary tract symptoms .Eighty eight patients were entered in to the study from AL-Kadhymia teaching hospital between October 2006 and May 2008. Eligible patients were men 40 years and older with a total IPSS of 12 or higher; An IPSS quality-of-life (QOL) item score of 3 or higher. Additional inclusion criteria were micturition frequency ( $\geq 8$  micturitions per 24 hours) and urgency (micturitions with urgency rating  $>3$  per 24 hours) for 3 or more months. Men with clinically significant bladder outlet obstruction (defined as a postvoid residual volume  $\geq 200$  mL and maximum urinary flow rate  $<5$  mL/s), or serum prostate-specific antigen of more than 4ng/mL with risk of prostate cancer were excluded. Other exclusion criteria included significant hepatic or renal disease; some neurological conditions (e.g., multiple sclerosis, spinal cord injury, parkinson disease); prostate cancer; Prostate surgery; History of acute urinary retention requiring catheterization; bladder outlet obstruction due to causes other than BPH; or any condition for which antimuscarinic use was contraindicated. Before commencing treatment patients were evaluated by physical and digital rectal examination, blood count, Blood urea, serum creatinine, urinalysis and culture, prostate specific antigen, Ultrasound imaging of the urogenital system and urodynamic study(flow rate , cystometrogram ) culture proved urinary tract infections treated before starting study medication. Patients who met all protocol criteria and were eligible to received study medication were randomly assigned using placebo drug (group 1, n=28), tamsulosin 0.4 mg once a day (group 2, n=30) tamsulosin 0.4mg per day

+ oxybutynin 5mg per day (group3, N=30) .all groups receive the treatment for three months. The primary efficacy end point was patient perception of treatment benefit at week 12. The Perception of Treatment Benefit question<sup>(10)</sup>, was administered after weeks 1, 6, and 12 of treatment. At each visit, We asked the patient, “Have you had any benefit from your treatment?” and if so, “Have you had little benefit or much benefit?” The following variables were also assessed: the change from baseline in urgency urinary incontinence episodes per 24 hours, Urgency episodes per 24 hours, Total micturition per 24 hours, and micturition per night. Patients were instructed to recorded the number of times at which urgency urinary incontinence &/or urgency episodes occurs and number of micturitions per day and nighttime. Secondary efficacy measures also included the IPSS, which was completed by patients at baseline and week 12 and assessed as the change from baseline. Postvoid residual volume was measured using ultrasound, and maximum urinary flow rate was measured using a flow meter. Both were assessed at baseline and week 12. Safety and tolerability were assessed also and all adverse events were recorded. Between-group differences for the percentage of patients answering “yes” to the questions related to treatment benefit at weeks 1, 6, and 12 were analyzed with a 2-sided Fisher exact test. Postvoid residual volume, Maximum urinary flow rate, and Changes on the IPSS total and QOL item from baseline value of the variable being analyzed by using chi square test and t test .p value considered significant if it  $< 0.05$  .

**RESULTES:**

Mean patient age  $\pm$ SD was comparable for all groups it was ( $62 \pm 7$  years, range 52 to 77 in group 1 and  $64 \pm 6$  years, range 50 to 75 in group 2 and  $64 \pm 5$  range 48 to 70 in group 3). Mean size of the prostate gland  $\pm$  SD was comparable in all groups as estimated by ultrasound ( $42.7 \pm 3.4$  gm. In group 1 and  $40.7 \pm 5.1$  in group 2,  $40.4 \pm 5$  in group 3 G1 VS G2 P=0.345, G2 VS G3 P=0.232, G1 VS G3 P=0.433. Patients baseline clinical characteristics are summarized in Table 1. At the end of three months of treatment, a total of 24 men (80%) receiving oxybutynin plus tamsulosin reported treatment benefit by week 12 compared with 13 patients (46.4%) receiving placebo (P=0.02), 16 (53.4%) receiving tamsulosin (P=0.45 vs. placebo), there is statistically significant difference between group 3 and group 2 with the p value 0.04. Patients receiving oxybutynin plus tamsulosin compared with placebo and tamsulosin only groups experienced significant reductions in urgency urinary

incontinence (-0.91 in G3 vs -0.41 in G 1, P=.005 , VS -0.52 in G 2 P=.03 )Figure 1, urgency episodes without incontinence (-3.55 in G3 vs. -1.95 in G1, P=.03 , -2.22 in G2 p=.04) Figure 2, micturitions per 24 hours (-3.52 in G3 vs. -1.51 in G1, P=.004 , -2.00 in G2 P=.043) Figure 3, and micturitions per night (-0.76 in G3 vs. -0.12 in G1, P=.002 , -0.33in G2 ,P=.04) Figure 4. Patients receiving oxybutynin plus tamsulosin demonstrated significant improvements on the total International Prostate Symptom Score (-7.22 vs. -3.46 in G1, P=.003) Figure 5, and QOL item (-2.21 vs -1.17, In G1 P=.003) Figure 6, there was also a significant difference in QOL item between oxybutynin plus tamsulosin group and tamsulosin only group (-2.21 vs. -1.44, P=.01) Figure 6 .There is no significant difference in total International Prostate Symptom Score between oxybutynin plus tamsulosin and tamsulosin only group (-7.22 vs. -6.46, P=.232) Figure 5. All interventions were well tolerated. The incidence of acute urinary retention requiring catheterization was low, in oxybutynin plus tamsulosin group the incidence was only 1 patient 3.3%; 3 patients(10.3%)

in placebo group, While in tamsulosin group there was no patient complain of acute urinary retention, 0%. The most frequent adverse event reported in patients receiving active treatment (G3) was dry mouth. No patients taking oxybutynin plus tamsulosin stopped treatment because of dry mouth .no other significant side effect was reported in all treatment groups. oxybutynin plus tamsulosin and tamsulosin only groups demonstrated significant increase in maximum urinary flow rate compared with baseline values these changes was significant in comparisons between any of these 2 groups with placebo group but there was no statistically significant difference between these 2 groups itself . Patients treated with oxybutynin plus tamsulosin demonstrated 6 to 8 mL increases in postvoid residual volume from baseline (placebo, 4.5; tamsulosin, 0.2; oxybutynin plus tamsulosin, 5.20). These increases were not statistically or clinically significant, and there were no significant differences in the change in postvoid residual volume between any 2 groups.

**Table 1: Baseline clinical characteristics**

	Placebo (n = 28)	Tamsulosin (n = 30)	oxybutynin + Tamsulosin(n=30)
Age Y. Mean (SD)	62(7)	64(6)	64(5)
Urgency episodes per 24 hr mean(SD)	7.2(3.08)	7.43(3.1)	7.23(3.0)
Micturitions per 24 hr mean(SD)	11.01(2.88)	12.2(3.1)	12.1(2.9)
Micturitions per night mean(SD)	2.7(1.3)	3(1.22)	2.9(1.24)
IPSS total mean(SD)	20.1(5.01)	19.8(5.34)	20.4(5.2)
IPSS QOL mean(SD)	4.1(0.95)	4.21(0.93)	4.6(0.99)
Maximum urinary flow rate, mean (SD) mL/s	13(6.9)	12.7(7.1)	13.1(7.2)
Postvoid residual volume, mean (SD) mL	35(33)	40(41.5)	38(36)

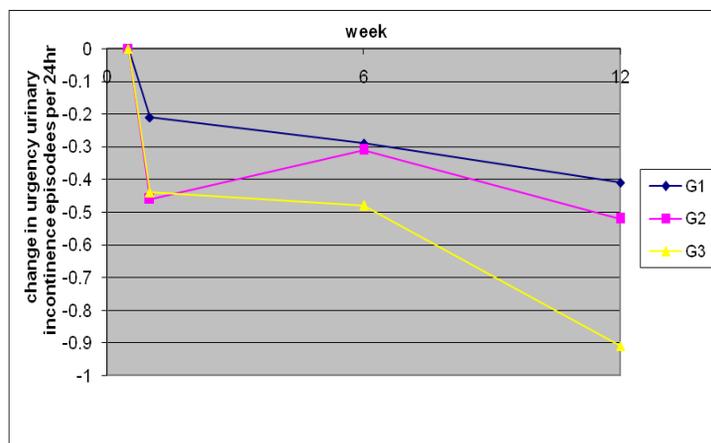


Figure 1: Change in urinary incontinence episodes per 24 hr.

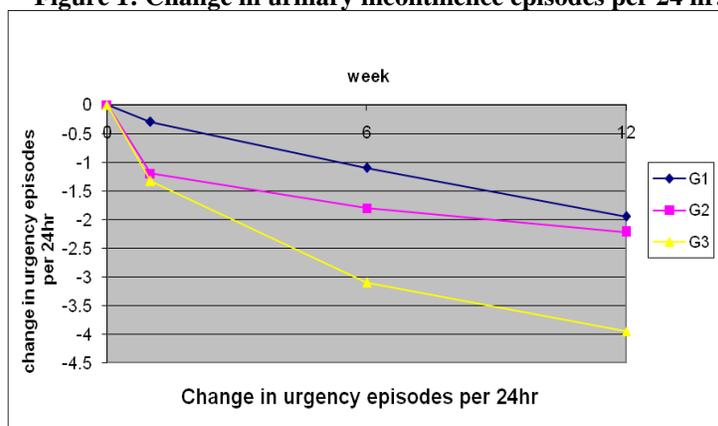


Figure 2: Change in urgency episodes per 24 hr.

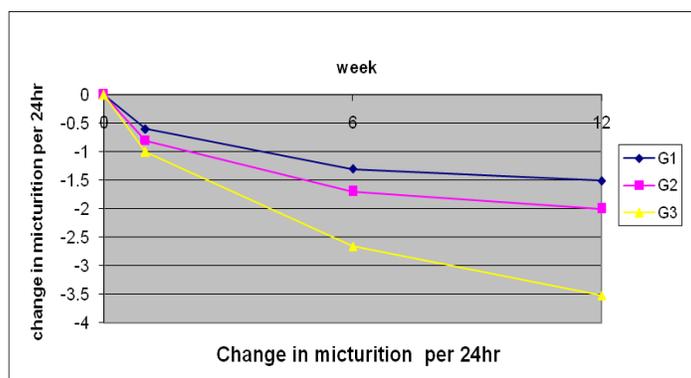


Figure 3: Change in micturition per 24 hr.

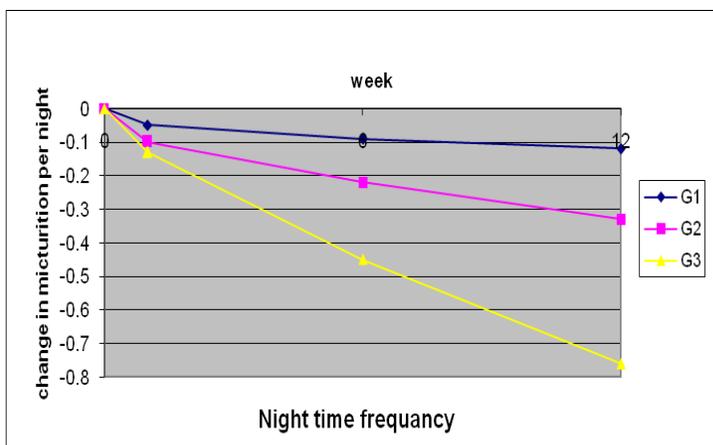


Figure 4: Change in night time frequency.

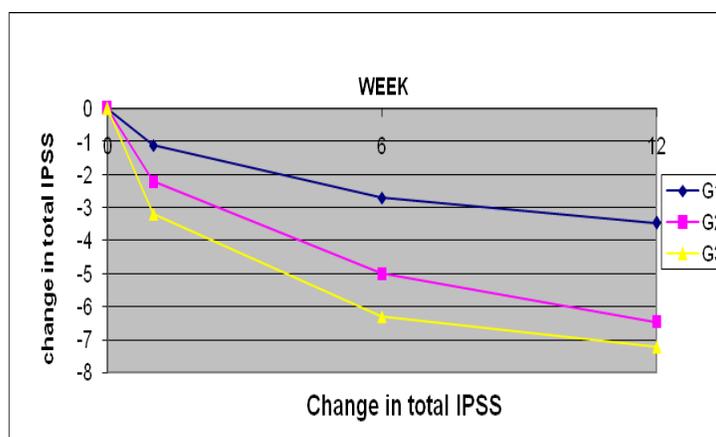


Figure 5: Change in total IPSS

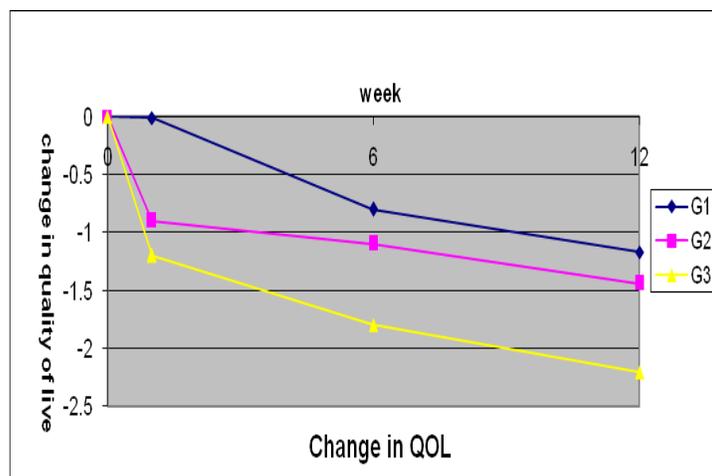


Figure 6: Change in QOL score.

**DISCUSSION:**

The incidence of OAB associated with BOO is 30–60%, and because the symptoms of the two are similar and overlapped it can be difficult to separate them diagnostically<sup>(11,14)</sup>. Irritative symptoms such as frequency, nocturia and urgency in patients with BOO are widely considered to be associated with OAB<sup>(15)</sup>. Neurogenically, histological evidence suggests that there is denervation in the obstructed detrusor, with a significant reduction in cholinergic receptors. Denervation supersensitivity has therefore been proposed as a possible mechanism for the OAB<sup>(16)</sup>. Moreover, In the rat, BOO can produce neurogenic bladder dysfunction, with remodelling of the neural pathways<sup>(17)</sup>. Brading<sup>(18)</sup> showed that human detrusor tissue from an OAB, of whatever cause, differs from that of normal bladder in activity and morphology. Electron microscopic studies show changes in intercellular junctions, and this has been proposed as a pathway of electrical coupling. These connections would allow propagation of action potentials, and thus synchronous contraction throughout the bladder, and involuntary detrusor activity<sup>(19,20)</sup>. Clinically, OAB has been reported to improve in 62% of men after prostatectomy but the reason why remains unknown<sup>(21, 22)</sup>. Whitjes et al<sup>(23)</sup>, examined the urodynamic and clinical effects of terazosin therapy over 6 months in symptomatic men with and without BOO, they found that even though those men who were unobstructed had no significant changes in the detrusor pressure at Qmax, both groups had a significant improvement in flow and voiding symptoms. Whitjes et al. concluded that urodynamic studies are not helpful in predicting the response to medical therapy, as the subjective outcome is similar in both obstructed and unobstructed patients<sup>(23)</sup>. However, the utility of urodynamics in men with symptomatic BOO with or without OAB before anticholinergic therapy remains to be addressed. This study shows a significantly greater proportion of patients in the oxybutynin plus tamsulosin group reported treatment benefit than the other 2 groups. The proportion of patients reporting treatment benefit in the tamsulosin monotherapy group was not significantly different from placebo. The question about the patient's perception of treatment benefit was selected as the primary end point because it is based on the assumption that the patient provides a global response that weighs the risks (e.g., adverse events) and benefits (e.g., symptom relief, life impact) of treatment<sup>(10)</sup>. The symptoms of urgency urinary incontinence, urgency, and 24-hour and nocturnal micturition frequency were also significantly improved by week

12 in the group receiving oxybutynin plus tamsulosin vs. placebo and the tamsulosin group. This can be explained by the antimuscarinic effect exerted by oxybutynin which can modulate the detrusor activity that alter by the action of BOO, age and /or neurological disease that cannot be overcome by the action of  $\alpha$ -blockers alone, so not surprisingly, Patients receiving oxybutynin plus tamsulosin demonstrated significant reductions in irritative bladder symptoms (urgency, urge incontinence and frequency). These results are comparable to results produced by other studies<sup>(24, 25)</sup>.

Compared with placebo group, The IPSS total and QOL item scores were significantly improved by week 12 among patients receiving oxybutynin plus tamsulosin. In the tamsulosin group, total IPSS was significantly improved by week 12, But the QOL item was not significantly improved compared with placebo. Although present study shows significant improvements on the total IPSS were observed by week 12 among patients receiving tamsulosin and among those receiving oxybutynin plus tamsulosin. However, Data from the tamsulosin group suggest that a significant change on the total IPSS does not necessarily correspond to a significant improvement on the IPSSQOL item in this population. There has been concern that the inhibitory effect of antimuscarinic agents on detrusor muscle contraction could theoretically aggravate the voiding difficulties or cause urinary retention and possible bladder outlet obstruction. To address this concern, maximum urinary flow rate, postvoid residual volume, and Incidence of acute urinary retention were evaluated. There were significant changes in maximum urinary flow rate in G2 and G3 rate compared with baseline value or G1. This result agrees with other studies that shows that Tamsulosin monotherapy significantly increased maximum urinary flow<sup>(25)</sup>. There were no significant changes in postvoid residual volume for any treatment group. These results prove that adding agent having antimuscarinic effect to  $\alpha$ -blockers in treatment of LUTS will not significantly alter the detrusor muscle contraction and aggravate the voiding difficulties or cause urinary retention and possible bladder outlet obstruction.

**CONCLUSION:**

This study suggests that for BPH/bladder outlet obstruction and concomitant detrusor instability the combination of an  $\alpha_1$ -adrenoceptor blocker with the anticholinergic drug significantly improves storage symptoms without compromising urine outflow

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