Combination Therapy Using an α-blocker Together with an Antimuscarinic Agent for Treatment of Men with Benign Prostatic Obstruction and Overactive Bladder: Results of Clinical Experience and a Mini-review

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ABSTRACT

This article shares our experience and reviews similar articles on the medical treatment of patients with combined benign prostatic hyperplasia (BPH) and overactive bladder (OAB) using an alpha-adrenergic blocker (α-blocker) with or without an antimuscarinic agent. A total of 140 men with BPH and moderate or severe lower urinary tract symptoms were included. The mean age was 74.5 years old. All were aged older than 50 years and had OAB together with urodynamically proven BPH obstruction. All had storage International Prostate Symptom Scores of 5 or higher and also had completed at least 6 months of medical treatment. Sixty-seven patients were treated with the α-blocker tamsulosin at 0.4 mg QD combined with an antimuscarinic agent (group A). Alternatively, 73 were treated with the α-blocker but without antimuscarinic agent (group B). Significant improvements were noted after treatment in both groups by comparing against baseline values for emptying IPSS, storage IPSS, quality of life index, maximum flow rate, voided volume, total prostate volume and transition zone index. However, group A showed a significantly greater improvement than group B only in the case of storage IPSS. *Key words:* overactive bladder, lower urinary tract symptoms, antimuscarinic treatment

INTRODUCTION

The prevalence of overactive bladder (OAB) in the western population has been estimated to be about 16% and the incidence increases with age in both sexes [1]. OAB is a symptom complex defined by the International Continence Society as urgency, with or without urge incontinence, usually with frequency and nocturia [2]. Non-surgical treatment should be the first priority when treating OAB and should include time voiding, biofeedback, pelvic floor muscle training, medication and a combination of these options. The mainstay of the pharmacological treatment of OAB is the use of an antimuscarinic agent, but this may not be suitable for male patients with benign prostatic hyperplasia (BPH) due to consideration of a possible deterioration of the emptying symptoms. However, antimuscarinic agents do not inhibit the normal micturition cycle, but rather diminish bladder sensation during the filling phase, which is confirmed by improvement in storage symptoms. A recent hypothesis suggests that antimuscarinic agents may act by other pathways too that are related to the afferent system as opposed to the efferent system [3].

The current standard treatment for men with BPH and lower urinary tract symptoms (LUTS) is an α-adrenergic receptor antagonist (α-blocker), which reduce smooth muscle tone from the prostate to the bladder neck, thus decreasing bladder outlet resistance. If the prostate is large (usually total prostatic volume ≥ 30 mL), a 5α-reductase inhibitor (5-ARI) may be added to reduce total prostatic volume (TPV) and transitional zone index (TZI). However, OAB symptoms may coexist with benign prostatic obstruction (BPO) or bladder outlet obstruction (BOO). Medications that reduce only the bladder outlet resistance may not alleviate OAB successfully [4]. Some results have indicated that although the treatment with either an α-blocker or a 5-ARI provides some improvement, many patients with LUTS that is associated with BPH still suffer from storage symptoms and these still affect their quality of life (QoL) [5,6]. Although some researchers have reported that either a combination α-blocker and 5-ARI or monotherapy with either drug results in some improvement in LUTS, few have focused on combined therapy with an α-blocker and an antimuscarinic agent when treating OAB. In this study, we evaluated and reviewed the efficacy and safety of the α-blocker and antimuscarinic agent combined therapy in patients with LUTS associated with BPH and OAB.

CLINICAL EXPERIENCE IN THE TREATMENT OF BPH WITH OAB

A total of 300 male patients with BPH and OAB were enrolled and these studied over a 6-month to 2-year follow-up. One hundred and sixty patients who had improved OAB symptoms, improved QoL or a storage International Prostate Symptom Score (IPSS) of less than 5 after treatment with an α-adrenergic receptor antagonist with or without 5-ARI were excluded from this study. The remaining 140 men were aged older than 50 years had OAB and urodynamically proven BPO. They also had a total storage IPSS of 5 or higher together with at least 6-months of medical treatment. These 140 men, after enrollment in the study, were divided into group A (67 men) who were treated with α-blocker (tamsulosin 0.4 mg QD) and an antimuscarinic agent (oxybutynin 7.5 mg QD or tolterodine 4 mg QD) and group B (73 men), who were treated with α-blocker alone. Furthermore, treatment with a 5-ARI (dutasteride 0.5 mg QD or finasteride 5 mg QD) was added to the treatment of patients with a TPV of more than 30 mL. The mean

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patient age was 74.5 years old.

Significant improvements in both groups were found compared to the baseline after treatment, the factors included emptying IPSS, storage IPSS, QoL index, maximum flow rate (Qmax), voided volume, TPV and TZI (Table 1 and 2). Compared to group B, patients in group A showed significantly greater improvement in storage IPSS (-1.26 ± 0.58, p=0.030, Table 3). There was no significant differences between the two groups in terms of age, emptying IPSS, QoL index, Qmax, voided volume, TPV, TZI and serum prostate-specific antigen (PSA). The main side effects of the antimuscarinic agents in our series were a dry mouth and constipation. The results suggest that treatment with an antimuscarinic agent plus an α-blocker provides therapeutic benefit when treating BPO with LUTS and OAB, especially in terms of storage IPSS.

REVIEW OF COMBINATION THERAPY FOR THE TREATMENT OF BPH WITH OAB

In a large series by Steven and his co-workers, they reported the first randomized, double-blind placebo-controlled study to investigate the efficacy of an antimuscarinic agent or an α-blocker or a combination therapy using the two agents in men with LUTS. A significantly greater proportion of patients, specifically men with moderate to severe LUTS (IPSS ≥ 12 and QoL ≥ 3) associated with OAB, who underwent the combination therapy (tolterodine ER 4 mg QD plus tamsulosin 0.4 mg QD) for 12 weeks reported a therapeutic benefit. This contrasted with the patients reporting therapeutic benefit in the tolterodine and tamsulosin monotherapy groups, which were not significantly different from the placebo group [4] (Table 4).

Results from previous small-scale non-placebo-controlled studies support the efficacy of a combination therapy of antimuscarinic agent plus α-blocker in men with BPO and OAB. Yang noticed the patient IPSS was significantly improved in both the α-blocker (terazosin 2 mg QD) and combination therapy (terazosin 2 mg QD plus tolterodine 2 mg BID) groups after 6-week treatment. The reduction in the IPSS in the combination group was significantly greater than that in the terazosin monotherapy group (p<0.01), especially for storage symptoms. Differences in the Qmax and postvoid residual (PVR) from the baseline values were also noted in both groups after medical treatment, but these were not significant. They concluded that patients with LUTS associated BPH showed improved IPSS after combined therapy after a 6-week follow-up [5]. Lee et al reported significant improvements in both groups (doxazosin 4 mg QD vs. doxazosin 4 mg QD plus propiverine 20 mg QD) after medical treatment for urinary frequency, Qmax, voided volume and total IPSS. Patient satisfaction rates were found to be significantly higher in combination group compared to the doxazosin monotherapy group over an 8-week period. It was concluded that the combination therapy provided an effective and safe therapeutic modality in patients with OAB coexisting with BPO [3]. Athanasopoulos et al presented a statistically significant reduction in maximum detrusor pressure, maximum unstable contraction pressure and improved QoL in the combination therapy group (tamsulosin 0.4 mg QD plus tolterodine 2 mg BID) compared to the α-blocker monotherapy group (tamsulosin 0.4 mg QD) over a 3-month follow-up; furthermore, in the 25 patients treated with tolterodine, no acute urinary retention was observed. Thus, combination therapy appears to be an effective and safe option in patients with BOO and detrusor overactivity (DO) [7].

DISCUSSION

Although previous clinical research has shown an improvement in urgency and urge incontinence to be a satisfactory end point in response to antimuscarinic treatment in patients with OAB [8], α-blocker monotherapy relieved both voiding and storage symptoms in BPO [9].

Table 1. Relationships of variables and therapeutic outcomes in group A with antimuscarinics (N=67)

	Baseline	6-month	p value
IPSS (emptying)	8.09±6.93	2.69±3.28	< 0.001
IPSS (storage)	7.57±3.87	5.04±2.85	< 0.001
QoL	3.58±1.41	2.19±1.00	< 0.001
Qmax (mL/sec)	9.99±4.46	11.59±5.23	0.009
Volume (mL)	151.20±102.6	163.40±108.7	0.356
PVR (mL)	78.80±72.1	71.00±60.5	0.505
TPV (mL)	44.80±22.9	38.00±15.7	0.001
TZI	0.45±0.12	0.41±0.13	0.003
PSA (ng/mL)	3.24±3.58	1.97±1.73	0.002

IPSS: International Prostate Symptom Score; QoL: quality of life; Qmax: maximum flow rate; PVR: postvoid residual; TPV: total prostate volume; TZI: transition zone index; PSA: prostate-specific antigen

Table 2. Relationships of variables and therapeutic outcomes in group B without antimuscarinics (N=73)

	Baseline	6-month	p value
IPSS (emptying)	9.15±6.11	4.59±4.52	< 0.001
IPSS (storage)	7.85±2.46	6.59±1.67	< 0.001
QoL	3.86±1.26	2.52±0.93	< 0.001
Qmax (mL/sec)	9.35±4.79	11.79±5.86	< 0.001
Volume (mL)	156.20±110.6	200.30±115.4	0.002
PVR (mL)	77.80±84.2	69.60±65.5	0.457
TPV (mL)	48.10±32.9	38.90±17.3	0.009
TZI	0.44±0.14	0.41±0.13	0.027
PSA (ng/mL)	3.23±3.83	2.62±3.28	0.147

IPSS: International Prostate Symptom Score; QoL: quality of life; Qmax: maximum flow rate; PVR: postvoid residual; TPV: total prostate volume; TZI: transition zone index; PSA: prostate-specific antigen

Table 3. Comparison of the changes in measured parameter for the two groups after 6-month follow-up

	Group A	Group B	P value
Age (years)	75.70±8.32	73.40±8.45	0.098
Δ IPSS (emptying)	5.40±6.53	4.56±6.48	0.446
Δ IPSS (storage)	2.52±4.06	1.26±2.67	0.030
Δ QoL	1.39±1.56	1.34±1.61	0.865
Δ Qmax (mL/sec)	-1.60±4.89	-2.44±5.70	0.350
Δ Volume (mL)	-11.52±101.45	-43.49±111.64	0.087
Δ PVR (mL)	6.38±77.95	7.90±90.35	0.915
Δ TPV (mL)	6.78±16.09	9.25±29.54	0.544
Δ TZI	0.04±0.11	0.03±0.11	0.493
Δ PSA (ng/mL)	1.27±3.25	0.61±3.56	0.252

IPSS: International Prostate Symptom Score; QoL: quality of life; Qmax: maximum flow rate; PVR: postvoid residual; TPV: total prostate volume; TZI: transition zone index; PSA: prostate-specific antigen

Table 4. Summary of similar trials

	Country	age	N	Study design	F/U	Results
Kuo 2008	Taiwan	74.5	73	BPH with LUTS and OAB → αB without antiM	6-24 mons	*Improved UDS parameters and QoL in the two groups *Combination → significantly decreased storage IPSS
			67	BPH with LUTS and OAB → αB with antiM		*No difference in PVR or Qmax
Steven et al 2007	USA	61.9	209	IPSS≥12 and QoL≥3 → αB without antiM	12 wks	*Improved urgency (-3.33), urge incontinence, IPSS (-8), and QoL (-1.61) in combination
			217	IPSS≥12 and QoL≥3 → αB with antiM		*AUR in only 0.4% with the combination therapy
Yang et al 2007	China	69.1	36	BPH with continued LUTS → αB without antiM	6 wks	*Improved IPSS in the two groups
			33	BPH with continued LUTS → αB with antiM		*No difference (vs. baseline and 2 groups) in PVR and Qmax
Lee et al 2005	Korea	66	67	BOO with OAB → αB without antiM	8 wks	*Improved UDS parameters and IPSS in the two groups without AUR
			131	BOO with OAB → αB with antiM		*greater reduction in storage IPSS with the combination therapy (-8.7%)
Athanasopoulos et al 2003	Greece	68	25	BOO with OAB → αB without antiM	3 mons	*Improved UDS parameters in the two groups
			25	BOO with OAB → αB with antiM		*Improved QoL and reduced OAB with the combination therapy

BPH: benign prostatic hyperplasia; LUTS: lower urinary tract symptom; OAB: overactive bladder; αB: α-blocker; antiM: antimuscarinic agent; UDS: urodynamic study; QoL: quality of life; IPSS: International Prostate Symptom Score; PVR: postvoid residual; Qmax: maximum flow rate; AUR: acute urinary retention; BOO: bladder outlet obstruction

Only a third of men undergoing treatment for BPO with OAB were helped by α-blocker monotherapy but 75% found that combining an antimuscarinic agent with an α-blocker was an effective therapy [10]. This supports the results in our study, where the combination therapy produced a significant reduction in storage IPSS compared with α-blocker alone (p=0.030).

The average baseline Qmax in our series was 9.66 mL/s, which suggests BOO [11]. The Qmax was significantly increased by 2.44 mL/s with α-blocker alone and by 1.60 mL/s with the combination therapy, but these results were not significantly different from the baseline values (p=0.350). Overall, this review suggests that antimuscarinic agents have predictable and tolerable adverse effects together with definite efficacy and safety in the treatment of BPH with OAB. Our results also reveal that the improvement in IPSS after antimuscarinic treatment would seem to reach a steady state after 6 months. However, no final conclusion can be reached about the duration of antimuscarinic therapy when treating patients with BPH and OAB.

There is a general impression that storage symptoms are more bothersome to the patients and affect their QoL profoundly; DO is considered a significant cause of storage symptoms. During the storage phase, acetylcholine may be released and then excite afferent nerves in the suburothelium and detrusor [12]. This mechanism may explain the pathophysiology of OAB and also seems to represent a likely target for antimuscarinic agents and botulinum toxin. Clinicians may be concerned that there might be an inhibitory effect of the antimuscarinic agents on detrusor contraction and that this might aggravate voiding symptoms. This would cause urinary retention in patients with low detrusor contractility. Theoretically unless the antimuscarinic dose is extremely high, these drugs should not impair bladder contractility. In our study, the incidence of difficult urination was only 10.4% and this difference was not statistically significance when compared with α-blocker alone. Balancing this, there was a significant improvement in Qmax, postvoid residual volume, total IPSS and QoL index even though an antimuscarinic agent was prescribed. Furthermore, serial research results have demonstrated that antimuscarinic agents are not associated with urinary safety concerns. A dry mouth is the adverse effect most frequently reported by patients receiving antimuscarinic treatment. In our study, there was an incidence rate for dry mouth of 22.4% among the combination group, which is similar to that reported in previous articles describing patients receiving antimuscarinic agent alone for OAB [4].

CONCLUSION

Combination therapy with an α-blocker and an antimuscarinic agent for men with BPH and LUTS associated with OAB provides a good therapeutic outcome by reducing IPSS and improving their QoL index. Treatment with an antimuscarinic agent produced a significantly greater improvement in storage IPSS in combination therapy group compared with the α-blocker alone group. Overall adverse effect rates were higher in combination group, but this was not statistically significant. Combination therapy appears to be an effective and relatively safe treatment choice for patients where BOO coexists with OAB.

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