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Efficacy and Safety of an Alpha-Blocker With and Without Anticholinergic Agent in the Management of Lower Urinary Tract Symptoms With Detrusor Overactivity

Nayan Kumar Mohanty, Anup Kumar, Manoj Jain, Sanjay Prakash, Rajender Prakash Arora
Department of Urology, Vardhman Mahaveer Medical College and Safdarjung Hospital, New Delhi, India
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ABSTRACT

INTRODUCTION: The purpose of the present investigation was to compare the efficacy and safety of a fixed dose of uroselective alpha blocker (tamsulosin) taken alone or in combination with a pure anticholinergic agent (tolterodine) in a group of patients with urodynamically and clinically proven lower urinary tract symptoms (LUTS) and detrusor overactivity (DO).

METHODS: The participants were 75 men with LUTS and DO, randomly assigned to 2 groups. Group 1 (n = 37) received tamsulosin (0.4 mg) orally; group 2 (n = 38) received tamsulosin (0.4 mg) and tolterodine (4 mg) orally. All patients took the medications daily for 3 consecutive months. Patients were evaluated before and after treatment by the International Prostate Symptoms Score (IPSS), ultrasound of the kidney and urinary bladder (KUB), prostate specific antigen (PSA), and urodynamic pressure flow study. Patients were also questioned about their perception of treatment benefits and quality of life (QoL). Group comparisons in response to treatment were analyzed statistically.

RESULTS: Patients in group 2 had significantly better response to treatment than patients in group 1 for 5 of the 8 main urodynamic variables studied: (1) mean reduction in maximum detrusor pressure during micturition ($P = .01$), (2) mean reduction in maximum unstable detrusor contraction pressure/end filling pressure ($P < .001$), (3) mean increase in maximum cystometric bladder capacity ($P = .007$), (4) mean increase in volume at first unstable bladder contraction ($P = .02$), (5) mean increase in bladder compliance ($P < .001$). The groups were similar in their response to therapy for maximum flow rate, postvoid residual volume, and total IPSS. No acute urine retention (AUR) was reported in either group. Positive response to treatment was reported by 51.4% of patients in group 1 and 85.7% of patients in group 2. Group 2 also had significantly higher mean QoL scores ($P = .02$). Group 2 had a significantly greater reduction in the DO symptoms of frequency in 24 hours, urgency in 24 hours, and nocturia when compared with patients in group 1 ($P = .02$, $P = .01$, and $P = .01$, respectively). Patients taking tamsulosin and tolterodine had significantly more side effects of constipation, dry mouth, and dry eyes.

CONCLUSION: Results of the study confirm the safety and efficacy of combination therapy for patients with LUTS and DO.

KEYWORDS: LUTS; Detrusor overactivity; Medical treatment

CORRESPONDENCE: Professor N.K. Mohanty, C – II /124, Motibagh, New Delhi, 110021 (nayankm@yahoo.co.in).

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original study

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common pathologic condition affecting elderly males that contributes to lower urinary tract symptoms (LUTS) [1]. Although the terms *benign prostatic hyperplasia* and *benign prostate enlargement* (BPE) are used interchangeably, BPH should only refer to microscopic demonstration of prostatic hyperplasia in the histology specimen. Men with BPE are presumed to have an increase in prostate volume due to BPH, which may cause LUTS and urodynamically proven bladder outlet obstruction (BOO).

BPH can be classified as microscopic or macroscopic. *Microscopic BPH* is a proliferative process of stromal and epithelial components of the prostate. *Macroscopic BPH* refers to an enlarged prostate (BPE). *Clinical BPH* includes LUTS, bladder dysfunction, and other clinical problems resulting from macroscopic BPH. Seventy percent of men older than 60 years with clinical BPH require treatment.

Patients with clinical BPH have a variety of lower urinary tract symptoms. These result from bladder outlet obstruction (BOO) [2] due to prostatic enlargement, storage or filling symptoms due to detrusor aging effects, and detrusor overactivity (ie, BOO-induced bladder dysfunction). Symptoms of BOO are hesitancy, straining, intermittency, narrow stream, and inadequate emptying of the bladder. Frequency and urgency with or without incontinence are due to detrusor overactivity (DO) [3]. BOO due to the aging process results in certain structural changes in the detrusor muscle, which causes DO. The combination of obstructive symptoms along with storage or filling problems occurs in 40-60% of men presenting with LUTS [4].

The physician needs to address the combination of obstructive and storage symptoms when planning medical management for patients with clinical BPH. Therefore, it would be logical to combine an alpha blocker with an anticholinergic agent in patients with LUTS associated with DO. Skepticism regarding this approach is based on the theoretical danger of impairment of obstructive symptoms and possible acute urine retention (AUR), but this concern is not definitively proven in the literature.

The purpose of the present investigation was to compare the efficacy and safety of a fixed dose of uroselective alpha blocker (tamsulosin) taken alone or in combination with a pure anticholinergic agent (tolterodine) in a group of patients with urodynamically and clinically proven LUTS and DO.

METHODS

Participants

The participants were 75 men with an average age of 64 years (range, 58 - 80 years) with mild to moderate LUTS and DO due to BPH. They were studied between July, 2007 and December, 2008. All patients passed the exclusion criteria: (1) no glaucoma, stricture urethra, neurogenic bladder, bladder or prostate malignancy; (2) no history of AUR, catheterization, bladder surgery, or prostate surgery; (3) no history of postural hypotension, syncopal attack, or significant renal or hepatic dysfunction; (4) no medical therapy for clinical BPH during the previous 6 months.

The patients were clinically assessed with an International Prostate Symptoms Score (IPSS) [5], digital rectal examination (DRE), and ultrasonography of the genitourinary system (GUS). The patients had a mean IPSS > 16 and postresidual urine (PRU) volume ≤ 200 mL. The number of frequency episodes was ≥ 8 times within 24 hours, urgency was ≥ 3 times in 24 hours, and maximum flow rate (MFR) was < 10 mL/sec. These features were present for at least the past 3 months. Biochemical evaluations of prostate specific antigen (PSA), kidney function test (KFT), hemogram, and urine (routine microscopy and culture sensitivity) were all within normal limits. Prostate size, echogenecity, bladder volume, and volume of post residual urine were evaluated with an ultrasound of the abdomen.

Procedures

All patients provided written consent to participate in the study. Patients were then randomly assigned to 2 groups, using a computer-generated randomized block design ratio 1:1. Group 1 (n = 37) received tamsulosin (0.4 mg) orally; Group 2 received a combination of tamsulosin (0.4 mg) and tolterodine (4 mg) orally. Patients in both groups took the medications daily for 3 consecutive months. They were evaluated at the beginning and end of the 3-month period.

Evaluation

Clinical Assessment. Clinical assessment of the efficacy of treatment included IPSS, PSA, urodynamic study, and ultrasound of the abdomen. The authors conducted a standard pressure-flow urodynamics study using instrumentation from Laborie Medical Technologies (Montreal, Quebec, Canada) with saline as the infusion medium at 10mL/min. The urodynamic parameters [6] included maximum detrusor pressure (MDP) during micturition, maximum flow rate (MFR), postvoid residual urine (PRU), maximum unstable detrusor contraction pressure (MUDP)/end filling pressure(EFP), maximum cystometric bladder capacity (MCC), volume at first unstable contraction (VUC), and

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Table 1. Urodynamic Variables for Each Group Before and After Treatment and Probability of Significant Group Differences (N = 70).
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Variable	Group 1 (n = 35)				Group 2 (n = 35)				*P*
	Before		After		Before		After		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Maximim detrusor pressure during micturition (cmH20)	66	3.2	60	3.1	65.8	3.3	34.4	3.25	.01
Maximum unstable detrusor contraction pressure/ end filling pressure (cmH20)	30	2.9	27	2.6	30.8	2.85	18.4	1.9	<.001
Maximum cystometric bladder capacity (mL)	302	21.4	375	22.1	308	21.7	430	23.1	.007
Volume at first unstable contraction (mL)	201	33.2	238	35.1	198	29.3	288	29.7	.02
Bladder compliance (mL/cmH20)	10.06	0.33	13.89	0.28	10	0.37	23.37	0.45	<.001
Maximum flow rate (mL/s)	8.8	1.32	13.4	1.55	8	1.64	12	1.44	.32
Postvoid residual urine volume (mL)	83.8	13.5	38	12.4	90	11.6	48	12.3	.45
Total IPSS	16	1.1	9	1.4	17	1.9	7	1.5	.21
Irritative symptoms	7.5	1.2	4.3	0.9	8.2	1.3	3.1	0.4	.02
Obstructive symptoms	8.5	1.1	4.7	0.8	8.7	0.9	3.7	0.5	.44

bladder compliance. Compliance was calculated by dividing MCC with MUDP/EFP.

Patient perception of treatment, quality of life, and symptoms of DO. To determine the patient's perception of treatment success at the end of therapy, each was asked the question, "Have you had any benefit from the treatment?" If the answer was yes, the patient was asked, "Have you had little benefit or many benefits?" These procedures were used in a previous study [7].

The patient's quality of life (QoL) was assessed before and after treatment by using the 9-item Urolife Questionnaire [8]. The questionnaire covers the topics of disruptions to daily activities, voiding frequency, energy level, and satisfaction with life, sexual desire, erections, and sexual activity. Each question has 2 possible ratings, which were presented to the patient as the extremes on a scale from 0 to 100. The patients provided a numerical score for each item. Patients were also asked to name their symptoms of DO.

Variables measured for group 1 and group 2 were compared using 2-sided multiple student *t* tests. The probability of statistical significance was set at $P < .05$. A power analysis was not conducted. Therefore, the ability to detect a significant difference with this sample size and variance is unknown and the possibility of statistical error exists.

RESULTS

Two patients from group 1 and 3 patients from group 2 dropped out of the study, resulting in a final N of 70 patients with 35 in each group.

Clinical Assessment

Table 1 contains the urodynamic parameters measured before and after therapy and the probability of significant group differences. Patients in group 2 had significantly better response to treatment than patients in group 1 for 5 of the 8 main urodynamic variables: (1) mean reduction in maximum detrusor pressure during micturition ($P = .01$), (2) mean reduction in maximum unstable detrusor contraction pressure/ end filling pressure ($P < .001$), (3) mean increase in maximum cystometric bladder capacity ($P = .007$), (4) mean increase in volume at first unstable bladder contraction ($P = .02$), (5) mean increase in bladder compliance ($P < .001$).

Mean MFR and mean postvoid residual volume improved from baseline in both groups, with no statistically significant group differences. The mean total IPSS score also improved for both groups. The mean irritative symptoms subscore for group 2 decreased significantly following treatment when compared with group 1 ($P = .02$), but there were no significant differences in the mean obstructive symptoms subscore.

Table 2. Quality of Life Score and Detrusor Overactivity Symptoms for Each Group Before and After Treatment; Probability of Significant Group Differences (N = 70). doi: 10.3834/uij.1944-5784.2009.12.02t2

Variable	Group 1 (n = 35)				Group 2 (n = 35)				*P*
	Before		After		Before		After		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Quality of life score	3	0.3	5	0.2	3	0.4	8	0.5	.02
Frequency in 24 hours	8.1	0.45	6.5	0.31	8.2	0.34	4.2	0.22	.02
Urgency in 24 hours	3.4	0.53	2.6	0.11	3.5	0.37	1.3	0.21	.01
Nocturia	3.2	0.2	2.3	0.14	3.3	0.25	1.1	0.53	.01

There were no significant group differences following treatment in mean PSA score or volume of prostate adenoma. There was no incidence of acute urine retention (AUR) reported in either group.

Patient perception of treatment, quality of life, and symptoms of DO

Patient responses to the question, "Have you had any benefit from the treatment?" showed that 18 patients (51.4%) in Group 1 and 30 patients (85.7%) in Group 2 felt they had benefitted. Responses to the second question, "Have you had more benefit or little benefit?" showed that 32 patients (94%) in group 2 felt they had more benefit, as compared to 20 patients (56%) in group 1. Therefore, patients in group 2 were more positive than patients in group 1 about their response to treatment.

Table 2 contains the pretreatment and posttreatment scores for both groups and the probability of significant group differences for the quality of life score and DO symptoms. Group 2 had a significantly larger improvement in QoL score from mean baseline value when compared with group 1 (P = .02). When compared with the baseline scores, patients in group 2 had a significantly greater reduction in the DO symptoms of frequency in 24 hours, urgency in 24 hours, and nocturia than patients in group 1 (P = .02, P = .01, and P = .01, respectively). The reduction in DO symptoms is mostly attributed to the anticholinergic agent taken by patients in Group 2.

Side Effects

The reported side effects are contained in Table 3. Group 2 had significantly more constipation, dry mouth, and dry eyes than patients in group 1 (P = .01 for each of the 3 side effects). Other side effects of dizziness, headache, and fatigue had similar rates of occurrence across groups.

DISCUSSION

Current standard medical management of patients with clinical BPH mainly addresses the relief of BOO symptoms by using an alpha blocker or 5-alpha reductase inhibitor, alone or in combination. Previously, little importance was given to relieving storage symptoms associated with lower urinary tract disorders, although these symptoms are very bothersome when due to DO. Recently, more attention is being given to treating the DO symptoms. Structural changes occurring in detrusor musculature may be due to the aging process and to BOO [9] resulting in DO [3,9,10]. Therefore, it is now recommended that the physician treat both the symptoms of BOO and DO in patients with LUTS [11].

Many urologists do not advocate the use of an antimuscarinic agent along with an alpha blocker for fear of risking AUR in patients with LUTS and DO. Recent literature [12,13] and post hoc analyses [14,15] suggest that tolterodine is not associated with an increased incidence of AUR in men with LUTS and DO. Results of several small-scale studies of men with urodynamically

Table 3. Side Effects Profile for Each Group and Probability of Significant Group Differences (N = 70).
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Side Effect	Group 1 (n = 35)		Group 2 (n = 35)		*P*
	n	%n	n	%n	
Constipation	0	0	6	17	.01
Dry mouth	0	0	7	20	.01
Dry eyes	0	0	5	14.5	.01
Dizziness	5	14.5	6	17	.32
Headache	4	11.4	5	14.5	.53
Fatigue	2	5.7	3	8.57	.45

confirmed detrusor overactivity and BOO have supported the use of combination treatment of an alpha blocker and an antimuscarinic agent [16,17]. These previous studies did not include a group receiving a placebo.

The results of the present study clearly indicate that the combination of an alpha blocker with an antimuscarinic agent greatly improves LUTS associated with DO by not only reducing maximum detrusor contraction pressure during voiding but also improving bladder capacity, volume at first unstable bladder contraction, bladder compliance, and maximum unstable bladder contraction pressure. The improvement in maximum flow rate (+4.6 and +4.0 in groups 1 and 2, respectively) was slightly greater than that reported previously (up to +3.5) [17,18]. However, there was no statistically significant difference between treatment groups.

Patients in the present study responded much more favorably to the combination of tamsulosin and tolterodine. Their perception of treatment benefit was 85.7%, compared with 51.4% for patients taking tamsulosin alone. The QoL score was also significantly higher for patients taking both medications.

Although minimal side effects were reported, dryness of mouth, constipation and dryness of eye were significantly more common in patients using tolterodine. AUR was not observed in any patients using tolterodine. However, the present study included only 75 patients followed for 3 months. Therefore, a prospective study enrolling a larger number of patients with longer follow-up is needed to validate the effect of the anticholinergic on AUR in these patients.

CONCLUSION

The current study confirms the efficacy and safety of treatment of LUTS associated with DO with a combination therapy of an alpha blocker and antimuscarinic agent.

Conflict of Interest: None declared.

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