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# Efficacy and Safety of Tamsulosin With and Without Flavoxate in the Treatment of Symptomatic Benign Prostastic Hyperplasia: A Randomized, Single-Blind Study

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## ABSTRACT

**INTRODUCTION**: The purpose of the study was to evaluate the efficacy and safety of tamsulosin plus flavoxate with tamsulosin plus a placebo for the treatment of clinically proven lower urinary tract symptoms (LUTS) in patients with benign prostatic hyperplasia (BPH).

**METHODS**: The participants were 120 patients with BPH and LUTS who were randomized into 2 equal groups. Group 1 received tamsulosin modified release (0.4 mg) once daily and flavoxate (200 mg) 3 times daily; group 2 received tamsulosin modified release (0.4 mg) once daily and a placebo 3 times daily. All patients took the medications orally for 12 weeks. Patients were evaluated before and after treatment by the total International Prostate Symptoms Score (IPSS), the irritative symptoms, voiding symptoms, and quality of life (QoL) IPSS subscores, maximum urinary flow rate (Qmax), and postvoid residual (PVR) urine volume. Adverse events were also summarized. The *t* test was used for group comparisons in response to treatment.

**RESULTS**: All patients responded positively to treatment. The group taking tamsulosin plus flavoxate had significant improvement in the mean total IPSS ($P < .001$), irritative symptom subscore ($P < .002$), and QoL score ($P < .002$) when compared with the group taking tamsulosin plus placebo. There was no significant group difference in the mean voiding symptom subscore, Qmax, or PVR volume. Group differences in mean frequency and nocturia at the end of 12 weeks approached statistical significance ($P = .05$); patients taking tamsulosin plus flavoxate had fewer episodes. There was no significant group difference in urgency. One patient withdrew from each group due to complaints of impotence and ejaculatory dysfunction; all other adverse events were mild and transient.

**CONCLUSION**: Taking a combination of tamsulosin with flavoxate improved IPSS, irritating symptoms, and QoL significantly more than taking the alpha blocker alone. The combined drugs had good safety and can be considered as a therapeutic option for treatment of LUTS associated with BPH.

**Abbreviations and Acronyms**

BPH = benign prostatic hyperplasia
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptoms
OAB = overactive bladder
PSA = prostate-specific antigen
PVR = postvoid residual
QoL = quality of life
Qmax = maximum urinary flow rate.

**KEYWORDS**: Tamsulosin; Flavoxate; Irritative symptoms; IPSS; LUTS

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original study

# Efficacy and Safety of Tamsulosin With and Without Flavoxate in the Treatment of Symptomatic Benign Prostastic Hyperplasia: A Randomized, Single-Blind Study

## INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases that affect elderly men and contribute to lower urinary tract symptoms (LUTS) [1]. LUTS include irritative *storage* symptoms (eg, urgency, frequency, nocturia, and urinary incontinence), and voiding *obstructive* symptoms (eg, slow stream, intermittent stream, hesitancy, straining, and terminal dribble) [2]. Irritative LUTS resemble the defining symptoms of overactive bladder (OAB) [2], although there is a degree of overlap between men with OAB and men with LUTS presumed secondary to BPH [3]. The EPIC study was a large multinational epidemiological study that was conducted in 4 European countries and Canada using current International Continence Society (ICS) definitions for LUTS [4]. The investigators found that irritative and voiding symptoms were experienced by 74% and 37% of men older than 60 years, respectively.

LUTS in men are commonly treated with medical therapies designed to alleviate prostatic enlargement (eg, alpha-receptor antagonists or 5α-reductase inhibitors). However, LUTS are not always attributable to prostatic pathology [5], and studies on the prevalence of OAB do not distinguish men with LUTS presumed secondary to BPH from those with isolated OAB symptoms [6]. Alpha-receptor antagonists targeting the prostate might not completely relieve OAB symptoms or storage symptoms of BPH [7]. The physician needs to address the combination of voiding and irritative symptoms when planning medical management for patients with symptomatic BPH.

Muscarinic receptor antagonists are currently the first-line medical treatment for OAB [8]. Data suggest that antimuscarinic agents are safe and effective in treating storage symptoms in men with LUTS [9-13]. However, there is skepticism regarding their use because of the concern of an increased risk of urinary retention [14].

Flavoxate hydrochloride was the first drug to be approved for OAB in 1970. This drug has no antimuscarinic activity. It has a moderate calcium antagonistic action, inhibitory effect on phosphodiesterase, and a local anesthetic and relaxant effect on smooth muscle [15-17]. In a Cochrane analysis in 2007 [17] designed to compare anticholinergic drugs with other types or classes of drugs for treating overactive bladder symptoms, 9 trials comparing flavoxate with anticholinergics were included. Although there was no evidence of a difference in cure rates between anticholinergics and flavoxate, adverse effects were more frequent in patients taking the anticholinergic than in patients taking the flavoxate. Flavoxate hydrochloride has been reported to activate spinal glycinergic neurons [18] that may become a treatment option for nocturia and irritative symptoms of LUTS.

The aim of the present study was to compare the efficacy and safety of a fixed dose of the uroselective $\alpha_{1A}$ blocker tamsulosin, taken alone or in combination with the urinary antispasmodic flavoxate in a group of patients with urodynamically and clinically proven LUTS.

## METHODS

The present investigation was a single-blind, randomized, parallel-group, placebo-controlled study. The protocol was reviewed and approved by the Institutional Ethics Committee of the college and was conducted in accordance with the Good Clinical Practice guidelines. The patients were given full information regarding the purpose, procedures, advantages and disadvantages, and other matters associated with the conduct of the trial. Written informed consent was obtained from all study participants. The study was conducted between April 2009 and January 2010.

### *Participants*

All adult male patients presenting with LUTS and irritative symptoms at the Outpatient Clinic of the Department of Urology and Department of Surgery, Sir Sunder Lal Hospital, Banaras Hindu University Varanasi, India (a tertiary care government medical center) were screened for eligibility. A total of 348 patients were assessed for eligibility; 120 patients were selected.

The inclusion criteria were: (1) male patients diagnosed as having BPH; (2) age ≥ 45 years; (3) at least a 12-month history of LUTS, including irritative symptoms such as frequency, nocturia, and urgency with or without urge incontinence; (4) an International Prostate Symptom Score (IPSS) ≥ 13; (5) a maximum urinary flow rate (Qmax) between 4 mL/s and 15 mL/s after 2 uroflowmetry determinations, with voided urine volumes ≤ 150 mL. The exclusion criteria were: (1) suspected or proven prostatic malignancy or prostate-specific antigen (PSA) > 4; (2) urinary retention, defined as a postvoid residual (PVR) urine volume ≥ 100 mL as measured on a bladder scan; (3) active, untreated, urinary tract infection or a history of prostatectomy; (4) significant, untreated or uncontrolled medical disease such as diabetes mellitus, hypertension, renal failure, hepatic dysfunction, cardiac failure, or senile dementia; (5) intake of any medication for the treatment of BPH (eg, α-blockers, 5α-reductase inhibitors, plant extracts) in the preceding 12 weeks; (6) intake of α-blockers (eg, doxazosin, terazosin, prazosin), 5α-reductase inhibitors, cholinergic agents, anticholinergic medications, or antispasmodic medications for any other reason.


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Table 1. Baseline Means and Standard Deviations for Patient Age, Prostate Size, Serum Prostate-Specific Antigen, and Number of Years Experiencing Lower Urinary Tract Symptoms; Probability of Significant Group Differences (N = 120). doi: 10.3834/uij.1944-5784.2010.08.09t1

| Characteristic | Group 1 (n = 60) | | Group 2 (n = 60) | | *P* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **Age (years)** | 62.57 | 8.32 | 64.23 | 9.82 | .13 |
| **Prostate size (cc)** | 30.53 | 7.94 | 32.37 | 6.36 | .33 |
| **Serum PSA (ng/mL)** | 2.73 | 1.32 | 3.28 | 2.25 | .26 |
| **Years With LUTS (No.)** | 3.76 | 1.06 | 3.5 | 1.57 | .46 |

Abbreviations: LUTS, lower urinary tract symptoms; PSA, prostate-specific antigen; SD, standard deviation.

Patients were randomly assigned to 2 groups, using a computer-generated 1:1 randomization ratio. Table 1 contains the baseline means and standard deviations (SD) for patient age, prostate size (assessed by ultrasound), serum PSA, and the number of years that the patient experienced LUTS for patients in both groups. There were no significant group differences for any baseline measure.

### *Procedures*

All patients completed a detailed medical history, including intake of medication. A physical examination was conducted.

Group 1 (n=60) received a combination of tamsulosin modified release (0.4 mg) once daily in the morning and flavoxate (200 mg) 3 times daily; group 2 (n=60) received a combination of tamsulosin modified release (0.4 mg) once daily in the morning and a placebo 3 times daily. The medications and placebo were taken orally for 12 consecutive weeks.

Patients were evaluated at the beginning for baseline values, at 4 weeks, and at the end of 12 weeks. They completed the IPSS questionnaire, a second questionnaire about adverse events, a bladder scan, and uroflowmetry.

### *Data Analysis*

The evaluations at baseline and the final visit at 12 weeks were compared within and between groups for the outcome measures of total IPSS, the irritative symptoms, voiding symptoms, and quality-of-life (QoL) subtests of the IPSS, Qmax, and PVR urine volume. Adverse events were also summarized and compared between groups.

A study sample size of 120 patients (60 in each arm) was calculated to have 80% power with a 95% confidence interval. Trial data were entered into a database using SPSS software version 15.0 (SPSS Inc, Chicago, IL, USA). The outcome measures were compared between the 2 groups using the *t* test; a conservative probability value of $P < .01$ was used to determine statistical significance because of the multiple number of paired comparisons.

## RESULTS

Out of 120 patients enrolled in the study, 118 patients completed it. One patient in each group was dropped due to adverse events, as described later.

### *IPSS, Qmax, and PVR Urine Volume*

Table 2 contains the means and standard deviations at baseline and at the end of 12 weeks for overall IPSS and the IPSS subscores of irritative symptoms and voiding symptoms; QoL, Qmax, and PVR are also included. The probability of significant differences is presented.

*IPSS*. There was no significant group difference in the mean total IPSS at baseline. Compared with the baseline IPSS, both groups showed significant improvement at the 12-week evaluation ($P < .001$). There was also a significant group difference at the end of 12 weeks; patients taking tamsulosin plus flavoxate had a significantly lower mean IPSS when compared with patients taking tamsulosin plus a placebo ($P < .001$).

There was no significant group difference in the mean irritative symptoms subscore or voiding symptoms subscore at baseline. Both groups had improved subscores at 12 weeks. There was a significant group difference in the mean irritative symptoms subscore at the end of 12 weeks; patients taking tamsulosin plus flavoxate had a significantly lower irritative symptoms subscore ($P < .002$). However, there was no significant group difference in the mean voiding symptom subscore at 12 weeks ($P = .14$).

There was no significant group difference in the mean QoL score at baseline. Patients in both groups had a significant improvement in QoL score at the end of 12 weeks ($P < .001$). There was also a significant group difference at the end of 12 weeks; patients taking tamsulosin plus flavoxate had a significantly lower QoL score when compared with patients taking tamsulosin plus a placebo ($P < .002$).

*Qmax.* There was no significant group difference in the mean Qmax at baseline. There was progressive increase in the Qmax of all patients during the treatment period ($P < .001$), with no significant group difference in the mean Qmax at the end of 12 weeks ($P = .68$).

Table 2. Means and Standard Deviations for Overall IPSS and Irritative and Voiding Symptom Subscores, QoL, Qmax, and PVR Urine Volume at Baseline and After 12 Weeks of Therapy; Probability of Significant Group Differences (N = 118). doi: 10.3834/uij.1944-5784.2010.08.09t2

| Outcome Measure | Group 1 Tamsulosin + Flavoxate (n = 59) | | Group 2 Tamsulosin + Placebo (n = 59) | | *P* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **IPSS (score)** | | | | | |
| **Baseline** | 21.08 | 3.58 | 20.57 | 2.62 | .61 |
| **12 weeks** | 10.93 | 3.11 | 13.07 | 3.08 | <.001 |
| **Irritative symptoms (score)** | | | | | |
| **Baseline** | 10.53 | 2.58 | 10.1 | 2.80 | .54 |
| **12 weeks** | 5.17 | 1.26 | 6.53 | 2.01 | <.002 |
| **Voiding symptoms (score)** | | | | | |
| **Baseline** | 10.55 | 4.15 | 10.47 | 3.71 | .70 |
| **12 weeks** | 5.77 | 1.26 | 6.53 | 2.01 | .14 |
| **QoL (score)** | | | | | |
| **Baseline** | 4.23 | 1.19 | 4.27 | 1.19 | .41 |
| **12 weeks** | 2.43 | 0.77 | 3.13 | 0.86 | <.002 |
| **Qmax (mL/s)** | | | | | |
| **Baseline** | 8.50 | 3.82 | 7.57 | 2.57 | .35 |
| **12 weeks** | 24.27 | 6.04 | 22.13 | 5.28 | .68 |
| **PVR urine volume (mL)** | | | | | |
| **Baseline** | 76.57 | 22.44 | 88.47 | 15.62 | .47 |
| **12 weeks** | 19.40 | 9.83 | 22.53 | 9.01 | .66 |

Abbreviations: IPSS, International Prostate Symptom Score; PVR, postvoid residual; Qmax, maximum urinary flow rate; QoL, quality of life; SD, standard deviation.

*PVR Urine Volume*. There was no significant group difference in the mean PVR volume at baseline. There was progressive decrease in the PVR volume of all patients during the treatment period ($P < .001$). There was no significant group difference in the mean PVR volume at 12 weeks ($P = .66$).

### *Episodes of Irritative Symptoms*

Table 3 contains the means and standard deviations for the number of episodes of irritative symptoms (frequency, urgency, and nocturia) at baseline and after 12 weeks of therapy for both patient groups. The probability of significant group differences is also displayed. There were no significant group differences at baseline for any of the measures. Both groups had significantly fewer episodes of frequency, urgency, and nocturia at the end of study when compared with baseline ($P < .001$). Group differences in mean frequency and nocturia at the end of 12 weeks approached statistical significance ($P = .05$); patients taking tamsulosin plus flavoxate had fewer episodes. There was no significant group difference in urgency.

### *Adverse Events*

Table 4 contains the number of adverse events reported by the patients in both treatment groups. A total of 22 adverse events were reported; 12 (20%) occurred in group 1 and 10 (16.7%) occurred in group 2. The most common adverse events were dizziness and headache. Two patients (1 from each group) were dropped from the study because they complained of impotence and ejaculatory dysfunction; these patients were switched to another therapy. All other adverse events were mild and transient. There was no statistically significant group difference in adverse event rate.

## DISCUSSION

Efficacy and safety of $\alpha_{1A}$ blockers like tamsulosin in treating LUTS in patients with BPH have been confirmed previously, but the results are not universal or adequate in alleviating the irritative symptoms due to detrusor overactivity. Literature and clinical practice show that many patients treated for LUTS caused by BPH continue to experience irritative LUTS [3]. Irritative

Table 3. Means and Standard Deviations (SD) for the Number of Episodes of Irritative Symptoms at Baseline and After 12 Weeks of Therapy; Probability of Significant Group Differences (N = 118).
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| Outcome Measure | Group 1 Tamsulosin + Flavoxate (n = 59) | | Group 2 Tamsulosin + Placebo (n = 59) | | *P* |
|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | |
| **Frequency (No.)** | | | | | |
| **Baseline** | 8.80 | 2.70 | 9.33 | 3.56 | .51 |
| **12 weeks** | 4.74 | 1.54 | 6.81 | 1.13 | .05 |
| **Urgency (No.)** | | | | | |
| **Baseline** | 3.57 | 0.82 | 3.83 | 0.92 | .15 |
| **12 weeks** | 2.21 | 1.37 | 2.50 | 1.14 | .23 |
| **Nocturia (No.)** | | | | | |
| **Baseline** | 4.03 | 1.29 | 3.90 | 1.32 | .56 |
| **12 weeks** | 1.83 | 1.01 | 2.89 | 1.12 | .047 |

Table 4. Number of Reported Adverse Events in Both Patient Groups (N = 120).
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| Adverse Event | Group 1 Tamsulosin + Flavoxate (n = 60) | Group 1 Tamsulosin + Placebo (n = 60) |
|---|---|---|
| **Dizziness** | 4 | 2 |
| **Headache** | 3 | 2 |
| **Syncope** | 0 | 1 |
| **Malaise** | 0 | 1 |
| **Hypotension** | 1 | 2 |
| **Dry mouth** | 3 | 1 |
| **Impotence** | 1 | 0 |
| **Ejaculatory disorder** | 0 | 1 |
| **Total Events** | 12 | 10 |

LUTS may be attributed to detrusor overactivity resulting from structural changes in detrusor muscles due to aging or to bladder outlet obstruction due to prostate enlargement [19,20]. Anticholinergics have been used in combination with alpha blockers for treatment of LUTS in patients with BPH. Studies have shown that anticholinergics in combination with alpha blockers are effective in treating irritative symptoms of LUTS [9-11;14]. However, anticholinergic drugs can cause residual urine and voiding difficulty in patients with BPH.

Flavoxate hydrochloride, a urinary spasmolytic drug that was approved for OAB, is commonly prescribed by physicians for treating irritative symptoms of LUTS. In the present study, the combination of tamsulosin and flavoxate was significantly more effective than tamsulosin and a placebo in improving the mean total IPSS, irritative symptom subscore, and QoL score.

Kato et al [21] studied flavoxate supplementation in patients with BPH who had nocturia that was resistant to the α-1 blockers tamsulosin and naftopidil. The patients were given 400 mg or 600 mg of flavoxate at bedtime. The results showed significant improvement in IPSS, QoL, and number of nocturnal micturations. In the present study, the patients were given flavoxate 200 mg, 3 times daily. The results were similar to those of the Kato et al study.

Flavoxate supplementation with $\alpha_{1A}$ blockers improves irritating symptoms of LUTS in patients with BPH. The advantage of flavoxate is that it is devoid of anticholinergic activity, with few side effects and no risk of increased PVR urine volume or acute urinary retention in patients with an enlarged prostate. It can be safely prescribed, especially in the elderly population where there may be compliance issues with anticholinergic drugs. There is also no danger of affecting cognitive functions. Therefore, supplemental administration of flavoxate hydrochloride with $\alpha_{1A}$ blockers appears to be safe and effective for the treatment of patients with LUTS due to BPH.

## CONCLUSIONS

The present study shows that taking a combination of tamsulosin with flavoxate improves IPSS, irritating symptoms, and QoL significantly more than taking the alpha blocker alone. The combined drugs had good efficacy and safety and can be considered as a therapeutic option for treatment of LUTS associated with BPH.

**Conflict of Interest**: none declared

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