Original Article

Comparison of Efficacy and Safety of a Combination of Tamsulosin and Mirabegron versus Tamsulosin Alone in the Management of Overactive Bladder in Males with Lower Urinary Tract Symptoms – TAME-Overactive Bladder: An Open-labeled Randomized Controlled Trial

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Abstract

Background: Overactive bladder (OAB) is a common condition in elderly men with coexisting benign prostatic enlargement (BPE), and it significantly impairs their quality of life (QoL). **Aim:** This study aimed to assess the safety and efficacy of adding beta-3 adrenergic receptor agonist (mirabegron 50 mg) to tamsulosin 0.4 mg for symptomatic men with BPE and OAB symptoms (OABS). **Materials and Methods:** It was an open-labeled randomized controlled trial. Ninety men with BPE and International Prostate Symptom Score (IPSS) of more than seven with predominant OABS were enrolled for the study. A detailed history, uroflowmetry, and baseline scores, including IPSS, OABS score (OABSS), and QoL assessment, were done for each patient. After written informed consent, patients were randomized into two groups of 45 each. Group-1 received tamsulosin 0.4 mg and placebo, and Group-2 received a combination of tamsulosin 0.4 mg plus mirabegron 50 mg once daily at bedtime. Follow-up of patients was done at 2nd, 4th, and 8th weeks. Efficacy at 8 weeks was assessed using repeat history for symptoms, uroflowmetry, IPSS, OABSS, and QoL score. **Results:** After 8 weeks of therapy, collected data were compared to baseline parameters in both groups. Significant improvement with respect to OABSS (P = 0.046), IPSS (P = 0.006), and QoL (P = 0.038) was observed with combination therapy versus tamsulosin alone. There were mild adverse effects, which were self-limiting. **Conclusions:** A combination of tamsulosin with mirabegron is effective and safe in improving the OABSS, IPSS, and QoL in men with BPE who have predominant OABS.

Keywords: *Benign prostatic enlargement, International Prostatic Symptom Score, mirabegron, overactive bladder, Overactive Bladder Symptom Score, quality of life, tamsulosin*

Introduction

Overactive bladder (OAB) is a common condition in the aging population, associated with detrimental effects on quality of life (QoL).[1] In men, OAB may be caused by bladder dysfunction or bladder-outlet obstruction (BOO).[2] According to the 2019 European Association of Urology Guideline for nonneurogenic male lower urinary tract symptoms (LUTS), patients with benign BOO and OAB symptoms (OABS) should use anticholinergic agents concurrently with alpha-adrenergic blockers.[3] Furthermore, systematic reviews and well-designed randomized controlled trials have demonstrated the efficacy of anticholinergic drugs.[4-6] Antimuscarinic drugs are frequently stopped by patients due to adverse effects such as blurring of vision, dryness of mouth, and constipation.[7]

Mirabegron is a β3-adrenoceptor agonist that may be used to treat symptoms of OAB.[8] Furthermore, compared to standard anticholinergic medications, the rate of side effects such as blurring of vision, dryness of mouth, and constipation with mirabegron is much lower.[9] Mirabegron has been shown to be effective as an add-on (postα-blocker medication) for controlling residual storage LUTS in benign prostatic enlargement (BPE) patients with coexisting persistent OAB in certain trials.[8,9] In this study, we analyzed the safety and efficacy of combination therapy (mirabegron 50 mg + tamsulosin 0.4 mg) versus tamsulosin alone in patients with BPE with OABS.

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Materials and Methods

Study setting and design

This randomized, double-blind, placebo-controlled study was conducted over 6 months (October 1, 2022–March 31, 2023) in a large tertiary care center in North India. The study was approved by the Institutional Ethics Committee and the Clinical Trial Registry, India (reference number CTRI/2022/09/045280 dated September 07, 2022).

Study subjects and sample size

A previous study from Japan had shown a mean change of 0.87 in monotherapy and 2.21 in the combination group in total OABS score (OABSS).[10] A total sample size of 43 patients (86 in each group) provides 80% power to conclude superiority using a one-sided 5% significance level and equivalence margin of 5%. This number was increased to 45 per group (a total of 90) to allow for a predicted dropout from treatment.

In the present study, 90 patients (18 years or older) with BPE with predominantly OABS (newly diagnosed uncomplicated BPE of any size with predominant OABS and an International Prostate Symptom Score (IPSS)[11] more than 7 without any medical contraindications to planned drug therapy or an absolute indication for surgery, who visited the outpatient department (OPD) or were admitted to the wards were included in the study. Patients with a prior history of anaphylaxis/hypersensitivity, drug therapy with metabolic interference to administered medication, prostatic/urethral surgery and other concomitant prostate disease/cancers, clinical neurological disorders, and/or neurogenic bladder were excluded from this study.

Data and sample collection

History pertaining to demographic parameters and clinical details of each patient was noted by a structured interview in a predesigned data questionnaire sheet. It was an open-labeled study. Patients were randomized by a computer-generated list and allocated to either the control Group A (tamsulosin 0.4 mg plus lactobacillus 1 capsules), or the intervention Group B (tamsulosin 0.4 mg plus mirabegron 50 mg tablet), administered at bedtime after meals for a study period of 2 months (8 weeks), considering the rapid onset of action of drugs in both arms and their major side effects if any would be exhibited within this study time frame. Patients were evaluated as per protocol (hemogram, liver function test, renal function test and urine routine, culture, electrocardiogram, ultrasound of the kidney, ureter, and bladder and uroflowmetry) during the initial visit (D0) before the initiation of therapy. Patients were followed up in OPD at the 2nd, 4th, and 8th weeks after initiation of therapy, and were interviewed as per the questionnaire in the predesigned pro forma for various outcome parameters and side effects.

The primary outcome studied was OABSS[12] and the secondary outcome parameters included mean change nocturnal voiding frequency, postvoid residual urine, and IPSS. Safety was assessed by monitoring for posttherapy treatment-emergent adverse event (TEAE).

Data analysis

Data were described in terms of range, mean ± standard deviation, frequencies (number of cases), and relative frequencies (percentages) as appropriate. To determine, whether the data were normally distributed, a Kolmogorov–Smirnov test was used. Comparison of quantitative variables between the study groups was made using Student's *t*-test and Mann–Whitney *U*-test for independent samples for parametric and nonparametric data, respectively. For comparing categorical data, Chi-square test was performed. A probability value (P value) < 0.05 was considered statistically significant. All statistical calculations were done using the Statistical Package for the Social Science (SPSS) 21 version (SPSS Inc., Chicago, IL, USA) statistical program for Microsoft Windows.

Results

The baseline characteristics of Group A (tamsulosin + placebo) and Group B (mirabegron + tamsulosin) were matched to adjust for any confounding effect on the outcomes. The various parameters, including mean age, renal function, and prostate-specific antigen, were comparable between the two groups. Prostatomegaly of Grade 2 was the most common, as seen among 55% of Group A and 62.5% of Group B patients. Similarly, the baseline OABSS, IPSS, and QoL scores were also comparable [Table 1].

The patients' voided volume (ml), maximum flow rate (ml/s), OABS, IPSS, and QoL were compared within each group postintervention. It was observed that Group A patients reported an increase in voided volume and maximum flow rate at 8 weeks. There was relative betterment in OABSS, IPSS, and QoL, but except for OABSS, nocturnal frequency, and urgency, improvement in the rest of all parameters was statistically not significant [Table 2a].

However, Group B, receiving a combination of tamsulosin and mirabergon, had significant improvement in OABSS, IPSS, and QoL at the end of 8 weeks of therapy [Table 2b].

When the outcome parameters were compared between the two groups after 8 weeks of therapy, a significantly better outcome was observed with respect to improvement in OABSS (P = 0.046), urgency (P = 0.035), and IPSS (P = 0.006). QOL postintervention was significantly improved for Group B compared to Group A (P = 0.038) [Table 3].

Three of the 90 patients, two (2/45; 6.7%) in Group A and one (1/45; 3.8%) in Group B suffered TEAE. One patient

Table 1: Comparison of baseline characteristics of Group A and Group B

Parameters	Mean±SD/*n* (% of patients)		*t*/*Z*/χ^2	*P*
	Group A (tamsulosin + placebo) (*n*=45)	Group B (mirabegron + tamsulosin) (*n*=45)		
Prostatomegaly				
Grade 1	13 (30)	9 (20)	0.964	0.617
Grade 2	25 (55)	28 (62.5)		
Grade 3	7 (15)	8 (17.5)		
Age (years)	72.5±8.3	71.3±7.8	−0.704	0.482
Voided volume (mL)	214.2±119.6	175.3±115.8	−1.568	0.121
Average flow rate (mL/s)	4.8±3.9	3.9±1.8	−0.163	0.871
Maximum flow rate (mL/s)	14.5±6.9	14.1±6.7	−0.279	0.781
Serum creatinine (mg/dL)	1.02±0.3	1.28±2.3	0.852	0.454
Serum PSA (ng/mL)	1.4±0.8	1.7±1.1	1.480	0.290
OABSS	7.41±2.79	7.92±2.58	0.900	0.370
Daytime frequency	0.73±0.67	0.74±0.56	0.077	0.939
Nighttime frequency	2.35±0.80	2.36±0.78	0.060	0.952
Urgency	2.99±0.93	3.35±0.96	1.807	0.074
Urgency incontinence	1.44±1.38	1.34±1.47	−0.333	0.740
IPSS	15.93±6.24	16.18±5.63	0.200	0.842
IPSS voiding sub score	5.67±3.49	5.81±3.42	0.193	0.848
IPSS storage sub score	9.13±3.44	9.85±2.86	1.080	0.283
QoL	3.48±1.27	3.70±1.49	0.754	0.453

PSA: Prostate-specific antigen, OABSS: Overactive Bladder Symptom Score, IPSS: International Prostate Symptom Score, QoL: Quality of life, SD: Standard deviation

Table 2a: Tamsulosin-only-based regimen (Group A): Comparison of parameters after 8 weeks of therapy versus baseline

Parameters	Group A (tamsulosin + placebo) (*n*=45), mean±SD		*t*/*Z*	*P*
	8 weeks	Baseline		
Voided volume (mL)	271.2±167.5	214.2±119.6	−1.858	0.067
Maximum flow rate (mL/s)	15.3±7.2	14.5±6.9	−0.536	0.591
OABSS	6.34±2.13	7.41±2.79	2.045	0.044
Daytime frequency	0.81±0.71	0.73±0.67	−0.550	0.584
Nighttime frequency	1.99±0.77	2.35±0.80	2.175	0.032
Urgency	2.42±1.23	2.99±0.93	2.480	0.015
Urgency incontinence	1.25±1.37	1.44±1.38	0.655	0.514
IPSS	15.57±8.13	15.93±6.24	0.236	0.814
IPSS voiding sub score	5.82±4.25	5.67±3.49	−0.183	0.855
IPSS storage sub score	8.78±3.46	9.13±3.44	0.481	0.632
QoL	3.39±1.30	3.48±1.27	0.332	0.741

PSA: Prostate-specific antigen; OABSS: Overactive bladder symptom score; IPSS: International Prostate Symptom Score; QoL: Quality of life; SD: Standard deviation

in Group A complained of postural hypotension and one patient in Group B experienced vertigo and tachycardia, respectively, which were mild and self-limiting, and were handled symptomatically with no need for drug discontinuation.

Discussion

This was an open-labeled, randomized controlled trial of mirabegron as a tamsulosin add-on medication, in patients with OAB. In this study, adding 50 mg/day of mirabegron to tamsulosin for 8 weeks was effective in significantly reducing OABS and led to improvement in IPSS, including voiding and storage subscores, besides improving the overall QoL.

Two previously published studies have compared this combination with the tamsulosin alone therapy; both have been done in Japanese and Korean males only. One study has shown a mean change of 0.87 in monotherapy and 2.21 in the combination group in total OABSS.[10] Another study (MATCH)[13] with primary objective as a change in the frequency of micturition showed improved outcome with combination therapy and similar benefits in improving

Table 2b: Tamsulosin + mirabegron combination therapy (Group B): Comparison of parameters after 8 weeks of therapy versus baseline

Parameters	Group B (mirabegron + tamsulosin) (*n*=45), mean±SD		*t*/*Z*	*P*
	8 weeks	Baseline		
Voided volume (mL)	289.4±157.7	175.3±115.8	3.912	0.0002
Maximum flow rate (mL/s)	15.9±6.4	14.1±6.7	22121.303	0.196
OABSS	5.45±2.03	7.92±2.58	5.047	<0.0001
Daytime frequency	0.61±0.57	0.74±0.56	1.091	0.278
Nighttime frequency	2.02±0.62	2.36±0.78	2.289	0.025
Urgency	1.89±1.12	3.35±0.96	6.639	<0.0001
Urgency incontinence	0.77±1.12	1.34±1.47	2.069	0.042
IPSS	11.34±5.82	16.18±5.63	3.983	0.000
IPSS voiding subscore	4.56±2.98	5.81±3.42	1.849	0.068
IPSS storage subscore	7.57±2.14	9.85±2.86	4.282	<0.0001
QoL	2.87±1.02	3.70±1.49	3.083	0.003

PSA: Prostate-specific antigen; OABSS: Overactive bladder symptom score; IPSS: International Prostate Symptom Score; QoL: Quality of life; SD: Standard deviation

Table 3: Comparison of 8 weeks posttherapy characteristics between tamsulosin-only therapy (Group A) and tamsulosin + mirabegron (Group B)

Parameters	Mean±SD		*t*/*Z*	*P*
	Group A (tamsulosin + placebo) (*n*=45)	Group B (mirabegron + tamsulosin) (*n*=45)		
Voided volume (mL)	271.2±167.5	289.4±157.7	0.531	0.597
Maximum flow rate (mL/s)	15.3±7.2	15.9±6.4	0.418	0.677
OABSS	6.34±2.13	5.45±2.03	−2.029	0.046
Daytime frequency	0.81±0.71	0.61±0.57	−1.474	0.144
Night time frequency	1.99±0.77	2.02±0.62	0.204	0.839
Urgency	2.42±1.23	1.89±1.12	−2.137	0.035
Urgency incontinence	1.25±1.37	0.77±1.12	−1.820	0.072
IPSS	15.57±8.13	11.34±5.82	−2.838	0.006
IPSS voiding subscore	5.82±4.25	4.56±2.98	−1.628	0.107
IPSS storage subscore	8.78±3.46	7.57±2.14	−1.995	0.049
QoL	3.39±1.30	2.87±1.02	−2.111	0.038

PSA: Prostate-specific antigen; OABSS: Overactive Bladder Symptom Score; IPSS: International Prostate Symptom Score; QoL: Quality of life; SD: Standard deviation

mean volume voided/micturition, OABSS (mean change of −0.65), IPSS (mean change −1.19), storage (mean change −0.78), QoL scores (mean change −0.29), OABS bother, and total health-related QoL. The difference in urgency, urgency urinary incontinence, and nocturia were not statistically significant in this Japanese study.[13]

Ours is the first study to analyze the clinical benefits and adverse effects of the drug combination (tamsulosin and mirabegron) in the Indian population. As we know, the pharmacodynamics of the drug may vary in people of different populations and different ethnicities, it is imperative to study the drug combination in our native population before getting the confidence of using it in a wider population.

In OAB, voiding is frequently utilized as an empirical and physiologic predictor of therapy success because the voided volume is thought to change in unison with a frequency of micturition when fluid intake remains constant, and a rise in voided volume is expected as the frequency of micturition falls.[14-18] The increased voided volume observed in this study suggests that the decrease in frequency of micturition is related to a drug therapeutic effect rather than a decrease in fluid consumption. Although OABSS, urgency, nighttime frequency, and urgency incontinence subscale scores showed statistically significant differences within the tamsulosin + mirabegron combination therapy group, the inter-group differences between combination and tamsulosin alone therapy did not reach classic thresholds of statistically significant for daytime frequency, nighttime frequency, and urgency incontinence.

In a voiding diary, the patient records discomfort on a real-time basis for 3 days; in the OABSS, the patient recalls the occurrence of OABS during the past 7 days. This could suggest that complaints of such an episodic nature that really does not show up in a 3-day observation might show up in a lengthier peek time. Furthermore, because tamsulosin improves urgency, it is probable that previous

tamsulosin administration altered the baseline intensity of urgency. This could have had a role in the lack of statistical significance for urgency incontinence. Previous studies of solifenacin added to tamsulosin showed statistically significant decreases in the urgency as compared to tamsulosin plus placebo combination and improvement in IPSS storage symptom score, and OABSS (except nighttime frequency) when compared to tamsulosin.[19]

In the therapy of OAB, improvements in QoL are the main goal. Patients with OAB are more likely to seek treatment if their QoL is compromised and are likely to adhere to prescribed treatment if they notice significant improvements in their QoL.[20]

The rates of drug-related TEAEs in the mirabegron 50 mg group were comparable to that in the placebo group, which is consistent with prior findings for men on mirabegron.[21,22]

Tachycardia was seen in 6.7% in the mirabegron group, showing that mirabegron had a low risk of anticholinergic adverse events, which are commonly associated with antimuscarinic medications. The frequency of cardiovascular TEAEs of particular concern did not differ significantly across treatment groups, matching the findings of a mirabegron trial in healthy males.[21-23] The safety profile of the add-on medication in this study was consistent with the known profiles of mirabegron and tamsulosin, with no newly disclosed adverse issues identified. The lack of antimuscarinic comparison (future studies could benefit from having a tamsulosin plus antimuscarinic comparison group), and omission of severe urgency as an inclusion criterion are limitations of this study.

Conclusions

In males with LUTS and OABS, mirabegron added to tamsulosin proves superior to tamsulosin alone in terms of increasing voided volume, as well as improvements in OABSS and IPSS total scores. Mirabegron addition also exhibited statistical significance and clinically important improvements in the QoL scores. Mirabegron was very well tolerated in combination therapy with tamsulosin, with no serious adverse effects, including cardiovascular events.

Ethical statement

The study was approved by the ethical committee of Dayanand Medical College and Hospital, Ludhiana, Punjab, India, vide approval number DMCH/DTEC/2022/1356, dated 17/8/2022, and the Clinical Trial Registry, India (CTRI) vide reference number CTRI/2022/09/045280 dated September 07, 2022.

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Conflicts of interest

There are no conflicts of interest.

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