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Original Article

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Mirabegron as add-on therapy for persistent storage symptoms under tamsulosin monotherapy for BEP

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Abstract

Background: *Antimuscarinic drugs are used for the treatment of overactive bladder (OAB), as it effectively reduces detrusor overactivity and bothersome storage symptoms in LUTS. However, the use of antimuscarinic agent is associated with several side effects such as dry mouth and constipation. Mirabegron is a selective beta-3 agonist that has good safety and tolerability profile with lower incidence of adverse events.*

Objective: *To evaluate the effectiveness and safety of Mirabegron as add-on therapy for persistent storage symptoms under tamsulosin monotherapy for benign enlargement of prostate.*

Methods: *This prospective observational study was conducted at OPD, Department of Urology, National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, from January 2021 to February 2022. Finally A total of 108 patients with persistent storage symptoms after 12 weeks of tamsulosin monotherapy with benign enlargement of prostate were purposively included in the study. Patients with post-void urine volume (PVR) >50 mL, prostate size < 40gm, history of urinary retention, neurogenic bladder, urethral stricture and taking any anti-muscarinic drugs, uncontrolled diabetic mellitus, bladder and prostate carcinoma were excluded from the study. Mirabegron (25 mg once daily) was added to Tamsulosin. Before and 12 weeks after addition of either drugs, International Prostate Symptom Storage Sub Score (IPSS-S), Overactive Bladder Symptom Score (OABSS), Quality of life(QOL) were assessed, Uroflowmetry and transabdominal ultrasound was done to assess maximum flow rate, voided volume (Qmax) and PVR respectively. Adverse events were recorded throughout the study period.*

Results: *The mean ages of the patients were 61 ±5.5. The mean IPSS-S, QOL, OABSS significantly reduced after three months of treatment (p<0.001). 13 (12%) patients developed adverse effects (dry mouth 1.8%, dysuria 2.8%, acute urinary retention 0.9%, constipation 2.8%).*

Conclusion: *Mirabegron with tamsulosin as add-on therapy for persistent storage symptoms significantly improved storage symptoms. There is no significant treatment emerging adverse events (TEAE) in mirabegron.*

Keywords: Mirabegron as add-on therapy, Lower urinary tract symptoms (LUTS), Tamsulosin, BEP, Overactive bladder (OAB), International Prostate Symptom Storage Sub Score (IPSS-S), Overactive Bladder Symptom Score (OABSS)

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Introduction:

Lower Urinary Tract Symptoms (LUTS) is a symptom complex composed of storage (frequency, urgency, nocturia, urge incontinence) and voiding (intermittency, hesitancy, weak stream, straining, sense of incomplete evacuation) symptoms. Lower Urinary Tract Symptoms (LUTS) are common with up to 41% of men reporting bothersome symptoms over age of 40 years[1]. Benign enlargement of Prostate (BEP), urethral stricture, urinary tract infection, overactive bladder, detrusor underactivity, bladder and prostate cancer, neurogenic bladder dysfunction, diabetes mellitus, bladder and distal ureteric stone are common causes of male LUTS[2].

In Asia, 77.8% of men aged ≥40 years have at least mild degree of LUTS according to IPSS assessment[3]. The prevalence of storage LUTS in men (51.3%) is greater than that for voiding (25.7%)[4] (Irwin et al., 2006).

Overactive bladder defines as urgency with or without urge incontinence, usually with frequency and nocturia. This term is usually used when there is no proven infection or other obvious pathology[5,6]. In men prevalence of overactive bladder is between 7% to 27%[7]. There is an association between overactive bladder and bladder outlet obstruction secondary to benign enlargement of prostate[8]. About 47% men with bladder outlet obstruction have overactive bladder[9].

Overactive bladder (OAB) or persistent storage symptoms are commonly found in men with lower urinary tract symptoms (LUTS) suggestive of benign enlargement of prostate (BEP)[9]. It has a significant impact on quality of life, sexual function, sleep and mental health[10].

For patients with benign enlargement of prostate and persistent storage symptoms, the key of treatment is inhibiting bladder contraction and reducing afferent sensation to improve storage symptoms[11].

Tamsulosin hydrochloride, an alpha1 adrenoreceptor antagonist, is an effective pharmacological treatment for benign enlargement of prostate[12]. Regardless of prostate size, á1-blockers alleviate dynamic obstruction of the prostate and urethra as well as storage symptoms[13]. Thus, in general, alpha1-blockers are the first line pharmacotherapy for male LUTS[14]. However, these therapeutics may fail to alleviate urinary storage symptoms when they are used as single agent[15].

Mirabegron is a selective beta-3 agonist that acts specifically on beta-3 receptors, the stimulation of which leads to active relaxation of detrusor muscle during storage phase with subsequent increase in bladder capacity without affecting bladder contractility during voiding phase[16]. It is an alternative treatment option to antimuscarinics for persistent storage symptoms, with proven efficacy in both men and women[17,18]. There are previous studies of mirabegron as add-on treatment to tamsulosin, showing that mirabegron add-on treatment is effective and well tolerated[19,20].

A phase II study shows that the urodynamic safety of mirabegron in male patients with lower urinary tract symptoms (LUTS) and bladder outlet obstruction (BOO). In that study, mirabegron 50 or 100 mg once daily had no negative effect on voiding parameters on urodynamics compares with placebo after 12 weeks of administration[8].

Another study shows that mirabegron to patients with persistent storage symptoms after tamsulosin monotherapy has significant efficacy to control these symptoms but mirabegron has better Quality of life (QOL) and overall patient satisfaction[21].

Mirabegron is more convenient to administer in elderly benign enlargement of prostate patients with persistent storage symptoms[8].

Materials and Methods:

This study was a prospective analytical study. The study was conducted from January 2021 to February 2022. The study was conducted at OPD, Department of Urology, National Institute of Kidney Diseases & Urology (NIKDU), Dhaka. Patients with persistent storage symptoms after 12 weeks of tamsulosin monotherapy for benign enlargement of prostate. **Inclusion criteria:** Male patients age > 45 years who has persistent storage symptoms after 12 weeks of tamsulosin monotherapy,IPSS storage sub score (IPSS-S) e" 5 , OABSS >3**,** Prostate size ≥40 gm**. Exclusion criteria:** Post-void residue (PVR) >50 mL, History of urinary retention, Urinary tract infection,Uncontrolled diabetes mellitus: HbA1c > 7%, Neurogenic bladder, Urethral stricture, Severe hypertension (systolic blood pressure e" 180 mmHg and/or diastolic blood pressure ≥ 110 mmHg) not well controlled by medication, Renal insufficiency (serum creatinine >1.4 mg/dl), Carcinoma prostate, Bladder carcinoma,Patients taking any anti-muscarinic drugs, Considered unsuitable for the trial by the treating physicians.

Sample size 128 participants. Purposive sampling technique was applied in this study. **Study procedure** done by Initial assessment of patient included history taking, general, physical, and genital examination, DRE, abdominal/pelvic ultrasonography, Uroflowmetry, Serum creatinine, Serum PSA, Urine R/M/E with C/S. Patient adviced mirabegron (25 mg once daily). Before and 12 weeks after addition of drug IPSS, IPSS-S, OABSS, QOL were assessed. Uroflowmetry was also done to assess Qmax, and trans-abdominal ultrasound was also done to assess PVR and Prostatic volume (PV). These subjective and objective parameters were observed. Treatment emergent adverse events (TEAE) were recorded throughout the study period.The statistical analysis was conducted using SPSS (statistical package for the social science) version 25 statistical software. Associations of categorical data were assessed using Chi square test. Associations of continuous data were assessed using Students t test and paired sample t test where p<0.05 was considered significant.

Results:

Table I shows that, 69 (63.9%) patients were from 56-65 years age group and 23 (21.3%) patients were from >65 years age group. The mean ages of the patients were 61.0 ±5.

Table-I: *Age distribution (N=108)*

Age group	N=108
(In years)	n (%)
46-55	16 (14.8)
56-65	69 (63.9)
>65	23 (21.3)

N= Total number of patients

Table II shows that, 57 (52.8%) patients had no comorbidity and 51 (47.2%) patients had comorbidities like Diabetes mellitus, Hypertension.

Table-II: *Comorbidities (N=108)*

Comorbidities	N=108 n (%)
Absent	57 (52.8)
Controlled diabetes mellitus	22 (20.4)
Hypertension	17 (15.7)
Both controlled diabetes mellitus and hypertension	12 (11.1)

N= Total number of patients

Table III shows that the mean of the International Prostate Symptom Storage Sub Score (IPSS-S), Quality of life (QOL) and Overactive Bladder Symptom Score (OABSS) of patients in group A significantly reduced after three months of treatment as p value was <0.001 (obtained by paired sample test).

Table-III : *Distribution of patients by mean of International Prostate Symptom Storage Sub Score (IPSS-S), Quality of life (QOL) and OABSS due to urinary symptoms at baseline and after three months (N=108)*

Criteria	At baseline mean ± SD	After three months mean ± SD	p value
IPSS-S	6.9 ±2.0	4.2 ±2.2	<0.001
QOL	2.7 ±0.7	1.8 ±0.8	<0.001
OABSS	7.8 ±1.6	5.1 ±1.6	<0.001

N= Total number of patients

Table IV shows that after 3 months of treatment, 13 (12%) patients developed adverse events.

Table IV: *Distribution of patients by occurrence of adverse events after 3 months of treatment (N=108)*

Adverse events	N=108 n (%)
Absent	95 (88.0)
Present	13 (12.0)

N= total number of patients

Figure I shows that, 2 patients had dry mouth, 3 for dysuria, 2 had headache, 1 had acute urinary retention, 3 had constipation.

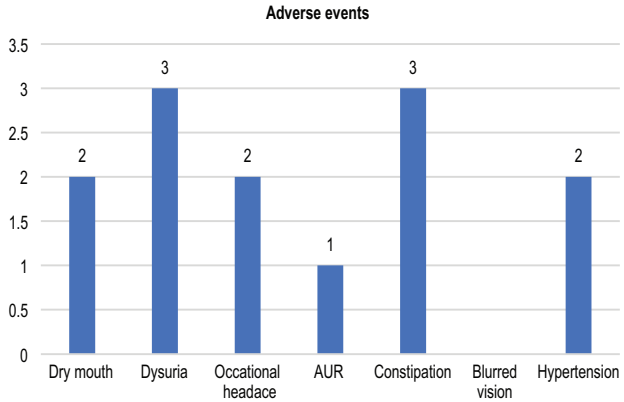

Figure 1: *Distribution of patients by occurrence of specific adverse events after 3 months of treatment (N=13)*

Discussion:

The present prospective observational study aimed to evaluate the effectiveness and safety of mirabegron as add-on therapy for persistent storage symptoms under tamsulosin monotherapy for benign enlargement of prostate. The study included 108 patients with persistent storage symptoms unders 12 weeks of tamsulosin monotherapy. Mirabegron as add-on therapy for persistent storage symptoms significantly improved storage symptoms. Moreover, mirabegron was found effective with negligible adverse events.

The mean age of the patients was 61.0 ±5.5 from 56-65 years age group. The study of Kaplan et al. (2013)[22] also observed that 55-64 years age group patients were more prevalent than others. Another study[23] found that the majority of patients were 65 years or older.

The mean of the IPSS, OABSS, overall QOL of patients significantly reduced after three months of treatment ($p<0.001$). Mirabegron, a â3-adrenergic receptor agonist, improves bladder storage capacity without impairing voiding function, resulting in its worldwide acceptance as a good therapeutic option for overactive bladder symptoms[24]. Kakizaki et al. (2020)[15] reported that mirabegron add-on therapy was superior to placebo in improving volume voided, International Prostate Symptom Score total, storage, quality of life. It has also been reported in several randomized trials that it significantly improves the overactive bladder symptoms with its all-sub scores and the IPSS storage symptoms, QOL index when used as add-on treatment after tamsulosin monotherapy[25,14,19,20].

Matsuo et al. (2016)[26] found that mirabegron additional therapy was effective regardless of patient age. Wada et al. (2016)[20] demonstrated that mirabegron add-on treatment with tamsulosin has efficacy and safety because it improves storage symptom without impairment of bladder contractility during voiding in male patients with OAB.

Mirabegron showed significant outcome in this study. Although the IPSS storage symptom score was significantly improved, there were no changes observed in the IPSS voiding symptom score. In this study the OABSS showed significant improvement (7.8 ±1.6 -5.1 ±1.6) which is close to Kaplan et al., 2020[23].

Common adverse effects included dry mouth (1.8%), dysuria (2.8%), acute urinary retention (0.9%), headache (1.8%), constipation (2.8%), hypertension (1.8%). Nitti et al. (2013) reported 1.5% incidence of dry mouth with mirabegron. Nitti et al. (2013)[8] and Soliman et al. (2020)[21] reported constipation in near about 2% with Mirabegron.

In the present study, patients who developed acute urinary retention were resolved by catheterization for seven days. Drugs were discontinued for them other than tamsulosin. Broad spectrum antibiotic was added. They were observed for refractory retention. Fortunately, no patient had further complications. They were further treated with tamsulosin alone.

Hypertension was observed in two patients who received mirabegron. They were treated with antihypertensive agents. Adverse effects in the study of Soliman et al. (2020)[21] with mirabegron included one case of tachycardia (2.2%) and two cases of hypertension (4.3%) which was not serious. Kakizaki et al. (2020)[15] reported even less cardiovascular side effects in only 1.1% of cases with no significant difference to the placebo and again none of them was serious.

Conclusion:

In conclusion this study finally demonstrates that Mirabegron with tamsulosin as add-on therapy for persistent storage symptoms significantly improves storage symptoms. Mirabegron is effective not only but also without any significant treatment emerging adverse events (TEAE)

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