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Efficacy and Safety of Add-on Treatment with Mirabegron for Benign Prostatic Hyperplasia Patients with Persistent Storage Symptoms after Alpha-blocker therapy

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Abstract:

Introduction: Introduction: Benign prostatic hyperplasia (BPH) is the most common benign disease in men with various lower urinary tract symptoms (LUTS). Clinically BPH results in LUTS, which can be classified as storage, voiding, and post-micturition, and often affect patients' quality of life (QoL)

Aim of the study: The study aims to evaluate the effect of adding mirabegron for benign prostatic hyperplasia patients complaining of persistent storage symptoms after alpha-blocker therapy.

Subjects and Methods: Our prospective study included 50 male patients with persistent storage LUTS after they were managed with a regular daily dose of α 1-adrenergic receptor blockers for 4 weeks. We added mirabegron 50 mg once daily for 8 weeks.

Results: Fifty men were enrolled in this study. Mirabegron additional therapy improved the total OABSS from 8.66 ± 2.28 to 5.12 ± 1.85 , total IPSS from 17.98 ± 2.9 to 10.88 ± 2.69 , and IPSS-quality of life (QOL) score from 5 (4- 5) to 2 (2- 3). The voided volume (VV) and Qmax improved from 10.90 (9.60-12.13) mL/s to 14.00 (12.48-15.05) mL/s after treatment in patients overall. However, there was no significant change in PVR.

Conclusions: Mirabegron's additional therapy is effective and safe for treating persistent storage symptoms after alpha blocker medication, Therefore, we recommend the combination therapy of AB and mirabegron as first-line therapy for patients with BPH who have persistent storage symptoms.

Keywords: Mirabegron, Elderly male, Overactive bladder, α 1-adrenergic blockers.

1. Introduction

According to Issa et al. (2006), benign prostatic hyperplasia (BPH) is the fourth most frequent disease among males 50 years of age and older and the most common benign disease in men with varied lower urinary tract symptoms (LUTS) [1]. Men's LUTS can occur

during storage, voiding, or the post-voiding phase and can come from the bladder, prostate, or urethra [2].

Age-related changes in the lower urinary tract, such as an increase in spontaneous bladder contractions, a decrease in the bladder's contractile function, a decrease in the feeling of the bladder filling, a reduction in bladder capacity, and comorbidities like bladder outlet obstruction (BOO) from benign prostatic hyperplasia, can be blamed for the rise in prevalence [3].

When treating LUTS in men with BPH, the most widely prescribed pharmacological treatment is an alpha-1adrenoceptor blocker (A1B). However, symptoms of OAB or storage may continue even after receiving treatment with A1B [4]. Nevertheless, poor treatment persistence and adherence, which are frequently linked to side effects including dry mouth and

constipation, may limit the positive therapeutic effects of antimuscarinics [5]. Providers may be reluctant to give antimuscarinics to some men because of the risk of acute urine retention (AUR), particularly in those with big prostates, a history of AUR, and elevated post-voiding residuals (PVR) [6]. The β 3-agonist mirabegron enhances bladder capacity by relaxing the detrusor smooth muscle without affecting PVR or micturition pressure [7].

Additionally, compared to patients taking anti-muscarinic therapy, individuals treated with mirabegron have demonstrated higher rates of durability and adherence [5].

The current study aimed to determine the expression levels of LncRNA NEAT-1 in the serum of psoriasis patients. Also, to investigate its function in the pathogenesis of the disease and whether it can be used as a potential diagnostic marker for psoriasis.

2. Subjects and methods

2.1. Subjects

50 male patients with persistent storage LUTS were included in our prospective trial after receiving daily doses of α 1-adrenergic receptor blockers for four weeks. For eight weeks, we also administered 50 mg of mirabegron once a day. Our study was performed at Fayoum University Hospital

(urology outpatient clinic) from October 2021 to September 2022. The study protocol has been approved by our faculty of medicine's ethical committee.

All our included patients signed informed consent. The patients were selected

according to the following inclusion and exclusion criteria.

Qualifications for inclusion

- Patient aged 50 years or above.
- Prostate volume > 30 ml or above.
- Patient complained of storage symptoms with failure of alpha-blocker therapy alone for one month.

Exclusion criteria

- Past surgical or urethral injuries.
- Prostatic surgery's past.
- Prostate cancer.
- Bladder cancer.
- Bladder stone.
- UTI.
- DM.

3. Results

All patients with persisting storage symptoms after taking a previous α 1-adrenergic receptor blocker for four weeks were included in this trial, which involved fifty men. The patients received an additional 50 mg of mirabegron once a day for eight weeks.

2.2. Study design

Prospective randomized clinical trial

2.3. Statistical Method

SPSS 28 was used to gather and tabulate the data. The statistical study was performed using IBM software for Windows. For categorical variables, descriptive statistics are displayed as percentages and frequencies. The numerical variables are presented using the mean and standard deviation. The numerical variables that are not evenly distributed are presented using the median and IQR. Patients with benign prostatic hyperplasia who continued to experience storage symptoms despite alpha blocker medication were compared before and after T with Mirabegron using the Paired T-test and the Wilcoxon Signed Rank Test. P-values less than 0.05 are regarded as statistically noteworthy.

Fifty patients in all took part in this investigation. They were 60.22 ± 7.06 years old on average. The PSA test findings had a median of 1.4 (1.075–2.00) ng/ml. Patients' median prostate volumes ranged from 45.00 to 66.25 (**Table 1**).

Table 1: Clinical characteristics of patients (N=50).

Variable	Control (n=20)
Age (mean± SD)	60.22±7.06
PSA (ng/ml) median (IQR)	1.4 (1.075 – 2.00)
PV (ml) median (IQR)	57.5045.00 – 66.25)

*Significant.

After adding mirabegron, the overall OABSS significantly improved. Furthermore, there was a notable improvement during the day and at night, there has been an improvement in both urgency and urgent incontinence (**Table 2**).

Table 2: Improvement of OABSS after adding mirabegron therapy.

Variable	Before	After	P-value
OABSS score	8.66± 2.28	5.12 ± 1.85	<0.001*
Day Frequency	1.6 ± 0.96	1.12 ± 0.77	<0.001*
Night Frequency	2.62± 1.25	1.64 ± 1.02	<0.001*
Urgency	3.22 ± 1.23	1.72 ± 0.94	<0.001*
Urge incontinence	1.22 ± 1.11	0.64 ± 0.69	<0.001*

*Significant.

IPSSs showed high statistically significant improvement after adding mirabegron therapy. There was a significant improvement in Frequency as well as nocturia and urgency (**Table 3**).

Table 3: Improvement of IPSSs after adding mirabegron therapy.

Variable	Before	After 2 months	P-value
IPSSs	9.6 ± 1.98	5.88 ± 1.78	<0.001*
Frequency	3.74 ± 0.96	2.34± 0.91	<0.001*
Nocturia	3.16 ±1.07	1.88 ± 1	<0.001*
Urgency	2.66 ± 1.06	1.64± 1.08	<0.001*

*Significant.

Total IPSS and IPSSv showed statically improvement in a weak stream as well as significant improvement after mirabegron Straining in addition to intermittency and additional therapy. There was significant Incomplete emptying (**Table 4**).

Table 4: Improvement of total IPSS and IPSSv after adding mirabegron therapy.

Variable	Before	After two months	P-value
Total IPSS score	17.98 ± 2.9	10.88 ±2.69	<0.001*
IPSSv	8.42 ± 1.62	5.02 ±1.55	<0.001*
Weak stream	3.42 ± 0.81	2.02 ±0.86	<0.001*
Straining	2.42 ± 0.9	1.42 ±0.99	<0.001*
Intermittency	1.5 ± 1.03	0.94 ±0.84	<0.001*
Incomplete emptying	1.08 ± 0.98	0.64 ±0.77	<0.001*

*Significant.

The amount of urine voided during each addition of mirabegron therapy ($p < 0.001$) micturition act was significantly increased from (Table 5). 191.58± 36.89 ml to 231.04±39.06 ml after the

Table 5: Voided volume (VV).

Variable	Before mirabegron	After mirabegron	P-value
Voided volume (VV)	191.58± 36.89	231.04±39.06	<0.001*

*Significant.

Qmax was significantly improved from 10.90 (9.60-12.13) mL/s to 14.00 (12.48-15.05) mL/s, after adding mirabegron therapy, $p < 0.001$ (Table 6). QoL showed significant improvement after mirabegron add-on treatment, from 5 (4- 5) to 2 (2- 3), $p < 0.001$ (Table 7).

Table 6: Maximum urinary flow rate (Qmax).

Variable	Before mirabegron	After mirabegron	P-value
Maximum urinary flow rate (Qmax) median (IQR)	10.9 (9.60-12.13)	14 (12.48-15.05)	<0.001*

*Significant.

Table 7: IPSS quality of life (Q. OL).

Variable	Before mirabegron	After mirabegron	P-value
IPSS quality of life (Q. OL) median, (IQR)	5(4- 5)	2 (2- 3)	<0.001*

*Significant.

PVR did not significantly change before or after receiving mirabegron medication. PVR displayed little variation in numbers. By the end of the 8-week follow-up period, the post-treatment volume had increased from (48.14±26.03ml) to (51.42±28.03ml) ($p < 0.274$) (Table 8).

Table 8: Voided volume (VV).

Variable	Before mirabegron	After mirabegron	P-value
Post voiding residual urine	48.14±26.03	51.42±28.03	<0.074

*Significant.

Only five patients (10%) had side effects after mirabegron therapy; One case suffered from headache (2%), while two cases complained of nasopharyngitis (4%), one case

suffered from constipation (2%), and a case agonized from tachycardia (2%). while the rest of the patients didn't have any side effects.

4. Discussion

Approximately 50% of elderly BPO patients have OAB [8]. Therefore, voiding symptoms can be greatly improved by treating BPO with a typical α 1-adrenergic receptor antagonist; yet, a portion of patients may still experience bothersome OAB symptoms like urgency and frequency [9]. A selective beta-3 agonist, mirabegron acts only on beta-3 receptors. When these receptors are stimulated, the detrusor muscle actively relaxes during the storage phase, increasing bladder capacity without compromising bladder contractility during the voiding phase [10].

In our study, we set the treatment duration to 8 weeks since it is thought to be sufficient for the effectiveness of mirabegron to reach a plateau. Many studies set the same duration [11, 12], However, other studies set a longer duration (12 weeks) for treatment [13].

The latest study showed a notable advancement in Overactive Bladder Symptom Score (OABSS) from 8.66 ± 2.28 to 5.12 ± 1.85 after additional mirabegron therapy, ($p < 0.001$). Similar to our study, a prospective study was carried out on 26 Japanese males who had continued OABS after eight weeks of tamsulosin medication [14]. With Mirabegron add-on medication, the authors reported a significant improvement in their OABSS from 8.5 ± 2.3 to 4.7 ± 2.5 ($P < .001$). The IPSS and IPSS-S also showed a similar improvement at the same time. which is consistent with recent research.

Singh et al. (2020) reported on an open-label randomized controlled clinical research that involved 80 BPH patients who had persistent OABS [15]. The authors showed a notable increase in the OABSS overall from

7.95 ± 2.80 to 2.33 ± 1.82 after adding on mirabegron, which is in harmony with our results.

In the current study after the addition of mirabegron therapy, there was significant improvement in total IPSS from 17.98 ± 2.90 to 10.88 ± 2.69 , and IPSS sub score IPSSv from 8.42 ± 1.62 to 5.02 ± 1.55 , IPSSs from 9.6 ± 1.98 to 5.88 ± 1.78 . In research comparable to ours, Matsuo et al. (2016) prospectively assessed fifty Japanese men over 65 who had been on α 1-blockers for BPH and had persisting OAB predominate LUTS [16]. Mirabegron 50 mg was administered to each patient, and they were monitored for 12 weeks. The total IPSS was significantly improved (from 15.1 ± 4.2 to 11.8 ± 4.6) by the mirabegron add-on medication. In our investigation, the maximum flow Qmax significantly improved with extra mirabegron medication, going from 10.90 (2.53) to 14.00 (2.58). Comparable to our findings, 26 Japanese males with OAB who had been receiving tamsulosin for BPH were prospectively assessed [14]. The initial dose of mirabegron for each patient was 50 mg. Qmax increased significantly after the 8-week follow-up period, from 10.7 ± 3.7 to 13.5 ± 6.4 mL/s. PVR urine showed no significant changes from 48.14 ± 26.03 to 51.42 ± 28.03 in our research, and there was no incidence of acute urinary

retention. Matsuo et al. (2016) stated that there was no discernible change in PVR between 23.1 ± 15.6 mL and 27.3 ± 21.5 mL, which was comparable to our outcomes [16]. Another study by Singh et al. (2020) showed that PVR with Mirabegron medication decreased numerically, but not significantly, from baseline values of 58.38 ± 68.79 to 51.17 ± 51.32 [15]. In contrast, three patients in the Kakizaki et al. (2020) trial had higher PVRs of 1.1% compared to one patient in the placebo group of 0.4%, with no occurrences of urine retention [13].

In this study Five cases had side effects, two cases of nasopharyngitis (4%), one case of dry mouth (2%), one case of constipation (2%), and one case of headache (2%). Similar to our results, the study conducted by Nitti et al. (2013), the incidence of dry mouth was 1.5%, and constipation in less than (2%) with mirabegron which was close to our incidence [17].

Conclusion

Mirabegron's additional therapy is efficient and secure for the management of persistent storage symptoms after alpha blocker medication. Therefore, for BPH patients who have persistent storage symptoms, we advise AB and mirabegron combination therapy as first-line treatment.

Ethical approval and consent to participate:

The ethical committee of our university hospital & Faculty of Medicine approved this study numbered, all the patients were informed about the drug and the possible drawbacks.

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Conflicts of Interest: All authors declare no conflict of interest.

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