

Add-on treatment with mirabegron may improve quality of life in patients with benign prostatic hyperplasia complaining of persistent storage symptoms after tamsulosin monotherapy

Tae Wook Kang  and Hyun Chul Chung

Abstract

Background: The aim of this study was to evaluate the change in lower urinary tract symptoms and quality of life (QoL) after combination therapy of solifenacin and mirabegron in patients with benign prostatic hyperplasia presenting with persistent storage symptoms after treatment with tamsulosin.

Material & Methods: We evaluated the International Prostatic Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), prostate-specific antigen, prostate volume, peak flow rate (Qmax), and post-voided residual volume (PVR) before and after treatment. Patients showing baseline OABSS ≥ 3 were included and treated with tamsulosin 0.2 mg as an initial drug for 1 month. After 1 month, add-on treatment with solifenacin 5 mg or mirabegron 50 mg was provided to patients who did not show improvement in OABSS with tamsulosin 0.2 mg. After 2 months, we evaluated changes in OABSS, IPSS, Qmax, and PVR.

Results: After combination therapy for 2 months, there were no significant differences between patients receiving add-on treatment with solifenacin and those receiving mirabegron. However, the IPSS QoL score improved in patients treated with mirabegron and tamsulosin more than in those treated with solifenacin and tamsulosin ($p < 0.05$).

Conclusion: A combination of tamsulosin and mirabegron might improve the QoL of patients presenting with persistent storage symptoms after tamsulosin monotherapy. Better QoL due to mirabegron compared with solifenacin could be associated with fewer adverse effects, such as dry mouth and constipation.

Keywords: benign prostatic hyperplasia, beta-3-receptor agonist, lower urinary tract symptoms, tamsulosin

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Introduction

Benign prostatic hyperplasia (BPH) is the most common benign disease in men with various lower urinary tract symptoms (LUTS) and is the fourth most common disease among men aged 50 years and older; the prevalence of BPH in men aged 70 years and older is more than 80%.^{1,2} BPH results in LUTS clinically, and symptoms can be classified as storage, voiding,

and postmicturition, and often affect patients' quality of life (QoL).³ Patients with BPH may have one predominant type of symptom rather than other symptoms, and symptoms often appear in different forms as the disease progresses.⁴ According to the EPIC study, the prevalence of storage (men, 51.3%; women, 59.2%), voiding (men, 25.7%; women, 19.5%), and postmicturition LUTS (men, 16.9%; women, 14.2%)

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are generally similar between men and women, and prevalence increases with age.⁵

According to Silva *et al.*, it is difficult to aim for more new effective and well-tolerated selective treatments for BPH/LUTS due to an incomplete understanding of the mechanism of the cause and progression of the disease.⁶ Overactive bladder (OAB) is classified as a symptom syndrome presenting with urinary urgency with or without urgency incontinence, and usually with frequency and nocturia. In addition, it worsens patients' QoL.⁷ The European Association of Urology offers practical evidence-based guidelines on the assessment and treatment of men aged 40 years and older who present with LUTS. They also recommend that medical history, validated symptom score questionnaires, voiding diary, physical examination, including digital rectal examination, urinalysis, prostate-specific antigen (PSA), and frequency volume chart are helpful as an initial assessment of BPH.⁸ The International Prostatic Symptom Score (IPSS) is used to assess urinary symptom severity and QoL. It is also used to document subjective responses to treatment.⁸⁻¹⁰ Measurement of urinary flow rates and residual urine is helpful in diagnostic evaluation and treatment response.^{8,9}

Many male patients with LUTS do not need medical management or surgical intervention, but patients with moderate-to-severe LUTS require medical or surgical treatment.⁸ Alpha-1-adrenoceptor blocker (A1B) is the most commonly used pharmacological agent to treat LUTS in men with BPH. However, even after treatment with A1B, storage or OAB symptoms may persist.¹¹ The 2015 European Urologic Association guideline recommends antimuscarinics or beta-3-adrenoceptor agonists (B3A) in men with BPH to treat moderate-to-severe LUTS with predominant bladder storage symptoms, and when both monotherapies are insufficient to relieve symptoms, a combination therapy of A1B and antimuscarinic agents is recommended.⁸

There are only a few studies comparing efficacy between combination therapy of tamsulosin and solifenacin and combination therapy of tamsulosin and mirabegron. Thus, we aimed to evaluate changes in LUTS and QoL after combination therapy of solifenacin and mirabegron in patients with BPH complaining of persistent storage symptoms and who had previously been treated with tamsulosin.

Material and methods

From May 2015 to May 2017, we retrospectively evaluated 88 patients aged 40 years and older who visited the urology department of Yonsei University Wonju Severance Christian Hospital because of LUTS due to BPH.

We defined BPH as a prostate volume (PV) of 20 ml or greater as assessed by transrectal ultrasonography (TRUS) or computed tomography (CT). PV measured by TRUS or CT was calculated by means of the ellipsoid formula [$PV = \pi/6$ width (cm) thickness (cm) length (cm)]. On the initial visit, baseline characteristics (e.g. age, body weight, and height) were recorded. Moreover, the IPSS, Overactive Bladder Symptom Score (OABSS), PSA, PV, peak flow rate (Q_{max}), and post-voided residual volume (PVR) were obtained.

We included 86 patients with an OABSS of 3 points or more who complained of urinary urgency at least once per week as the main symptom. Moreover, we treated patients with tamsulosin 0.2 mg as an initial drug for 1 month. After 1 month, we added solifenacin 5 mg or mirabegron 50 mg to patients who did not show improvement in OABSS after tamsulosin 0.2 mg monotherapy. We categorized the combination of tamsulosin and mirabegron as group A and tamsulosin and solifenacin as group B.

We excluded patients who were diagnosed with neurogenic bladder due to neurogenic causes, those with a history of urethral injury, or those with a history of prostate surgery such as transurethral resection of the prostate (TURP) and Holmium enucleation of the prostate, those who were suspected of having urinary tract infection, those requiring inpatient treatment due to severe cardiopulmonary disorder, or those requiring bronchodilator therapy due to severe asthma.

The primary endpoint was change in total IPSS. Secondary endpoints were changes in voiding symptom score of IPSS (IPSS_v), IPSSs, QoL (IPSS-QoL subscore), and Q_{max}.

We use the independent sample *t*-test to compare the baseline characteristics and treatment outcome at 3 months between the two groups. In addition we used the paired sample *t*-test to compare changes in parameters in each group. Standard deviation *p* values of < 0.05 were considered as statistically acceptable. We used the Statistical Package for the Social Sciences

Table 1. Baseline characteristics of patients according to medication.

	Group A (n = 17)	Group B (n = 18)	p value
Age, years	68.35 ± 9.99	66.13 ± 7.78	0.493
BMI	24.21 ± 3.28	23.78 ± 3.69	0.729
PV	25.93 ± 6.01	26.36 ± 5.52	0.848
PSA	1.19 ± 1.29	1.41 ± 1.30	0.645
IPSSv	11.24 ± 5.53	9.64 ± 4.67	0.400
IPSSs	8.94 ± 3.19	9.29 ± 3.07	0.763
QoL (IPSS-QoL)	4.79 ± 1.25	4.38 ± 1.60	0.224
IPSS overall	20.18 ± 7.67	18.93 ± 7.10	0.645
OABSS	6.5 ± 2.33	5.0 ± 1.73	0.342
Qmax	10.37 ± 4.47	11.55 ± 9.66	0.685

Values are presented as mean ± standard deviation. Group A: tamsulosin + mirabegron; group B: tamsulosin + solifenacin. BMI, body mass index; IPSS, International Prostate Symptom Score; IPSSs, storage symptom score; IPSSv, voiding symptom score; OABSS, Overactive Bladder Symptom Score; PSA, prostate-specific antigen; PV, measured prostate volume; Qmax, peak flow rate, QoL, quality of life.

(version 20.0 IBM, Armonk, New York, USA) for all statistical analyses in this study. A *p* value of < 0.05 was considered statistically significant.

This study was approved by the Ethics Committee of Yonsei University Wonju Severance Christian hospital (Approval no. CR319066).

Results

A total of 86 patients were included in this study. We excluded 51 patients who showed OABSS symptom improvement after tamsulosin monotherapy for 1 month and who did not require add-on treatment.

A total of 17 patients were included in the mirabegron add-on treatment after tamsulosin monotherapy group (group A), and 18 patients were included in the solifenacin add-on treatment after tamsulosin monotherapy group (group B).

Patient demographics are presented in Table 1. Mean patient's age was 68.35 ± 9.99 years and 66.13 ± 7.78 years in groups A and B, respectively. Mean PV of group A was 25.93 ± 6.01 ml and that of group B was 26.36 ± 5.52 ml. The mean PSA

was 1.19 ± 1.29 and 1.41 ± 1.30 for groups A and B, respectively. The mean IPSS was 20.18 ± 7.67 and 18.93 ± 7.10 for groups A and B, respectively. The mean QoL was 4.79 ± 1.25 and 4.38 ± 1.60 for groups A and B, respectively (Table 1). There were no significant differences in background characteristics between groups A and B.

After 2 months of additional treatment, the mean IPSS at 3 months was 16.64 ± 7.50 and 19.25 ± 4.23 in groups A and B, respectively. Mean IPSSv and IPSSs were 9.07 ± 5.21 and 10.13 ± 3.36, respectively, in group A and 7.57 ± 3.20 and 9.13 ± 2.64, respectively, in group B (Table 2). Mean QoL and Qmax at 3 months were 3.64 ± 1.55 and 4.25 ± 0.71, respectively, in group A and 12.04 ± 5.92 and 13.41 ± 4.91, respectively, in group B (Table 2). Moreover, there were no significant statistical differences between the two groups. The mean changes in treatment outcomes of both groups after 2 months of additional treatment are shown in Table 3.

The results of the paired *t*-test and comparison of the two groups at 3 months showed IPSSs, IPSSv, IPSS, and Qmax were improved in group B, but there was no statistically significant difference

Table 2. Difference in values at 3 months between the two groups.

	Group A (n = 17)	Group B (n = 18)	p value
IPSSv	9.07 ± 5.21	10.13 ± 3.36	0.615
IPSSs	7.57 ± 3.20	9.13 ± 2.64	0.259
IPSS overall	16.64 ± 7.50	19.25 ± 4.23	0.379
QoL (IPSS-QoL)	3.64 ± 1.55	4.25 ± 0.71	0.311
Qmax	12.04 ± 5.92	13.41 ± 4.91	0.607

Values are presented as mean ± standard deviation. Group A: tamsulosin + mirabegron; group B: tamsulosin + solifenacin. IPSS, International Prostate Symptom Score; IPSSs, storage symptom score; IPSSv, voiding symptom score; Qmax, peak flow rate; QoL, quality of life.

Table 3. Difference between groups in mean change from baseline at 3 months.

	Initial	3 months later	Mean change from baseline	p value
Group A (n = 17) IPSSv	10.29 ± 5.61	9.07 ± 5.21	-1.21 ± 4.09	0.288
IPSSs	8.50 ± 3.06	7.57 ± 3.20	-0.93 ± 4.36	0.440
QoL (IPSS-QoL)	4.79 ± 1.25	3.64 ± 1.55	-1.14 ± 1.61	0.02
IPSS overall	18.27 ± 8.31	10.85 ± 6.90	-2.14 ± 8.03	0.37
Qmax	8.83 ± 4.72	16.21 ± 20.14	2.45 ± 7.11	0.304
Group B (n = 18) IPSSv	9.44 ± 3.54	9.33 ± 3.94	-0.38 ± 5.24	0.95
IPSSs	9.67 ± 3.32	8.33 ± 3.43	-0.88 ± 2.53	0.18
QoL (IPSS-QoL)	4.38 ± 1.60	4.25 ± 0.71	-0.13 ± 1.36	0.057
IPSS overall	19.11 ± 6.29	17.67 ± 6.18	-0.50 ± 6.19	0.52
Qmax	9.26 ± 4.18	13.55 ± 4.56	4.74 ± 7.87	0.03

Values are presented as mean ± standard deviation. Group A: tamsulosin + mirabegron; group B: tamsulosin + solifenacin. IPSS, International Prostate Symptom Score; IPSSs, storage symptom score; IPSSv, voiding symptom score; Qmax, peak flow rate; QoL, quality of life.

between the two groups (Table 3). Mean changes from baseline IPSS at 3 months were -2.14 and -0.5 in groups A and B, respectively, showing no significant difference between the two groups. However, mean changes from baseline QoL at 3 months were -1.14 ± 1.61 and -0.13 ± 1.36 in groups A and B, respectively, which showed a significant difference between the two groups ($p=0.02$). Mean changes from baseline Qmax at 3 months were 2.45 and 4.74 in groups A and B, respectively, which showed a significant difference ($p=0.03$).

In group A, there were no significant differences in IPSS, IPSSv, IPSSs, and Qmax before and after treatment, but there was a difference in QoL ($p=0.02$) (Table 3). In group B, there were no significant symptom score improvements, but Qmax improved from 9.26 ± 4.18 to 13.55 ± 4.56 ($p=0.03$).

There were no adverse events in the mirabegron add-on group, but there were a few adverse events in the solifenacin add-on group. Overall, 7 of 18 (39%) participants experienced a minor adverse event such as a weak urinary stream (11%) and

dry mouth (11%). Interestingly, three participants had storage symptoms such as nocturia (11%) and frequency (6%). At the end of trial, nine participants in group B decided to have mirabegron therapy (44%) and TURP (6%), respectively.

Discussion

In this study, we evaluated the clinical effects of additional therapy with A1Bs and B3As and A1Bs and anticholinergics in patients with BPH presenting with persistent storage symptoms after tamsulosin monotherapy. We observed a significant improvement in QoL among patients with persistent storage symptoms after tamsulosin monotherapy and in group A patients receiving mirabegron add-on therapy. Traditionally, alpha-blockers (ABs) have been used widely to regulate the LUTS of BPH. Nonetheless, storage symptoms may still persist in many patients.¹² Male OAB symptoms are often caused by bladder dysfunction due to detrusor overactivity.¹³ This is a common cause of OAB symptoms and is characterized by the involuntary contraction of the bladder detrusor in the bladder filling phase.¹¹

Alpha-receptor antagonists have been considered the first-line drug for LUTS.⁹ In an randomized controlled trial, Elhilali *et al.* reported that terazosin showed a significant increase of Qmax ($p < 0.001$) and did not affect the change in PVR at 24 weeks.¹⁴ In previous studies with placebo-controlled trials, A1Bs typically reduced IPSS by about 35–40% and Qmax increased 20–25% approximately.^{15–17} In a meta-analysis of 14 studies comparing tamsulosin and placebo, the tamsulosin 0.4 mg group showed a 12% IPSS improvement compared with the placebo, and the tamsulosin 0.8 mg group showed a 16% improvement in IPSS.¹⁸ The more recent drug, silodosin, showed comparable results with tamsulosin at the end of the study, but only silodosin significantly reduced nocturia compared with placebo (attrition from baseline was 0.9, 0.8, and 0.7 for silodosin, tamsulosin, and placebo, respectively; $p < 0.013$).¹⁹

There were four comparative studies of combination therapy with ABs (tamsulosin, doxazosin, or alfuzosin) and antimuscarinic (tolterodine 4 mg) therapy *versus* AB monotherapy in patients with LUTS and OAB symptoms. All studies reported that the mean change in all IPSS scores was similar in both groups (weighted mean difference = -0.19).^{20–23} Several 12-week studies

compared solifenacin with tamsulosin *versus* tamsulosin monotherapy in men with LUTS and OAB symptoms.^{24–28} Moreover, five studies used solifenacin 5 mg,^{26–28} two used solifenacin 6 mg,^{24,25} four used tamsulosin 0.2 mg,^{26,27} and three studies used tamsulosin 0.4 mg as a daily dose.^{24,25,28} All studies reported that the combination therapy decreased the IPSS QoL score more than the tamsulosin monotherapy, but there was no significant difference found clinically between the two groups.^{24–28}

Anticholinergic combination therapy seems to be a good treatment for LUTS, but it also has side effects, such as constipation and dry mouth, which are well-known and common complications of combination therapy. According to a previous study on the combination therapy of solifenacin with tamsulosin, 47% of patients complained of treatment-related side effects, with constipation, dry mouth, and dyspepsia being the most common. Moreover, they reported 86 serious adverse events occurring in 64 patients, which included 3 deaths, 6 (0.7%) cases of acute urinary retention, and 3 cases of intervertebral disc protrusion.²⁹ In our study, the side effects were slightly lower than in other studies. Memon *et al.* reported that acute urinary retention was a rare complication ($\leq 1\%$), and only one patient in each of their study groups required catheterization.²⁰ Otsuki *et al.* reported that mirabegron had an efficacy rate of 85.2%. Significant improvements were observed in each domain of OABSS, and there was no significant difference between patients treated with and those treated without antimuscarinic agents.³⁰

According to a study on the efficacy and safety of daily therapy of mirabegron 50 mg in male patients with OAB, mirabegron 50 mg showed improvements in frequency, urgency, and incontinence similar to solifenacin 5 mg, and was well tolerated for antimuscarinics. Moreover, mirabegron 50 mg showed significant improvement in frequency symptoms compared with placebo.³ However, several side effects have been reported with mirabegron, including two cases of dry mouth, and one case of palpitations, headache, dysuria, insomnia, dizziness, increase of residual urine, constipation, cystitis, left leg paresis, and erectile dysfunction; the incidence rate of side effects was 8.4%.³⁰

This present study differed from other previously published studies. First, the previous studies identified changes in IPSS among patients with BPH

who had OABSS of 3 or more. However, in our study, patients were classified according to the IPSSs. Second, other studies evaluated patients with BPH who complained of OAB symptoms and who had OABSS of 3 or more. However, we evaluated patients with OABSS of 3 or more who were suffering from OAB symptoms and who had an IPSSs of 4 or more. Our study evaluated the clinical efficacy of B3A combination therapy in patients with BPH who had persistent storage symptoms, therefore focusing on the assessment of changes in the IPSSs instead of OABSS. Moreover, our study reported the improvement of IPSS QoL in the mirabegron add-on group.

However, our study has some limitations. First, the small number of patients might have affected the results. Further studies with large numbers of patients are required to determine the detailed clinical relevance of our results. Second, limitations pertain to the retrospective study design. These include the risk of unidentified confounding factors and missing data. Third, this study had a short-term follow-up period of 3 months. Therefore, we believe that long-term follow up and multicenter trials are required for further evaluation and for a better understanding of major prognostic determinants of the disease as well as its treatment options.

In conclusion, we found that the B3A mirabegron add-on treatment improved IPSS QoL of patients with BPH presenting with persistent storage symptoms after tamsulosin monotherapy. However, the Qmax was shown to improve only in the anticholinergic add-on group. Patients receiving mirabegron showed a better QoL, which could be associated with few adverse effects, such as constipation and dry mouth, compared with patients receiving solifenacin. Therefore, we carefully recommend the combination therapy of tamsulosin and mirabegron as a first-line therapy for patients with BPH who have persistent storage symptoms.

Author contributions

Hyun Chul Chung: conceptualization; methodology; writing–review and editing.

Tae Wook Kang: data curation; formal analysis; methodology; writing original draft.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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