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Original Article

Therapeutic efficacy of mirabegron 25 mg monotherapy in patients with nocturia-predominant hypersensitive bladder

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Abstract

Objective: The objective of this study was to evaluate the efficacy of mirabegron 25 mg daily in patients with nocturia-predominant hypersensitive bladder (HSB). **Materials and Methods:** This study prospectively investigated 219 consecutive patients with nocturia-predominant HSB and treated with mirabegron 25 mg daily from July 2015 to 2016. Patient with nocturia episode decreased by ≥1/night after treatment was considered successful. The subjective symptom score, such as International Prostate Symptom Score (IPSS), Quality of life index, Overactive Bladder Symptom Score (OABSS), Urgency Severity Scale, patient perception of bladder condition (PPBC), and nocturia episodes per night, was assessed before and 1 month after mirabegron treatment and between successful and failed groups. **Results:** A total of 219 patients, including 51 women and 168 men, were enrolled. The mean age of the population was 72.3 ± 11.0 years. Totally, 58 (26.5%) of the patients had improvement in nocturia at 1 month after treatment. Among them, 14 (27.5%) women and 44 (26.2%) men had improvement in nocturia episodes after treatment (P = 0.858). Compared the clinical data between successful and failed group, the baseline symptom scores were more severe in successful group, including IPSS-storage subscore (4.84 ± 2.09 vs. 4.11 ± 2.19, P = 0.031), OABSS (3.21 ± 0.67 vs. 2.91 ± 1.00, P = 0.037), and nocturia episodes (3.81 ± 0.95 vs. 3.095 ± 1.32, P = 0.000). Multivariate analysis revealed only a higher nocturia episodes (P = 0.046) predict a successful treatment result. Mirabegron 25 mg daily significantly improved PPBC score along the 3 months' follow-up (P < 0.05), and postvoid residual volume did not increase after mirabegron treatment in overall patients. **Conclusions:** Mirabegron 25 mg daily treatment showed a limited therapeutic effect on nocturia-predominant HSB patients. The patients with higher OAB symptoms predict a successful result.

Keywords: *Hypersensitive bladder, Mirabegron, Nocturia, Therapeutic efficacy*

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Introduction

Hypersensitive bladder (HSB) is defined as a symptom complex of increased bladder sensation, associated with urinary frequency, with or without bladder pain or urgency [1]. Among the symptoms of HSB, nocturia is one of the most bothersome lower urinary tract symptoms (LUTS) [2]. In the elderly with LUTS, nocturia is the most common core symptoms, which comprise 29.9% of men with LUTS [3]. The prevalence of nocturia is high in both genders and increases with age [4]. Nocturia may be caused by sleep disorder, psychological factor, nocturnal polyuria, reduced bladder capacity, a combination of nocturnal polyuria and reduced bladder capacity, and polyuria due to systemic diseases such as diabetes mellitus (DM), congestive heart failure (CHF), or chronic obstructive pulmonary diseases (COPD) [5]. Urodynamic study of patients with nocturia revealed detrusor overactivity (DO) incontinence in 26% of women and DO in 64% of men. Nocturnal polyuria was noted in 55% of patients with nocturia [6]. Nocturia may cause sleep deprivation in night time and increase daytime sleepiness and loss of energy, which may have great impact on the health-related quality of life in the elderly [7].

There has been no consensus in managing nocturia. Since nocturia is highly prevalent in male LUTS suggestive of benign prostatic hyperplasia (BPH), alpha-blocker is usually prescribed

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for men with voiding LUTS and nocturia can be improved in part of the patients treated [8]. For men and women with nocturia-predominant LUTS and no voiding symptoms, the antimuscarinic agent is usually used because nocturia is a common symptom related to overactive bladder (OAB) or urodynamic DO. Antimuscarinic agents are commonly used as the first-line pharmacotherapy for OAB [3,4]. In patients with OAB and nocturia, antimuscarinic agents can effectively reduce nocturia episodes [9]. However, this medication is often marked by less efficacy, poor compliance, low patient satisfaction, and bothersome side effects such as dry mouth or constipation [10]. The international OAB guidelines emphasize behavioral modification and lifestyle therapy as the first-line treatment, although there is lacking of data regarding the effectiveness of this treatment [11].

β3-adrenergic receptor agonist is a new class drug for OAB with less bothersome adverse effects existed in the market [12,13]. β3-adrenergic receptor agonist was initially approved for the treatment for OAB with the symptoms of urgency or urgency urinary incontinence in 2012. Now, the only launched drug, mirabegron, has been widely approved for the treatment of OAB-associated storage symptoms. Previous studies revealed three β-adrenoceptor subtypes (mRNAs), β1, β2, and β3 in the detrusor muscle and urothelium [12]. Among them, β3-adrenoreceptor is the predominant β-receptor subtype in the human bladder [13]. β3-adrenergic receptor agonist relaxes detrusor smooth muscle during the bladder storage phase and increases bladder capacity without affecting maximum urinary flow rate (Qmax), detrusor pressure at Qmax (Pdet.Qmax), and residual volume [14]. β3-adrenergic receptor agonist plays an important role in relaxing the detrusor smooth muscle during bladder storage phase and increasing bladder capacity. In several Phase III trial, mirabegron has been shown effective in improvement of urgency, urgency incontinence, urinary frequency, and nocturia episodes, compared with placebo or active antimuscarinic agent [15].

Since nocturia is a storage symptom and usually associated with DO, it seems reasonable to use mirabegron in treatment of nocturia-predominant LUTS. However, if patients do not have urgency or urgency incontinence, but only present with severe daytime frequency and nocturia, it will be interesting to know whether mirabegron can be effective or not. Since the recommended initial dose of mirabegron in the US and Taiwan FDA is 25 mg daily, this study was conducted to investigate the effectiveness of mirabegron 25 mg daily in the treatment of nocturia-predominant HSB in Taiwanese patients.

Materials and methods

We prospectively investigated the therapeutic efficacy of mirabegron 25 mg daily on consecutive male and female patients' age ≥20 years and had nocturia-predominant HSB from July 2015 to 2016. All candidates had the symptoms of urinary frequency ≥8 times/day and nocturia >1 per day, without urgency, urgency urinary incontinence, or bladder pain, and the symptoms had sustained for at least 12 weeks. Patients with frank neurogenic voiding dysfunction, stress urinary incontinence, urinary tract infection, urolithiasis, proven interstitial cystitis/bladder pain syndrome, or malignancy were precluded at enrollment. Mirabegron 25 mg was prescribed once daily before bedtime, and the therapeutic effect was evaluated. The Institutional Review Board and the Ethics Committee of the hospital (IRB-104-16-A) approved this study. The patients signed informed consent and were informed of the possible adverse events after taking mirabegron.

The patient with nocturia episodes improved more than once per day after mirabegron treatment was considered having good therapeutic effect and was grouped as the successful treatment group. In contrast, patients whose nocturia episode did not improve were grouped in the failed treatment group. The subjective symptom score, such as International Prostate Symptom Score (IPSS), quality of life index, OAB Symptom Score (OABSS), Urgency Severity Score (USS), patient perception of bladder condition (PPBC), and uroflowmetry parameters, including Qmax, voided volume (Vol.), postvoid residual volume (PVR), total prostate volume (TPV), transitional zone index (TZI), and nocturia episodes per day, was assessed before and after the treatment. Those subjective symptom scores and parameters were compared between successful and failed groups and from baseline, 1 to 3 months after treatment. The same research assistant assessed the questionnaire by face-to-face interview. Moreover, the gender, age, comorbidities such as BPH, DM, COPD, coronary artery disease, cerebrovascular accident, chronic kidney disease (CKD), Parkinson disease (PD) and early dementia, and concomitant medications such as antimuscarinic agent, alpha-blocker, or 5-alpha-reductase were also evaluated as predictor factors for better therapeutic effectiveness.

In the analyses, the mean and standard deviations were calculated for the continuous variables. Continuous data of therapeutic outcomes were compared between the groups at different time points. Paired *t*-tests and Pearson Chi-square tests were used to compare the measured parameters from baseline to each time point. $P < 0.05$ is considered statistically significant. Univariate and multivariate analysis were used to investigate the predictive factor for a successful treatment outcome. Statistical analyses were performed using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL, USA).

Results

A total of 219 patients were enrolled in the study, including 51 (23.3%) women and 168 (76.7%) men. Among these patients, only 58/219 (26.5%) had successful therapeutic effect in nocturia-predominant symptoms, including 14/66 (27.56%) women and 44/173 (26.2%) men. Tables 1 and 2 show the demographics of the successful and failed treatment groups. Patients' gender distribution, age, baseline total IPSS, USS, TPV, TZI, Qmax, Vol., PVR, comorbidities, and concomitant lower urinary tract medication history were comparable between two groups. However, the baseline subjective storage symptom scores were significantly higher in the successful group compared to failed group, including IPSS-S (4.84 ± 2.09 vs. 4.11 ± 2.19, $P = 0.031$), OABSS (3.21 ± 0.67 vs. 2.91 ± 1.00, $P = 0.037$), and nocturia episodes per night (3.81 ± 0.95 vs. 3.09 ± 1.32, $P = 0.00$). Multivariate analysis revealed only a

Table 1: Patient demographics, baseline subjective score, and parameters

	Successful (*n*=58)	Failure (*n*=161)	Univariate	Multivariate	Odds ratio (Exp 95% range)
			P	*P*	
Male (%)	44 (26.2)	124 (73.8)	0.858	1.000	0.000 (0.000-)
Female (%)	14 (27.5)	37 (72.5)			
Age	71.5 ± 12.7 (38-94)	72.3 ± 11.3 (24-96)	0.661	0.598	0.981 (0.912-1.054)
IPSS-V	5.25 ± 5.24	5.55 ± 5.27	0.703	0.982	0.998 (0.873-1.142)
IPSS-S	4.84 ± 2.09	4.11 ± 2.19	0.031	0.915	1.027 (0.625-1.690)
IPSS-T	10.1 ± 6.00	9.66 ± 6.15	0.649	-	-
OABSS	3.21 ± 0.67	2.91 ± 1.00	0.037	0.639	0.772 (0.262-2.278)
USS	0.00 ± 0.00	0.01 ± 0.16	1.000	-	-
PPBC	2.67 ± 1.80	2.51 ± 1.68	0.542	0.339	1.327 (0.743-2.372)
QoL-I	2.77 ± 1.17	2.77 ± 1.23	0.976	0.755	0.863 (0.342-177)
Nocturia/day	3.81 ± 0.95	3.09 ± 1.32	0.000	0.046	2.223 (1.014-4.875)
Qmax	12.6 ± 7.76	11.8 ± 8.29	0.536	0.534	1.039 (0.920-1.174)
VoL	198.9 ± 129.7	186.5 ± 139.2	0.567	0.695	0.998 (0.991-1.006)
PVR	64.4 ± 79.0	61.4 ± 80.7	0.809	0.821	1.001 (0.991-1.011)
TPV	39.0 ± 17.3	43.8 ± 23.5	0.359	0.300	0.980 (0.943-1.018)
TZI	40.0 ± 12.2	38.5 ± 17.1	0.697	0.437	6.711 (0.055-817.23)

P<0.05 considered significant difference. IPSS: International Prostate Symptom Score, IPSS-V: IPSS voiding subscore; IPSS-S: IPSS storage subscore, IPSS-T: IPSS total score, QoL-I: Quality of life index, OABSS: Overactive Bladder Symptom Score, USS: Urgency Severity Scale, PPBC: Patient perception of bladder condition, Qmax: Maximum flow rate, Vol: Voided volume, PVR: Postvoid residual volume, TPV: Total prostate volume; TZI: Transition zone index

Table 2: Comorbidity and concomitant medication in patients with successful and failed treatment results

	Successful (*n*=58), *n* (%)	Failed (*n*=173), *n* (%)	*P*
BPH	33 (56.9)	98 (60.9)	0.597
DM	17 (29.3)	40 (24.8)	0.506
COPD	3 (5.2)	7 (4.3)	0.727
CAD	6 (10.3)	17 (10.6)	0.964
CVA	6 (10.3)	11 (6.8)	0.398
CKD	8 (13.8)	20 (12.4)	0.789
PD	1 (1.7)	1 (0.6)	0.460
Dementia	2 (3.4)	4 (2.5)	0.657
Antimuscarinics	0	1 (0.6)	1.000
Alpha-blocker/5ARI	25 (43.1)	73 (45.3)	0.769

BPH: Benign prostatic hyperplasia, DM: Diabetes mellitus, COPD: Chronic obstructive pulmonary disease, CAD: Cardiac arterial disease, CVA: Cerebrovascular disease, CKD: Chronic kidney disease, PD: Parkinson's disease, 5ARI: 5-alpha-reductase inhibitor

higher nocturia episode per night (P = 0.046) could predict a successful treatment result, with odds ratio of 2.223 (ranged 1.014–4.875).

Table 2 shows the comorbidities of patients and concomitant medication in successful and failed treatment groups. The comorbidities had no effect on the therapeutic efficacy of mirabegron on nocturia-predominant HSB patients. In male patients already treated with alpha-blocker and/or 5-alpha-reductase inhibitor for LUTS/BPH, or antimuscarinics for OAB, adding mirabegron also showed no significant additional therapeutic effect (P = 0.999 and P = 0.380, respectively).

The treatment results of mirabegron on successful and failed groups at 1 month are summarized in Table 3. In the successful group, nocturia episodes decreased from 3.81 ± 0.95 to 2.52 ± 0.96 (P < 0.05). Interestingly, in the failed treatment group, the storage symptoms, including IPSS-S, OABSS, USS, and nocturia episodes got worse at 1 month after mirabegron treatment. Nevertheless, the PVR significantly decreased after 1-month mirabegron treatment, in both successful (65.9 ± 80.0 vs. 38.0 ± 43.1 mL, P < 0.05) and failed treatment (61.4 ± 81.2 vs. 47.1 ± 55.8 mL, P < 0.05) groups (P = 0.202). The patients with the long-term prescription of mirabegron 25 mg daily showed significant improvement in PPBC and GRA score from 1 to 3 months of follow-up (P = 0.029 and P = 0.000, respectively). However, patients who continued to take mirabegron for nocturia-predominant HSB for up to 3 months did not show further improvement in nocturia episodes or storage symptom scores after 1 month [Table 4].

Discussion

This study revealed that mirabegron 25 mg daily monotherapy is effective only for 26.5% of patients in reduction of nocturia episodes by ≥1 per night. Mirabegron 25 mg daily is equally effective in female and male in treating nocturia-predominant HSB. Patients with baseline higher storage symptoms and high nocturia episodes may predict a successful treatment result.

The prevalence of nocturia is higher with increasing age [16]. Female has higher prevalence of nocturia than male in the age 18–49 years old, however, men have higher prevalence for nocturia after 60 years of age, possibly due to increased prostate size after this age. Among 70–79 years old men, nearly 50% of them have more than two nocturia episodes per night [17]. Previous phase 2 and phase 3 clinical trials all revealed that mirabegron 50 mg daily was superior to placebo in mean volume voided, mean number of incontinence episodes, nocturia episodes, and urgency episodes [18]. This study further shows that mirabegron at the dose of 25 mg daily is effective in the treatment of nocturia in 26.5% of old patients with the mean age of 72.3 years.

Nocturia can be attributed to OAB, age-related low bladder volume, increased urine output during nighttime, or underline sleeping disorder [19]. Around 50% of obstructive sleep apnea patients might suffer from bothersome nocturia [20].

Table 3: Changes of symptom scores and uroflow parameters from baseline to 1 month in patients with successful and failed treatment results

Variable	Time point	Successful (*n*=58)	Failed (*n*=161)	*P* Between groups
IPSS-V	Baseline	5.25 ± 5.24	5.55 ± 5.27	0.743
	1 month	4.33 ± 4.81	4.38 ± 4.85*	
IPSS-S	Baseline	4.84 ± 2.09	4.11 ± 2.19	0.000 *
	1 month	3.37 ± 2.11*	4.60 ± 2.33*	
IPSS-T	Baseline	10.1 ± 6.00	9.66 ± 6.15	0.058
	1 month	7.70 ± 5.34*	8.99 ± 5.72	
OABSS	Baseline	3.21 ± 0.67	2.91 ± 1.00	0.297
	1 month	4.00 ± 2.61*	4.10 ± 2.48*	
USS	Baseline	0.00 ± 0.00	0.01 ± 0.16	0.821
	1 month	0.84 ± 1.47*	0.81 ± 1.46*	
PPBC	Baseline	2.67 ± 1.80	2.51 ± 1.68	0.039*
	1 month	1.67 ± 1.23*	2.08 ± 1.39*	
QoL	Baseline	2.77 ± 1.17	2.77 ± 1.23	0.024*
	1 month	2.02 ± 0.77*	2.51 ± 0.98*	
Nocturia/day	Baseline	3.81 ± 0.95	3.09 ± 1.32	0.000*
	1 month	2.52 ± 0.96*	3.58 ± 1.25*	
Qmax (mL/s)	Baseline	12.9 ± 7.87	12.0 ± 8.46	0.997
	1 month	13.5 ± 8.47	12.6 ± 7.81	
VoL (mL)	Baseline	201.4 ± 132.9	189.2 ± 141.0	0.837
	1 month	216.2 ± 145.1	199.8 ± 137.5	
PVR (mL)	Baseline	65.9 ± 80.0	61.4 ± 81.2	0.202
	1 month	38.0 ± 43.1*	47.1 ± 55.8*	

P<0.05, significant difference. IPSS: International Prostate Symptom Score, IPSS-V: IPSS voiding subscore, IPSS-S: IPSS storage subscore, IPSS-T: IPSS total score, QoL-I: Quality of life index, OABSS: Overactive Bladder Symptom Score, USS: Urgency severity scale, PPBC: Patient Perception of Bladder Condition, Qmax: Uroflowmetry, Vol: Voided volume, PVR: Postvoid residual volume. *Indicates significant difference between groups or from baseline to 1 month

Patients with OAB or HSB have been associated with low bladder volume voiding, and mirabegron plays an important role in eliciting detrusor relaxation in the bladder. On the other hand, diuretics, nocturnal polyuria due to age-related bladder volume changes, and the abnormal secretion and action of arginine vasopressin and polyuria have limited therapeutic effects from mirabegron due to different underlying pathophysiology. Mirabegron is important in reducing OAB symptoms with low incidence rate of adverse effects given to a better quality of life and directly improved the patient's perception of their bladder function [21].

The results of this study indicated that higher nocturia episode per day and greater IPSS storage subscore at baseline might predict a successful treatment outcome at 1 month. These results implied that the therapeutic effect of mirabegron on nocturia in the successfully treated patients might be owing to mild OAB rather than other causes. Patients with mild OAB might not report urgency symptoms on interview because they used to void at a small bladder volume without eliciting detrusor contractions. However, because the successful group only comprises 27.6% of overall patients, it is likely that the other patients with nocturia-predominant HSB might have other pathophysiology accounting for the nocturia.

The detrusor muscle, interstitial cells, and intramural innervation play an important role for initiating, coordinating, and modulating micromotions [22]. However, the loss of efferent inhibition might lead to upregulating of micromotion and afferent stimulation and predisposing to urinary urgency was noted in the OAB patients [23]. Mirabegron relaxes the detrusor smooth muscle and therefore have a prominent effect on OAB patients but not imply on our study. These prove the difference of pathophysiology of HSB and OAB.

A previous study indicated that mirabegron at the dose of 50 or 100 mg once daily had statistically significant improvements in daily incontinence episodes, number of micturition per day, urgency, and voided volume compared to placebo [15]. The previous study has shown that the absolute bioavailability of

Table 4: The changes of variables at different time points after treatment with mirabegron 25 mg daily in patients who were followed up to 3 months

	Baseline	1 month	3 months	*P* Baseline to 1 month	*P* 1-3 months
Nocturia/day	3.3 ± 1.3	3.3 ± 1.3	3.2 ± 1.2	0.802	1.000
Qmax (mL/s)	12.0 ± 8.3	12.7 ± 8.0	12.5 ± 8.4	0.074	0.979
Vol (mL)	188 ± 138	203 ± 139	195 ± 150	0.094	0.634
PVR (mL)	62.4 ± 80.2	44.5 ± 52.3	48.7 ± 60.1	0.000	0.558
IPSS_V	5.4 ± 5.2	4.4 ± 4.8	3.7 ± 4.4	0.002	0.094
IPSS_S	4.3 ± 2.2	4.3 ± 2.3	4.1 ± 2.3	0.861	0.826
IPSS_T	9.8 ± 6.1	8.6 ± 5.6	7.8 ± 5.5	0.006	0.124
QoL-I	2.8 ± 1.2	2.4 ± 0.9	2.0 ± 1.0	0.000	0.002
OABSS	3.0 ± 0.9	4.1 ± 2.5	4.1 ± 2.4	0.000	0.929
USS	0.0 ± 0.1	0.8 ± 1.5	0.8 ± 1.5	0.000	0.785
PPBC	2.5 ± 1.7	2.0 ± 1.4	1.6 ± 1.3	0.000	0.029
GRA	0.0 ± 0.0	1.0 ± 1.4	1.6 ± 1.4	0.000	0.000

IPSS: International Prostate Symptom Score, IPSS-V: IPSS voiding subscore, IPSS-S: IPSS storage subscore, IPSS-T: IPSS total score, QoL-I: Quality of life index, OABSS: Overactive Bladder Symptom Score, USS: Urgency Severity Scale, PPBC: Patient Perception of Bladder Condition, GRA: Global response assessment, Vol: Voided volume, Qmax: Maximum flow rate

mirabegron is dose dependent and affected by gender [24]. The DRAGON study also revealed a dose-dependent decrease in mean number of micturition per day was seen in patients treated with mirabegron [25]. However, in this study, we prescribed mirabegron 25 mg once daily and found only 26.5% of patients could benefit from it. The real mechanism of the action of mirabegron on the storage bladder symptoms should be the minute detrusor contractions during storage phase. If patients with nocturia and HSB but not having DO during bladder storage phase, mirabegron should not have any benefit.

There are several studies indicating the efficacy of mirabegron with other concomitant medication in treating OAB patients. In MILAI study, solifenacin 2.5 mg or 5 mg once daily add-on therapy with mirabegron 25 mg once daily for 16 weeks significantly improved OABSS, number of micturition per day, urgency, urinary incontinence episodes, and number of nocturia [26]. In this study, we did not find concomitant alpha-blocker or 5-alpha-reductase inhibitor with 25 mg mirabegron provides the improvement in the reduction of nocturia in HSB patients. It is also possible that the dose used in this study was 25 mg, lower than that used in previous clinical trials. Some previous studies have demonstrated that a further improvement of OAB symptoms was found after mirabegron dosage adjustment from 25 mg to 50 mg, indicating that mirabegron 50 mg could have more clinical benefit for patients who had limited efficacy with 25 mg mirabegron [27,28]. Patients who failed mirabegron 25 mg treatment for nocturia-predominant HSB might benefit from adding-on antimuscarinics or escalating mirabegron dose to 50 mg.

Limitation of this study is the absence of placebo control group in which the placebo effect of mirabegron cannot be excluded, especially in the subjective symptoms score evaluation. Lacking of a higher mirabegron dose such as 50 mg for patients included in this study also limited the evaluation of the therapeutic efficacy of the efficacy of mirabegron on patients with nocturia-predominant HSB.

Conclusions

The etiology of nocturia is heterogeneous and the underlying pathophysiology might be different from OAB. The therapeutic effect on mirabegron 25 mg daily on the reduction of nocturia episodes per day was noted in only 26.5% of patients; nevertheless, patients with higher storage symptoms and higher nocturia episodes may predict a successful outcome.

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Conflicts of interest

There are no conflicts of interest.

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