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Original Article

Comparison of Two Different Drugs for Overactive Bladder, Solifenacin and Mirabegron: A Prospective Randomized Crossover Study

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To assess the efficacy and safety of 2 drugs for overactive bladder (OAB), solifenacin and mirabegron. Forty-seven female OAB patients were randomized into 2 groups. Twenty-three patients were initially prescribed solifenacin for 4 weeks, followed by mirabegron for 4 weeks (group S). The other 24 patients were initially prescribed mirabegron for 4 weeks, followed by solifenacin for 4 weeks (group M). Evaluations included clinical determination of the OAB symptom score (OABSS), International Prostate Symptom Score (IPSS), and Visual Analog Scale. The IPSS significantly improved after the administration of solifenacin in both groups. The OABSS significantly improved in both groups after 4 weeks. In group M, the OABSS after eight weeks was significantly improved compared to that after 4 weeks. However, in group S, it was not significantly improved. Twelve patients experienced adverse events during the solifenacin treatment, while 2 patients experienced adverse events during the mirabegron treatment. Both solifenacin and mirabegron led to improved OAB symptoms. Switching from mirabegron to solifenacin significantly improved the OABSS. However, mirabegron led to fewer adverse events than solifenacin. We recommend that mirabegron be prescribed first for OAB patients. If patients are not satisfied with mirabegron, solifenacin should be used.

Key words: overactive bladder, randomized crossover study, solifenacin, mirabegron

Overactive bladder (OAB) is defined as urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence (UUI) [1].

OAB is common among elderly women [2] and affects health-related quality of life [3]. The current pharmacological approach to OAB treatments involves many drugs, mainly anti-muscarinic agents. However, anti-muscarinic agents are associated with relatively high rates of adverse events such as dry mouth and constipation. In 2011, mirabegron, a β3-adrenoceptor agonist, was developed for the treatment of OAB, with a mechanism of action distinct from that of anti-muscarinics. β3-adrenoceptor is responsible for promoting human detrusor relaxation and urine storage in the bladder [4-7]. Mirabegron demonstrated significant efficacy in treating the symptoms of OAB, and had a low rate of adverse events. The incidence of dry mouth is similar to that seen with a placebo, and is between three- and five-fold less than that seen when tolterodine is used as an anti-muscarinic [8]. Several studies have shown that both mirabegron and anti-muscarinics improve OAB symptoms, with no statistically significant differences observed between the 2 treatments [9-12].

Although anti-muscarinic agents are used as the first-line therapy for OAB, they may be accompanied by bothersome adverse effects, leading to poor adherence to the prescribed medications. Specifically, dry

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mouth is the most common reason for discontinuation [10]. Considering this, we must ask which drugs should be used first for OAB. The answer is not yet clear. We assessed the efficacy and safety of 2 drugs, solifenacin succinate and mirabegron, in the treatment of OAB from a clinical point of view.

Material and Methods

Patients and study protocol. This study was conducted with the approval of the Institutional Review Board of Okayama Rosai Hospital. After written informed consent was obtained, the subjects were registered and randomly divided into the following 2 groups. Patients were divided with using the envelope method. The solifenacin-preceding group (group S) received 5 mg of solifenacin once daily for 4 weeks followed by mirabegron 50 mg once daily for 4 weeks. The mirabegron-preceding group (group M) received 50 mg of mirabegron once daily for 4 weeks followed by solifenacin 5 mg once daily for 4 weeks. Patients were switched to the alternative treatment quickly, meaning they had no drug clearance period. The subjects enrolled in this study comprised 47 consenting female OAB patients who visited Okayama Rosai Hospital between April 2012 and March 2014 and satisfied the following conditions: 20 years old or older, an OABSS of 3 or higher, and urgency once or more per week [13]. They had not previously received treatment for OAB. The exclusion criteria included patients with the presence of residual urine ≥ 50 ml, neurogenic bladder, stress urinary incontinence, mixed urinary incontinence, or contraindications for either drug. Patients who did not visit the hospital were judged as having dropped out.

Pre- and post-operative evaluation. Evaluations included the clinical determination of the OABSS, International Prostate Symptom Score (IPSS), Visual Analog Scale (VAS), maximum flow rate (Qmax) and postvoid residual urine volume (PVR) before and after treatment. IPSS is a questionnaire used for benign prostatic hypertrophy, but it is also used for women and is useful for recognizing the presence or absence of dysuria. The IPSS can be used to evaluate female lower urinary tract symptoms, and the IPSS is well correlated with the OABSS [14].

A VAS of 0 corresponds to no symptoms, and a VAS of 10 corresponds to severe symptoms. PVR was measured by transabdominal ultrasonography. After patients had taken both medications, we asked them which drug they preferred, and why they chose it.

Statistical analysis. Based on the data characteristics, the median (min-max) was calculated. In terms of statistical analysis, the Wilcoxon signed rank test was performed to compare data pre- and post-administration in each group. The Mann-Whitney *U* test was used for inter-group comparisons. *P* values of less than 0.05 were considered significant. Data analysis was carried out with the Statistical Package for Social Sciences (SPSS).

Results

Patients' backgrounds. Of the 47 patients who registered, 23 patients were assigned to group S (S to M) and 24 patients were assigned to group M (M to S). Seven patients who did not visit the hospital and two patients who stopped taking the assigned drug due to adverse events could not be assessed and were excluded. Thirty-eight (80.9%) completed the two cross-over protocols (Fig. 1). Table 1 shows pre-administration background factors for the 47 patients. There were no significant differences between the 2 groups.

Evaluation. Table 2 shows the change in the IPSS, OABSS, and VAS from pre- to post- administration and comparisons of the degree of change between the 2 groups. The IPSS was significantly improved after the subjects received solifenacin. After they received mirabegron, the IPSS was also improved, but not sig-

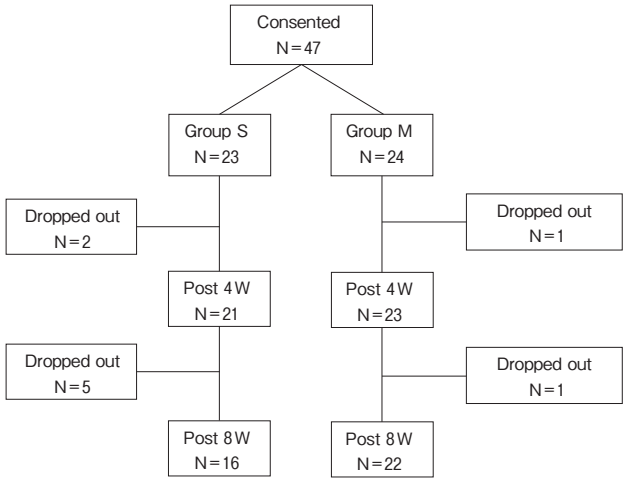

Fig. 1 Disposition of patients.

Table 1 Pre-administration background factors of patients in group S and group M

		Group S (n=23)	Group M (n=24)	Inter-group
Age (years)		70.0 (34.0–84.0)	75.0 (42.0–88.0)	0.333
Subjective symptom	Total IPSS	8.0 (3.0–27.0)	9.0 (2.0–34.0)	0.814
	OABSS	8.0 (5.0–12.0)	9.0 (5.0–15.0)	0.588
Objective symptom	Voiding volume (mL)	95.0 (20.0–215.0)	128.0 (79.0–208.0)	0.503
	Max flow rate (mL/sec)	12.0 (7.0–24.0)	16.9 (9.0–34.0)	0.570
	Postvoid residual urine volume (mL)	0.0 (0.0–16.0)	0.0 (0.0–41.0)	0.918

Median (min-max). Pre-administration background factors were compared inter-group by the Mann-Whitney *U* test.

Table 2 Change in IPSS, OABSS and VAS from pre- to post- administration and comparisons of the degree of change among the 2 groups

			Baseline	4 weeks after	8 weeks after
Total IPSS		S-M	8.0 (3.0–27.0)	5.0 (0.0–23.0)	3.0 (0.0–35.0)
		Intra-group		0.017*	0.531
		M-S	9.0 (2.0–34.0)	6.5 (0.0–23.0)	4.0 (0.0–19.0)
		Intra-group		0.100	0.001*
		Inter-group	0.814	0.300	0.385
OABSS		S-M	8.0 (5.0–12.0)	4.0 (0.0–14.0)	3.0 (0.0–11.0)
		Intra-group		< 0.0001*	0.494
		M-S	9.0 (5.0–15.0)	6.0 (0.0–11.0)	3.5 (0.0–9.0)
		Intra-group		< 0.0001*	< 0.0001*
		Inter-group	0.588	0.143	0.656
VAS	Urgency	S-M	5.0 (1.0–10.0)	5.0 (0.0–10.0)	4.3 (0.2–6.2)
		Intra-group		0.055	0.362
		M-S	5.0 (2.5–10.0)	5.0 (0.0–10.0)	2.5 (0.0–10.0)
		Intra-group		0.009*	0.006*
		Inter-group	0.605	0.872	0.089
	Incontinence	S-M	4.5 (0.0–9.0)	2.5 (0.0–10.0)	1.9 (0.0–5.0)
		Intra-group		0.266	0.637
		M-S	5.0 (0.5–10.0)	2.0 (0.0–7.5)	1.0 (0.0–5.0)
		Intra-group		0.001*	0.059
		Inter-group	0.205	0.939	0.510

Median (min-max). Intra-group: The changes pre- and post 4W-administration, post 4W- and post 8W-administration were compared by the Wilcoxon singed rank test Inter-group: The changes pre- and post 4W-, 8W-administration were compared in each group by the Mann-Whitney *U* test. *$p < 0.05$.

nificantly. The OABSS was significantly improved in both groups after treatment. There were no significant differences between the 2 groups.

In group M, the OABSS after 8 weeks was significantly improved compared to that after 4 weeks. On the other hand, in group S, it was not significantly improved. In group M, the VAS values for urgency and incontinence were significantly improved after treatment. In addition, the VAS values for urgency and incontinence after 8 weeks were significantly improved compared to those after 4 weeks. In group S, on the other hand, they were not significantly improved.

Table 3 Change in dry mouth and constipation from pre- to post- administration and comparisons of degree among the 2 groups

			Baseline	4 weeks after	8 weeks after
VAS	Constipation	S-M	0.0 (0.0–5.0)	0.5 (0.0–10.0)	0.3 (0.0–9.0)
		Intra-group		0.028*	0.504
		M-S	1.5 (0.0–10.0)	0.3 (0.0–10.0)	1.5 (0.0–10.0)
		Intra-group		0.683	0.166
		Inter-group	0.197	0.809	0.549
	Dry mouth	S-M	0.7 (0.0–10.0)	5.0 (0.0–10.0)	2.5 (0.0–9.0)
		Intra-group		0.010*	0.064
		M-S	2.0 (0.0–6.5)	0.0 (0.0–10.0)	3.3 (0.0–10.0)
		Intra-group		0.105	0.023*
		Inter-group	0.422	0.001*	0.589

Median (min-max). Intra-group: The changes pre- and post 4W-administration, post 4W- and post 8W-administration were compared by the Wilcoxon singed rank test Inter-group: The changes pre- and post 4W-, 8W-administration were compared in each group by the Mann-Whitney *U* test. *$p < 0.05$.

Qmax and PVR were not significantly changed between before and after treatment in both groups (data not shown).

Table 3 shows the VAS values for constipation and dry mouth; both conditions were worsened during the administration of solifenacin in both groups. The details of these and other adverse events in both groups were as follows. Twelve patients (26.0%) experienced adverse events during the solifenacin treatment. Four patients complained of dry mouth, 3 patients complained of difficulty with urination, and 3 patients complained of constipation. One patient had eczema, and one patient had itching. On the other hand, 2 patients experienced adverse events during mirabegron treatment. One patient complained of itching. The patient experienced itching even during the administration of sorifenacin. She stopped taking both drugs. One patient complained of stomach ache, and she also stopped both drugs.

After taking both medications, 17 patients preferred solifenacin, 18 preferred mirabegron, and the others hoped for the development of other drugs. Four patients preferred mirabegron due to the side effects of solifenacin, even though solifenacin was effective. Patients who hoped for the development of other drugs were not satisfied with either treatment.

Discussion

Mirabegron is the first β3-adrenoceptor agonist used in clinical practice for the treatment of OAB. It has a mechanism of action different from that of anti-muscarinic agents. Many studies have shown that mirabegron exhibits significant efficacy in treating the symptoms of OAB, and that its efficacy is equivalent to that of anti-muscarinic agents. Khaled *et al.* reported that Bayesian mixed treatment comparisons (MTCs) were performed to evaluate drugs for OAB efficacy and tolerability [10]. The MTCs showed that mirabegron 50 mg was as efficacious as anti-muscarinics in reducing the frequency of micturition incontinence and UUI episodes, with the exception of solifenacin 10 mg, which was more efficacious than mirabegron 50 mg for the improvement of micturition frequency and the frequency of UUI. This paper also showed that the mean change in the baseline number of micturitions for solifenacin 5 mg versus mirabegron 50 mg was −0.24 micturition episodes per day. The number of UUI episodes per day was −0.294. Solifenacin 5 mg treatments tended to be more effective than mirabegron 50 mg, but the difference was not significant.

Our study also showed that both drugs were effective for OAB symptoms, and the VAS and OABSS scores for OAB symptoms after 4 weeks of treatment showed no significant differences between group S and group M. In group M, the OABSS and VAS of urgency after eight weeks was significantly improved compared to that after four weeks. On the other hand, in group S, there was no significant difference in the OABSS or VAS between these 2 time points. When the subjects switched from solifenacin to mirabegron, there was no significant difference, but switching from mirabegron to solifenacin

significantly improved the OABSS. It was found to be more effective to change the medicine from mirabegron to solifenacin.

In group S, it decreased markedly to 4 points of OABSS after four weeks, whereas the OABSS value decreased to 6 points in group M, so it is possible that significant changes in the OABSS did not occur easily after the change to mirabegron. If so, solifenacin may have been the more effective drug. However, because the number of cases was small, this was impossible to determine definitively. Additionally, in our study, patients switched to the alternative treatment quickly, meaning that they had no drug clearance period, so it is possible that the effect of the first drug remained. Since there was no clearance period, it is possible that the effect cannot be accurately evaluated. However, this situation seems to be similar to the clinical situation.

Mirabegron had lower incidences of dry mouth and constipation. These adverse events are also reported with anti-muscarinics, and indeed they are one of the main causes of the treatment discontinuation in patients receiving anti-muscarinics. Hypertension is the most commonly reported adverse event in patients treated with mirabegron [15]. β3-adrenoceptors are expressed in cardiovascular tissues, and there are concerns that treating OAB with β3-adrenoceptor agonists may affect the heart and vasculature. In this study, there were no side effects such as hypertension or cardiovascular disorders. Gian *et al.* reviewed 20 papers, and they showed that the safety of mirabegron for cardiovascular-associated adverse events appears to be acceptable at the therapeutic doses and comparable with that of anti-muscarinic agents [16]. Kobayashi *et al.* evaluated the comparative efficacy and tolerability of anti-muscarinics and mirabegron as the primary and salvage therapy in patients with OAB. They found that mirabegron seems to have priority as an initial therapy with a distinct efficacy/tolerability balance [17]. In our study, mirabegron also improved OAB symptoms and showed fewer adverse events than solifenacin during the treatment period.

This study has some limitations. First, the number of patients was small. Second, we did not include a placebo control group. Therefore, further study is necessary.

Both solifenacin succinate and mirabegron improved OAB symptoms. Switching from mirabegron to solifenacin significantly improved the OABSS, and mirabegron showed fewer adverse events than solifenacin during the treatment period. We therefore recommend that mirabegron be prescribed first for OAB patients. When patients are no longer satisfied with mirabegron, solifenacin can be used.

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