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A Prospective Paired Comparison Trial of Mirabegron and Anticholinergics in Patients With Low Bladder Compliance

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Purpose: Low bladder compliance (BC) poses a significant clinical challenge. Nevertheless, studies exploring pharmacological mechanisms to improve BC remain limited. We investigated the efficacy of a β3-adrenoceptor agonist, mirabegron, on BC in comparison with anticholinergics.

Methods: This prospective single-arm paired comparison trial included 14 patients with low BC (≤20 mL/cm H_2O) despite anticholinergics treatment. After a 2-week anticholinergics-washout period, patients were treated with mirabegron for 8 weeks and then returned to 8 weeks of anticholinergics. Major treatment effect was assessed with urodynamic studies performed at baseline, 8 weeks after mirabegron treatment, and 8 weeks after consecutive anticholinergics treatment (McNemar test, Paired t-test; mean [95% confidence intervals]).

Results: Following mirabegron, 71.43% of patients exhibited a BC of >20 mL/cm H_2O, compared to 54.55% after switching back to anticholinergics (P=0.317). BC improved significantly from 12.02 (9.52–14.52) to 39.67 (21.60–57.73) mL/cm H_2O after mirabegron treatment (P=0.007), but subsequently declined to 20.94 (15.78–26.10) mL/cm H_2O after reintroduction of anticholinergics (P=0.075). Maximum cystometric capacity increased from 352.21 (282.78–421.65) to 442.71 (348.95–536.48) mL after mirabegron (P=0.091), but decreased to 402.00 (315.92–488.08) mL after returning to anticholinergics (P=0.218). Notably, detrusor pressure at end-filling decreased significantly with mirabegron, from 30.50 (25.61–35.39) to 14.43 (10.79–18.06) cm H_2O (P<0.001), while increasing to 20.36 (16.26–24.46) cm H_2O after returning to anticholinergics (P=0.056).

Conclusions: A β3-adrenoceptor agonist, mirabegron, was more effective than anticholinergics in improving BC. Among the two components of improved BC — increased bladder volume and reduced detrusor filling pressure — the β3-adrenoceptor agonist showed a more pronounced effect on lowering detrusor filling pressure, compared to anticholinergics. These findings suggest that β3-adrenoceptor agonists might play an important role in reducing the tension of the bladder wall by controlling detrusor muscle tone, and this may be an important target for future research.

Keywords: β3-adrenoceptor agonist; Cholinergic antagonist; Compliance; Detrusor muscle; Mirabegron; Muscle tone

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- **Research Ethics:** This study was conducted at Yonsei University Severance Hospital, a tertiary referral center. It was registered at ClinicalTrials.gov (NCT05745584) and was approved by the Institutional Review Board of Yonsei University Severance Hospital (4-2015-0938). All participants provided written informed consent.
- **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

INTRODUCTION

Low bladder compliance (BC) is a urological challenge that can compromise renal function, not to mention storage disorders [1]. BC is determined by structural (passive) components related to the viscoelastic properties of the bladder wall and neuro-

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functional (active) components that determine the dynamic bladder resting pressure [2-4]. Various surgical and medical treatments can be provided to convert the bladder into a low-pressure reservoir. Although structural and neurofunctional components are not completely independent, the target of future research should be the development of noninvasive drug therapy that modulates neurofunctional components, considering surgical complications and long-term safety [1]. Nevertheless, few studies have explored how BC can be improved through pharmacological treatment.

The two major drug classes currently used for patients with low BC are anticholinergics and β3-adrenoceptor agonists, which were initially developed for the treatment of overactive bladder [5-7]. However, even with long-term use of both drug classes, their mechanisms of action in improving BC have not been clearly demonstrated. Little is known regarding the drug properties that may contribute to BC improvement, and which of the two drug classes, with different unique mechanisms of action, is more effective for improving BC.

Few studies have compared these two drug classes in terms of BC, particularly in prospective settings. Here, we performed a prospective study to assess the effect of a β3-adrenoceptor agonist, mirabegron, compared with that of anticholinergics on BC.

MATERIALS AND METHODS

Study Design and Patient Enrollment

This prospective single-arm paired comparison trial was conducted at a tertiary referral center, Yonsei University Severance Hospital, between January 2016 and March 2023. The study enrolled β3-adrenoceptor agonist-naïve patients with BC ≤20 mL/cm H_2O [8], in urodynamic studies performed while they were taking anticholinergics for more than 1 month.

The patient inclusion/exclusion criteria are provided in Supplementary Table 1.

Intervention

To eliminate potential additive effects of anticholinergics and assess mirabegron's pure therapeutic effect, a 2-week washout period was implemented. Subsequently, patients received 50 mg of mirabegron daily for 8 weeks. Then, anticholinergics treatment with the same regimen used in the baseline assessment was performed for another 8 weeks. Given mirabegron's pharmacokinetics (~99% eliminated within 11–14 days), no additional washout period was implemented at this stage [9, 10]. Urodynamic studies and patient evaluations were performed at baseline, 8 weeks after mirabegron, and 8 weeks after anticholinergics treatment (Fig. 1).

Urodynamic Study

Urodynamic studies were performed in accordance with the "Good Urodynamic Practices" suggested by the International Continence Society [11]. Using body-temperature saline, bladder instillation was performed at a mean rate of 20–30 (range, 5–40) mL/min [11]. BC was defined as the change in bladder volume divided by the change in detrusor pressure (Pdet) [12]. The change in bladder volume was defined as the maximum cystometric capacity (MCC) when there was no terminal detrusor overactivity; the volume at detrusor leak point pressure, when autonomic dysreflexia occurred, or when the patient

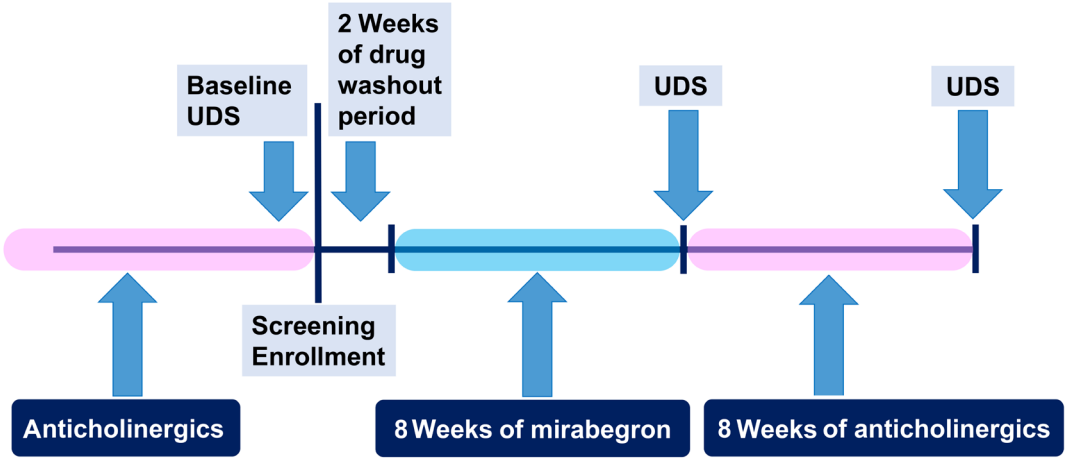

Fig. 1. Study design. UDS, urodynamic study.

complained of discomfort. When there was terminal detrusor overactivity, cystometric capacity was determined at the point immediately before involuntary detrusor contraction [12]. At the start of the urodynamic study, Pdet was set to 0 cm H_2O; therefore, the BC was determined by dividing the cystometric capacity by the Pdet at cystometric capacity (Pdet end-filling).

Endpoints and Outcome Assessments

We set two primary endpoints: a comparison of the proportion of patients with improved BC higher than 20 mL/cm H_2O after mirabegron and anticholinergics treatment (McNemar test) and the change in BC during each treatment period (paired t-test). The secondary endpoints were changes in the MCC and Pdet end-filling during each treatment period (paired t-test). Additionally, changes in the International Consultation on Incontinence Questionnaire (ICIQ) score and functional capacity on a bladder diary were evaluated (paired t-test). To explore potential relationships between the duration of the neurological deficit and treatment outcomes, Pearson correlation analysis was performed.

Sample Size Determination and Statistical Analysis

The sample size was established using retrospective data of patients who received anticholinergics and were then switched to mirabegron or add-on mirabegron therapy to anticholinergics in an unplanned manner. A sample size of 9 pairs achieved 80% power for a 1-sided McNemar test with a significance level of 0.025, with a proportion of discordant pairs of 0.75, specifically found in cell 1,2. Considering a 30% dropout rate, the target number of patients was set to 13. Data are expressed as mean with 95% confidence interval (CI) or range. Statistical analyses were performed using IBM SPSS Statistics ver. 27.0 (IBM Co., USA) and SAS 9.4 (SAS Institute Inc., USA). Statistical significance was set at $P < 0.05$.

RESULTS

Study Participants

Seventeen candidates met the inclusion criteria, but 3 were excluded because of irregular anticholinergics medication at the time of baseline assessment. Fourteen patients were enrolled. Three patients dropped out after 8 weeks of mirabegron because of protocol violations; 1 refused to resume anticholinergics for fear of suffering severe dry mouth; 1 arbitrarily switched to mirabegron 7 days after returning to anticholinergics due to aggravated urinary incontinence; and 1 missed follow-up because of impaired ambulation caused by a fall. Finally, 11 patients completed all study sessions. Analysis included all 14 enrolled patients, including the 3 patients who dropped out after completion of mirabegron treatment (Fig. 2).

General Characteristics of Patients

The patients' age was 54.4 (range, 23.9–78.3) years; 57.4% (8 of 14) had neurological disorders of spinal cord origin, 14.3% (2 of 14) had diseases of brain origin, and 7.1% (1 of 14) had neurofibromatosis involving both the brain and spine. 21.4% (3 of

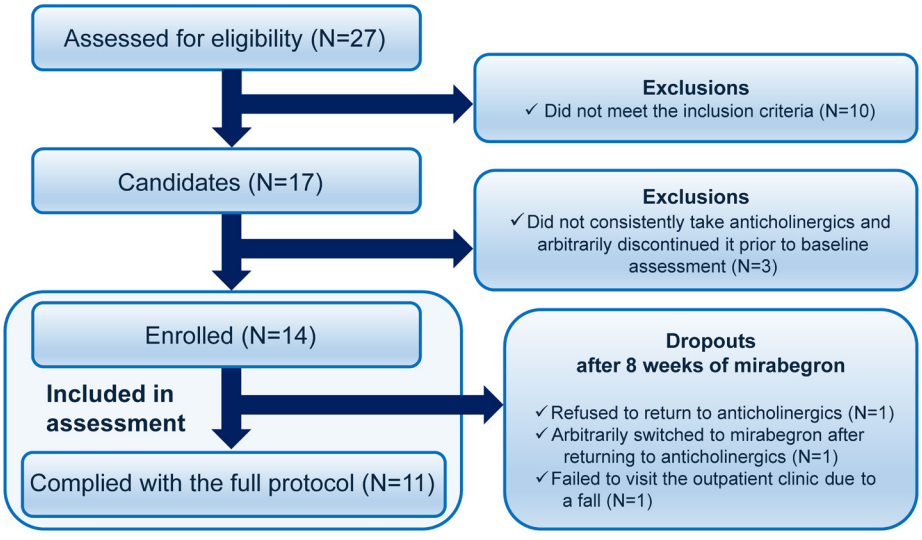

Fig. 2. Participant flow diagram.

14) had bladder dysfunction following radical pelvic surgery (1 cervical cancer, 2 rectal cancer). Both rectal cancer patients underwent pelvic radiation. The estimated duration of neurological deficit — defined as the time from symptom onset (for neurological diseases), date of trauma (for spinal cord or brain injury), or date of surgery (for patients who underwent radical pelvic surgery) — was 16.7 (range, 1.7–37.0) years. The body surface area-adjusted estimated glomerular filtration rate was 102.6 (range, 55.0–153.0) mL/min. At the baseline urodynamic study, the anticholinergics treatment duration was 10.1 (range, 2.1–72.1) months. No participants received any urological drugs other than the study medications that might affect bladder function (Table 1 and Fig. 3).

Table 1. Patient baseline characteristics (N = 14)

Characteristic	Value
Sex, male:female	8:6
Age (yr)	54.4 (23.9–78.3)
Etiology	
Traumatic spinal cord injury	4
Spinal stenosis	1
Spina bifida	3
MSA	1
Traumatic ICH, MSA suspected	1
Neurofibromatosis involving both the brain and spine	1
Radical pelvic organ surgery for cancer	3
Estimated duration of neurological deficit (yr)	16.7 (1.7–37.0)
Urodynamic pattern	
LMN lesion type	10
UMN lesion type	3
Normal except for low compliance	1
Voiding pattern	
CIC	7
CIC & self-urination	4
Self-urination	3
Pelvic radiation	2
Body surface area-adjusted eGFR (mL/min)	102.6 (55.0–153.0)
Anticholinergics	
Solifenacin 5 mg/day	9
Solifenacin 10 mg/day	1
Propiverine 20 mg/day	1
Fesoterodine 4 mg/day	1
Oxybutynin 10 mg & fesoterodine 8 mg/day	1
Oxybutynin 15 mg & propiverine 10 mg/day	1
Duration of anticholinergics medication at baseline urodynamic study (mo)	10.1 (2.1–72.1)

Values are presented as mean (range) or number.
MSA, multiple system atrophy; ICH, intracranial hemorrhage; LMN, lower motor neuron; UMN, upper motor neuron; CIC, clean intermittent catheterization; eGFR, estimated glomerular filtration rate.

Primary Endpoints; Changes in BC

After 8 weeks of mirabegron treatment, 71.43% (10 of 14) achieved BC >20 mL/cm H_2O (95% CI, 45.35%–88.28%). Eight weeks after returning to the previously administered anticholinergics, 54.55% (6 of 11) achieved BC >20 mL/cm H_2O (95% CI, 28.01%–78.73%). The absolute effect size (risk difference) was 16.88% (95% CI, -20.88% to 54.64%), and the relative effect size (relative risk) was 1.31 (95% CI, 0.70–2.47), indicating a 31% higher likelihood of achieving BC >20 mL/cm H_2O with mirabegron compared to anticholinergics. However, this difference between the two treatment sessions was not statistically significant (P = 0.317).

After 8 weeks of mirabegron treatment, BC increased significantly from 12.02 mL/cm H_2O (95% CI, 9.52–14.52) to 39.67 mL/cm H_2O (95% CI, 21.60–57.73), with a significant mean

Patient ID	Sex/age (yr)	Etiology
1	M/57	MSA
2	M/77	SS, C3/4
3	M/24	SCI, C6
4	M/49	SCI, L4/5
5	M/56	Rectal cancer, RTx
6	M/32	Neurofibromatosis involving both the brain and spine
7	M/75	Traumatic ICH, MSA suspected
8	F/78	Cervical cancer
9	F/77	Rectal cancer, RTx
10	F/60	SB
11	M/36	SB
12	F/37	SB
13	F/77	SCI, L2
14	F/27	SCI, C4/5/6

Fig. 3. Clinical profile of patients. MSA, multiple system atrophy; SS, spinal stenosis; SCI, spinal cord injury; C, cervical spine; L, lumbar spine; RTx, pelvic radiation therapy; ICH, intracranial hemorrhage; SB, spina bifida.

difference of +27.65 mL/cm H_2O (95% CI, 8.78–46.51; P = 0.007) (N = 14). Eight weeks after returning to the previously administered anticholinergics, BC decreased from 39.63 mL/cm H_2O (95% CI, 17.04–62.21) to 20.94 mL/cm H_2O (95% CI, 15.78–26.10), with a mean difference of -18.68 mL/cm H_2O (95% CI, -39.63 to 2.26; P = 0.075) (N = 11) (Fig. 4).

Secondary Endpoints; Changes in MCC, Pdet End-Filling, and Others

After 8 weeks of mirabegron, MCC increased from 352.21 mL (95% CI, 282.78–421.65) to 442.71 mL (95% CI, 348.95–536.48), with a mean difference of +90.50 mL (95% CI, -16.69 to 197.69; P = 0.091) (N = 14). After returning to the previously administered anticholinergics for 8 weeks, MCC decreased from 447.64 mL (95% CI, 332.72–562.56) to 402.00 mL (95% CI, 315.92–488.08), with a mean difference of -45.64 mL (95% CI, -122.97 to 31.69; P = 0.218) (N = 11). There was no statistically significant difference in MCC for either treatment session (Fig. 5).

After 8 weeks of mirabegron, a significant decrease in Pdet

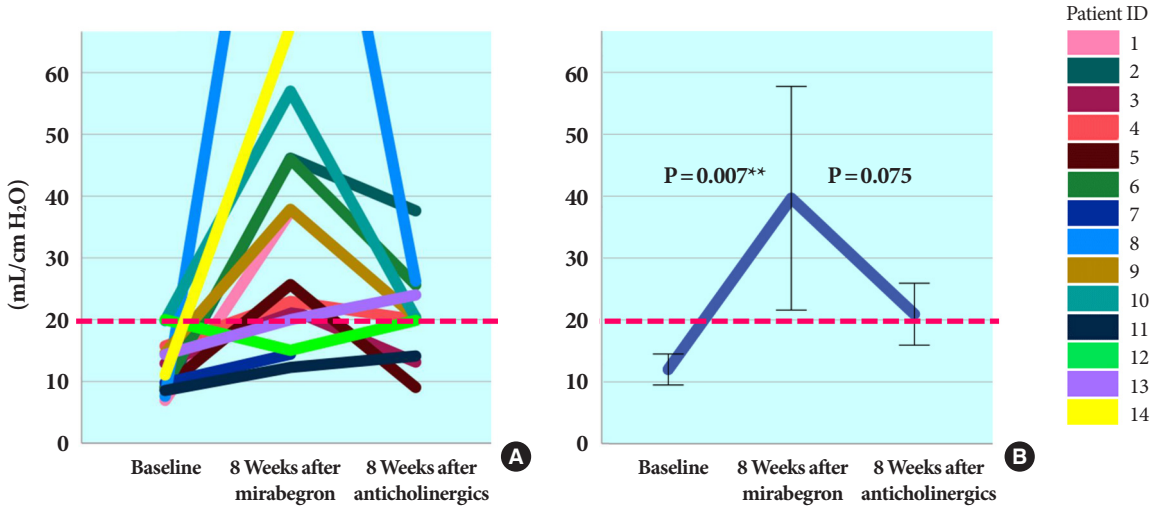

Fig. 4. Changes in bladder compliance. (A) Changes in bladder compliance of each patient. (B) Mean value (95% confidence interval) of bladder compliance. The red dotted line indicates '20 mL/cm H_2O,' the minimum standard for normal compliance set in this study; paired t-test. **Statistically significant at P < 0.01.

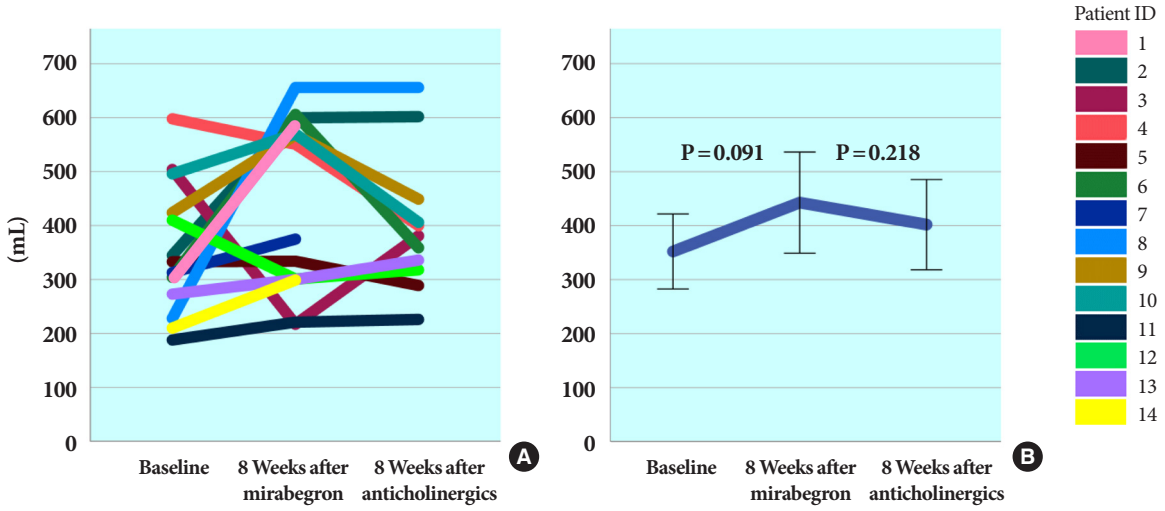

Fig. 5. Changes in maximum cystometric capacity. (A) Changes in maximum cystometric capacity of each patient. (B) Mean value (95% confidence interval) of maximum cystometric capacity; paired t-test.

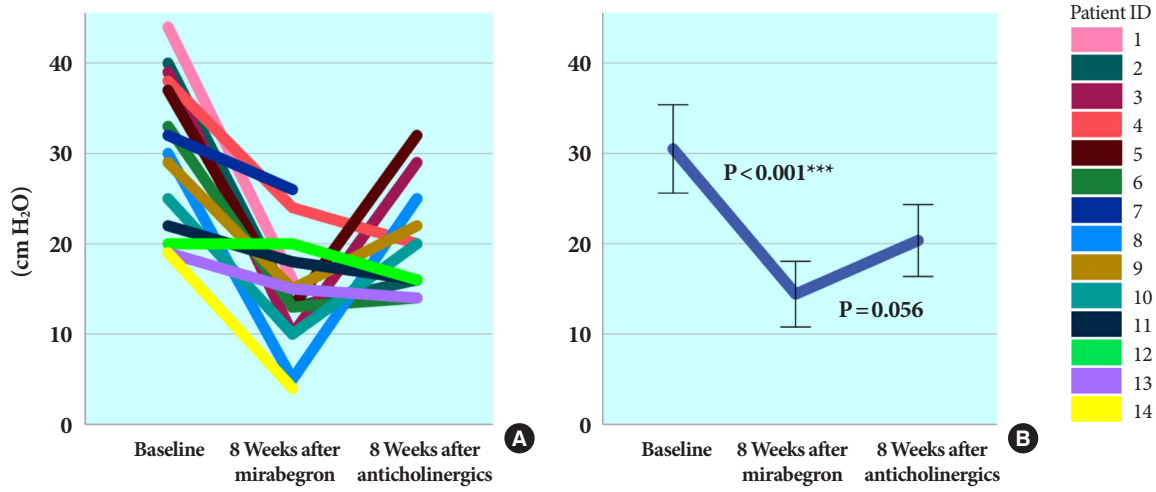

Fig. 6. Changes in detrusor pressure at end-filling. (A) Changes in detrusor pressure at end-filling of each patient. (B) Mean value (95% confidence interval) of detrusor pressure at end-filling; paired t-test. ***Statistically significant at P < 0.001.

end-filling was observed, from 30.50 cm H_2O (95% CI, 25.61–35.39) to 14.43 cm H_2O (95% CI, 10.79–18.06), with a significant mean difference of -16.07 cm H_2O (95% CI, -21.73 to -10.41; P < 0.001) (N = 14). After returning to the previously administered anticholinergics for 8 weeks, Pdet end-filling increased from 14.18 cm H_2O (95% CI, 10.69–17.67) to 20.36 cm H_2O (95% CI, 16.26–24.46), with a mean difference of +6.18 cm H_2O (95% CI: -0.18 to 12.55; P = 0.056) (N = 11), approaching conventional significance (Fig. 6).

ICIQ scores were assessed in 13 patients, excluding one patient who was using a urethral clamp for true urinary incontinence. After 8 weeks of mirabegron, the ICIQ score decreased significantly from 10.92 (95% CI, 7.70–14.14) to 6.62 (95% CI, 2.70–10.53), with a mean difference of -4.30 (95% CI, -7.88 to -0.74; P = 0.022) (N = 13). Subsequently, the ICIQ score increased from 5.30 (95% CI, 0.74–9.86) to 8.90 (95% CI, 3.34–14.46), with a mean difference of +3.60 (95% CI, -1.76 to 8.96; P = 0.163) (N = 10) after returning to anticholinergics.

Based on bladder diaries, functional capacity increased significantly from 375.83 mL (95% CI, 248.57–503.09) to 522.50 mL (95% CI, 335.44–709.56), with a mean difference of +146.67 mL (95% CI, 29.31–264.02; P = 0.019) (N = 12) after 8 weeks of mirabegron. Subsequently, functional capacity decreased from 489.00 mL (95% CI, 267.63–710.37) to 453.00 mL (95% CI, 279.66–626.34), with a mean difference of -36.00 mL (95% CI, -164.64 to 92.64; P = 0.542) (N = 10) after returning to anticholinergics.

Impact of Duration of Neurological Deficit on Mirabegron Effect

After 8 weeks of mirabegron treatment, significant changes in BC and Pdet end-filling were observed. However, the amount of change varied among patients. Correlation analyses revealed a significant negative correlation between the duration of the neurological deficit and the amount of decrease in Pdet end-filling (Pearson r = -0.566; 95% CI, -0.843 to -0.051; P = 0.035), indicating that patients with a longer duration of neurological deficit experienced a smaller decrease in Pdet end-filling. However, there was no significant correlation between the duration of neurological deficit and the amount of increase in BC (Pearson r = 0.009; 95% CI, -0.524 to 0.537; P = 0.977) or MCC (Pearson r = 0.128; 95% CI, -0.432 to 0.617; P = 0.664).

Treatment-Emergent Adverse Events

Two patients experienced treatment-emergent adverse events (palpitations, skin rash) after starting mirabegron. Both were mild, resolved without intervention, and had no lasting effects. Consequently, both patients completed the planned 8-week mirabegron treatment and subsequent anticholinergic protocol as scheduled.

One Patient Who Showed No Improvement in BC Despite Mirabegron Administration

Unlike the 13 patients whose BC increased with mirabegron, one spina bifida patient showed decreased BC after mirabegron, with a notable decrease in MCC (patient ID 12; Figs. 3–6).

Eight months after study completion, pelvic ultrasonography and magnetic resonance imaging revealed a large uterus (724.4 mL), with myomas, the largest of which was 11 cm in diameter on the anterior uterine wall.

DISCUSSION

Mirabegron, a β3-adrenoceptor agonist, showed superior effects on BC compared to anticholinergics. Eight weeks of mirabegron significantly improved BC in patients with persistently low BC despite prior anticholinergics. However, BC improvement was not sustained after switching back to anticholinergics. Compared to anticholinergics, mirabegron's effect on BC was more pronounced in reducing Pdet end-filling.

Factors That May Have Caused Differences Between the two Drug Classes

As researches progress to date, it is known that there are many common aspects in the distribution of receptors and the ultimate mechanisms of action through each unique pathway of anticholinergics and β3-adrenoceptor agonist [6, 13-15]. Here, detrusor contraction during the storage phase and detrusor muscle tone should be considered separately [2, 14, 16-18]. Both anticholinergics and β3-adrenoceptor agonists are believed to act on detrusor contraction during the storage phase. By suppressing afferent Aδ or C fiber excitation [6, 14, 15], both agents increase the bladder volume where 'bladder filling awareness' occurs, inhibit involuntary detrusor contraction, and finally increase MCC [16, 19]. Therefore, among the two functions that comprise BC, both anticholinergics and β3-adrenoceptor agonists might have effect in improving the bladder capacity. The lack of a statistically significant difference in MCC between anticholinergics and mirabegron observed in this study may be attributed to these phenomena. However, these two groups of agents are believed to have different effects on detrusor muscle tone, which is believed to be induced by the intramural movement of the bladder, known as 'micromotion' [13, 16, 17, 20, 21].

Micromotion and Detrusor Muscle Tone

Micromotion is a disinhibited, autonomous, and localized movement inherent to the bladder — observed in animals, including humans — and is well-controlled in a normally innervated bladder [16, 22]. Microdistortion of the bladder wall caused by micromotion is a basic component for activating mechanosensitive afferents [16, 23], and is assumed to prevent stretching of the microvasculature during bladder distention, thereby producing bladder wall tension [24].

Micromotion is different from the nonvoiding fluctuation of intravesical pressure, which can be observed on cystometrograms in neurologically intact or partially denervated bladders. To detect pure micromotion, reflected as intravesical pressure oscillations on a cystometrogram, the bladder should be completely denervated, theoretically [16, 22, 25]. However, micromotion of the human bladder is difficult to observe on cystometrograms because the terminal neural ganglia are believed to exist inside the bladder wall [26, 27]. In the human bladder, micromotion has been confirmed using electrodes, demonstrating higher activity in patients with hypersensitive bladder [23].

Unlike human, rodents have extravesical terminal neural ganglia known as the major pelvic ganglion (MPG) [28, 29]. We previously developed a living micromotion rat model whose nonvoiding oscillation of intravesical pressure was the closest to micromotion by excising bilateral MPGs. A systemically administered β3-adrenoceptor agonist significantly suppressed micromotion, but nonselective anticholinergics oxybutynin could not control micromotion significantly [30].

Consistent with the differential effects of β3-adrenoceptor agonists and anticholinergics on micromotion, prior studies have reported similar distinctions in their effects on detrusor muscle tone, which is thought to be micromotion-related. One study performed with live dogs suggested little relationship between cholinergic components and detrusor tone [18]. A later study performed with isolated whole bladders of mice implied the possibility that the cholinergic pathway acts on bladder afferents through a mechanism independent of changes in detrusor tone [14]. Contrary to anticholinergics, an experiment performed with live rats denervated at the L6 dorsal root level showed a decrease in afferent firing simultaneously with amelioration of microcontraction and a decrease in intravesical pressure after β3-adrenoceptor agonist administration, whereas these effects were not observed with anticholinergics [31]. Several *in vitro* studies have shown that β3-adrenoceptor agonists can ameliorate detrusor tone via various mechanisms unique to the β3-adrenergic pathway [32].

What Remains to Be Answered

Caution should be exercised when interpreting the results of individual experiments conducted with different animals and under various conditions, as the response may vary depending

on the species and pathological condition, even when the same agent is used [33]. Further research is required to verify the relationships between β3-adrenoceptor agonists and micromotion, detrusor muscle tone, and BC for application to the human bladder.

The exploratory analysis revealed a significant negative correlation between the duration of neurological deficit and mirabegron's effect on reducing Pdet end-filling, suggesting that longer disease duration may reduce responsiveness. However, as these analyses were not prespecified, the findings should be interpreted cautiously. Additionally, one patient with a large pelvic mass showed a paradoxical decrease of BC after mirabegron. While the mass may have influenced MCC, its direct relationship with BC remains unclear, warranting cautious interpretation. Prespecified hypotheses-driven studies may validate these findings.

An unplanned finding outside the original study design revealed that BC and Pdet end-filling remained significantly improved compared to baseline after the reintroduction of anticholinergics, although the effect was weaker than during mirabegron treatment. Considering mirabegron's pharmacokinetics, the improvement observed 8 weeks after discontinuation — far beyond complete elimination from the bloodstream — is unlikely to be attributable to mirabegron's effect on the neurofunctional (active) components of BC, such as the dynamic modulation of micromotion or detrusor tone [9, 10]. However, the possibility of longer-lasting effects of mirabegron on the structural (passive) components of BC, potentially mediated through partial reversal of fibrosis, cannot be excluded [34]. Whether such changes persist after drug elimination and contribute to sustained improvement in BC warrants further investigation.

Limitations and Remarkable Points

This study has limitations, including the use of a 20 mL/cm H_2O cutoff as an endpoint. Although 20 mL/cm H_2O is commonly used to define low BC, a critical dichotomization bias may exist because as BC approaches 20 mL/cm H_2O, there can be an increased risk that the results may be misjudged [35]. This study found no significant difference in the proportion of patients with BC >20 mL/cm H_2O after mirabegron and anticholinergics, but the findings warrant cautious interpretation.

As the study included only mirabegron-naive patients who exhibited BC ≤20 mL/cm H_2O despite anticholinergics, patients who were anticholinergics-naive or who might have responded favorably to anticholinergics were not represented, reflecting a limitation in the spectrum of the study population.

When determining the sample size, 9 pairs were sufficient to differentiate the effects of the two drug classes; therefore, this study was performed with a confined number of 14 patients. Additional studies with a large number of patients are required to support these results, more robustly.

Despite these limitations, this study provides valuable insights into the potentially different effects of the two drug classes on detrusor muscle tone. It indicates that the regulation of detrusor muscle tone via the modulation of bladder micromotion, which is believed to be predominantly mediated through the β3-adrenergic pathway, may play a crucial role in improving BC. To the best of our knowledge, this study is the first to prospectively compare a β3-adrenoceptor agonist and anticholinergics regarding BC.

Conclusion

A β3-adrenoceptor agonist, mirabegron, was more effective than anticholinergics in improving BC. Among the two components of improved BC — increased bladder volume and reduced detrusor filling pressure — the β3-adrenoceptor agonist showed a more pronounced effect on lowering detrusor filling pressure, compared to anticholinergics. These findings suggest that β3-adrenoceptor agonists might play an important role in reducing the tension of the bladder wall by controlling detrusor muscle tone, and this may be an important target for future research.

SUPPLEMENTARY MATERIAL

Supplementary Table 1 is available at https://doi.org/10.5213/inj.2550050.025.

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AUTHOR CONTRIBUTION STATEMENT

· Conceptualization: *HSS, JHK*
· Data curation: *HSS, JHK*
· Formal analysis: *HSS, JHK*

· Methodology: *HSS, JHK*
· Project administration: *HSS, JHK*
· Visualization: *HSS, JHK*
· Writing - original draft: *HSS*
· Writing - review & editing: *HSS, JHK*

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