Original Article

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Long-Term Efficacy of Mirabegron Add-On Therapy to Antimuscarinic Agents in Patients With Spinal Cord Injury

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Objective To evaluate the long-term efficacy of mirabegron add-on therapy in patients with spinal cord injury (SCI) based on an urodynamic study.

Methods This retrospective study involved a chart audit of individuals with SCI who underwent two consecutive urodynamic studies between April 1, 2015 and April 1, 2018. After adding 50 mg of mirabegron once a day to the pre-existing antimuscarinic therapy for a period of, at least 6 months, the following variables were analyzed: change in cystometric capacity, change in bladder compliance, change in maximal detrusor pressure, change in reflex volume, and presence of significant leakage during filling cystometry.

Results A total of 31 participants with a mean age of 41±15 years were included in the analysis. A significant increase in cystometric capacity (mean, 362 to 424 mL; p=0.03), reflex volume (mean, 251 to 329 mL; p=0.02), and bladder compliance (median, 12 to 18 mL/cmH_2O; p=0.04) was observed. The presence of leakage during filling cystometry was significantly reduced (29% to 10%; p=0.03). Likewise, a non-significant decrease in the change in maximal detrusor pressure was observed (mean, 31 to 27 cmH_2O; p=0.39).

Conclusion Adding mirabegron to conventional antimuscarinics further improved urodynamic parameters in patients with chronic SCI, and sustained efficacy was observed in long-term use.

Keywords Spinal cord injuries, Urodynamics, Mirabegron, Muscarinic antagonists

INTRODUCTION

Neurogenic lower urinary tract dysfunction (NLUTD) is a major concern for patients with spinal cord injury (SCI). It can cause renal function deterioration and renal failure, urinary tract infection, and vesicoureteral reflux

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[1]. Therefore, the goals of care in this population are the protection of the upper urinary tract and prevention of renal damage by increasing detrusor capacity and lowering detrusor pressure [2].

Successful pharmacological management of NLUTD leads to an improvement in the activities of daily living, psychosocial well-being, and long-term persistence, along with the adverse effects of drugs [3]. In current clinical guidelines, antimuscarinic agents such as propiverine, tolterodine, oxybutynin, fesoterodine, and solifenacin are often initially prescribed. Antimuscarinics have been proven to increase bladder capacity and detrusor compliance and to lower the risk of upper urinary tract damage, thus improving patients' quality of life [4]. However, people with SCI require an increased dosage of antimuscarinic agents to obtain sufficient therapeutic effect, which, in turn, may exacerbate the adverse events (i.e., dry mouth, constipation, blurred vision, and cognitive impairment). Due to lack of efficacy and the side effects of the drugs, the administration of antimuscarinics for the treatment of NLUTD in patients with SCI often leads to poor treatment compliance, resulting in the termination of therapy [5].

Mirabegron, a β3-adrenoceptor selective agonist, has been proven to have a similar efficacy as antimuscarinics. Because of its different mode of action from that of antimuscarinics, this agent does not lead to antimuscarinic-related adverse events [6]. Owing to these advantages, the frequency of mirabegron administration for SCI patients with NLUTD has increased over the years. A study showed improvements in urodynamic and clinical parameters when switching from conventional antimuscarinic treatment to mirabegron monotherapy for a short period of time [7]. However, objective evidence to prove the effectiveness of drug when prescribed for long-term use in people with SCI is currently unavailable. In this study, we tested the hypothesis that adding mirabegron to conventional antimuscarinic therapy in SCI patients with NLUTD would be effective in the long term.

MATERIALS AND METHODS

Subjects and study design

This longitudinal retrospective study included individuals with SCI at a rehabilitation hospital in Korea and was approved by the Institutional Review Board of the rehabilitation hospital. The participants underwent two consecutive urodynamic studies (UDSs) between April 1, 2015 and April 1, 2018 and the interval between the consecutive UDSs was, at least, 6 months.

Among those considered, 31 were surveyed based on the following inclusion criteria: individuals who (1) had a neurological impairment secondary to traumatic or non-traumatic SCI that occurred at least 12 months prior to the first UDS; (2) had received pre-existing antimuscarinics on a stable dose throughout the preceding 3 months; (3) had never taken any β3-adrenoceptor selective agonist before first UDS; (4) had a stable medical condition that would not interfere with interpretation of study results; and (5) were aged at least 18 years. Individuals with other neurologic disorders or a history of urologic surgery or intravesical Botox injection were excluded.

Prior to UDS, each participant was examined according to the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) guideline [8,9], and the clinical characteristics, including the neurological level of injury, the American Spinal Injury Association impairment scale (AIS), and bladder emptying method, were collected. All the participants received 50 mg of mirabegron once a day for, at least, 6 months. Mirabegron administration was initiated subsequent to the day of the first UDS.

Urodynamic protocol

All the participants underwent a multichannel UDS using the Duet Logic G2 (Mediwatch, Rugby, UK) urodynamic measurement system. UDS was conducted by clinicians (mostly spinal cord medicine residents, who received the ISNCSCI training by senior SCI physicians), and the results were reviewed by senior SCI physicians.

During the UDS, each participant was positioned supine on a urological chair. An 8-French dual-lumen urethral catheter was inserted for filling and intravesical pressure recording. The intra-abdominal pressure was simultaneously measured using a 12-French rectal balloon catheter. The detrusor pressure was measured by subtracting the intra-abdominal pressure from the intravesical pressure [10]. Filling cystometry was performed at an infusion rate of 30 mL/min with room-temperature sterile saline. Videourodynamic investigation under fluoroscopy was performed to detect vesicoureteral reflux. The UDSs were performed and reported in accordance

with the standardization subcommittee of the International Continence Society [11,12].

Efficacy assessments

The primary efficacy endpoint referred to change in cystometric capacity (mL) during filling cystometry. Cystometric capacity was defined as the bladder volume at which the investigator decided to terminate filling if the participant could no longer delay micturition because of a strong desire to void, if significant leakage was noted, or if 550 mL of normal saline had been infused. At any signs of adverse effects, such as autonomic dysreflexia, or patient intolerance, the filling was also terminated immediately.

Secondary efficacy variables derived from the consecutive UDSs included a change in bladder compliance (mL/cmH_2O), change in maximal detrusor pressure (cmH_2O), change in reflex volume (mL), and presence of significant leakage during filling cystometry.

Compliance was defined as volume increment per detrusor pressure increment and was calculated by dividing the volume change by the change in detrusor pressure during that change in bladder volume. Maximal detrusor pressure, as the name implies, was defined as the maximum value of detrusor pressure during the filling cystometry. Reflex volume was defined as the infused volume that induced the first involuntary detrusor contraction. All the definitions were based on the report from the standardization subcommittee of the International Continence Society [11].

Statistical analysis

To calculate the sample size, we referred to two previous studies conducted in the Swiss Paraplegic Center. These retrospective studies included 15 and 35 people treated with mirabegron and solifenacin, respectively [7,13]. Based on the primary outcome, a minimum sample size of 27 individuals provided a power of 80% with an alpha error probability of 0.05 using the paired t-test [14,15].

Statistical analyses were performed using SPSS software version 20.0 (IBM, Armonk, NY, USA). The significance level for statistical tests was set at a two-sided 95% level. The data are presented as mean±standard deviation for continuous variables and as a percentage for categorical parameters. The normality of the distribution of variables was assessed using the Kolmogorov-Smirnov test. All relevant parameters (changes in cystometric capacity, maximal detrusor pressure, and reflex volume), except for the change in compliance, were normally distributed. Thus, the primary and secondary efficacy endpoints (change in maximal detrusor pressure and change in reflex volume, respectively) were analyzed using a paired t-test. Wil-

Table 1. Characteristics of the participants (n=31)

Characteristic	Value
Age (yr)	41±15
Sex	
Male	20 (65)
Female	11 (35)
Neurological level of injury	
Cervical	16 (52)
Thoracic	14 (45)
Lumbar	1 (3)
AIS classification	
A	22 (71)
B	5 (16)
C	4 (13)
D	0 (0)
Etiology	
Trauma	25 (81)
Others	6 (19)
Bladder emptying method	
CIC	20 (64)
Indwelling catheter	
Transurethral	8 (26)
Suprapubic	3 (10)
Antimuscarinics prescribed[a)]	
Fesoterodine	13 (42)
Oxybutynin	10 (32)
Propiverine	18 (58)
Solifenacin	6 (19)
Tolterodine	3 (10)
Trospium	3 (10)
Duration of injury (mo)	47 (32–69)

Values are presented as mean±standard deviation, number (%) or median (interquartile range).
AIS, American Spinal Injury Association (ASIA) impairment scale; CIC, clean intermittent catheterization.
[a)]Sum of frequency (%) may exceed 100% because some patients received more than one antimuscarinic agent.

coxon signed-rank test was used to analyze the change in compliance. The presence of significant leakage during filling cystometry was analyzed using the McNemar test.

RESULTS

Baseline demographics and clinical characteristics of the participants

Between April 1, 2015 and April 1, 2018, 81 patients underwent two consecutive UDSs in our urodynamic unit. Among them, 31 (age 41±15 years; 11 women) were found to be eligible for this study. The demographic characteristics and the clinical information of the participants are presented in Table 1. A total of 22 participants had complete injuries and 9 had incomplete injuries. The neurological level of injury was cervical in 16, thoracic in 14, and lumbar in 1 participant. The median duration of SCI at the first UDS was 47 months (interquartile range, 32–69 months). The etiology of the SCI was traumatic in 25 cases (81%). Other etiologies included vascular, syringomyelia, and tumoral. A total of 20 participants used clean intermittent catheterization for bladder emptying, whereas 8 and 3 had a suprapubic and transurethral indwelling catheter, respectively.

Efficacy

Urodynamic evaluation revealed a significant increase in cystometric capacity (mean, 362 to 424 mL; p=0.03) and reflex volume (mean, 251 to 329 mL; p=0.02) and improvement in bladder compliance (median, 12 to 18 mL/cmH_2O; p=0.04). Moreover, a non-significant decrease in maximal detrusor pressure was noted (mean, 31 to 27 cmH_2O; p=0.39). The presence of leakage during filling cystometry was significantly reduced (29% to 10%; p=0.03). Changes in the UDS parameters before and after long-term mirabegron treatment are presented in Table 2 and Figs. 1, 2.

DISCUSSION

NLUTD is a common sequela of neurological disorders including SCI. It has been reported that over 80% of individuals with SCI experience impaired bladder function, including detrusor overactivity and detrusor sphincter dyssynergia, within 1 year after injury [16]. The high prevalence and severity of NLUTD negatively affect all aspects of the patient's life and the importance of the proper management of NLUTD in the long-term is now being recognized in neurological practice [17]. The goals of management are to prevent urinary tract infection and autonomic dysreflexia, maintain dryness to improve quality of life, and preserve the upper urinary tract by increasing detrusor capacity and lowering intravesical pressure [18].

The current mainstay of pharmacotherapy for NLUTD has focused on antimuscarinic agents for several decades [19]. The primary action of antimuscarinics is to inhibit the effects of acetylcholine at the postganglionic autonomic receptors on detrusor muscle cells, which results in detrusor relaxation, lower intravesical pressure, and

Table 2. Urodynamic results and the number of antimuscarinics prescription of study subjects

	Before mirabegron	After mirabegron	p-value
Cystometric capacity (mL)	362±178	424±124	0.03*
Reflex volume (mL)	251±172	329±158	0.02*
Maximal detrusor pressure (cmH_2O)	31±16	27±21	0.39
Bladder compliance (mL/cmH_2O)	12 (6–23)	18 (12–24)	0.04*
Presence of leakage during filling CMG (%)	9 (29)	3 (10)	0.03*
Number of antimuscarinics prescribed			
0	0 (0)	4 (13)	
1	15 (49)	16 (52)	
2	10 (32)	7 (22)	
3	6 (19)	4 (13)	

Values are presented as mean±standard deviation, median (interquartile range) or number (%).
CMG, cystometry.
*p<0.05.

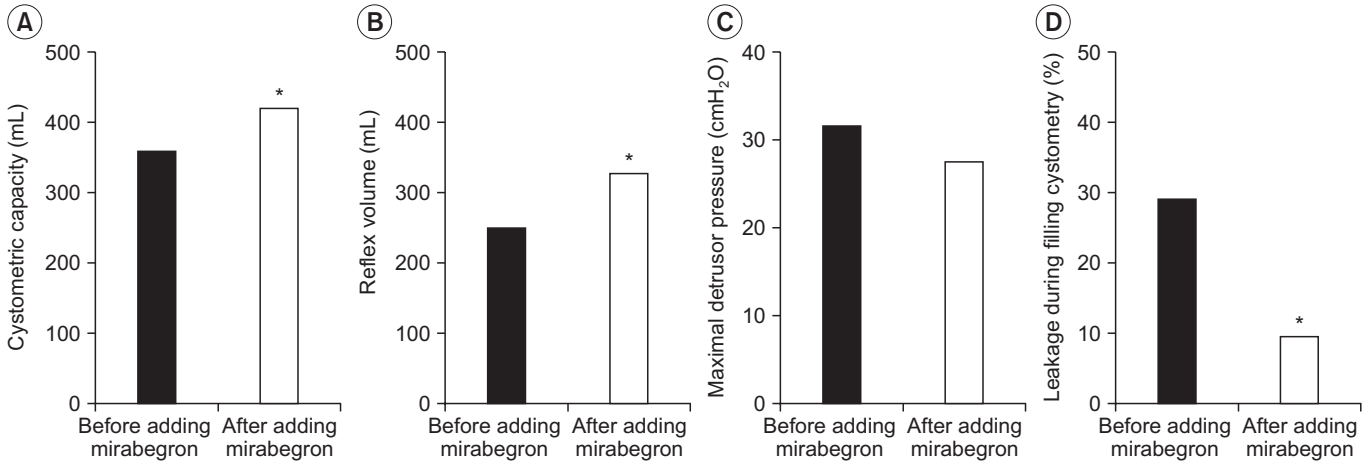

Fig. 1. Changes in cystometric capacity (A), reflex volume (B), maximal detrusor pressure (C), and leakage during filling cystometry (D) in participants before and after adding mirabegron (50 mg a day). *p<0.05.

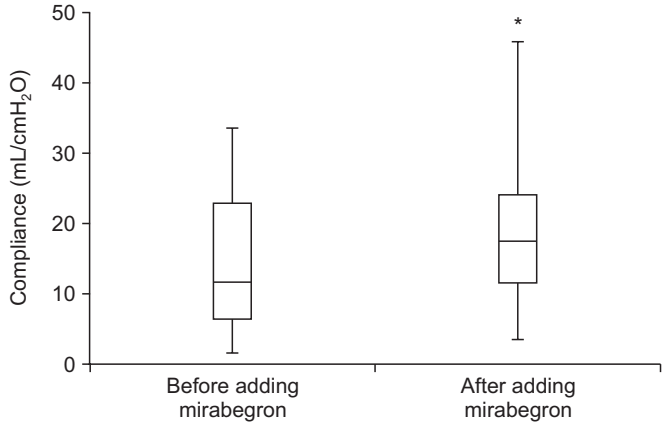

Fig. 2. Box plots of compliance (mL/cmH_2O) in participants before and after adding mirabegron (50 mg a day). *p<0.05.

storage symptoms [4]. These therapies have been proven to ameliorate bladder storage function and improve urodynamic variables in individuals with NLUTD [20]. However, despite their well-established effect, the rate of discontinuation of these drugs is high for several reasons. First, they affect organs outside the lower urinary system, including the gastrointestinal system, eyes, and central nervous system, resulting in adverse events such as dry mouth, constipation, blurred vision, and deterioration of cognition in the elderly [21,22]. Second, antimuscarinics are often administered at higher doses to patients with SCI than to the individuals with overactive bladder (OAB), resulting in more severe side effects and termination of therapy [23].

Mirabegron, a β3-adrenoceptor selective agonist, was recently licensed for the treatment of OAB and is a recognized novel pharmacological compound with a better efficacy/side-effect profile to overcome the limitations of antimuscarinics [24]. Among the three subtypes of β adrenoceptors (β1, β2, and β3) in human detrusor muscle, β3 adrenoceptors account for 97% of total β adrenoceptor mRNA [25], and activation of β3 adrenoceptors elicits detrusor relaxation [24]. Therefore, it is hypothesized that mirabegron could increase bladder capacity without causing antimuscarinic side effects and is expected to play a vital role in the management of NLUTD in patients with SCI. Maman et al. [6] reported that mirabegron at a dose of 50 mg had a similar efficacy to that of antimuscarinics, with a lower incidence of dry mouth and constipation in individuals with OAB.

The urodynamic effects of antimuscarinic agents in OAB and NLUTD have been well documented in previous studies [26], but the clinical experience and evidence of mirabegron efficacy as demonstrated by UDS are still inadequate. Matsukawa et al. [27] and Vecchioli Scaldazza and Morosetti [28] reported a significant increase in cystometric capacity by an average of 37 mL and 41 mL, respectively, in women with OAB who received mirabegron 50 mg once a day for 12 weeks. In a study involving men with OAB, mirabegron add-on therapy with tamsulosin significantly increased cystometric capacity (by 24%, from 170 to 212 mL) [29]. Wollner et al. [7] conducted a retrospective study by including 12 people with SCI who took mirabegron for at least 6 weeks and observed im-

provements in urodynamic variables: cystometric capacity (+54 mL), bladder compliance (+17 mL/cmH_2O), and maximal detrusor pressure (−16 cmH_2O). Krhut et al. [30] examined 66 people with SCI or multiple sclerosis who were randomized to mirabegron 50 mg once a day group and placebo. After 4 weeks, the change from baseline in cystometric capacity and compliance was +55 mL and +24 mL/cmH_2O, respectively.

Theoretically, mirabegron add-on therapy to conventional antimuscarinic therapy may increase efficacy compared to the sole increase in the dosage of antimuscarinics and possibly reduce antimuscarinic burden because they block completely different bladder receptors, and mirabegron does not affect muscarinic receptors outside the lower urinary system. In our treatment concept, we added mirabegron to pre-existing anticholinergics for patients who had been refractory to maximally tolerated anticholinergic therapy and considered lowering the number or dose of pre-existing anticholinergics, especially for patients who experienced antimuscarinic side effects through outpatient clinic visit. As a result, the subjects showed a significant increase in cystometric capacity, reflex volume, and bladder compliance. The presence of leakage during filling cystometry was significantly reduced. Although maximal detrusor pressure also decreased after adding mirabegron, the difference was not significant. In addition, the number of antimuscarinics prescribed showed a decreased tendency (Table 2). The recorded antimuscarinic side effects were dry mouth (n=5, 16%) and constipation (n=2, 6%). The lessening of antimuscarinic burden was noted in these patients and no antimuscarinic adverse effects were observed after adding mirabegron.

The present study has several limitations. Because of the retrospective design of the study, data regarding adverse events or adherence/persistence were unavailable. For the further clinical application of long-term mirabegron add-on therapy, studies on side-effect profiles and adherence to multidrug therapy are required. The heterogeneity of composition of antimuscarinics also pertains to the limitations of the present study. However, it was inevitable in the long-term clinical situation to further increase efficacy, while keeping the side effects profile low. Furthermore, this study is limited by the relatively small sample size. Although mirabegron has emerged as an alternative to overcome the limitations of antimuscarinic agents, the most widely prescribed medications as first-line therapy are antimuscarinics according to international guidelines, and many people still benefit from them. The relatively high cost and concerns about cardiac side effects may also restrict the use of mirabegron. Our results suggest that mirabegron should be considered as a complement and not as a substitute for conventional therapy. Further factors which may contribute, in part, to the treatment effect such as muscle relaxants, concomitant medication, smoking, and alcohol use should be considered in future studies.

In conclusion, in patients with SCI and NLUTD, who had previously been exposed to antimuscarinic therapy, adding a long-term β3 adrenoceptor selective agonist provided urodynamic improvements in efficacy compared with previous therapies. Compared to previous studies, our study demonstrated the persistence of mirabegron efficacy for more than 6 months and the superiority of add-on therapy with mirabegron over conventional antimuscarinic therapy in patients with chronic SCI, based on UDS. We anticipate that the results of this study would provide the basis for further well-designed prospective trials with mirabegron and may help patients with NLUTD.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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