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ORIGINAL ARTICLE

Efficacy and safety of mirabegron, a β3-adrenoceptor agonist, for treating neurogenic bladder in pediatric patients with spina bifida: a retrospective pilot study

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Abstract

Purpose Antimuscarinics are the first pharmacological treatment option for neurogenic bladder in children with spina bifida but side effects limit their use. Mirabegron, a new β-3 adrenoceptor agonist with a distinct mechanism of action, is a potential agent for the treatment of neurogenic bladder; however, it has yet to be studied in the pediatric population. This study evaluated the efficacy and safety of mirabegron for treating neurogenic bladder in children with spina bifida.

Materials and methods Clinical and urodynamic parameters were retrospectively studied in 66 children (under 18 years of age) with spina bifida who were treated for neurogenic bladder with mirabegron at Severance Children's Hospital between July 2015 and December 2017. Pediatric patients received 50 mg mirabegron daily for at least 6 weeks either in addition to or instead of antimuscarinic therapy. Urodynamic parameters, including compliance, involuntary detrusor contraction, and maximum cystometric capacity, as well as patient-reported efficacy and adverse events, were measured.

Results In both groups post-treatment, incontinence significantly improved. In addition, maximum cystometric capacity and compliance significantly increased post-treatment. Six patients reported side effects (constipation, 4.5%; headache, 3.0%; and hypertension, 1.5%) and three patients discontinued treatment.

Conclusion We evaluated the efficacy and safety of mirabegron for treating neurogenic bladder in pediatric patients with spina bifida. All clinical and urodynamic parameters improved with treatment. Prospective, placebo-controlled studies are necessary to confirm these findings.

Keywords Mirabegron · β3-Adrenoceptor agonist · Spina bifida · Neurogenic detrusor overactivity

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Introduction

Spina bifida, one of the most common birth defects, has an incidence of 0.3–4.5 per 1000 births worldwide [1, 2]. Most children with spina bifida have major urological problems that disrupt voluntary control of bladder and bowel function, resulting in impaired quality of life [3]. Over the years, studies in pediatric patients with spina bifida have identified renal scarring and renal failure as important issues. According to current recommendations, to prevent renal damage, clinicians should begin treatment of a neurogenic bladder immediately after birth by lowering bladder pressure [2, 4]. Antimuscarinic therapy, which is the first pharmaceutical treatment, has both short- and long-term effects on the pediatric neurogenic bladder but the compliance of treatment is poor due to its adverse side effects [5].

One potential therapy for this condition is mirabegron, a β3-adrenoceptor (β3-AR) agonist. It is the first of a new class

of compounds with a distinct mechanism of action: targeting adrenergic transmission [6]. Mirabegron is approved for treating overactive bladder (OAB) symptoms in adults [6]. However, only two studies have evaluated mirabegron for treating neurogenic bladder symptoms [7, 8]. Wollner et al. demonstrated the effectiveness of mirabegron for neurogenic detrusor overactivity due to spinal cord injury in adults [7]. To date, its efficacy in pediatric patients with neurogenic bladder has not been studied. Mirabegron was tested in one pediatric study by Blais et al. that reported the efficacy and safety of the drug in children with OAB [9].

Although antimuscarinic therapy is currently the mainstay of medical management for pediatric neurogenic bladder, mirabegron could be an effective treatment option in children with neurogenic bladder, as shown in adult populations. Our study considered mirabegron as an additional treatment option for managing neurogenic bladder via the adrenergic pathway in children with spina bifida. Therefore, the objective of our study was to evaluate the efficacy and safety of mirabegron for treating neurogenic bladder in children with spina bifida.

Materials and methods

A total of 66 patients with spina bifida under 18 years of age were treated for neurogenic bladder with mirabegron for at least 6 weeks between July 2015 and December 2017 at our institution. The following data were recorded and retrospectively evaluated: demographics, mode of bladder management, and previous neurogenic bladder therapy, as well as voiding cystourethrogram and urodynamic parameters before and after treatment. All patients were evaluated regularly throughout the follow-up period, including blood pressure assessments, urine analysis, therapy effectiveness, and any side effects. Patients with a previous bladder operation, botulinum toxin injection [10], or intravesical electrical stimulation [11] were excluded from this study. Primary outcome of this study is to demonstrate the therapeutic effect of mirabegron which could be objectively shown by the voiding cystourethrogram and urodynamic parameters. Secondary outcome of this study is to demonstrate the therapeutic effect on incontinence and side effects of the therapy. The study design and protocols were approved by the Institutional Review Board.

Pediatric patients included in this study were previously prescribed trospium chloride, propiverine, solifenacin, or oxybutynin. If side effects or a lack of efficacy were observed with one of these medications, mirabegron was prescribed. For those with side effects and no efficacy on trospium chloride, propiverine, solifenacin, or oxybutynin, mirabegron monotherapy was used. For those with partial responses to trospium chloride, propiverine, solifenacin, or oxybutynin, antimuscarinic plus mirabegron combination therapy was used. All patients received mirabegron 50 mg once daily. Only children that could swallow the mirabegron pill whole were included in this study. These patients could be divided into two groups: group 1 ($n=30$) took mirabegron in addition to antimuscarinic therapy; group 2 ($n=36$) stopped antimuscarinic therapy and initiated mirabegron.

The urodynamic investigation was conducted according to the International Children's Continence Society (ICCS) guidelines [12] and any patients with symptomatic urinary tract infections were excluded before urodynamic study (UDS). UDS was performed with Duet Logic G2 (Medi-watch, Rugby, UK). We used 6-Fr double-lumen catheters for the urethra and 12-Fr fluid-filled balloon catheters for the rectum. A saline solution was warmed to body temperature and mixed with a contrast medium for infusion at filling rates of 5–10% of a known or predicted capacity (mL/min). Patients had a bowel clean-out before the UDS. Procedure was performed by two experienced nurse practitioners. Interpretation was done by two experienced pediatric urologists. To consider the effect of intervals between UDS, we calculated age-adjusted maximum cystometric capacity (MCC) using measured MCC divided by the expected bladder capacity for age ($30\times$[age in years + 1] ml) [12]. This formula is useful up to age 12 years, after which age-expected bladder capacity is maintained at 390 ml. Clean intermittent catheterization (CIC) was performed in 47 (71.2%) patients. Those not undergoing CIC, parents or patients rated subjective incontinence symptom relief following the ICCS classification [12]. They reported efficacy as complete cure (defined as complete dryness), improvement (at least 90% reduction in incontinence episodes), partial improvement (50–89% reduction), or failure (< 50% reduction) [9, 12]. For patients undergoing CIC, incontinence reported during interval between regular CIC was assessed.

The statistical analysis was performed with SPSS software version 24.0 (IBM Corp., Armonk, NY, USA). Ordinal and continuous data are expressed as the medians with interquartile ranges (IQRs). The Kolmogorov–Smirnov test was used to test the normal distribution. Differences were assessed using the *t* test and Wilcoxon sign-ranked test for continuous variables and the Chi square test or Fisher's exact test for categorical variables. A p value less than 0.05 was considered statistically significant and all tests were two sided.

Results

A total of 66 patients (42 boys, 24 girls) with neurogenic bladder due to spina bifida were treated with mirabegron for at least 6 weeks. The patient characteristics are listed in Table 1. The median age at initiation of mirabegron was

Table 1 Patient characteristics

Patients	
Male, *n*	42
Female, *n*	24
Type of spinal lesion	
MMC, *n* (%)	21 (31.8%)
LMMC, *n* (%)	41 (62.1%)
Sacral agenesis, *n* (%)	4 (6.1%)
Age at UDS	
Pre-mirabegron treatment, years	10.0 (6.0–14.0)[a]
Post-mirabegron treatment, years	12.0 (8.0–15.0)[a]
Duration of mirabegron treatment before post-treatment UDS, mo	10.0 (5.0–16.0)[a]
Interval of UDSs, mo	13.5 (7.8–24.3)[a]

LMMC lipomeningocele, *MMC* myelomeningocele, *UDS* urodynamic study, *VUR* vesicoureteral reflux

[a]Data presented as the medians (interquartile range)

11.0 years (IQR 7.8–14.0 years). The median duration of treatment with mirabegron before post-treatment UDS was 10 months (IQR 5.0–16.0 months).

Urodynamic results

Urodynamic data are reported in Table 2. Compliance was significantly increased after the addition of or change to mirabegron. Involuntary detrusor contraction (IDC) was significantly decreased in the group 1 post-treatment; however, for the group 2, although the frequency of IDC was decreased, this change was not significant. Furthermore, in both groups, significant increases in measured MCC and age-compensated MCC were observed post-treatment. Although the frequency of vesicoureteral reflux (VUR) was decreased in both groups post-treatment, this change was not significant.

Clinical results

The efficacy of mirabegron was defined as parent- or patient-reported incontinence relief. Among 62 patients (93.9%) that were incontinent at enrollment, after the post-treatment, 23 patients (37.1%) experienced complete dryness; 11 patients (17.7%), > 90% reduction in incontinence episodes; and 16 patients (25.8%), 50–89% reduction in episodes. Failure (< 50% reduction in episodes) occurred in 12 patients (19.4%).

Most of the patients (90.9%) reported no side effects. The exception was a subgroup of six patients (9.1%) who described the following side effects: constipation (4.5%), headache (3.0%), and hypertension (1.5%). Among those who reported side effects, three patients (those who reported headache and hypertension) discontinued the treatment.

Discussion

Our study demonstrated significant improvements in clinical and urodynamic data when treating neurogenic bladder with mirabegron in pediatric patients with spina bifida. To the best of our knowledge, this is the first study to report the efficacy and safety of mirabegron in pediatric patients with neurogenic bladder due to spina bifida using urodynamic parameters (including compliance, IDC, and MCC). Our study showed significant improvements in MCC and compliance for both groups. Furthermore, measured MCC and age-adjusted MCC increased after the addition of or change to mirabegron. The improvement in compliance and MCC

Table 2 Changes in urodynamic parameters after mirabegron add-on therapy ($n = 30$) or after substituting antimuscarinic therapy for mirabegron ($n = 36$)

	Mirabegron add-on therapy ($n = 30$)			Substitution for mirabegron therapy ($n = 36$)		
	Antimuscarinic Tx	Antimuscarinic + mirabegron Tx	*p* value[a]	Antimuscarinic Tx	Mirabegron Tx	*p* value[a]
Age at evaluation, years	9.0 (6.0–12.3)[c]	11.0 (7.8–14.0)[c]	< 0.001	11.0 (6.0–14.8)[c]	12.5 (9.0–15.0)[c]	< 0.001
Measured MCC, ml	242.0 (175.8–318.0)[c]	333.5 (287.5–432.5)[c]	< 0.001	180.5 (151.0–286.3)[c]	300.5 (232.0–388.3)[c]	< 0.001
Age-adjusted MCC[b], ml	0.9 (0.6–1.0)[c]	1.1 (0.8–1.3)[c]	0.001	0.6 (0.4–0.9)[c]	0.8 (0.6–1.1)[c]	0.001
Compliance, ml/cm H_2O	10.5 (7.1–26.7)[c]	32.4 (18.1–43.3)[c]	0.001	8.7 (5.6–17.3)[c]	20.3 (11.3–41.5)[c]	< 0.001
IDC (%)	11 (36.7%)	4 (13.3%)	0.037	13 (36.1%)	10 (27.8%)	0.448
VUR (%)	3 (10.0%)	1 (3.3%)	0.612	5 (13.9%)	3 (8.3%)	0.710

IDC involuntary detrusor contraction, *MCC* maximum cystometric capacity, *Tx* treatment, *VUR* vesicoureteral reflux

[a]Differences assessed using the Wilcoxon sign-ranked test for continuous variables and Chi square test or Fisher's exact test for categorical variables

[b]Age-adjusted MCC = measured MCC/(age in years + 1) × 30 ml

[c]Data presented as the medians (interquartile range)

is crucial for protecting the upper urinary tract. According to the current European Association of Urology guidelines, antimuscarinics are the first pharmaceutical line of treatment for neurogenic bladder in children with spina bifida [4, 13]. However, patient compliance of antimuscarinic treatment is poor, with a high discontinuation rate due to its associated side effects [14]. A meta-analysis of adverse events by antimuscarinics reported that as many as 40% of patients may discontinue antimuscarinic treatment due to adverse events [14]. Among these adverse events, gastrointestinal side effects, including dry mouth, dry throat, and constipation, were most frequently reported [14].

β3-AR agonists, a new class of compounds with a distinct mechanism, significantly innovated OAB treatment [8]. β3-AR is the predominant subtype in the bladder, representing 97% of total β-AR mRNA expression in the human bladder. β3-AR agonists relax the detrusor muscle, allowing for increased bladder capacity without disturbing micturition pressure, residual volume, or voiding contraction [15–18] Several phase 2 and 3 studies reported that clinical OAB symptoms significantly improved in adults treated with mirabegron [19–22] leading to its worldwide approval for the treatment of OAB in adults [23]. However, only a single study demonstrated the effect of mirabegron in children, showing promise for treating urinary incontinence in children with OAB [9]. In this study by Blais et al., a total of 58 patients with a median age of 10.1 years were recruited and received mirabegron at a median daily dose of 1.00 mg/kg for a median duration of 11.5 months. Mirabegron improved continence in 89.7% of patients and the median bladder capacity rose from 150 to 200 ml. In addition, no side effects were reported in 86% of patients and mild side effects were described in 9% (transient abdominal colic, 3.4%; constipation, 3.4%; and blurred vision, 1.7%). However, 5% of patients discontinued the treatment due to significant nasopharyngitis (1.7%), nausea (1.7%), and behavior change (1.7%), which were not observed in our study [9].

To date, only two studies have investigated the effects of mirabegron in patients with neurogenic bladder [7, 8]. Both studies reported reductions in incontinence episodes and improvements in urodynamic parameters [7, 8]. Wada et al. added mirabegron in cases where antimuscarinic therapy was insufficient to reduce neurogenic detrusor overactivity [8]. By contrast, Wollner et al. stopped antimuscarinic therapy and then initiated mirabegron [7]. Whereas these two studies studied adults, our study reported the effects of mirabegron for treating neurogenic bladder in children. Moreover, we demonstrated that both methods of mirabegron treatment, in addition to or instead of antimuscarinic therapy, were effective for neurogenic bladder treatment.

Similar to previous studies, our data showed significant improvements in MCC and compliance for both groups. Furthermore, measured MCC and age-adjusted MCC increased after the addition of or change to mirabegron. Although group 1 patients who added mirabegron in addition to antimuscarinic therapy showed more pronounced differences (mean difference in pre- and post-treatment UDS measured MCC: 114.6 ml; mean difference in pre- and post-treatment UDS age-adjusted MCC: 0.20 ml) than group 2 patients who stopped antimuscarinic therapy and initiated mirabegron (mean difference in pre- and post-treatment UDS measured MCC: 85.7 ml; mean difference in pre- and post-treatment UDS age-adjusted MCC: 0.18 ml), these differences were not statistically significant (measured MCC $p = 0.214$; age-adjusted MCC $p = 0.738$). For compliance, group 2 patients showed larger increases (mean difference in pre- and post-treatment UDS compliance: 17.0 ml/cm H_2O) than group 1 patients (mean difference in pre- and post-treatment UDS compliance: 17.0 ml/cm H_2O); however, this difference was also not significant ($p = 0.607$). Although some authors have reported synergistic effects of a combination of mirabegron and antimuscarinic therapy for treating OAB [22], our study did not show any synergistic effects. In addition, there were no differences in urodynamic parameters according to the different types of antimuscarinic used in addition to mirabegron. Furthermore, significant decreases in IDC were observed in the group 1 patients.

The reason for these different results is probably due to the different mechanisms of action of the two drugs mediating detrusor relaxation via different intracellular pathway [24]. Antimuscarinics decrease the activity of afferent nerve which inhibits urothelially released acetylcholine and autonomous bladder contractions generated by both neuronal and non-neuronal sources. On the other hand, mirabegron inhibits Aδ and C-fiber activity during filling as well as autonomous contractile activity [7, 24]. Theoretically, since the two drugs have different mechanisms, the combination of antimuscarinic with mirabegron would sufficiently relax the bladder. However, similar to our study, previous combination treatment studies do not appear to be overwhelming, suggesting that the different mechanism of action may not be clearly complimentary [25]. Our results also showed similar findings that synergistic effects of two drugs have resulted in more increased bladder capacity of mirabegron-added group that changed to mirabegron although it was not significantly different and this suggests possible plateau of combination effect of two drugs on nerve activity. However, for compliance, mirabegron monotherapy seems to be more beneficial according to our results. The one possible explanation could be drug–drug interaction; however, the clear mechanism is unknown.

Regarding side effects, we did not observe severe side effects in this study. The most commonly reported side effect was constipation. Only one patient exhibited hypertension after taking mirabegron. This patient had elevated blood

pressure of 10–15 mmHg. This patient did not have underlying chronic kidney disease or cardiac disease that could be associated with high blood pressure. Since we have not fully evaluated the cause of elevated blood pressure, we do not know the exact cause of the elevated blood pressure. The blood pressure of this patient have been returned to normal after discontinuation of mirabegron monotherapy. Due to the limitations of a retrospective study, the exact values for blood pressure and heart rate were not recorded when they were within the normal range. These values were only recorded when the patient exhibited hypertension. A previous study demonstrated that side effects commonly reported with antimuscarinics—including headache, dry mouth, and constipation—were observed no more often with mirabegron than with a placebo [21]. However, the potential interaction of mirabegron with β receptors in the intestine should be considered and may possibly explain the three patients who reported constipation in our study. In a phase 3 trial by Nitti et al., the three most commonly reported side effects of mirabegron were hypertension, nasopharyngitis, and urinary tract infection [26]. In addition, Blais et al. reported no significant increase in heart rate and blood pressure in pediatric patients; however, they reported that mirabegron increases mean heart rate and blood pressure of 1 beat/min and 0.4–0.6 mmHg and this small change would not have affected the patients enough to reach the range indicating hypertension [8].

The primary limitations of this study are its retrospective design and small sample size. However, even with these limitations, significant clinical and urodynamic improvements were observed. Therefore, we believe that mirabegron may be a therapeutic option for pediatric patients with neurogenic bladder due to spina bifida. Prospective randomized studies are required to investigate the efficacy and safety of this therapy in these patients. Moreover, the dose of mirabegron administered in our study was 50 mg because 25 mg mirabegron pills were unavailable in our country. Mirabegron must be swallowed whole and should not be chewed, divided, or crushed and, therefore, its usage is limited. Clinical trials are now underway to demonstrate the efficacy of syrup-based liquids and these results may be especially helpful for this pediatric population.

Conclusion

Our study supports mirabegron as an alternative treatment option in pediatric patients with neurogenic bladder due to spina bifida. Mirabegron treatment for at least 6 weeks improved clinical and urodynamic parameters of neurogenic bladder, with minimal side effects. Following the drug's recent approval for treating OAB in the adult population, future prospective studies are needed to confirm its efficacy and safety in children.

Author contributions PJS: protocol/project development, data collection or management, data analysis, manuscript writing/editing. LYS: protocol/project development, manuscript editing. LCN: data collection or management. KSH: data collection or management. KSW: protocol/project development, manuscript editing. HSW: protocol/project development, manuscript editing.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest pertaining to this study.

Ethical approval All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent The Institutional Review Board of Yonsei University College of Medicine waived the requirement of obtaining informed consent because this study retrospectively reviewed anonymous patient data and did not involve a patient intervention or the use of human tissue samples.

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