



Efficacy and tolerability of mirabegron compared with solifenacin for children with idiopathic overactive bladder: A preliminary study

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Purpose: To compare the efficacy and tolerability of mirabegron and solifenacin in pediatric patients with idiopathic overactive bladder (OAB) and to identify factors affecting OAB symptom improvement after treatment.

Materials and Methods: We retrospectively reviewed 103 patients (5–15 years old) who visited our hospital with OAB symptoms between July 2017 and March 2019. All participants had received solifenacin or mirabegron. Those who had secondary OAB or who did not complete the frequency-volume chart either before or after treatment were excluded. The age-adjusted bladder capacity ratio was used to evaluate bladder capacity. Efficacy was assessed on the basis of patient reports and changes in the frequency-volume chart, and $\geq 90\%$ reduction was regarded as “responding to medication.” Tolerability was assessed by obtaining reports from patients about the adverse effects of the drug.

Results: After the exclusion of 58 patients, 45 patients (29 in solifenacin-group and 16 in mirabegron-group) were included in the primary analysis. The age-adjusted bladder capacity ratio increased from 0.71 to 0.96 ($p < 0.001$) and from 0.57 to 0.97 ($p = 0.002$) after solifenacin and mirabegron use, respectively. Decreased bladder capacity before medication was associated with responding to medication (odds ratio, 7.41; $p = 0.044$). There was no significant difference in efficacy between the two drugs. Drug-induced adverse effects were reported in only 3 (10.3%) of the solifenacin-treated patients.

Conclusions: Mirabegron showed comparable efficacy to solifenacin in pediatric patients with idiopathic OAB. Additionally, only few adverse effects were reported, suggesting that mirabegron can be a safe alternative for the treatment of idiopathic pediatric OAB.

Keywords: Child; Enuresis; Urinary bladder, overactive

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INTRODUCTION

Overactive bladder (OAB) is a common symptom in pediatric patients, with an overall prevalence of less than 17% [1-3]. Pediatric OAB patients must be managed aggressively

because OAB affects health-related quality of life [4]. Treatment includes urotherapy and pharmacotherapy, and anti-muscarinics are the first pharmaceutical option [5]. However, these drugs have a poor response rate and cause adverse effects, such as dry mouth, constipation, and urinary reten-

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tion. In addition, prolonged use of antimuscarinics can lead to adverse effects on the central nervous system, such as cognitive and memory dysfunction. Therefore, most parents reject the use of these drugs, causing the majority of pediatric OAB patients to discontinue antimuscarinic use [6,7].

Mirabegron, a β_3 -adrenoreceptor agonist, is a new drug for controlling OAB symptoms. It has been used as an alternative to antimuscarinics in patients with OAB because it increases bladder capacity without impairing detrusor contractility [8]. Studies comparing mirabegron with antimuscarinics in adults with OAB have shown that mirabegron has similar efficacy to antimuscarinics but has better tolerability [9,10]. However, only a few studies have investigated these properties in pediatric OAB patients; therefore, mirabegron is currently not licensed for pediatric use [11-13]. Hence, the primary objective of this study was to compare the efficacies of mirabegron and solifenacin in pediatric OAB patients. The secondary objectives were to evaluate mirabegron tolerability and identify factors contributing to symptom improvement in pediatric OAB patients after treatment.

MATERIALS AND METHODS

This was a retrospective observational study approved by Institutional Review Board of the Ulsan University Hospital (approval number: UUH 2020-03-010), which waived the need for informed consent. We reviewed 103 pediatric patients, aged between 5 and 15 years, who visited Ulsan University Hospital with OAB symptoms from July 2017 to March 2019. OAB was diagnosed on the basis of what patients and/or parents described. Inclusion criteria were having taken an OAB medicine (solifenacin 5 mg or mirabegron 50 mg) and having completed a frequency-volume chart (FVC) both before and after medication use. Exclusion criteria included secondary OAB, lack of a complete FVC either before or after medication use, and loss to follow-up. We evaluated age, sex, medication (solifenacin 5 mg, mirabegron 50 mg), previous history of antimuscarinic use, incontinence, nocturnal enuresis, duration of symptoms, duration of medication, medication adverse effects, and FVC factors (maximal voided volume [MVV], maximal voided volume during daytime [MVVDT]). To overcome the age-dependent change in bladder capacity, the change was expressed as an age-adjusted bladder capacity ratio (aBCR) by using measured actual bladder capacity (MVV and $1.25 \times \text{MVVDT}$) divided by the expected bladder capacity (eBC) for age. The eBC was calculated by using the following formula: "bladder capacity (mL) = (age + 1) \times 30" [14]. Children with a BCR < 0.65 were considered to have decreased bladder capacity [15].

Efficacy was assessed by reports from patients and/or parents and by changes in the aBCR as estimated from FVCs. To evaluate OAB symptom relief, patients and parents reported efficacy as complete dryness, improvement (90%–99% reduction), partial improvement (50%–89% reduction), or failure ($< 50\%$ reduction). A reduction of more than 90% was regarded as "responding to medication" [15]. Tolerability was also assessed by obtaining reports from patients and parents about drug adverse effects. Adverse effects were described by using the common terminology criteria for adverse events (CTCAE), version 5.0.

We hypothesized that, as in adults, mirabegron would have similar efficacy but fewer adverse effects than solifenacin in pediatric OAB patients. Wilcoxon's signed-rank test was used to compare matched variables before and after treatment. Continuous variables were presented as medians with interquartile ranges (IQRs) and categorical variables as frequencies with percentages. The chi-square test or Fisher's exact test was used to evaluate differences in the categorical variables, and the independent t-test was used to compare the means of continuous variables. Pearson's correlation coefficient and linear regression analysis were used to calculate correlations between baseline aBCR and the rate of change after medication. Multivariate binary logistic regression analysis was used to assess the factors affecting medication response. Kaplan–Meier analysis was performed to compare drug maintenance according to medications, and the Cox proportional hazards method was used to determine predictive factors for medication discontinuation. A $p < 0.05$ indicated statistical significance. SPSS version 25.0.0 (IBM Corp., Armonk, NY, USA) was used.

RESULTS

1. Patient characteristics

A total of 103 patients were enrolled, of whom 58 were excluded because 38 were patients with secondary OAB, 14 did not have an FVC before or after medication, and 6 were lost to follow-up (Fig. 1). The remaining 45 patients were included in the primary analysis. The median age at first visit was 7.1 years (IQR: 6.0–9.4) and 22 (48.9%) of the patients were male. Twenty-nine patients were enrolled in the solifenacin group and 16 in the mirabegron group. The patients in the mirabegron group were older, had a longer duration of symptoms, and had a lower aBCR before starting medication than did the patients in the solifenacin group (Table 1).

2. Clinical outcomes

After solifenacin treatment, the aBCR obtained by using

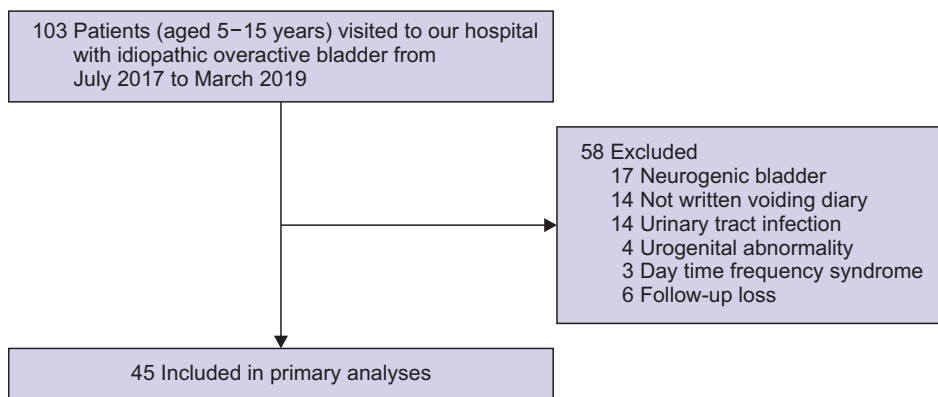


Fig. 1. Overview of the study population.

Table 1. Patient characteristics

Variable	Solifenacin 5 mg (n=29)	Mirabegron 50 mg (n=16)	p-value
Age (y)			
Median	6.6	9.8	
Range	5.0–14.7	5.6–12.3	
IQR	5.6–7.1	8.3–11.0	
Sex, male (%)	41.4	62.5	0.175
Previous drug history, n (%)	5 (17.2)	2 (12.5)	>0.999 ^a
Incontinence, n (%)	12 (41.4)	3 (18.8)	0.105
Nocturnal enuresis, n (%)	19 (65.5)	16 (100.0)	0.008 ^a
Duration of symptom (mo)			0.005
Median	6.0	12.0	
Range	1.0–18.0	1.0–36.0	
IQR	6.0–12.0	12.0–24.0	
Duration of medication (d)			0.570
Median	193	239	
Range	30–772	72–466	
IQR	158–351	114–328	
Frequency			0.261
Median	7	6	
Range	4–15	4.5–10	
IQR	5.5–8.5	5–7.5	
aBCR (MVV/eBC)			0.015
Median	0.60	0.56	
Range	0.37–1.43	0.27–0.76	
IQR	0.52–0.82	0.44–0.64	
Decreased bladder capacity, n (%)	15 (51.7)	13 (81.3)	0.051
aBCR (1.25×MVVDT/eBC)			0.072
Median	0.66	0.55	
Range	0.11–1.46	0.29–0.95	
IQR	0.57–0.95	0.49–0.69	
Decreased bladder capacity, n (%)	13 (44.8)	12 (75.0)	0.051

IQR, interquartile range; aBCR, age-adjusted bladder capacity ratio; MVV, maximal voided volume; eBC, expected bladder capacity by using age; MVVDT, maximal voided volume during daytime.

^a:Fisher’s exact test.

both MVV and MVVDT improved significantly from 0.68 to 0.87 (MVV, p<0.001) and from 0.71 to 0.96 (MVVDT, p<0.001), respectively (Fig. 2A, B). The proportion of patients with

decreased bladder capacity was also reduced from 51.7% to 24.1% and from 44.8% to 13.8%, respectively (Supplementary Table 1). Similar to solifenacin, mirabegron improved aBCR

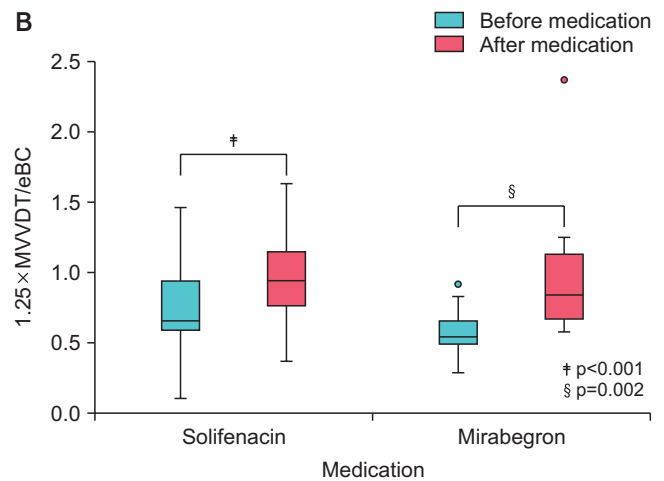
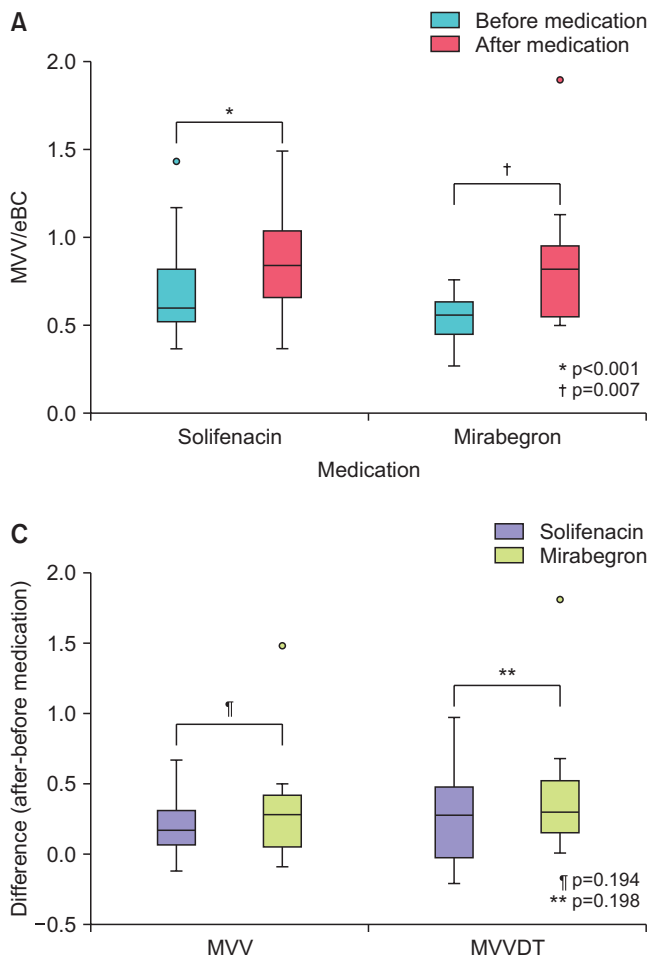


Fig. 2. Differences in bladder capacity before and after treatment according to drug used. The aBCR uses (A) MVV or (B) MVVDT divided by eBC. (C) Changes in aBCRs obtained using both MVV and MVVDT before and after medication between two drugs. aBCR, age-adjusted bladder capacity ratio; MVV, maximal voided volume; MVVDT, maximal voided volume during daytime; eBC, expected bladder capacity by using age.

(MVV and MVVDT) from 0.54 to 0.83 (MVV, $p=0.007$) and from 0.57 to 0.97 (MVVDT, $p=0.002$) and reduced the proportion of patients with decreased bladder capacity from 81.3% to 31.3% and from 75.0% to 18.8%, respectively (Fig. 2A, B, and Supplementary Table 1). However, the changes in aBCR obtained by using MVV and MVVDT before and after treatment did not differ significantly between the solifenacin and mirabegron groups (MVV: 0.19 ± 0.19 vs. 0.30 ± 0.37 , $p=0.194$; MVVDT: 0.25 ± 0.31 vs. 0.40 ± 0.42 , $p=0.198$) (Fig. 2C). Fig. 3 represents a scatter plot of the aBCR (MVVDT/eBC) change rate before and after treatment versus baseline aBCR (MVVDT/eBC), showing a moderate negative correlation ($r=-0.578$). Linear regression analysis was carried out using the following formula: $Y=-1.69X+2.73$ (Y =rate of change in aBCR after medication, X =baseline $1.25 \times MVVDT/eBC$, $r^2=0.334$, $p<0.001$).

Assessment of symptom relief revealed that incontinence improved in all patients in both treatment groups. Urgency and nocturnal enuresis also improved in both groups, but there was no significant difference in the response to medication between solifenacin 5 mg and mirabegron 50 mg (69.0% vs. 81.3%, $p=0.491$, and 63.2% vs. 87.5%, $p=0.233$)

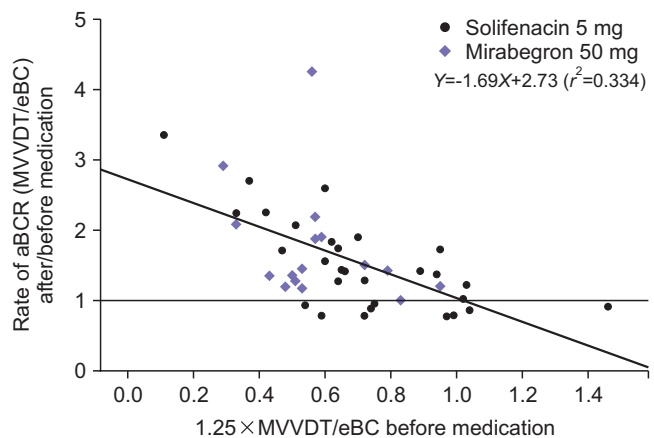


Fig. 3. Correlation between baseline aBCR (MVVDT/eBC) and change rate after treatment. aBCR, age-adjusted bladder capacity ratio; MVVDT, maximal voided volume during daytime; eBC, expected bladder capacity by using age.

(Supplementary Table 2). Multivariate binary logistic regression analysis showed that decreased bladder capacity before treatment was associated with improvement in OAB symptoms after medication (odds ratio [OR], 7.41; 95% confidence interval [CI], 1.05–52.18; $p=0.044$) (Table 2).

Table 2. Results of multivariate binary logistic regression analysis for determining factors associated with improvement in OAB symptoms after medication

Variable	OR	95% CI	p-value
Decreased bladder capacity Yes vs. no	7.41	1.05–52.18	0.044
Medication Mirabegron vs. solifenacin	0.20	0.01–3.17	0.251
Sex Female vs. male	0.41	0.08–2.13	0.287
Age Continuous variable	0.82	0.45–1.51	0.523
Duration of medication Continuous variable	0.99	0.99–1.01	0.385
Duration of symptom Continuous variable	1.07	0.95–1.20	0.270

OAB, overactive bladder; OR, odds ratio; CI, confidence interval.

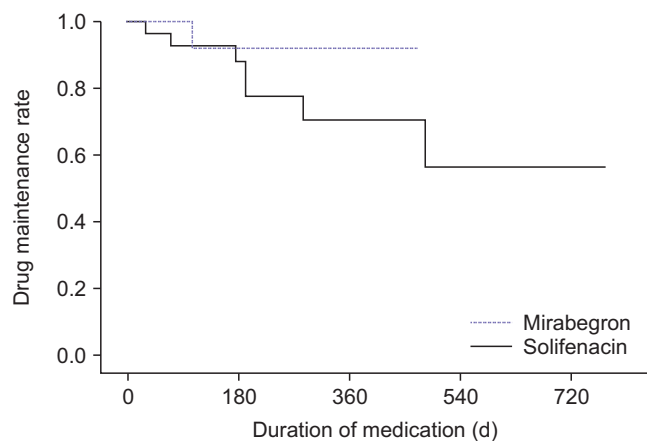


Fig. 4. Kaplan–Meier analysis of the relationship between drug maintenance and medications (solifenacin vs. mirabegron).

Drug-induced adverse effects were reported in only three patients (10.3%) in the solifenacin group. These three patients reported adverse effects of CTCAE grade 2 (abdominal cramps in 1, anorexia in 1, and nausea in 1). There were no cases of hypertension, hypotension, or voiding difficulty. The medication (mirabegron vs. solifenacin) did not make a significant difference in drug maintenance, which was 92.3% and 88.1% at 6 months after treatment, respectively (OR, 0.30; 95% CI, 0.04–2.48; $p=0.263$) (Fig. 4).

DISCUSSION

Antimuscarinic agents have been used as first-line treatment for idiopathic OAB; however, because of their short- and long-term adverse effects, new alternatives have been investigated [16]. Mirabegron, an alternative to antimuscarinics, has comparable efficacy with favorable tolerability [17]. It has, therefore, been recommended as a medication for adult idiopathic OAB, but more studies are needed to investigate its efficacy and tolerability in pediatric OAB patients [9,10]. This study had the strength that the effects of mirabegron and solifenacin were directly compared in pediatric patients, including patients administered only 5 mg solifenacin.

cin.

In this study, participants in the mirabegron group were older than those in the solifenacin group, and an important factor for drug selection in pediatric patients is whether they can swallow a tablet. Solifenacin can be prescribed as a powder; therefore, it can be administered to younger children who are unable to swallow a tablet. Mirabegron can only be prescribed to older children (around 9 years old), as a powdered formulation is not available [8,18]. Owing to the age difference between the two treatment groups, the factors affected by age (e.g., bladder capacity) were first adjusted and then compared. We adjusted for bladder capacity using the ratio of measured MVV to eBC, which is a widely used method for evaluating bladder volume [13].

Most children with OAB have nocturnal enuresis. In these patients, the first morning voided volume does not represent a full bladder owing to unconscious bladder emptying during sleep; therefore, their bladder capacity is predicted to be less than that of children without nocturnal enuresis [19]. In the present study, the aBCR (MVV/eBC) differed between patients with and without nocturnal enuresis (0.58 ± 0.17 vs. 0.84 ± 0.31 , $p=0.042$), but the aBCR (MVVDT/eBC) did not (0.52 ± 0.18 vs. 0.56 ± 0.26 , $p=0.746$) (Supplementary Table 3). In this respect, MVVDT (except for the first morning voided volume) can be used for more accurate evaluation when analyzing bladder capacity in patients with nocturnal enuresis.

Previous mirabegron studies in pediatric OAB evaluated only changes in symptoms [12,20] or in bladder capacity without considering patient age [11]. This study used age-adjusted bladder capacity and compared its change in pediatric OAB patients taking either solifenacin or mirabegron. Both drugs significantly increased the age-adjusted bladder capacity, 1.35 times and 1.70 times, which reduced the rate of decreased bladder capacity by 31% and 56%, respectively. This effect depended on bladder capacity before treatment; for instance, the lower the bladder capacity before medication, the better the treatment effect. Interestingly, as the

pre-treatment bladder capacity approached the age-eBC, both solifenacin and mirabegron were ineffective, suggesting that these drugs have little effect in patients with normal bladder capacity. This study showed no significant difference in the ability of the two drugs to increase bladder capacity.

In addition to an increase in bladder capacity, improvement in OAB symptoms was also observed. This study showed that incontinence improved in all patients, and urgency and nocturnal enuresis also improved in 65% and 80% of cases, respectively. These effects were not significantly different between children administered solifenacin 5 mg and those administered mirabegron 50, which is in line with the results of a previous meta-analysis in adult OAB patients [8,10]. The results showed that OAB symptoms are more likely to improve if bladder capacity before treatment is already reduced, as these drugs act in patients with decreased bladder capacity. Similar results were found in a previous study based on urodynamic study. The study showed that lower bladder capacity at the first sensation to void correlated with better improvement in OAB symptoms after taking mirabegron, suggesting a correlation between bladder capacity before medication and improvement in OAB symptoms [21].

In the present study, the incidence of adverse effects was low in both treatment groups, but owing to the small sample size, this finding should be reviewed cautiously. In addition, only short-term adverse effects could be evaluated as the duration of drug administration was less than 6 to 8 months. In the case of solifenacin, most adverse effects were mild (CTCAE grade 2) gastrointestinal problems (e.g., nausea and vomiting). This finding is similar to that of a Korean prospective study, confirming the tolerability of solifenacin 5 mg in pediatric idiopathic OAB patients [18]. Patients taking mirabegron did not report any adverse effects. Despite these results, there was no significant difference in drug maintenance, possibly due to the mild adverse effects in the solifenacin group and the drug tolerability observed in both groups.

Limitations of the present study included its retrospective design and small sample size owing to the fact that in Korea solifenacin and mirabegron are used off-label for pediatric patients. Therefore, because only a few studies have investigated the effects of mirabegron in pediatric OAB patients, it is difficult to conduct prospective studies. In addition, we could not show improvement in OAB symptoms by using objective methods such as the patient's perception of bladder condition scale. Thus, the results were based on the degree of improvement described by parents and children, which could not be compared numerically. Third, we did not

use an objective questionnaire to assess the tolerability of each medication; therefore, it is likely that adverse events were underreported owing to the lack of an adverse effect profile questionnaire. Finally, this study did not assess patient quality of life, which is seriously impacted by OAB [22].

CONCLUSIONS

Mirabegron has similar efficacy to solifenacin in pediatric patients with idiopathic OAB. In particular, OAB symptoms improved more effectively when the bladder capacity was already impaired before treatment. Additionally, mirabegron caused only a few adverse effects, suggesting it is a safe alternative for the treatment of pediatric patients with idiopathic OAB.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Seong Cheol Kim. Data acquisition: Myungchan Park, Chongsok Chae, Ji Hyung Yoon, and Sejun Park. Statistical analysis: Seong Cheol Kim. Data analysis and interpretation: Kyung Hyun Moon, Sang Hyeon Cheon, Taekmin Kwon, Seong Cheol Kim, and Sungchan Park. Drafting of the manuscript: Seong Cheol Kim. Critical revision of the manuscript: Seong Cheol Kim and Sungchan Park. Supervision: Seong Cheol Kim and Sungchan Park. Approval of the final manuscript: Seong Cheol Kim and Sungchan Park.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via <https://doi.org/10.4111/icu.20200380>.

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