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Comparison of the efficacy and safety of onabotulinum toxin A and mirabegron for overactive bladder in elderly patients

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Abstract. – OBJECTIVE: This study aimed to investigate the efficacy and tolerability of mirabegron and onabotulinum toxin A (BoNT/A) injections for overactive bladders. The treatment we provided was to patients over the age of 65 years who were not satisfied with the results of anticholinergic monotherapy.

PATIENTS AND METHODS: This multicenter retrospective observational study was conducted between March 2017 and December 2021. Thirty patients who were unable to take anticholinergics or mirabegron due to side effects received a total of 100-unit intravesical injections of BoNT/A. Furthermore, 30 patients receiving 50 mg of mirabegron daily were compared. Micturition frequency, urgency of urinary incontinence, pad usage, and nocturia were all evaluated for efficacy. Patients' health-related quality of life and subjective satisfaction ratings were assessed before and six months after treatment using an incontinence-quality-of-life questionnaire. We documented all adverse events for all subjects.

RESULTS: There was a statistically significant decrease in the frequency, daily pad usage, and incontinence episodes of both groups. The median (interquartile range) voiding frequency after onabotulinum toxin A treatment was lower than that after mirabegron treatment [9.4 (6.83-10.0) *vs.* 10.5 (8.37-11.67); $p = 0.01$]. Incontinence episodes showed similar differences [1.3 (1.17-3.67) *vs.* 2.53 (2.0-5.67); $p = 0.05$]. There was no significant difference in nocturia or maximum urine flow rate between the groups before and after treatment.

CONCLUSIONS: We determined that mirabegron led to lower urinary retention, hematuria, infection and post-void residual urine volume rates than BoNT/A in the older patient population. In addition, mirabegron treatment had comparable incontinence-quality-of-life scores at six months post-treatment.

Key Words:
Overactive bladder, Elderly, Onabotulinum toxin A, Mirabegron.

Introduction

Overactive bladder (OAB) is a complex symptom characterized by frequent urination, urgency, and nocturia, with or without urinary incontinence and without a demonstrable organic cause[1]. OAB affects more than 500 million people worldwide, with 35.6% of men and women aged 40 years. This rate increases with age[2]. OAB is associated with significant social limitations, loss of self-confidence, depression, anxiety, and adverse sexual health-related effects in the younger population and significantly reduces health-related quality of life (HRQoL). OAB symptoms and urinary leakage in elderly patients are associated with an increased risk of falls and fractures. Additionally, they are associated with recurrent urinary infections, skin deterioration, and ulceration[3-5].

The initial treatment for OAB is behavioral therapies and lifestyle changes; however, it is difficult to maintain these treatments in geriatric patients because of the lack of proper treatment centers and trained personnel[6]. Oral pharmacological treatment is considered for patients who do not benefit from this treatment. The most important among them is anticholinergic therapy, which is particularly effective in older people but can lead to unendurable side effects (AEs) and contribute to anticholinergic load. Exposure to anticholinergic drugs has also been associated with adverse cognitive effects, especially in people over 65 years of age[7].

Mirabegron, a β3-receptor agonist, has been introduced as an alternative to anticholinergics, with similar efficacy and a lower side effect profile. There is also clinical evidence[8] that mirabegron may be administered after the failure of anticholinergic treatment. In 2013, onabotulinum

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toxin A (BoNT/A) was approved as a tertiary treatment option for patients with OAB who did not benefit from oral pharmacological treatment[9].

Since BoNT/A does not affect muscarinic and adrenergic receptors in the bladder, it does not affect cognitive function[6]. Although OAB treatment options are different, patients prefer oral drugs because of their ease of use and access[10]. Despite numerous studies[11] comparing mirabegron with anticholinergics for OAB, no comparison involving BoNT/A and mirabegron has been conducted in elderly patients. In this study, we aimed to compare the efficacy and tolerability of mirabegron *vs.* BoNT/A injection for the treatment of OAB in patients aged > 65 years who were not satisfied with anticholinergic monotherapy for at least 8 weeks.

Patients and Methods

Study Design and Participants

We conducted a retrospective observational study from March 2017 to December 2021. The study was conducted in accordance with the principles of the Declaration of Helsinki. After the approval by the local Research Ethics Committee of Firat University Institutional Ethical Board (Number: 2023/01-09, Date: 12.01.2023), 30 patients who could not use anticholinergics and mirabegron due to side effects (owing to the possibility of unfavorable side effects on the cardiovascular and gastrointestinal systems as well as on cognitive functions, uncontrolled hypertension, mirabegron intolerance, etc.) received 100 intravesical BoNT/A injections and 30 patients who received 50 mg mirabegron daily were compared. Informed consent regarding the potential side effects of injections and oral therapy was obtained from all individual participants included in the study.

All study participants underwent a thorough examination and were subjected to necessary laboratory tests (urine culture, biochemistry, etc.), imaging (urinary ultrasound), and specific tests (urodynamics, uroflow, and voiding diary, among others).

Patients with at least eight or more daily urinations, one nocturia and one incontinence who used at least two different anticholinergics for at least three months and did not obtain the desired response or had to stop the treatment due to side effects were included in the study. Patients who could not perform clean intermittent catheterization (CIC) by themselves or their caregivers, who had interstitial cystitis/painful bladder syndrome, genuine stress urinary incontinence, neurogenic bladder, a history of pelvic radiotherapy, or who could not be administered BoNT/A due to reasons such as pregnancy or allergy and patients with bladder outlet obstruction [maximal flow rate (Qmax) < 15 mL/sec for women, < 10 mL/s for men] and patients who had > 150 mL post-void residual urine volume or bleeding tendency were excluded from the study. Urge urinary incontinence, nocturia, pad use, and voiding frequency demographic data, including age, sex, body mass index, duration of symptoms, and comorbidities, were recorded to evaluate treatment effectiveness. Patient health-related quality of life (HRQoL) and subjective satisfaction with the treatment were assessed using an incontinence quality of life (I-QoL) questionnaire. We recorded all adverse events for all subjects. A positive urine culture (> 10^5 colonies mL/U) and positive urine analysis [> 5 leucocytes/High Power Field (HPF)] with dysuria were considered urinary infections, and a post-void-residual (PVR) volume > 200 mL or the inability to void after the procedure was accepted as urinary retention.

Surgical Technique

The procedure was performed under sedation anesthesia in the lithotomy position. Onabotulinum toxin A (100 U) was diluted with 10 mL of isotonic NaCl. During rigid or flexible cystoscopy, the 10 mL BoNT-A solution was injected 4 mm into the bladder wall (including the trigone) at 10 different points approximately one centimeter apart from one another[12].

Statistical Analysis

The SPSS 18.0 (SPSS Inc., Chicago, IL, USA) package program was used for statistical analysis. Data are expressed as the mean, standard deviation, and percentage (%). Nominally measured variables were analyzed with the Chi-square test. Whether the numerically measured variables showed a normal distribution was analyzed with the Shapiro-Wilk test. To compare the groups with each other, Student's *t*-test was used for normally distributed numerical variables and the Mann-Whitney U test was used for nonnormally distributed variables. Comparisons of groups within themselves (6 months preop and postoperative) were analyzed by Student's *t*-paired test for those with normal distribution and Wilcoxon tests for those with normal distribution. A $p < 0.05$ value was considered significant.

Results

Overall, 60 patients were included in the study and received either mirabegron (n = 30) or BoNT/A (n = 30). In our study, there were 17 (56.7%) men and 13 (43.3%) women in the mirabegron group and 15 (50%) men and 15 (50%) women in the BoNT/A group and there was no difference between the groups in terms of sex. While 7 patients in the mirabegron group (23.4%) had diabetes mellitus (DM) and 4 had coronary artery disease (CAD) (13.4%), 9 patients in the BoNT/A group (30%) had DM and 3 (10%) had CAD, there was no significant disparity between the groups in terms of comorbid diseases ($p = 0.979$). In the mirabegron group, 11 of the patients (36.7%) smoked, and 9 of the patients in the BoNT/A group smoked (30%), and there were no statistically significant differences between the two groups ($p = 0.784$). Table I shows the description of the cohorts of patients. There was no significant difference in the groups' demographic and pre-study baseline characteristics. Comparing the pretreatment data with the 6-month post-treatment duration, a statistically significant decrease was recorded in both groups' frequency, daily pad usage, and incontinence episodes. The median (interquartile range) voiding frequency was lower after BoNT/A than after mirabegron [9.4 (6.83-10.0) *vs.* 10.5 (8.37-11.67); $p < 0.01$] at 6 months post-treatment. Similar differences were seen in incontinence episodes [1.3 (1.17-3.67) *vs.* 2.53 (2.0-5.67); $p < 0.05$]. When comparing before and after treatment, no significant change was observed in nocturia or maximum flow urine rate in either group. Urinary tract infection (31% *vs.* 11%; $p = 0.0003$) and voiding difficulty requiring self-catheterization (16% *vs.* 4%; $p = 0.003$) were more common after BoNT/A. While no hematuria was observed in mirabegron users, three patients in the BoNT/A group encountered hematuria, which improved with short-term follow-up. The findings of I-QoL scores indicate that the use of mirabegron and BoNT/A as second-line therapy has similar positive effects on quality of life (64.3 and 66.1, respectively, $p > 0.05$) (Table II).

Discussion

Although OAB affects one in every six people in the entire population, it is more common in older individuals and can cause more serious effects. These include an increased risk of falling, recurrent urinary tract infections, skin lesions, deterioration in quality of life and psychoso-

Table I. Comparison of demographic and baseline characteristics of study groups.

Variables	Groups	Mean	Std. Deviation	Std. Error Mean	*p*-value
Age (years)	BoNT/A	73.2	5.86	1.07	$p > 0.05$
	Mirabegron	72.4	4.57	0.83	
Weight (kg)	BoNT/A	71.67	8.13	1.48	$p > 0.05$
	Mirabegron	74.43	9.58	1.74	
Height (cm)	BoNT/A	166.56	5.85	1.06	p > 0.05
	Mirabegron	167.66	7.08	1.29	
Duration of disease (years)	BoNT/A	9.07	2.67	0.48	$p > 0.05$
	Mirabegron	7.97	1.47	0.26	
Pretreatment I-Qol scores	BoNT/A	43.96	4.61	0.84	$p > 0.05$
	Mirabegron	43.10	4.21	0.76	
Pretreatment PVR (ml)	BoNT/A	67.50	22.23	4.05	$p > 0.05$
	Mirabegron	53.33	11.09	2.02	
Pretreatment Qmax (ml/sn)	BoNT/A	14.23	3.23	0.59	$p > 0.05$
	Mirabegron	13.83	3.16	0.57	
Pretreatment daily pad usage (n)	BoNT/A	2.00	1.78	0.32	$p > 0.05$
	Mirabegron	2.53	1.22	0.22	
Pretreatment frequency (n)	BoNT/A	14.13	1.90	0.34	$p > 0.05$
	Mirabegron	13.60	1.71	0.31	
Pretreatment nocturia (n)	BoNT/A	3.60	0.89	0.16	$p > 0.05$
	Mirabegron	3.43	1.04	0.19	
Pretreatment incontinence episodes (24 hours)	BoNT/A	3.47	2.86	0.52	$p > 0.05$
	Mirabegron	4.33	1.76	0.32	

BoNT/A: onabotulinum toxin A, I-Qol: incontinence quality of life, PVR: postvoid residual volume, Q max: maximal flow rate.

Table II. Comparison of clinical outcomes of mirabegron *vs*. onabotulinum toxin A.

Variables	Groups	Mean	Std. Deviation	Std. Error	*p*-value
Post-treatment daily pad usage (n)	BoNT/A	0.63	1.03	0.18	***p* < 0.01**
	Mirabegron	1.30	0.79	0.14	
Post-treatment frequency (n)	BoNT/A	9.4	1.54	0.28	***p* < 0.01**
	Mirabegron	10.56	1.67	0.30	
Post treatment nocturia (n)	BoNT/A	1.900	1.02	0.18	$p > 0.05$
	Mirabegron	2.167	1.05	0.19	
Post-treatment incontinence episodes (24 hours)	BoNT/A	1.3	1.57	0.28	***p* < 0.05**
	Mirabegron	2.53	0.86	0.15	
Post-treatment PVR (ml)	BoNT/A	90	58.29	10.64	***p* < 0.0**1
	Mirabegron	57.5	10.72	1.95	
Post-treatment Qmax (24 hour)	BoNT/A	12.43	3.42	0.62	$p > 0.05$
	Mirabegron	13.83	3.16	0.57	
Post-treatment I-Qol scores	BoNT/A	66.1	10.51	1.91	$p > 0.05$

BoNT/A: onabotulinum toxin A, I-Qol: incontinence quality of life, PVR: post-void residual volume, Q max: maximal flow rate.

cial problems such as depression, social isolation and anxiety in elderly individuals. It has been revealed[13,14] that it brings with it a health expenditure of more than 80 billion dollars as of 2020.

Age-related bladder endothelial dysfunction, atherosclerosis, oxidative stress, disruption in the functioning of afferent receptors that sense filling, and reduced suprapontin inhibition of processing reflexes are among the reasons for the pathophysiology. Pharmacotherapy, especially the oral anticholinergic approach, is the most commonly used method in the treatment of this complex symptom[15].

In the conducted studies[16], compared to younger individuals, higher drug doses were needed to obtain similar pharmacological treatment efficacy in elderly individuals. In particular, side effects such as constipation and dry mouth, which may lead to treatment discontinuation, may cause patients to abandon treatment quickly. In addition, if anticholinergics are used simultaneously with other anticholinergic drugs that patients should use, they may cause interactions, also defined as anticholinergic burdens. Delirium, confusion, and dizziness are associated with undesirable conditions such as impaired cognitive functions[17]. The age-related decline in cholinergic transmission raises concerns about cognitive burden. Concerns related to the formation of anticholinergic load in elderly patients have led to an interest in adrenergic beta-receptors, another dominant receptor in the bladder. Stimulation of β3 adrenergic receptors relieves OAB symptoms by relaxing the detrusor muscle in the filling phase and inhibiting uninhibited contractions. Mirabegron, a beta-3 receptor agonist, has been used for this purpose for over a decade. In the PILLAR study[18] evaluating the use of mirabegron in the population over 65 years of age, it was shown to be more effective than a placebo in improving the symptoms of OAB. Moreover, this study also found that mirabegron did not hurt the side-effect profile, especially on cognitive functions. Although not yet included in guidelines, there is evidence[8,19,20] in clinical practice that mirabegron can be given with fewer adverse effects when treatment with anticholinergics fails. Moreover, mirabegron has been claimed to be superior in improving most urodynamic parameter outcomes compared to antimuscarinic agents. Another study[21] claimed that mirabegron was superior in improving most urodynamic parameter outcomes compared to antimuscarinic agents.

Intradetrusor BoNT/A injection has come to the fore as a different treatment option in patients with significant side effects or inadequate symptom control with oral treatments, with its proven efficacy and minimally invasive technique in recent years. In a limited number of randomized and nonrandomized studies[22-24], it has been revealed that there is no significant difference between young and elderly patients in terms of effectiveness, but undesirable side effects such as urinary infection in women and an increase in residual urine after micturition in men are more common. Furthermore, it has been discovered[22-24] that unfavorable side effects, particularly residual urine after micturition, increase with increasing age, frailty, comorbidities, and dose administered. Few studies[25,26] have compared these two commonly used OAB treatments. These studies are conducted indirectly. Initial differences in baseline values between mirabegron and BoNT/A

studies, such as gender distribution, urinary incontinence, and the number of urgency episodes, were significant factors limiting study homogenization.

Network meta-analysis (NMA) is a statistical method used in these studies[25,26] that combines previously published clinical trials to compare these key differences. In a meta-analysis of 100 units of BoNT/A by Freemantle et al[26], 25 and 50 mg mirabegron for an average of 12 weeks without head-to-head was found to be more effective in daily urinary incontinence attacks, urinary incontinence daily urgency attacks, urgency and urinary frequency. While it was effective, no significant difference was found in nocturia.

A meta-analysis by Drake et al[25] of 56 studies comparing BoNT/A to other oral options, including mirabegron, found that BoNT/A was more successful in terms of care or > 50% improvement in voiding frequency with episodes of incontinence and urgency. None of the aforementioned studies compared injection and oral side effects.

In the meta-analysis of Lozano-Ortega et al[27], the efficacy of oral mirabegron by BoNT/A injection was evaluated in patients who had previously received anticholinergic therapy but did not benefit. In this study, the network meta-analysis method was used in terms of homogenization of groups and pretreatment symptoms, and BoNT/A showed a significant superiority compared to mirabegron in terms of reduction in 24-hour voiding frequency and fewer incontinence attacks. Regarding the frequency of nocturia, there was no difference in efficacy with either agent. Unlike other studies[25-27], BoNT/A was found to be associated with urinary tract infection three times more than mirabegron when side effects were evaluated. However, although an event of urinary retention was reported in two-thirds of the BoNT/A group, the absence of this event in the mirabegron group resulted in an incomplete quantitative assessment of the relative safety of mirabegron against BoNT/A.

There were no differences in the initial demographic and baseline characteristics of the patients in our study. This situation is critical for the study's homogenization and distinguishes it from other studies. When treatment efficacy was assessed, it was discovered that BoNT/A was more effective than mirabegron in terms of daily pad use, frequency, and incontinence attacks, which is consistent with previous meta-analyses[25,26]. Regarding the frequency of nocturia, there was no significant difference between the two groups in treatment effectiveness. When safety and adverse effects were considered, there was no difference in maximum urine flow rate. However, the post-voiding residue was significantly higher in the BoNT/A group. Furthermore, urinary tract infection (31% *vs.* 11%; $p = 0.0003$) and voiding difficulty, which requires self-catheterization (16% *vs.* 3.3%; $p = 0.003$), were more prevalent in BoNT/A patients. While mirabegron users did not experience hematuria, three patients in the BoNT/A group did, and they improved with short-term follow-ups. When comparing the quality of life before and after treatment, both groups showed significant improvements, with no significant difference. The importance of muscle strength (including the detrusor muscle) for the quality of life of older adults has been demonstrated in many studies[28]. Although mirabegron left less residual urine than Intradetrusor BoNT/A injection, the short-term effect of the injection may be one of the factors that caused no significant difference in terms of quality of life. Mirabegron can be used in patients who are resistant to anticholinergics because of its low risk of side effects, although it is not as effective as BoNT/A. It is more potent than traditional anticholinergics. However, randomized placebo-controlled trials are required to demonstrate mirabegron's efficacy in cases where BoNT/A cannot be used.

There are some limitations to our study. The inability to use the frailty index for patients, the small number of cases (especially due to the COVID-19 pandemic), the lack of placebo and sham groups and the lack of 3-month results in the study are among these limitations. Since patients with hypertension were excluded from the study in the mirabegron group, the inability to evaluate side effects and safety was another limiting aspect of the study.

Conclusions

BoNT/A is a viable option after failed or intolerable anticholinergics for OAB[18]. However, our study determined that mirabegron led to less urinary retention, hematuria, infection and PVR rates when compared to BoNT/A in the older patient population. In addition, mirabegron treatment had comparable I-QoL scores at post-treatment 6 months. However, randomized, placebo-controlled studies are needed to demonstrate the efficacy of mirabegron in these cases where BoNT/A cannot be applied.

Conflict of Interest
The authors declare that they have no conflict of interests.

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Ethics Approval
The study was approved by the Ethics Committee of Firat University, Institutional Ethical Board, Number: 2023/01-09, Date: 12.01.2023.

Informed Consent
Informed written consent form was obtained from all participants.

Authors' Contribution
Ahmet KARAKECI: Data collection, Manuscript writing/editing, Project Development; Ahmet KELES: data collection, data analysis, project development; Rahmi ONUR: data analysis, methodology, project development.

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