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Intravesical Injection of OnabotulinumtoxinA (Botulinum Toxin Type A) in Japanese Patients With Refractory Overactive Bladder

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Abstract. *Background/Aim: Botulinum toxin intravesical injection therapy (hereafter, botulinum therapy) is approved in Japan for treating urinary urgency, frequency, and urinary incontinence due to refractory overactive bladder or neurogenic bladder. Although botulinum therapy is classified as urinary incontinence surgery, it is minimally invasive, effective, and safe. However, there are few reports on the actual use of botulinum therapy and examination of its effects and side-effects. Herein, we report real-world data on botulinum therapy. Patients and Methods: Patients who received botulinum therapy for refractory overactive bladder at the Nara Medical University and affiliated facilities from May 2020 to May 2022 were enrolled. The patient background, treatment efficacy, and safety were retrospectively reviewed. Results: Twenty-three cases of refractory overactive bladder (age: 68.4±14.1 years; 7 males, 16 females; 17 outpatient, 6 hospitalized) were enrolled. Pretreatment, the overactive bladder symptom score (OABSS) was 10.1±2.7, and post-void residual urine volume was 27.1±31.6 ml. Botulinum was administered once, twice, thrice, and four times in 11, eight, three, and one cases, respectively. OABSS decreased to 6.1±3.2 2 weeks after botulinum therapy (p<0.0001), and the effect persisted at 6.6±3.2 after 12 weeks (p<0.0001). Post-void residual urine volume increased to 74.6±79.2 ml after 2 weeks (p=0.0010), but subsequently improved to 33.9±42.0 ml after 12 weeks (p=0.0002). Adverse events included post-void residual urine volume of 200 ml or more in three patients (7.5%) and urinary retention grade 2 in two (5.0%). Conclusion: Botulinum therapy is effective and relatively safe for refractory overactive bladders.*

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Key Words: Botulinum toxin type A, intravesical injection, refractory overactive bladder, urinary incontinence.

Overactive bladder (OAB) was defined by the International Continence Society in 2002 as follows: "The essential symptom of OAB is urinary urgency, which may or may not be accompanied by urge urinary incontinence but is usually accompanied by frequent urination and nocturia. It is one of the symptom syndromes defined as overactive bladder syndrome, urge syndrome, or urgency-frequency syndrome (1). In Japan, the overactive bladder clinical guidelines (3rd edition), revised in September 2022, state that overactive bladder is a symptom syndrome classified by urinary urgency, usually accompanied by nocturia and frequency. Diagnosis is only possible after excluding localized diseases with similar symptoms.

According to the Japanese guidelines, refractory OAB refers to an overactive bladder that fails to respond to behavioral and drug therapy, including various anticholinergic drugs (oral drugs and patches) and β3 adrenoreceptor agonists, either alone or in combination. Resistance, defined as a failure to achieve "patient-assessed efficacy" or "a 50% or more improvement in urge incontinence frequency", can be defined after as little as 12 weeks.

Recent changes in OAB treatment include the issue of side-effects of anticholinergic drugs, particularly the possibility of cognitive impairment due to long-term administration, and their safety has recently been questioned (2, 3). However, reports show that β3 adrenoreceptor agonists are highly effective and safe (4). In Japan, sacral neuromodulation (SNM) for refractory OAB was first approved in September 2017, while botulinum toxin type A intravesical injection therapy was first approved in April 2020. SNM is a neuromodulation therapy in which an

electrical stimulation device is implanted in the sacral foramen, and continuous electrical stimulation is repeated. This stimulates the afferent pathways in the sacral spinal cord region, suppressing the reflexes of the parasympathetic pelvic nerves or stimulating the sympathetic nerves to suppress the contraction of the detrusor muscle. Botulinum toxin intravesical therapy for OAB comprises injecting 100 units of botulinum toxin into 20 locations (5 units per location) of the detrusor muscle under cystoscopy. This toxin inhibits neuromuscular transmission by inhibiting the release of acetylcholine within nerve endings, thereby achieving muscle-relaxing effects.

Botulinum toxin intravesical injection therapy is more straightforward to administer than SNM, and the number of cases in Japan is increasing. Still, real-world data regarding safety and outcomes is lacking. In this study, we report the results of intravesical botulinum injection therapy for refractory OAB at our hospital and related facilities.

Patients and Methods

Patients. This retrospective observational study included patients admitted to the Nara Medical University and related facilities. Patients were selected from the electronic medical record database between May 2020 and May 2022. The inclusion criteria were patients diagnosed with refractory OAB due to insufficient response to anticholinergic drugs or β3 adrenoreceptor agonists who underwent intravesical injection therapy of botulinum toxin type A (5). Exclusion criteria were patients whose primary symptom was stress urinary incontinence due to bladder stones, interstitial cystitis, urinary cancer, urinary tract infection, or urethral obstruction, and patients with a post-void residual urine volume of 100 ml or more (6-8). Efficacy measures included an overactive bladder symptom score (OABSS) at baseline and 2 and 12 weeks after intravesical injection therapy of botulinum toxin type A. The OABSS is a four-item questionnaire that quantifies daytime frequency (OABSS 1, score, 0-2), nocturia (OABSS 2, score, 0-3), urgency (OABSS 3, score, 0-5), and urgency urinary incontinence (OABSS 4, score, 0-5) that collectively expresses OAB symptoms as a single score. The OABSS was initially developed and validated psychometrically in Japan (9). Safety was evaluated based on participant-reported adverse events and post-void residual urine volume during visits.

Administration method. The injection was performed using a rigid or flexible cystoscope, with an Olympus single-use injector (NM-221C-0427) as the puncture needle. In some patients, local anesthesia was administered, comprising an injection of 4% xylocaine (20 ml, 20 min) into the bladder. Thereafter, the inside of the bladder was washed with physiological saline, and 100 units of Botox were dissolved in 10 ml of physiological saline and injected into the muscularis of the posterior wall of the bladder at 20 preset locations, avoiding the trigone and apex of the bladder. Recent studies have reported that even if the number of administration sites is reduced, the effectiveness is the same as long as the number of administration units is maintained. In addition, the effectiveness of administration to the bladder trigone and submucosal administration rather than the muscularis is also being investigated, but there is little evidence of superiority (10).

Table I. *Patient characteristics*.

Characteristic		Average±SD or number (%)
Age (years)		68.3±14.1
OABSS		10.1±2.7
Post-void residual (ml)		27.1±31.6
Sex	Male	7 (30.4)
	Female	16 (69.6)
Embodiment	Outpatient	17 (73.9)
	Inpatient	6 (26.1)
Anesthesia method	Local	17 (73.9)
	General	4 (17.4)
	Lumber	2 (8.7)
Number of botulinum toxin administrations	One	11 (47.8)
	Two	8 (34.8)
	Three	3 (13.0)
	Four	1 (4.3)

OABSS: Overactive bladder symptom score.

Statistical analysis. All values are expressed as the mean±standard deviation. The Wilcoxon matched pairs and Mann-Whitney *U* tests were used to evaluate statistical differences. Prism software version 9.5.1 (GraphPad Software, San Diego, CA, USA) was used for statistical analyses and data plotting. Statistical significance was set at $p<0.05$.

Ethical considerations. This study was approved by the Institutional Ethics Committee of Nara Medical University (protocol approval no. 3352). The study protocol and procedures were performed in accordance with the tenets of the Declaration of Helsinki and its later amendments. The requirement for informed consent was waived because of the retrospective nature of this study.

Results

Participants. We included 23 patients with a mean age of 68.3±14.1 years, a baseline OABSS of 10.1±2.7, and a baseline post-void residual urine volume of 27.1±31.6 ml. This cohort comprised seven male (30.4%) and 16 female (69.6%) patients. Seventeen patients (73.9%) underwent the procedure as outpatients, and six (26.1%) underwent the procedure as inpatients. The anesthesia methods used were local anesthesia in 17 cases (73.9%), general anesthesia in four cases (17.4%), and lumbar anesthesia in two cases (8.7%). Botulinum was administered once in 11 cases (47.8%), twice in eight cases (34.8%), three times in three cases (13.0%), and four times in one case (4.3%) (Table I).

Outcomes at 2 and 12 weeks post-treatment. The total OABSS was significantly lower at 2 weeks than at baseline (6.1±3.2 *vs*. 10.1±2.7, $p<0.0001$) and continued to decrease at 12 weeks (6.6±3.2 *vs*. 10.1±2.7, $p<0.0001$). OABSS 1 was significantly lower at 12 weeks than at baseline (0.4±0.5 *vs*. 0.7±0.7, $p=0.0215$). OABSS 2 was significantly lower at 2

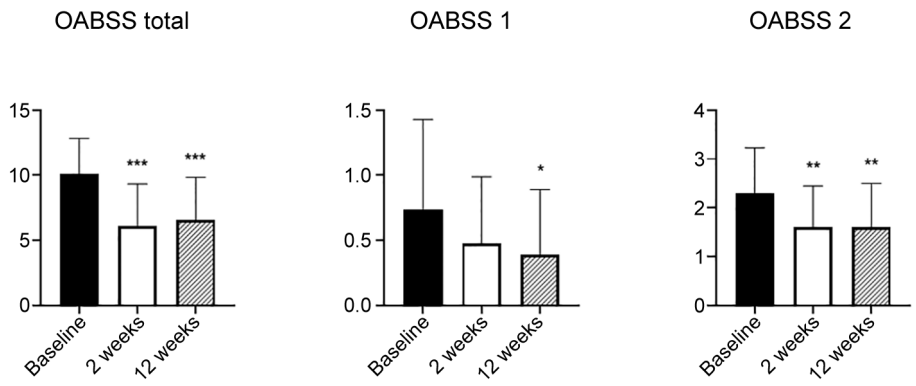

Figure 1. *The results of OABSS total, OABSS 1, and OABSS 2 for first treatment of botulinum therapy. The total OABSS was significantly lower at 2 weeks than at baseline and continued to decrease at 12 weeks. OABSS 1 was significantly lower at 12 weeks than at baseline. OABSS 2 was significantly lower at 2 weeks than at baseline and continued to decrease at 12 weeks. OABSS: Overactive bladder symptom score. *p<0.05, **p<0.01, ***p<0.001 vs. baseline.*

weeks than at baseline (1.6±0.8 *vs.* 2.3±0.9, p=0.0013) and continued to decrease at 12 weeks (1.6±0.9 *vs.* 2.3±0.9, p=0.0013) (Figure 1). OABSS 3 was significantly lower at 2 weeks than at baseline (2.5±1.4 *vs.* 4.0±1.0, p<0.0001) and continued to decrease at 12 weeks (2.7±1.3 *vs.* 4.0±1.0, p=0.0001). OABSS 4 was significantly lower at 2 weeks than at baseline (1.5±1.5 *vs.* 3.0±1.4, p=0.0003) and continued to decrease at 12 weeks (1.9±1.6 *vs.* 3.0±1.4, p=0.0122) (Figure 2).

Initial treatment results treated once vs. twice or more. Baseline OABSS total and OABSS 4 were higher. The decrease at 12 weeks was more significant in the group administered botulinum two or more times than in the single administration group (OABSS total: 11.5±2.0 *vs.* 8.7±2.4, p=0.0084, OABSS 4: 3.7±1.0 *vs.* 2.5±1.3, p=0.0456, and the change in OABSS 4: –2.0±1.6 *vs.* –0.5±1.3, p=0.0409) (Figure 3).

Initial treatment effected by sex. In female patients, the total OABSS was significantly lower at 2 weeks than at baseline (5.8±2.9 *vs.* 9.9±2.8, p=0.0002) and continued to decrease at 12 weeks (6.5±3.1 *vs.* 9.9±2.8, p=0.0042). In male patients, the total OABSS was significantly lower at 2 weeks than at baseline (6.6±4.1 *vs.* 10.6±2.6, p=0.0313) and continued to decrease at 12 weeks (6.9±3.7 *vs.* 10.6±2.6, p=0.0313) (Figure 4).

Safety. Post-void residual urine volume was significantly higher at 2 weeks than at baseline (74.6±79.2 *vs.* 27.1±31.6 ml, p=0.0010) and was significantly improved at 12 weeks compared to 2 weeks (33.9±42.0 *vs.* 74.6±79.2 ml, p=0.0002) (Figure 5). Adverse events included post-void residual urine volume of 150 ml or more in eight patients (20.0%), post-void residual urine volume of 200 ml or more

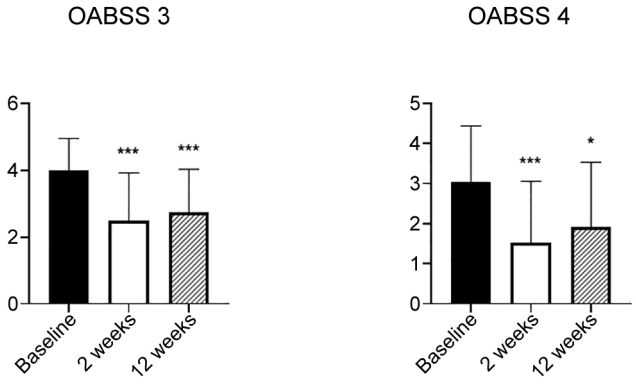

Figure 2. *The results of OABSS 3 and OABSS 4 for first treatment of botulinum therapy. OABSS 3 was significantly lower at 2 weeks than at baseline and continued to decrease at 12 weeks. OABSS 4 was significantly lower at 2 weeks than baseline and continued to decrease at 12 weeks. OABSS: Overactive bladder symptom score. *p<0.05, **p<0.01, ***p<0.001 vs. baseline.*

in five patients (12.5%), requirements for α1 blocker in eight patients (20.0%), urinary retention (grade 2) in three cases (7.5%), and sepsis (grade 3) in one case (2.5%).

Discussion

Botulinum toxin, produced by the *Clostridium botulinum* bacterium, is a protein known to relax smooth and striated muscles by inhibiting the release of acetylcholine from cholinergic nerve terminals (11). Beyond this primary action, this toxin also suppresses the release of neurotransmitters, including substance P (12) and adenosine triphosphate (ATP) (13) in the bladder, triggering downregulation of P2X3 receptors and transient receptor potential vanilloid 1 (TRPV1) receptors in the suburothelial nerve terminals,

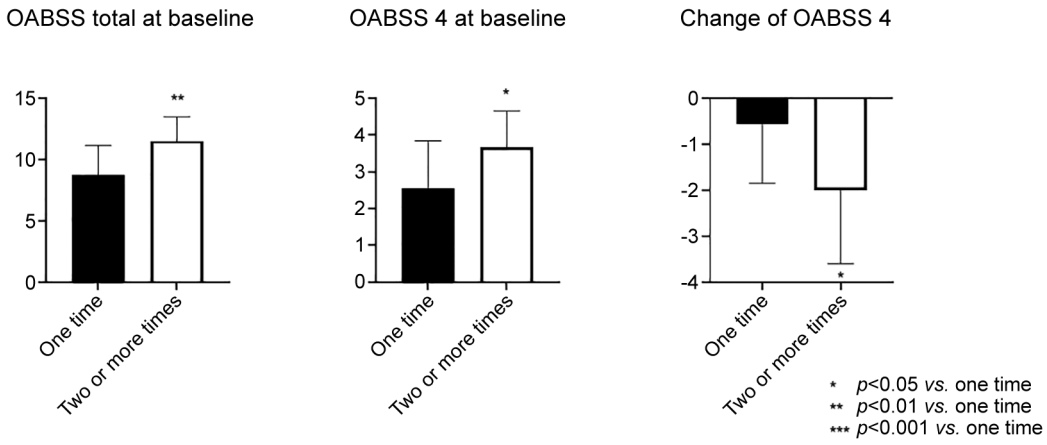

Figure 3. *The results for OABSS total at baseline, OABSS 4 at baseline, and change in OABSS 4 through 12 weeks for first treatment of botulinum therapy for patients receiving one dose of botulinum and two or more doses. Baseline OABSS total and OABSS 4 were higher, and the decrease in OABSS 4 at 12 weeks was more significant in the botulinum administration group of two or more doses than in the one dose administration group. *p<0.05, **p<0.01, ***p<0.001 vs. one dose.*

potentially inhibiting bladder afferents (14). Among the seven types of botulinum toxins (A to E), type A exhibits the highest biological activity per unit weight in humans, making it the preferred choice for medical applications.

The application of botulinum therapy for OAB has been widely reported. According to a review by Leong *et al.*, this therapeutic regimen is effective in approximately 80% of patients, reducing urination frequency by 12-53% and reducing urinary incontinence by 35-87%. The duration of response was 6-14 months, and the treatment interval was 14-23 months (15). Although it is difficult to calculate the duration of the effect precisely due to a lack of standardized dosage and definition, effects are thought to last approximately 4-8 months. Recent reports also suggest that botulinum treatment may modulate bladder inflammatory responses and reduce fibrosis (16).

In one Japanese domestic phase III trial comparing the effects of botulinum therapy and placebo on OABs resistant to anticholinergic drugs and β3 adrenoreceptor agonists, a more significant change in the primary endpoint (change in the number of urinary incontinences per day) at week 12 was more significant in the botulinum therapy group (6). In addition, significant improvements were observed in the reduction rate of urinary incontinence frequency, change in urge incontinence frequency, change in urinary urgency frequency, and change in urination frequency (6). These results have further been confirmed in international phase III trials (7, 8).

In this study, OABSS scores improved 2 weeks after botulinum therapy, and the effect continued until 12 weeks, indicating the efficacy of this treatment modality. Among them, 12 cases received botulinum therapy more than once.

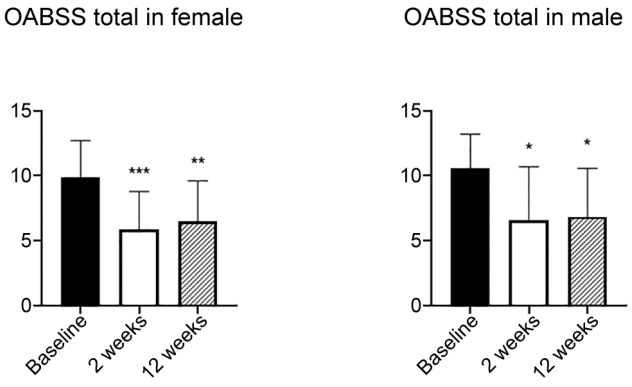

Figure 4. *The results of OABSS total in female and in male patients for first treatment of botulinum therapy. In female patients, OABSS total was significantly lower at 2 weeks than baseline and continued to decrease at 12 weeks. In male patients, the OABSS total was significantly lower at 2 weeks than baseline and continued to decrease at 12 weeks. *p<0.05, **p<0.01, ***p<0.001 vs. baseline.*

Patients who received botulinum therapy two or more times had a worse original OABSS score and showed a more significant improvement in urge urinary incontinence after treatment than those who received a single dose only. The decision to administer botulinum was collaboratively made by the patient and the attending physician, reflecting a consensus to continue treatment due to its effectiveness. This suggests that the patient may have been satisfied with the effects of botulinum treatment and wished to continue treatment.

In previous phase III trials of botulinum treatment, the proportion of women among all patients was high, and efficacy and safety were sufficiently evaluated (6-8). In this

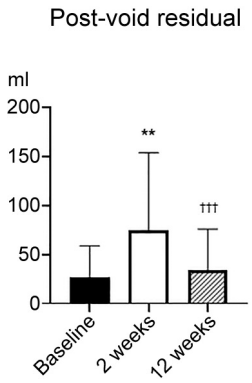

Figure 5. *The results of post-void residual urine volume for first treatment of botulinum therapy. Post-void residual urine volume was significantly higher at 2 weeks than at baseline and was significantly improved at 12 weeks compared to 2 weeks. OABSS: Overactive bladder symptom score. *p<0.05, **p<0.01, ***p<0.001 vs. baseline. †p<0.05, ††p<0.01, †††p<0.001 vs. 2 weeks.*

study, as in previous reports, OABSS scores improved after 2 weeks of botulinum treatment in female patients, and the effect continued until 12 weeks. However, it should be noted that in previous large-scale phase III trials, the ratio of male to female patients was low, and the evaluation of efficacy and safety was insufficient (6-8). Although there were only seven male cases in this study, the OABSS score improved after 2 weeks of botulinum treatment, and the effect continued to 12 weeks. Although the number of cases in this study was small, a benefit of treatment was observed regardless of sex.

Botulinum therapy's most common side effects are urinary tract infections and difficulty urinating. Karsenty *et al*. previously reported that the incidence of post-treatment urinary tract infections ranged from 2% to 32% and that the frequency was correlated with post-treatment post-void residual urine volume. Urinary retention ranged from 0 to 33%, and transient hematuria was observed in 2-21% of patients (17). The frequency of clean intermittent catheterization use in actual clinical practice is about 1-2% (18, 19). Further, it has been reported that the increase in post-void residual urine volume peaks 2 weeks after treatment and gradually decreases thereafter (20). Botulinum therapy has also been reported to have the effect of reducing salivary flow, but such symptoms were not observed in this study (21).

In this study, post-void residual urine volume peaked after 2 weeks and improved after 12 weeks. This therapy could be considered safe as there were almost no severe complications. Three cases required temporary self-catheterization, and no serious side-effects of hematuria were observed.

Despite its strengths, this study has some limitations that should be mentioned. Firstly, this was a retrospective, non-randomized study without a placebo control. Second, our sample size was too small to draw a definitive conclusion. Studies with a larger sample size are required to confirm our findings. Third, in this study, we did not perform cystometry, but since cystometry is not essential for diagnosing overactive bladder, we believe that it does not significantly affect the final results.

Conclusion

We reported a practical botulism treatment involving multiple doses for refractory OAB. The results of this study demonstrate that botulinum therapy is effective for urinary urgency, frequency, and urge incontinence associated with refractory overactive bladder, and is a simple, safe treatment method that can be implemented in daily clinical practice.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

All Authors participated in the design of the study. DG and KT designed the study. DG, KO, YM, SH, YN, and MM collected the clinical data. DG performed the statistical analysis. DG drafted the paper. KT and KF revised the manuscript. All Authors read and approved the final manuscript.

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