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Original Article

Botulinum Neurotoxin-A therapy in patients with refractory overactive bladder

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Abstract

Aim: The aim of this study was to evaluate the clinical efficacy and safety of intravesical botulinum neurotoxin-A injection in patients with refractory overactive bladder to conservative treatment and anti-muscarinic drugs.

Material and Methods: The data of 62 patients, who received botulinum neurotoxin-A (BonTA) injection (100 U) for overactive bladder (OAB) between 2015 and 2019, were reviewed retrospectively. For 55 patients included into the study, the urinary frequency and urgency, the number of incontinence and nocturia episodes, the maximum flow rate (Qmax), the post-void residual volume (PVR), and the Urinary Incontinence Quality of Life (I-QoL) scores were evaluated before the treatment and at the third month after the treatment.

Results: The comparison of the pre-treatment and posttreatment 3rd-month follow-up data revealed a statistically significant decrease in the urinary frequency and urgency, and the number of incontinence and nocturia episodes ($p < 0.05$). There were no statistically significant differences in Qmax and PVR in the posttreatment 3rd month ($p > 0.05$). The mean I-QoL score increased significantly in the posttreatment 3rd month compared to the pre-treatment scores (43.62 ± 11.2 and 75.2 ± 12.6, $p = 0.001$, respectively). After the treatment, hematuria developed in 3 female and 2 male patients and urinary tract infections developed in 4 females and 2 male patients.

Conclusion: BonTA injection significantly improves the daily urinary frequency, incontinence, and quality of life scores in patients with OAB.

Keywords: Botulinum Neurotoxin Type-A; overactive bladder; quality of life

INTRODUCTION

The International Continence Society describes overactive bladder (OAB) as "a feeling of urgency with or without urinary incontinence and an increase in urinary frequency during the day and at night" (1). OAB is a chronic disease that poses negatively effects on the quality of life (QoL), especially when accompanied by urinary incontinence (2). In epidemiological studies, the incidence of OAB varies between 12.4% and 53.1%, depending on the target population and the OAB definition (3,4).

The first-line treatment of OAB is behavioral therapy. Anti-muscarinic medications can be used either in combination with behavioral therapy for the treatment of OAB or when treatment success cannot be achieved with behavioral therapy alone (5). Recently, the Food and Drug Administration (FDA) approved the use of β3-adrenergic agonist effective mirabegron in OAB patients (6). Oral mirabegron relaxes the detrusor muscle, causing decrease in OAB symptoms such as urgency, urinary incontinence and frequency of voiding and it has been studied as both monotherapy and as combination therapy as a treatment for OAB (7).

Inappropriate treatment response to anti-muscarinic medications or inability of the patient to tolerate their side effects is qualified as "refractory", introducing refractory OAB. Refractory OAB is diagnosed in patients; who failed the treatment and/or cannot tolerate the side effects after receiving one or more types of anti-muscarinic medications for 3 months (8). Botulinum toxin type A (BonTA) into the detrusor muscle, sacral neuromodulation and posterior tibial nerve stimulation are recommended for the treatment of OAB refractory to anti-muscarinic drugs (5,9,10). In the European Urinary Incontinence Guidelines, there is no recommendation as to which of these options should be preferred for refractory OAB cases (10). However, in the American guidelines, BonTA is referred to as the standard treatment option for refractory OAB, whereas the other two options are at the recommendation level (5).

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The symptoms associated with botulism were first described by Kerner in the years between 1817 and 1822. In 1895, Van Ermengen isolated this strongest neurotoxin for humans from anaerobic gram-positive Clostridium botulinum (11). Botulinum toxin acts by inhibiting the release of acetylcholine from the presynaptic vesicles in the neuromuscular junction. BonTA can be used in urological diseases, such as overactive bladder (OAB), neurogenic detrusor overactivity (NDO), detrusor sphincter dyssynergia (DSD), benign prostatic hyperplasia (BPH), interstitial cystitis (IC), and chronic pelvic pain (CPP) (12,13).

This retrospective study evaluated the efficacy and safety of intravesical BonTA injection in patients with OAB.

MATERIAL and METHODS

Study procedure

The data of 62 patients who were admitted to the Urology Outpatient Clinic of Sütçü İmam University due to the diagnosis of refractory OAB and who received BonTA injections between January 2015 and October 2019 were analysed retrospectively. Of these patients, 7 were excluded from the study because they did not attend the follow-up visits. Therefore, the study was continued with 55 patients. The study was approved by the Ethics Committee of Sütçü İmam University Faculty of Medicine (2019/21/06) and eligible patients were included into the study after informing them. The patients who experience OAB symptoms such as urinary urgency and/or urge urinary incontinence, urinary frequency, and nocturia for at least 6 months; patients who recorded urination for more than 8 times in 24 hours or more than once in one night in a 3-day voiding diary and who experienced a sudden feeling of urgency whether or not they experienced urgency urinary incontinence within 24 hours; and patients, who failed the treatment despite conservative treatments or medications (having received treatment with two different types of anti-muscarinics and/or beta-3 antagonists for 3 months or longer) were included in the study. Patients were excluded, if they had previously known or newly diagnosed urinary retention or urinary tract obstruction; metabolic diseases, neurogenic diseases causing urinary incontinence, refractory or recurrent urinary infections, history of interstitial cystitis, bladder cancer, history of bladder augmentation surgery, spinal cord injury, or neuropathic disorders. Detailed anamneses of patients were taken for OAB; information was obtained about their surgical history and previous drug therapies, and the patients underwent urologic, gynecologic, and neurologic examination. The common lab tests (complete urinalysis and urine culture) were requested. Biochemical, radiological, and urodynamic tests were carried out for differential diagnosis. The patients, who were diagnosed with OAB based on the physical examination and test findings, were given a 3-day voiding diary to be filled in before the start of the treatment. They were asked to note their daily fluid intake, their urinary output volume, and the number of urination during the day and night, and the number of incontinence episodes for three days.

Surgical Technique

Antibiotic prophylaxis was administered to the patients during the procedure. The procedure was performed in lithotomy position under one of the following anesthesia methods, including local, general, or sedation anesthesia. A dose of 100 U BonTA (Botox® Allergan, Dublin, Ireland) was diluted with 10 ml of saline solution containing no preservatives. Using a 20-French rigid cystoscope (Karl Storz; Tuttlingen, Germany), injections of 0.5 ml volume from the prepared solution were applied at 1-1.5 cm distances apart to 20 regions into the walls of the urinary bladder; including the trigone and the bladder base. No injections were made into the bladder dome to avoid perforations and accidental injections to the intestine. Most of the patients who had no difficulty in urinating were discharged from hospital on the day of operation.

Clinical Efficacy of BonTA

Observation of hematuria, urinary tract infections (UTI) developing due to the procedure (> 5 leucocytes/HPF), and post-void residual volumes > 200 ml were recorded as postoperative complications. Patients' responses to the BonTA treatment and the efficacy of the treatment were evaluated both in the pretreatment period and in the posttreatment 3rd month with the symptoms of OAB (urgency, urinary incontinence, frequency, and nocturia), maximum flow rate (Q-max), post-void residual volume (PVR), and the Urinary Incontinence Quality of Life (I-QoL) questionnaire scores.

Statistical analysis

The data were analyzed using the IBM SPSS version 20.0 software (IBM Inc., Chicago, IL, USA). Data were presented as mean ± SD values. The Mann-Whitney U test was used for the comparison of non-parametric values and Pearson's chi-square test was used for analyzing the categorical variables. A p-value of <0.05 was considered to be statistically significant.

RESULTS

Of the 55 patients, 20 were males and 35 were females. The mean age was 52.24 ± 16.4 years. The mean duration of OAB symptoms was 7.4 ± 5.81 years. All demographic data of the patients are presented in Table 1.

The posttreatment voiding diary findings are presented in Table 2. There were significant reductions in the pre-treatment urinary incontinence (UI), frequency, and nocturia complaints compared to the posttreatment findings in the 3rd month after the procedure ($p<0.05$). The comparison of the Q-max and PVR levels did not reveal any statistically significant differences between the pretreatment and posttreatment findings ($p=0.25$ and $p=0.47$, respectively). The mean I-QoL score increased significantly in the posttreatment 3rd month compared to the pre-treatment score (43.62±11.2 vs. 75.2±12.6, $p = 0.001$, respectively).

Table 1. Patients' baseline demographic data

Variable	Value
Age, years (± SD)	52.24±16.4
Gender, n (%)	
Female	35 (63.6%)
Male	20 (36.4%)
Duration of symptoms, years (± SD)	7.4±5.8
Mean lenght of using drug, years (± SD)	2.6±1.8
Comorbidity, n (%)	
Hypertension	5 (9 %)
Diabetes mellitus	3 (12 %)
Coronary artery disease	2 (2 %)

SD: standard deviation; n: number of patients

Table 2. Patients' voiding parameters and I-QoL scores at baseline and 3rd month

	Baseline	3rd month	P value
Frequency (± SD)	13.76±5.24	7.42±3.52	0.007
Urgency (± SD)	8.76±4.8	3.24±2.72	0.001
UI (± SD)	6.42±4.64	2.65±1.47	0.003
Nocturia (± SD)	3.58±0.89	1.24±0.72	0.001
Qmax (± SD) (mL/s)	21.17±10.7	20.64±9.8	0.254
PVR (± SD) (mL/s)	32.45±30.24	36.52±35.46	0.478
I-QoL scores (± SD)	43.62±11.2	75.2±12.6	0.001

p < 0.05 values are statistically significant; SD: Standard deviation; UI: Urinary incontinence; Qmax: Maximum flow rate; PVR: Post-void residual; I-QoL: Incontinence quality of life

After the Botox injection, hematuria was observed in 3 female and 2 male patients. These patients received conservative treatment with oral and parenteral fluid replacement therapy. UTI developed in 4 female and 2 male patients after the treatment. There was no growth in the urine cultures of any of these patients and they were treated with appropriate antibiotics. Clean intermittent catheterization (CIC) was initiated for three patients, who developed urinary retention after the procedure. CIC was terminated in the 4th week on the average.

DISCUSSION

The findings of our study showed that BonTA injection is an effective and safe treatment option in patients with OAB. Nearly 40% of patients treated with anticholinergics due to OAB do not respond to the treatment appropriately or remain refractory (14). Mirabegron offer a drug option with a better side effect profile. A placebo-controlled study on 1978 patients with OAB revealed that mirabegron caused decrease in voiding frequency and incontinence attacks compared to placebo (15). There are very few studies involving a combination of β 3-adrenoceptor agonist and antimuscarinic drug. In the Symphony study, Abrams et al. compared combinations of mirabegron and solifenacin with monotherapy in OAB patients. As a result of the study, the combination of two drugs was found to be more effective in patients with OAB than those given only solifenacin (16). However, data on long-term use for the effectiveness and safety of combination therapy are currently insufficient. As far as we know, there are no studies in the literature comparing mirabegron with BoNTA and using it in combination with other antimuscarinics other than solifenacin.

BonTA is one of the second-line treatments in these patients, who fail standard treatments. It has been shown in many randomized controlled trials (RCTs) and patient series that the use of BonTA is effective and safe treatment option of primary OAB. Dmochowski et al. (17) reported a 47.9% (12.5%) improvement in the frequency of daily urination at the end of 12 weeks compared with placebo. In a placebo-controlled study on 43 patients, it was reported that the number of incontinence episodes decreased in 72% of the patients after the administration of 200 U botulinum toxin into the detrusor muscle (18). In a recent multicenter placebo-controlled study with 200 U of botulinum toxin, a significant reduction was reported in the frequencies of daily urination and incontinence in the treatment-receiving patients (19). In a long-term follow-up study reporting a mean clinical recovery period between 6-14 months with botulinum toxin injections made in 14-23 month-intervals; recurrence rates were reported to vary from 27 to 66% (20). A multicenter study on 313 patients with refractory OAB compared various doses of botulinum toxin to placebo. After 12 weeks, the decrease in the number of urinary incontinence episodes per week was 17.4 with placebo; however, it was 20.7, 18.4, 23.0, 19.6, and 19.4 for the injections of 50 IU, 100 IU, 150 IU, 200 IU, and 300 IU botulinum injections, respectively. There was no significant increase in the efficacy with botulinum toxin doses above 150 IU, but increased urinary retention and urinary infection rates (21). In a placebo-controlled study conducted by Sahai et al., the urinary frequency and urgency were reduced by 40% and 70%, respectively (22). Nitti et al. evaluated 557 patients and found a significant decrease in urge incontinence and OAB symptoms in the group of patients; who were administered a dose of 100 IU BonTA in a placebo-controlled phase 3 study (23). In a prospective study, Onem et al evaluated the patients at 3 and 9 months after BonTA injection and reported that the OAB symptoms such as urinary frequency, urgency and, urge incontinence decreased in all patients (24). Mangera et al. study demonstrated a significant decrease in the frequency and urgency, and incontinence episodes after BonTA injections (p <0.02) (25). Confirming those findings; our study results showed that urinary frequency and

urgency, and the symptoms of urinary incontinence were significantly reduced in the 3rd month after the injection of 100 IU BonTA in line with the literature (p<0.05).

Intravesical Botox treatment is generally well-tolerated and major complications are rare. The most common adverse effects are increased urinary retention and urinary tract infection. In a study comparing placebo with botulinum toxin injection therapies at 50 IU, 100 IU, 150 IU, 200 IU, and 300 IU doses, the postvoid urine volume increased by 0%, 12.5%, 14.5%, 20.0%, 28.8%, and 27.3%, respectively (26). The meta-analysis conducted by López et al. found that urinary retention was higher in the group receiving a 100 IU dose of BoNT-A injection compared to the placebo group (p = 0.00001) (27). Mangera et al. concluded that the need for CIC was higher in patients receiving BonTA injections compared to the placebo group (12% vs. 0%, p <0.01) (25). Again, in a placebo-controlled study by Tincello et al. on 240 patients, the most common side effects in the BonTA group were reported to be urinary tract infections and the need for CIC at rates of 31% and 16%, respectively (19). In the meta-analysis performed by Sun et al., it was concluded that urinary tract infections were observed at higher rates and with increased severity in the BonTA injection group (6.4% and 22.1%, respectively, p <0.0001) (28). Onem et al. reported that they started CIC in 3 out of 80 patients treated with BonTA due to high PVR (> 200ml) and that no patient needed CIC after 4 weeks. They also reported that hematuria and urinary tract infections developed in five patients and they were treated with appropriate antibiotics (24). In our study, hematuria was observed in 3 female and 2 male patients after BonTA injection. These patients were treated with oral and parenteral fluid replacement therapy. In the second week after the treatment, urinary tract infections developed in 4 female and 2 male patients. These patients were treated with appropriate antibiotics according to urine culture results. CIC was started for 3 patients who developed urinary retention after the procedure and it was terminated in the 4th week on the average. None of these patients required CIC at later follow-ups.

As a chronic and displeasing situation, OAB has a significant effect on the QoL affecting the social, physical, psychological, occupational, and sexual lives of individuals. Tincello et al. study found significant improvements in I-QoL scores in the patient group receiving a 200 IU dose of BonTA compared to the placebo (p<0.0001) (19). In a meta-analysis conducted by Anger, BonTA treatment was reported to improve QoL scores compared to placebo-injected patients (29). In our study, the initial I-QoL scores were re-evaluated in the 3rd postoperative month and it was found out that they increased significantly in line with the literature (p=0.001).

One of the major limitations of our study was its retrospective design. Other limitations included the lack of a placebo control group, the short follow-up period, and the study conduct at a single site with a small number of patients.

CONCLUSION

In conclusion, BonTA injections improve the daily urinary frequency, incontinence, and QoL scores significantly in patients with OAB. Patients should be informed that hematuria, urinary retention, and urinary tract infections may develop after the injections. Further high-quality, multi-centered, and randomized-controlled trials are needed to confirm these results.

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