Randomized, double-blind, placebo controlled pilot study of intradetrusor injections of onabotulinumtoxinA for the treatment of refractory overactive bladder persisting following surgical management of benign prostatic hyperplasia

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Introduction: *We assessed the efficacy of onabotulinumtoxinA (BOTOX, Allergan Inc., Irvine, CA, USA) in patients with refractory overactive bladder (OAB) after treatment for benign prostatic hyperplasia (BPH).*

Materials and methods: *This was a two-center, randomized, double-blinded pilot study conducted in patients with OAB secondary to bladder outlet obstruction (BOO), refractory to anticholinergic medication and persistent for greater than 3 months after surgical intervention to relieve obstruction, with an International Prostate Symptom Score (IPSS) > 12. Patients were randomized in 1:1 fashion to either 200 units of onabotulinumtoxinA versus placebo. Fifteen patients received onabotulinumtoxinA versus 13 who received placebo. Follow up was performed at 1 week and then 1, 3, 6, and 9 months. The primary endpoint was reduction in the frequency of micturition per 24 hours by 3-day voiding diary. Secondary endpoints were maximum flow rate (Qmax), post-void residual (PVR), and IPSS scores.*

Results: *Patients receiving onabotulinumtoxinA demonstrated significantly improved quality of life scores at 180 and 270 days after treatment ($p = 0.02$ and 0.03, respectively) as well as significantly lower International Consultation on Incontinence Questionnaire (ICIQ) scores ($p < 0.05$). Baseline urinary frequency was 10.5 versus 11.0 voids/day ($p = 0.47$). Frequency episodes improved from 11 episodes per day to 8 episodes per day in the treatment arm. The placebo arm did not have a decrease in frequency episodes. This response was durable up to 90 days, although this was not statistically significant. IPSS, PVR, and urgency were unchanged postoperatively in both groups.*

Conclusions: *OnabotulinumtoxinA was safe in patients with refractory irritative lower urinary tracts symptoms after surgical treatment of BPH. There were improvements in daily frequency, although the results were not statistically significant. Larger trials are needed to help characterize the utility of onabotulinumtoxinA in the treatment of OAB secondary to BPH.*

Key Words: botulinum toxin, benign prostatic hyperplasia, overactive bladder

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Introduction

Overactive bladder (OAB) is defined by the International Continence Society as a symptom complex of "urgency, with or without urge incontinence (UI), usually with frequency and nocturia".[1] Urinary incontinence associated with idiopathic overactive bladder (IOAB) can markedly impact quality of life for patients. First-line treatment is typically non-surgical and consists

of behavioral modification (reduction of oral fluid intake and spreading fluid intake throughout day), pelvic muscle training, and oral medications, i.e. anticholinergics. Unfortunately, anticholinergics often cause side effects, leading to a relatively high rate of discontinuation. Second line treatment includes sacral nerve electrical stimulation, while third line treatment consists of higher-risk surgical bladder augmentation.[2,3]

OAB is a problem that can follow chronic prostatic bladder outlet obstruction and is part of the benign prostatic hyperplasia (BPH) syndrome in men. Unfortunately, it may not resolve after treatment of the outlet obstruction. The use of anticholinergic agents in these patients may not be effective, and different treatment modalities may be of benefit in these cases.

This study investigated the efficacy and safety of onabotulinumtoxinA (BOTOX, Allergan Inc., Irvine, CA, USA) in the treatment of OAB in men with BPH refractory to treatment (i.e., three antimuscarinic therapies).

Materials and methods

After IRB approval was obtained, 28 subjects with refractory OAB symptoms persistent after treatment for BPO participated in this study. Of the 28 subjects, 16 underwent laser transurethral resection of the prostate (TURP) and 12 underwent TURP. Subjects underwent surgical treatment 3 months prior to participation in this study. This was a randomized, double-blind study comparing intravesical injection of 200U onabotulinumtoxinA to placebo (200U saline, see Figure 1). Study subjects were randomized in 1:1 fashion. Follow up was performed at 7, 30, 90, 180, and 270 days post-injection.

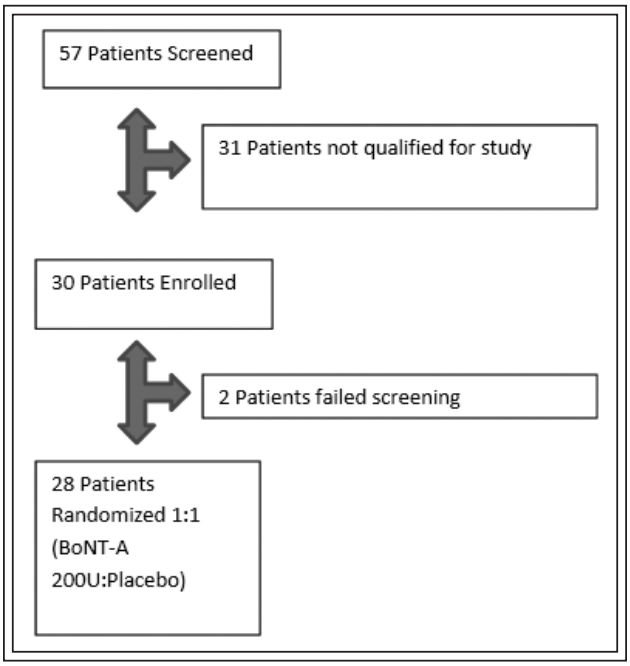

Figure 1. Block diagram.

The primary endpoint of the study was a reduction in the frequency of micturition by 3-day voiding diary. Secondary endpoints included average daily frequency of incontinence episodes over 3 days, total volume voided, post-void residual (PVR), flow meter test, International Prostate Symptom Score (IPSS), International Consultation on Incontinence Questionnaire (ICIQ). The ICIQ is a brief validated instrument that is comprehensive for the assessment of incontinence and measures frequency, severity, and impact on quality of life.[4]

The inclusion criteria consisted of males between 40 and 90 years of age with clinical signs and symptoms of frequency (> 8 micturitions/day) and urgency (> 2 episodes/day); urinary urgency incontinence > 3 episodes over 3 consecutive days of voiding diary recordings during the screening period; urodynamic history consistent with OAB that developed in conjunction with BPO and that persisted for at least 3 months post TURP or other obstruction relieving procedure; OAB inadequately controlled with anticholinergic medications, as per investigator opinion; Qmax > 12mL/s with a voided volume of > 125 mL; and IPSS > 12, with IPSS QoL > 3 (due to remaining irritative symptoms, not to obstructed symptoms) at study Visit 1.

Patients with known history of interstitial cystitis, uninvestigated hematuria, bladder outlet obstruction due to vesical neck contracture, mullerian duct cysts, urethral obstruction due to stricture, valves, sclerosis of urethral tumor, radiation cystitis, genitourinary tuberculosis, bladder calculi, or detrusor-sphincter dyssynergia were excluded. In addition, those with known history of clinically significant cardiovascular disease, cerebrovascular disease, or arrhythmia, history of spinal cord injury or multiple sclerosis, or other neurological disease which may contribute to OAB were also excluded.

Statistical analyses were conducted on an intent-to-treat basis. All statistical tests were two-sided and interpreted at a 5% significance level. Comparisons between treatment groups were performed using an ANCOVA technique with the baseline value as the covariate. The Wilcoxon Rank-Sum test was used for non-parametric tests.

TABLE 1. **Baseline characteristics**

	Placebo (n = 13)	OnabotulinumtoxinA (n = 15)	p value
Age (years), median (range)	68 (53-83)	80 (48-87)	0.16
BMI (lbs/in^2), median	32.5 (24-38)	25.7 (20-30.4)	< 0.01
Baseline IPSS, median (IQR)	20 (12-23)	16 (13-23)	0.78
Baseline Qmax, (mL/s) mean ± SD	16.0 ± 5.8	21.1 ± 10.5	0.15
Baseline voided volume (mL) mean ± SD	212.6 ± 74.5	265.4 ± 132.3	0.23
PVR (mL), mean ± SD	34.8 ± 31.2	38.3 ± 39.5	0.93
Voiding frequency preprocedure, median (IQR)	10.5 (8-13)	11 (9-14)	0.47
Type of procedure: TURP	6	6	
Type of procedure: laser TURP	7	9	

BMI = body mass index
IPSS = International Prostate Symptom Score
PVR = post-void residual
TURP = transurethral resection of the prostate

TABLE 2. **Voiding outcomes after onabotulinumtoxinA versus placebo injections in patients with overactive bladder and benign prostatic hyperplasia**

	Frequency (IQR)	Urgency (IQR)	QoL score (IQR)	ICIQ score (IQR)	PVR	Qmax	IPSS (IQR)
Baseline							
Placebo	10.5 (8-13)	4.5 (1-10)	90 (79-93)	7 (5-12)	34.8	16.0	20 (12-23)
OnabotulinumtoxinA	11 (9-14)	2 (2-4)	73 (60-92)	9 (4-15)	36	21.1	16 (13-23)
p value	0.47	0.51	0.14	0.58	0.93	0.15	0.78
Day 7							
Placebo	12 (9-14)	0.5 (0-3)	97.5 (82.5-100.5)	5 (3-7)	41.7	14	13.5 (8-20)
OnabotulinumtoxinA	8.5 (7-12.5)	1 (0-6)	81.5 (47-92)	8 (5-11)	137.1	15.7	15.5 (13-25)
p value	0.30	0.35	0.08	0.09	0.06	0.68	0.16
Day 30							
Placebo	12 (8-13)	0 (0-2)	92 (90-94)	4.5 (1-8)	26.3	12.7	13 (11-18)
OnabotulinumtoxinA	8 (7-10)	0 (0-1)	82.5 (63-94)	7 (5-10)	73.1	16.5	15 (8-18)
p value	0.12	0.78	0.28	0.25	0.25	0.34	0.85
Day 90							
Placebo	13 (7-13)	0 (0-1)	91 (66-103)			13.9	16 (10-24)
OnabotulinumtoxinA	8 (7-12)	0 (0-1)	88 (61-91)			10.3	5 (10-17)
p value	0.35	0.83	0.24			0.40	0.60
Day 180							
Placebo	10 (8-14)	1 (0-3)	**97.5 (88.5-105.5)**	4 (1-6)	151.6	8.7	14.5 (11-19.5)
OnabotulinumtoxinA	9 (8-12)	1.5 (0-4)	**79 (59-86)**	4 (4-7)	168.6	12.8	17 (13-22)
p value	0.70	0.74	**0.02**	0.68	0.85	0.27	0.35
Day 270							
Placebo	8.5 (5-10)	0 (0-1)	**99 (93-107)**	4 (3-4)	21.2	9.3	17 (10-18)
OnabotulinumtoxinA	9.5 (7-10)	0 (0-7)	**79 (67-87)**	8.5 (6-13)	54.4	12.9	15 (12-15)
p value	0.46	0.52	**0.02**	0.05	0.39	0.59	0.78

Sample size calculation

In order to detect a difference of 3 episodes between treatment groups in the mean change from baseline in the average daily frequency of micturition (1° endpoint; 3-day voiding diary), with an attrition rate of 20%, it was necessary to enroll 34 subjects (17 subjects/ treatment group).

Results

Baseline characteristics were similar between the treatment groups, although body mass index (BMI) was higher in the placebo group ($p < 0.01$). The median age in the placebo arm was 68 versus 80 years in the onabotulinumtoxinA arm ($p = 0.16$, see Table 1. In comparison between groups at baseline and after treatment with regard to the urge incontinence episodes measured by 3-day voiding diary, both groups displayed a slight decrease; the botox group went from 1.06 at baseline to .98 after treatment and the placebo group went from 1.08 at baseline to .99 after treatment. These were not statistically significant. Patients receiving onabotulinumtoxinA demonstrated significantly improved quality of life scores at 180 and 270 days after treatment ($p = 0.02$ and 0.03, respectively) as well as significantly lower ICIQ scores ($p < 0.05$).

Baseline urinary frequency was 10.5 versus 11.0 voids/day ($p = 0.47$). Frequency episodes improved from 11 episodes per day to 8 episodes per day in the treatment arm. The placebo arm did not have a decrease in frequency episodes. This response was durable up to 90 days, although this was not statistically significant finding. IPSS, PVR, and urgency were unchanged postoperatively in both groups, Table 2.

Adverse events included hematuria in 1 patient (3.5%), acute urinary retention in 2 patients that resolved with catheter placement (7%), and 1 patient with a UTI that resolved with oral antibiotics (3.5%), Table 3. Complications did not exceed grade I on the Clavien Classification System (CCS).[5]

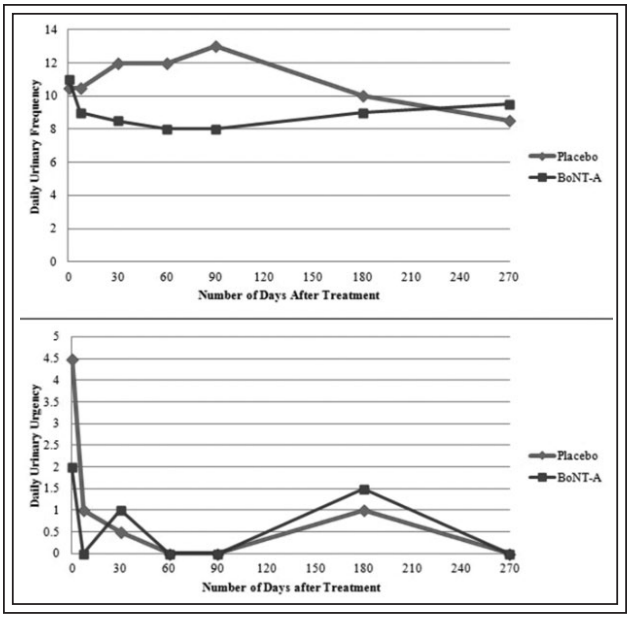

Figure 2. Post-procedural median daily frequency and urgency.

Discussion

This randomized, double blind, placebo controlled pilot study investigates the use of intradetrusor onabotulinumtoxinA for refractory OAB symptoms. There was improvement in frequency episodes from 1 week to 90 days. At 6 months there was a return to a baseline in frequency episodes. This finding was not statistically significant, Figure 2. Additionally, a decrease in IPSS scores at 90 days in the treatment arm was found; this finding was not statistically significant, Figure 3.

The efficacy of onabotulinumtoxinA is supported by published data on idiopathic OAB. Sahai, et al published the first double blind placebo controlled trial of 200 units in idiopathic OAB, which showed safety and efficacy over a 24 week study period.[6]

TABLE 3. **Adverse events**

Adverse event	Number of patients	Percent	Intervention	CCS grade
Hematuria	1	3.5%	Catheter drainage and clot evacuation	I
Acute urinary retention	2	7%	Catheter placement	I
Urinary tract infection	1	3.5%	Oral antibiotics	I

CCS = Clavien classification system[5]

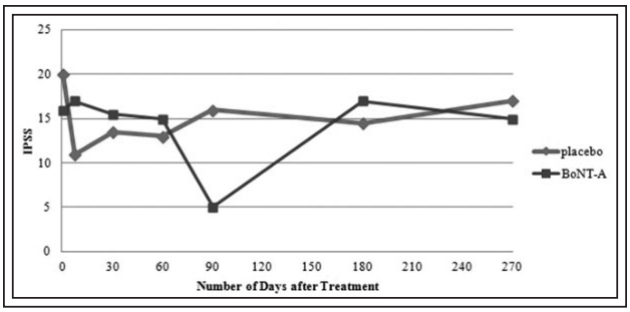

Figure 3. Post-procedural median International Prostate Symptom Score.

In a multinational randomized, placebo controlled study by Dmochowski et al, 313 patients with OAB and urgency incontinence episodes received 50, 100, 150, 200 or 300U intradetrusor onabotulinumtoxinA, or placebo.[7] The primary endpoint was weekly urinary urgency incontinence episodes in 3 months. OnabotulinumtoxinA in amounts of 100U or greater demonstrated durable efficacy in OAB and UUI episodes while maintaining safe PVRs.

Treatment with onabotulinumtoxinA was well tolerated, Table 3. There were no urinary tract infections reported as defined by greater than 10^5 cfu on urine culture. There were two patients who went into transient urinary retention that resolved with catheter drainage. One patient had hematuria significant enough to justify catheter placement and clot evacuation. This resolved without surgical intervention or need of blood transfusions.

Several trials have demonstrated the tolerability of intradetrusor onabotulinumtoxinA. Current trials have reported an incidence of UTIs of 1.3%-64%, rates of retention requiring intermittent catheterization of 1.3%-42.2%.[7-9] The data presented in this group had lower reported rates, likely secondary to the small sample size in this study. This study has several limitations. Primarily, based on the initial sample size calculation, there were not enough patients recruited for the primary endpoint. This was partially due to the uncommon nature of patients with OAB-like symptoms secondary to surgery for BOO.

The onabotulinumtoxinA group was both older and had a lower BMI than the placebo group. This study was conducted with 200 units of onabotulinumtoxinA; the current standard is to treat idiopathic OAB with 100 units of onabotulinumtoxinA. This study was conducted with 3-day voiding diaries. While consistent in most other trials, a 7-day diary may have unmasked other changes in voiding habits, incontinence episodes, etc. Larger, properly powered and matched trials are needed to further characterize the role of onabotulinumtoxinA in the cohort. □

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