HHS Public Access

Author manuscript

Neurourol Urodyn. Author manuscript; available in PMC 2016 February 16.

Published in final edited form as:

Neurourol Urodyn. 2015 September ; 34(7): 675–678. doi:10.1002/nau.22642.

Urinary Retention Rates after Intravesical OnabotulinumtoxinA Injection for Idiopathic Overactive Bladder in Clinical Practice and Predictors of this Outcome

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Abstract

Aims—The purpose of this study was to find the rate of urinary retention in clinical practice after treatment with onabotulinumtoxinA (BTN/A) for refractory overactive bladder (OAB) symptoms and determine factors that predict this outcome.

Methods—This is a retrospective study of BTN/A for treatment of non-neurogenic, refractory OAB symptoms. Patients were analyzed with respect to their first and second BTN/A injections. The primary outcome measure was postoperative urinary retention. Statistical significance was assessed with multivariate logistic regression.

Results—Based on inclusion and exclusion criteria, the study population was 160. Mean age was 64 ± 13.2 years and 24% of the patients were men. The rate of urinary retention was 35% (n = 56). For the first BTN/A treatment, multivariate analysis revealed that preoperative PVR (post-void residual volume) (OR 1.27, 95% CI 1.13–1.43, $P < 0.001$) and preoperative bladder capacity (OR 1.05, 95% CI 1.01–1.08, $P = 0.005$) were associated with postoperative urinary retention. In patients with a preoperative PVR of ≥100 ml, 94% (n = 17) went into urinary retention. For those who underwent a second BTN/A treatment, preoperative PVR, BTN/A units injected and retention after the first BTN/A were associated with an increased rate of postoperative retention.

Conclusions—Increased preoperative PVR was associated with urinary retention. The retention rate is higher than that reported in recent clinical trials. The inclusion of patients with a preoperative PVR ≥100 ml and a lower threshold to initiate clean intermittent catheterization contributed to this high rate of retention.

Keywords

Botox; complication; intermittent catheterization; post-void residual

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Eric Rovner led the peer-review process as the Associate Editor responsible for the paper.

Conflict of interest: none.

Author Contributions: All of the above authors made: (1) Substantial contributions to conception and design, (2) Drafting and revising the article critically for important intellectual content, (3) Final approval of the version to be published.

INTRODUCTION

The initial treatment of overactive bladder (OAB) symptoms usually involves conservative interventions such as fluid management and lifestyle modification.[1] If these interventions are unsuccessful, AUA guidelines suggest initiation of pharmacologic treatment with an anticholinergic medication.[2] If pharmacologic treatment does not yield adequate response, the patient typically undergoes a diagnostic evaluation beyond the typical urinalysis and post-void residual volume (PVR) measurement. This step often involves a cystoscopy and urodynamics. If no anatomic or contraindicated functional abnormalities are discovered, one of the available third-line treatment modalities is intradetrusor injection with onabotulinumtoxinA (BTN/A). This mode of therapy has been shown to be efficacious and safe in two recent randomized, placebo-controlled trials.[3,4]

One of the most common side effects of intradetrusor BTN/A injection is urinary retention. Ranging from 5.4% to 43%, the rate of urinary retention in published studies is highly variable and dependent on how retention is defined, the patient population and the units of BTN/A administered.[3–10] The purpose of this study was to find the rate of urinary retention in clinical practice after treatment with BTN/A for medication-refractory OAB symptoms and determine whether or not there are factors that predict this outcome.

MATERIALS AND METHODS

After obtaining Institutional Review Board (IRB) approval (IRB#130288), electronic medical records were queried for the following CPT (current procedural terminology) codes over the 10-year study period of 2003–2012: 53899 (cystoscopy with Botox injection into bladder) and 64640 (destruction by neurolytic agent). A secure database was created with all patients identified by the CPT search.

The demographic information collected included patient age at the time of the first BTN/A treatment and gender. In addition to body mass index (BMI), a prior history of the following comorbid medical conditions was also evaluated: pelvic radiation, diabetes, neurologic disease, intermittent urinary catheterization, and urinary retention. Data were also collected on lower urinary tract symptoms and the presence of urgency incontinence. The results of preoperative urodynamics were also collected. Outcome measures included urinary retention, urinary tract infection, repeat BTN/A treatment, subjective improvement in symptoms (>50% reduction in voiding symptoms) and length of time of intermittent catheterization measured in weeks. Postoperative urinary retention was defined as any patient who was started on daily intermittent catheterization or had an indwelling catheter placed. PVR volumes were measured by bladder scanner ultrasonography or intermittent catheterization.

Patients were included in this study if they underwent trial and failure or were intolerant of at least one anticholinergic medication prior to their BTN/A treatment. Also, patients had to demonstrate preoperative persistent complaints of urgency urinary incontinence and urinary frequency. In addition, all patients included in the database needed to have a preoperative PVR measurement prior to BTN/A treatment.

Patients were excluded from analysis if they had a history of neurogenic bladder or a neurologic condition that is known to affect voiding. In addition, patients were also excluded if they had a preoperative PVR >200 ml or if they had a history of urinary retention treated with intermittent catheterization or an indwelling urethral catheter. Lastly, patients were excluded if they had less than 4 weeks of follow up, received BTN/A prior to being treated at our institution, received more than 200 units of BTN/A during their first treatment or participated in an earlier clinical trial.

STATISTICAL ANALYSIS

Initial statistical analysis of continuous variables such as age was performed using the T-test mean comparison test and analysis of categorical variables was carried out using Pearson's Chi-Squared test. The eligible cohort of patients was separated into two groups, patients who experienced urinary retention and patients who did not experience urinary retention after their first BTN/A treatment. The associations between postoperative retention and age, gender, BMI, dosage of BTN/A (100 or 200 units), diabetes, pelvic radiation, type of anesthesia (BTN/A in clinic under local vs. general anesthesia), preoperative PVR (10 ml increments), bladder capacity (10 ml increments) during urodynamics, and maximum detrusor pressure at peak flow during urodynamics (pDet at Qmax) were assessed with multivariate logistic regression.

RESULTS

Of the 405 patients identified in the initial collection of medical record numbers based on the screened CPT codes, 160 patients met eligibility for inclusion. The most common reasons for exclusion were a history of a neurologic condition, a history of high PVR (> 200 ml) or urinary retention and greater than 200 units of BTN/A injected. Figure 1 displays the results of patient inclusion and exclusion into the study.

The average age was 64.0 ± 13.2 years and 76% of patients were female. Although not part of the inclusion criteria, all patients underwent urodynamics prior to the BTN/A injection. In addition, all patients had tried at least one anticholinergic medication prior to their BTN/A treatment, had complaints of urgency incontinence, complaints of urinary frequency and had a PVR checked preoperatively and at their initial postoperative visit. Table I lists results of baseline demographic and preoperative characteristics in the study population, no retention and retention groups.

Postoperatively, 56 (35%) patients experienced urinary retention and required initiation of intermittent catheterization for a mean duration of 16 weeks (1–40 weeks). Of note, nine patients performed once-daily CIC to aid in emptying their bladders at night for at least 20 weeks after surgery. Patients who received 100 units and had a preoperative PVR of <100 ml demonstrated a 21% rate of urinary retention. Twenty-six (16%) patients experienced a postoperative urinary tract infection and 117 (74%) patients had improvement in urgency incontinence. Also, 102 (64%) patients reported subjective improvement and 87 (54%) patients in the study population underwent a second BTN/A treatment. Of those with urinary

retention, 32 (57%) patients reported subjective success of the procedure and 28 (50%) had further BTN/A injections. The overall median follow-up was 12.5 (IQR 22.5) months.

Of the 56 patients with retention, 48 were started on CIC and eight had an indwelling catheter placed. Five (9%) patients had an indwelling catheter placed by a primary care physician or in an emergency room because the patient presented with lower urinary tract symptoms perceived to have resulted from urinary retention. The other 51 patients were instructed to initiate CIC or had an indwelling catheter placed by the treating physician. This decision was made in any patient with an elevated PVR volume and symptoms consistent with urinary retention or if the provider felt that that the patient was experiencing asymptomatic urinary retention based only on a high PVR volume. Lastly, eight (14%) of the patients in the retention group were instructed to perform CIC only once per day to aid in emptying the bladder. Of note, four of these patients had asymptomatic retention. Table II lists the proportion of patients that were determined to have retention and the corresponding postoperative PVR.

Overall, 12 (21%) patients had asymptomatic retention and were started on CIC or had an indwelling catheter placed because of a high postoperative PVR value in the absence of retention symptoms. The average PVR in patients with asymptomatic retention was 442.7 ± 102.1 ml. The range in PVR of these asymptomatic retention patients was 300–637 ml. Pearson chi-squared analysis revealed that the 41 patients with a preoperative bladder capacity of >400 ml (range 401–844 ml) were more likely to have asymptomatic retention ($P = 0.01$). In addition, analysis also revealed that these large capacity bladder patients were more likely than other patients to have any retention (49% vs. 35%, $P = 0.032$). Lastly, there were a significantly lower percentage of large capacity bladder patients than other patients with DO on preoperative urodynamic testing (63% vs. 87%, 0.001).

A multivariate analysis was performed on the study population in order to determine factors that may predict urinary retention. The results of this analysis are displayed in Table III. A separate multivariate analysis analyzing the risk of postoperative retention was performed on just those patients that received 100 units of BTN/A and these results are displayed in Table IV.

Another multivariate logistic regression analysis was performed on the 87 patients who underwent a second BTN/A treatment. This analysis demonstrated that PVR prior to the second BTN/A treatment (OR 1.19, 95% CI 1.03–1.38, $P = 0.02$), BTN/A units injected (OR 4.22, 95% CI 1.15–15.49, $P = 0.03$), and retention after the first BTN/A (OR 30.20, 95% CI 5.18–175.92, $P < 0.001$) were associated with increased rate of postoperative urinary retention.

DISCUSSION

Analogous to the two recent randomized clinical trials of BTN/A for non-neurogenic OAB, in this study herein described, all patients who had symptoms consistent with urinary retention after BTN/A treatment were started on intermittent catheterization or had an indwelling foley placed.[3,4] The above-mentioned trials were designed with limits on

postoperative PVR for urinary retention, however, clinicians were allowed to start patients on intermittent catheterization if clinical judgment warranted this decision. Our study revealed an overall 35% rate of postoperative urinary retention following BTNA treatment for idiopathic OAB. This is much higher than the urinary retention rates of 6.9% and 6.1% in the first 12 weeks of the two randomized, placebo-controlled trials. Of all the variables evaluated, only an elevated preoperative PVR and an elevated preoperative bladder capacity were associated with urinary retention after the first treatment. In 2009, Sahai et al.[11] found that maximum urinary flow and bladder contractility were associated with urinary retention. However, in the study herein described we did not find this relationship to be significant.

The mean length of urinary retention was 16 weeks, however, in the literature, the mean duration of urinary retention is only 9 weeks.[8,9] The longer length of urinary retention in this trial may be due to a tendency by our clinicians to keep patients on a once-daily CIC regimen. This was often intended to help patients with complaints of nocturia.

Unlike the previously mentioned clinical trials, we did include 18 patients who had a pre-operative PVR of >100 ml and interestingly, 17 (94%) of these patients went into urinary retention.[3,4] An earlier randomized clinical trials in which patients with a preoperative PVR up to 200 ml were included had a higher rate of intermittent catheterization (10.2%) than the more recent studies.[10] The inclusion of patients with a PVR of >100 ml more closely mirrors how intravesical BTN/A might be employed in clinical practice and these patients need to be counseled about the high risk of urinary retention. In addition, patients who received 200 units of BTN/A were included to evaluate the risk of retention for that higher dosage. The higher dosage of BTN/A was not associated with an increased rate of retention after the first BTN/A, but it did with the second BTN/A treatment. Overall, pertaining to the first BTN/A treatment, patients who received only 100 units and had a preoperative PVR of <100 ml still demonstrated a 21% rate of urinary retention.

In this study, 31% of patients had a postoperative PVR ≥200 ml. This was higher than the 10.2% of patients that had a postoperative PVR ≥200 ml in the 2013 European randomized, placebo-controlled trial of 277 patients by Chapple et al.[4] This higher postoperative PVR certainly contributed to the high rate of CIC herein reported. In our study the decision to recommend a patient perform CIC was based on the patient's urinary complaints and PVR. This resulted in 23% of patients with a PVR between 100 and 200 ml, and 92% of the patients with a PVR of >200 ml being started on CIC. If these same percentages were applied to the previously mentioned Chapple et al. trial, the rate of retention in their trial would increase from 6.9% to 15.0%.[4] In that trial only 2% (1/53) of patients with a PVR of between 100 and 200 ml, 41% (7/17) of patients with a PVR between 200 to 350 ml and 90.9% (10/11) of patients with a PVR ≥350 ml were initiated on CIC. Therefore, the much higher rate of urinary retention seen our trial and others may have partially resulted from a lower threshold to initiate a patient on CIC.[5–7] Going forward the true rate of urinary retention in clinical practice will likely exceed the rates demonstrated in the recent clinical trials.

Preoperative bladder capacity was also significantly associated with retention after the first BTN/A treatment. It is possible that patients with a large capacity bladder are more likely to

have CIC recommended because they have a more difficult time emptying their bladders after BTN/A treatment and thus have a higher postoperative PVR. Interestingly, the rate of urinary retention was 49% in patients with a bladder capacity >400 ml and these patients were significantly more likely to have asymptomatic urinary retention ($P = 0.003$). Patients with these large capacity bladders were also less likely to have DO on preoperative urodynamic testing. Even though the presence of DO was not significantly associated with an increased rate of urinary retention, the lower percentage of DO seen in the large capacity bladder patients may have contributed to their higher rate of urinary retention. It is unclear what the true relationship is between the presence of DO and urinary retention in patients with large capacity bladders.

Lastly, 57% of the patients with postoperative urinary retention demonstrated subjective improvement and 50% went on to have more BTN/A treatments. Therefore, similar to a study by Kessler et al. looking at outcomes after BTN/A treatment, retention patients may have a better quality of life with catheterization after BTN/A treatment than before BTN/A treatment with no catheterization.[12]

CONCLUSIONS

Though the retrospective nature of this study is a limitation, the rate of urinary retention demonstrated in this manuscript is much higher than the rates reported in recent randomized, placebo-controlled trials. This higher rate of urinary retention appears to primarily result from a lower threshold to initiate CIC and the inclusion of patients with >100 ml preoperative PVR. This analysis additionally reveals a significant correlation between preoperative PVR and bladder capacity on postoperative urinary retention. Patients with an elevated PVR (particularly over 100 ml) and a high bladder capacity (particularly over 400 ml) should be counseled that they have a higher likelihood of requiring postoperative CIC. Interestingly, the majority of patients who initiated CIC reported subjective improvement and elected to undergo more BTN/A treatments.

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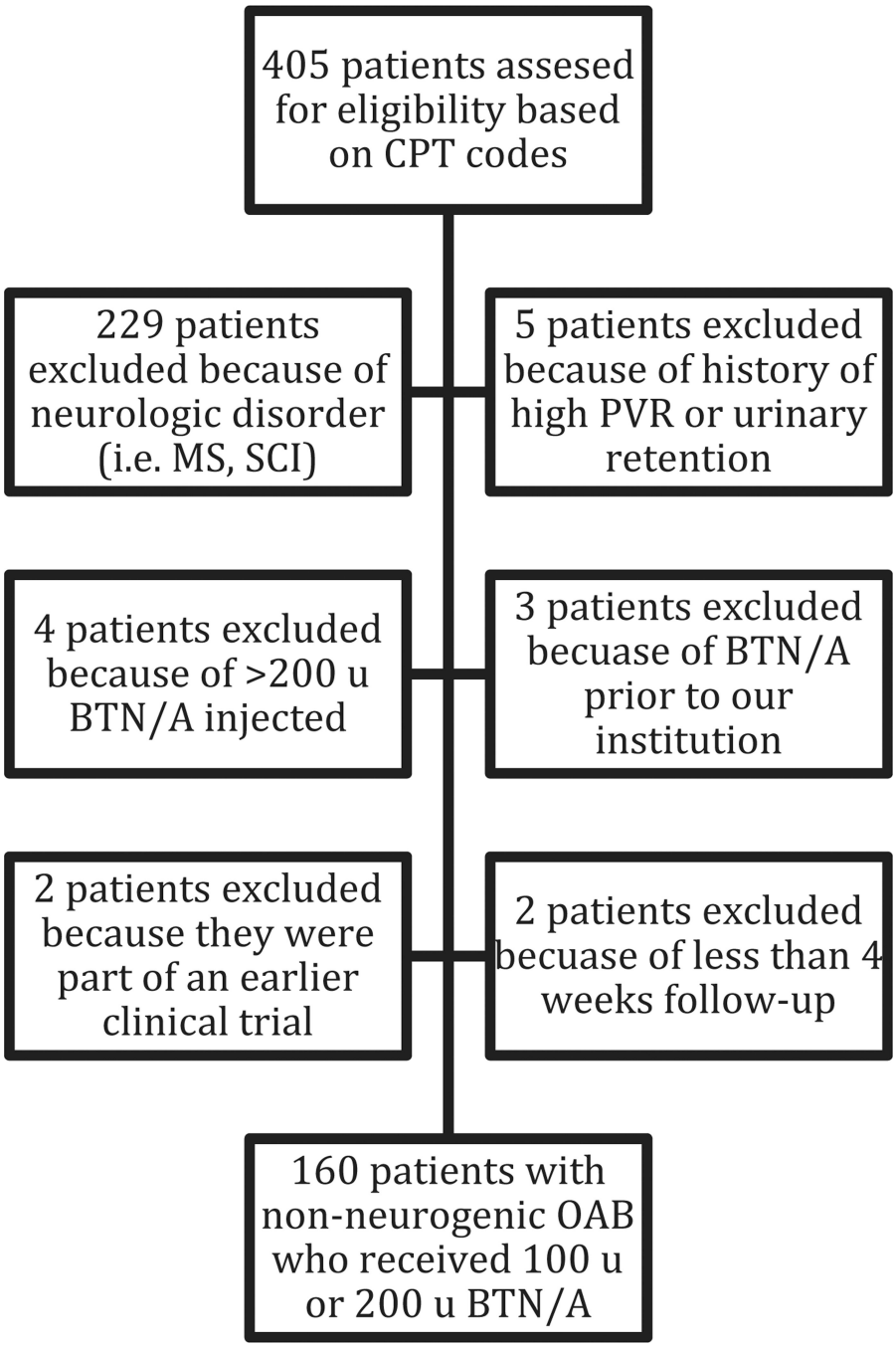

Fig. 1.
Consort diagram for inclusion or exclusion into retrospective study.

TABLE I

Baseline Demographic and Preoperative Characteristics of Study Population and no Retention and Retention Groups (First BTN/A Treatment)

Characteristic	Study population	No retention	Retention	*P*-value
Patients	160	104	56	
Age (yrs)	64 ± 13.2	64 ± 13.6	65 ± 12.5	0.701
Female	121 (76)	74 (71)	47 (84)	0.073
Diabetes	36 (23)	20 (20)	16 (29)	0.158
Prior pelvic radiation	10 (6)	8 (8)	2 (4)	0.304
Body mass index	31 ± 8.0	32 ± 8.6	30 ± 6.1	0.044
Preoperative urodynamic findings				
Bladder capacity (ml)	298 ± 163.6	264 ± 162.2	357 ± 146.7	0.001
Bladder capacity >400 ml	41 (26)	21 (20)	20 (36)	0.032
Qmax (ml/s)	13.1 ± 9.3	12.8 ± 10.2	13.8 ± 7.4	0.536
DO during urodynamics	129 (81)	89 (86)	40 (71)	0.082
pDet at Qmax (cmH_2O)	25.6 ± 16.4	24 ± 15.2	28 ± 18.1	0.117
PIP(1) (females only)	37.3 ± 18.4	35.1 ± 17.7	40.6 ± 19.2	0.126
BOOI (males only)	13.7 ± 15.8	13.1 ± 16.6	15.4 ± 13.9	0.733
Preoperative PVR	33.5 ± 46.5	18 ± 21.6	63 ± 63.5	<0.001
Preoperative PVR >100 ml	18 (11)	1 (1)	17 (30)	<0.001
Local anesthesia	42 (26)	27 (26)	15 (27)	0.813
Units of BTN/A injected	137 ± 48.4	134 ± 47.5	143 ± 49.9	0.253
BTN/A injected: 100 u	101 (63)	69 (66)	32 (57)	0.250
BTN/A injected: 200 u	59 (37)	35 (34)	24 (43)	0.250

Mean ± SD, n (%).

Qmax (maximum urinary flow), PIP(1) (projected isovolumetric pressure; pDet at Qmax + Qmax), BOOI (bladder outlet obstructive index; pDet at Qmax − 2× Qmax), DO (detrusor overactivity).

TABLE II

Proportion of Patients Initiated on CIC for each Postoperative PVR (First BTN/A Treatment)

Postoperative PVR	Proportion CIC initiated
≤100 ml	1/80 (1%)
>100 and <200 ml	7/30 (23%)
≥200 and <350 ml	23/25 (92%)
≥350 ml	25/25 (100)

TABLE III

Logistic Regression Multivariate Analysis of Postoperative Urinary Retention for First BTN/A Treatment (100 and 200 Unit Patients)

	Odds ratio	95% Confidence interval	*P*-value
Age	1.02	0.98–1.06	0.349
Gender	2.32	0.65–8.26	0.192
Diabetes	1.60	0.50–5.04	0.425
BMI	0.96	0.90–1.01	0.134
pDet Qmax	1.03	0.99–1.06	0.062
DO on urodynamics	0.50	0.16–1.63	0.253
Bladder capacity[a]	1.05	1.01–1.08	0.005
Preoperative PVR[a]	1.27	1.13–1.43	<0.001
Local anesthesia	1.23	0.43–3.58	0.698
BTN/A units[b]	2.31	0.87–6.12	0.092

[a] 10 ml increments.

[b] 100 unit increments.

TABLE IV

Logistic Regression Multivariate Analysis of Postoperative Urinary Retention for the First BTN/A Treatment (101 Patients that Received 100 Units)

	Odds ratio	95% Confidence interval	*P*-value
Age	1.02	0.97–1.07	0.42
Gender	3.12	0.58–16.83	0.19
Diabetes	0.55	0.10–3.09	0.49
BMI	0.94	0.87–1.03	0.20
Pelvic radiation	1.94	0.13–28.96	0.63
pDet Qmax	1.01	0.98–1.04	0.62
Bladder capacity[a]	1.06	1.01–1.10	0.02
Preoperative PVR[a]	1.39	1.15–1.67	0.001
Local anesthesia	0.55	0.12–2.47	0.43

[a]10 ml increments.