Very Low, Real-Time Rate of Urinary Retention after Intradetrusor Botox® for Non-Neurogenic Overactive Bladder

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Abstract

Introduction: According to the most recent AUA/SUFU guidelines, intradetrusor onabotulinumtoxinA (BTN/A) is a standard, evidence strength grade B, third line treatment option for refractory non-neurogenic overactive bladder (OAB). Urinary retention is the most common clinically significant reported side effect ranging from 5.4% to 43% in previous studies. The aim of this study was to investigate the real-time rate of urinary retention in patients treated with BTN/A for refractory non-neurogenic OAB in a multi-institutional study. Methods: Retrospective chart review identified 71 patients who were treated with 100U BTN/A for refractory non-neurogenic OAB from August 2011 to July 2015 at two institutions. Using a flexible cystoscope, 100U Botox® reconstituted with 10 ml normal saline was administered. Injections of 1 ml (10 units/mL) were administered in 10 evenly distributed sites sparing the trigone. Pre and post BTN/A post-void residuals (PVR) were reviewed. Urinary retention was defined as PVR > 200 mL requiring clean intermittent catheterization (CIC).

Results: After exclusion, the study group consisted of 66 patients with a mean age of 67 years and 30% were men. Mean pre and post-procedural PVR were 14.06 mL and 69.21 mL. Eight patients (12.12%) were noted to have elevated PVR > 200 mL post injection however only one patient (female) required initiation of CIC. The rate of urinary retention was 1.5% (N = 1). There was no correlation with age, history of previous radiation, diabetes or prior use of a neuromodulator device. Conclusions: To the best of our knowledge, this is the first study to demonstrate a very low risk of real-time urinary retention rates in appropriately selected patients treated with BTN/A for refractory non-neurogenic OAB outside of a clinical trial setting.
1. Introduction

Non-neurogenic or idiopathic overactive bladder (OAB) is a symptom complex, which is defined by the International Continence Society (ICS) standardization committee as urgency, with or without urgency incontinence, usually with frequency and nocturia, in the absence of proven infection or other obvious pathology [1]. Although non-life threatening, it is a chronic, costly and debilitating disorder and can have a significant impact on quality of life.

While no standard definition exists for “refractory OAB”, it is a term often used to describe patients who have either failed or were unable to tolerate conservative therapy and/or anticholinergic/beta 3 agonist therapy. Available third line options now include pharmacologic use of intradetrusor onabotulinumtoxinA [Botox®, Allergan, Inc., Irvine, CA, USA/(BTN/A)].

Safety, efficacy and durability of BTN/A have been demonstrated in previously published randomized controlled trials [2] [3] [4]. However, one of the most common side effects of therapy is urinary retention. In previously published literature, urinary retention was reported to occur in 5% - 43% of patients and was shown to be dose-dependent [2]-[7]. The purpose of this study was to assess the real-time rate of urinary retention in clinical practice after administration of BTN/A for refractory non-neurogenic OAB in a multi-institutional clinical setting.

2. Methods

Retrospective chart review identified 71 patients who were treated with 100 units (U) BTN/A for refractory non-neurogenic OAB from August 2011 to July 2015 at two institutions. These institutions included a 178-bed community hospital, part of a large health care network that averaged more than 70,000 admissions in 2016. The second institution is a large 900-bed academic center that averages greater than 25,000 annual admissions.

Given the retrospective nature of the study, along with confidential chart review in accordance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the use of pre-existing patient data and records, our study met criteria for exemption from further ethical clearance. Therefore approval from institutional review boards was not pursued.

Our technique was in accordance with previously described principles [8] [9] [10]. Using a flexible cystoscope, 100 U of Botox® reconstituted with 10 ml normal saline was administered in an office setting without use of general anesthesia. Local anesthesia using 20 mL of 1% Lidocaine was utilized at one institution. Using a 27 gauge injection needle, aliquots of 1 ml (10 units/mL) were adminis-
tered in 10 evenly distributed sites sparing the trigone. In accordance with pre-
viously published randomized control trials [2], pre and post BTN/A post void re-
siduals (PVR) were reviewed at 2 and 6 weeks post treatment or at any other visit 
depending on clinical need. A PVR ≥ 200 mL was considered elevated. Clean inter-
mittent catheterization (CIC) was initiated at PVR ≥ 200 ml with associated symp-
toms or PVR ≥ 350 mL regardless of symptoms. Urinary retention was defined as 
any PVR of ≥200 mL that required CIC in accordance with previously published 
methodology in the phase 3 randomized controlled trail by Nitti et al. [2].

Secondary variables assessed included age, history of previous radiation, diabetes, 
and prior use of a neuromodulator device [Interstim™ neuromodulator (Med-
tronic, Minneapolis, MN, USA) or peripheral tibial nerve stimulation].

Exclusion criteria included elevated pre-procedural PVR ≥ 100 mL, history of re-
current urinary tract infections (UTIs), predominant stress incontinence symp-
toms, lack of follow up, patients who were unable or unwilling to perform CIC, 
patient’s with neurogenic bladder and/or any nervous system pathology that may 
induce lower urinary tract symptoms such as Parkinson’s disease, Alzheimer’s dis-
ease, cerebrovascular accidents, spinal cord injuries etc.

3. Results

After exclusion, the study group consisted of 66 patients with a mean age of 67 
years ± 1.61 years. Of the 66 patients, 46 (69.7%) were female and 20 (30%) were 
men. Mean pre and post-procedural PVR was 14.06 mL ± 24.06 mL [95% CI 
(19.86, 8.26)] and 69.21 mL ± 1.61 mL [95% CI (90.26, 48.16)]. Eight patients 
(12.1%) were noted to have elevated PVR ≥ 200 mL post injection and all were 
asymptomatic. Only one patient (female) required initiation of CIC. The rate of 
urinary retention was 1.5% (N = 1). Demographics of the eight patients with 
elevated PVRs are listed in Table 1. Data was obtained by detailed and confiden-
tial review of retrospective patient records.

Demographics of the single patient who required CIC for elevated PVR are 
outlined in Table 2. The patient did not have any history of diabetes or radiation.

Table 1. Demographics of the eight patients with elevated PVRs.

<table>
<thead>
<tr>
<th>Demographics of Patients with Elevated PVRs</th>
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<tbody>
<tr>
<td>PVR &gt; 200</td>
<td>8 (12.1%)</td>
</tr>
<tr>
<td>Male</td>
<td>3 (37%)</td>
</tr>
<tr>
<td>Female</td>
<td>5 (62.5%)</td>
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<tr>
<td>Average age</td>
<td>69.88 years ± 4.3 years</td>
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<tr>
<td>Diabetes</td>
<td>1 (12.5%)</td>
</tr>
<tr>
<td>Radiation</td>
<td>0</td>
</tr>
<tr>
<td>Prior sacral neurostimulator (Interstim™)</td>
<td>3 (37%)</td>
</tr>
<tr>
<td>Prior peripheral tibial nerve stimulation</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Avg pre-procedural PVR</td>
<td>26 mL ± 13.14 mL [95% CI (51.75, 0.25)]</td>
</tr>
<tr>
<td>Avg post-procedural PVR</td>
<td>249.88 mL ± 22.55 mL [95% CI (294.08, 205.67)]</td>
</tr>
<tr>
<td>Use of local anesthesia (Lidocaine)</td>
<td>Per investigator discretion</td>
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Table 2. Clinical characteristics of single patient with urinary retention.

<table>
<thead>
<tr>
<th>Demographics of Single Patient with Urinary Retention</th>
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<tbody>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Diabetes</td>
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<tr>
<td>Radiation</td>
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<tr>
<td>Prior sacral neurostimulator (Interstim™)</td>
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<tr>
<td>Prior peripheral tibial nerve stimulation</td>
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<tr>
<td>Pre-procedural PVR</td>
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<tr>
<td>Post-procedural PVR</td>
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<tr>
<td>Use of local anesthesia (Lidocaine)</td>
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However she did fail prior sacral neuromodulation (Interstim™). Her pre-procedural PVR was 70 mL and CIC was initiated for asymptomatic elevated post-procedural PVR of 379 mL. In addition, no local anesthesia was utilized during injection.

Secondary variables assessed included age, history of previous radiation, diabetes and prior use of a neuromodulator device (Interstim™ neuromodulator or peripheral tibial nerve stimulation). Of the 66 patients, 15 (22.7%) were diabetic, 12 (18%) had history of prior radiation, 10 (15%) had prior sacral neuromodulation (Interstim™) and one (0.1%) had previous peripheral tibial nerve stimulation.

4. Discussion

In 2007, OAB was one the most common urologic disorders, accounting for more than 2 million physician office visits in the United States [11]. The negative impact on health-related quality of life (HRQL) has shown to have a considerable social and financial impact.

Less work productivity, higher rates of depressive symptoms, less sexual satisfaction, erectile dysfunction and lower levels of overall health have been shown to be correlated with OAB [12] [13]. In addition, the economic footprint associated with this condition is staggering. Total national cost, including community and institutional costs, was estimated at $65.9 billion in 2007 and is expected to increase to $82.6 billion by 2020 [14].

Finding an ideal treatment for OAB has been a challenge in the realm of voiding dysfunction. While no perfect treatment exists, there are several options available. An algorithm has been set forth by the AUA/SUFU Guidelines [15] [16]. The guidelines state that third line therapies should be pursued if first line (fluid management and behavioral modification) and second line (anticholinergics/beta 3 agonists) are insufficient, unable to be tolerated and/or do not result in acceptable symptom improvement. Third line treatment options include neuromodulation and chemical denervation. Chemodenervation with pharmacologic use of onabotulinumtoxinA (Botox®, BTN/A) was approved by the FDA.
in 2013 for use in patients with OAB who did not adequately respond to oral medications. It was recently upgraded and received the stronger rating of “standard” (strength of evidence grade B) by the amended 2014 AUA/SUFU guidelines [15] [16].

Our study evaluated the real-time rate of urinary retention in clinical practice outside of a regimented clinical study. We demonstrate that the real-time rate of urinary retention in clinical practice is far less than previously reported. Another unique aspect of our study is that 30% of the study population was male, which is significantly higher than the 8% - 10% previously reported [2] [6].

Osborn et al [5] recently reported an overall urinary retention rate of 35% in a clinical study consisting of patients with non-neurogenic OAB that were treated with 100 - 200 U of BTN/A. They defined urinary retention as any patient who was started on daily intermittent catheterization or had an indwelling catheter placed. Bladder drainage with CIC or indwelling catheter was recommended based on the patient’s urinary complaints and PVR or on clinical judgment of asymptomatic urinary retention based on PVR alone. In that study, 23% of patients were noted to have post-procedure PVRs between 100 and 200 mL and 92% of the patients with a PVR of >200 ml were started on CIC. Demographic review of the patient population in the study revealed that 24% of the patient population was male, 26% underwent BTN/A under local anesthesia, 63% received 100 U and 37% received 200 U. Further subgroup analysis revealed a 21% rate of urinary retention in patients who received 100 U and had a preoperative PVR of <100 mL. The authors further concluded “going forward the true rate of urinary retention in clinical practice will likely exceed the rates demonstrated in the recent clinical trials”.

However our study does not support these findings. Despite having a high number of male patients (30%), only one patient in our study group required initiation of CIC yielding a urinary retention rate of 1.5%. This is significantly lower than any previously reported studies. In addition, there was no correlation with age, history of previous radiation, diabetes or prior use of neuromodulation.

We hypothesize that our favorable rate of urinary retention may differ from previous studies due to differences in technique, inclusion of patients who received >100 units of BTN/A for refractory non-neurogenic OAB in prior studies, difference in threshold to initiate CIC, definition of urinary retention and patient selection.

Some limitations of our study include the retrospective nature and small patient cohort. Although our study population is small, we feel that there is a paucity of information on real-time adverse effects of BTN/A in actual clinical practice. Therefore we believe that our data is still interesting and highlights the importance of patient selection. We believe that careful patient selectivity plays a major role in dramatically diminishing the chances of urinary retention.

Further evaluation in a prospective fashion with a large cohort of patients should be undertaken to verify our results.
5. Conclusion

To the best of our knowledge, ours is the first study to demonstrate an extremely low rate of real-time urinary retention in patients treated with BTN/A for refractory non-neurogenic OAB outside of a clinical trial setting. We hypothesize that our favorable rate of urinary retention may differ from previous studies due to differences in technique, inclusion of patients who received >100 units of BTN/A for refractory non-neurogenic OAB in prior studies, difference in threshold to initiate CIC, definition of urinary retention and patient selection.

References


