Intravesical botulinum toxin: Practice patterns from a survey of Canadian urologists

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ABSTRACT

Introduction: The objectives of this study were to conduct a survey of intravesical botulinum toxin administration practices in Canada, to compare practices based on level of training, and to identify barriers to delivery.

Methods: A voluntary online survey was sent to all members of the Canadian Urology Association. Respondents who provide intravesical botulinum toxin were questioned on training, surgical volume, workup, technique, and followup practices. Those with formal training in functional urology were compared to those without. Barriers to treatment delivery were identified.

Results: The overall response rate was 26% (148/570). Most providers (59%) perform one to 10 treatments/month. Preoperatively, 51% perform cystoscopy and 43% perform urodynamics. A majority (66%) give routine antimicrobial prophylaxis; however, regimen and duration varied. Most (79%) perform some treatments under local anaesthetic, and 66% instill lidocaine solution for analgesia. There was a wide variation in technique with regards to the number of injections administered (range <10 to >20), volume administered per injection (range 0.5 mL to 2 mL), location of injections (bladder body vs. trigone vs. both), and depth of injection. Postoperative

KEY MESSAGES

- No formal guidelines exist on intravesical botulinum toxin evaluation, administration, or followup, and as such, there is a wide range of practice patterns among Canadian urologists.
- Further research is required to identify appropriate evidence-based practices for patients undergoing intravesical botulinum toxin injections.
- Several barriers to administration of intravesical botulinum toxin exist among providers and non-providers within the Canadian healthcare system.
followup ranged from three days to three months. Respondents with fellowship training in functional/reconstructive urology performed more treatments per month and administered fewer injections per treatment. Common barriers to delivery included lack of experience/training among non-providers (45%), lack of resources (34%), and lack of medication funding (32%).

**Conclusions:** Despite intravesical botulinum toxin being a widely accepted treatment, significant variability in practices and several barriers to delivery exist in Canada. Further study is required to optimize treatment access and quality.

**INTRODUCTION**

Intravesical botulinum toxin (BoNT) is a safe and effective treatment option for patients suffering from idiopathic overactive bladder and neurogenic lower urinary tract dysfunction refractory to conservative measures and oral pharmacotherapy. Intravesical BoNT studies have consistently demonstrated a significant improvement in urinary symptoms, urodynamic parameters, and quality of life. As a result, intravesical BoNT has gained widespread acceptance and use among urologists.1–7

Although no formal standard of practice guidelines exists, initial clinical trials advocated for the use of higher doses (200-300 units vs 100 to 200 units) and more injections per treatment (30 injections of 1mL aliquots vs 20 injections of 0.5mL aliquots) in neurogenic vs idiopathic overactive bladder.5–8 Aside from these general recommendations, there is limited data on best practices and no formal national or international guidelines for the administration of intravesical BoNT with regards to pre-procedural, peri-procedural and post-procedural practices. In addition, barriers to administration within the universal Canadian health care system have not been extensively explored in intravesical BoNT providers and non-providers and may be further impacted by provincial variability in resources and medication funding.

The primary objective of this study is to characterize the intravesical BoNT practice patterns of Canadian urologists via a comprehensive online survey. We hypothesize that Canadian urologists will vary widely with regards to evaluation, administration, and follow-up. Secondary objectives are to identify barriers to intravesical BoNT administration within the Canadian healthcare system as well as to assess for differences in practice patterns between providers with formal fellowship training in functional urology and those without.
METHODS
An anonymous, web-based, bilingual survey was administered to all practicing Canadian urologists who are members of the Canadian Urology Association (CUA) through the internal membership directory. Separate approval to access the directory was obtained from the CUA. The survey was distributed using the LimeSurvey platform (www.limesurvey.org). Urology residents, fellows, or Canadian urologists who do not practice in Canada were excluded. The survey was created and reviewed by three staff urologists at The Ottawa Hospital with formal fellowship training in functional/reconstructive urology who regularly perform intravesical BoNT (HV, DH, CM) as well as one urology fellow in functional and reconstructive urology at the same institution (JR). No formal pilot testing was performed. Approval from institutional research ethics board was obtained.

For urologists who do not perform intravesical BoNT, the survey was divided into two main segments: 1) basic demographic and practice information (highest level or training, location and type of practice) and 2) barriers to providing intravesical BoNT. For urologists who perform intravesical BoNT, the survey was divided into five main segments: 1) demographic and practice information (highest level of training, location and type of practice), 2) pre-procedural practices (investigations and antimicrobial prophylaxis), 3) intra-procedural practices (analgnesia, number, volume, and site of injections), 4) post-procedural practices (follow-up interval and testing), and 5) barriers to providing intravesical BoNT. The impact of the COVID-19 pandemic on the administration of intravesical BoNT was also assessed.

All data was collected and stored on the secure LimeSurvey server. The proportion of respondents for each answer was calculated. Respondents who reported specific training in functional urology were identified and practice patterns were compared to those without specific training using the Chi-square test for nominal and Mann Whitney U test for ordinal variables. All statistical analysis was performed using SAS software version 9.4.

RESULTS
The survey was administered to 570 Canadian urologists; 148 urologists completed the survey for an overall response rate of 26%. Of the respondents, 119 (80.4%) perform intravesical BoNT and 29 (19.6%) do not.

Providers of intravesical BoNT (n=119)

Demographics
The majority of respondents completed a urology residency only (38.7%), were from Central Canada (including Ontario and Quebec – 52.9%) and described having a general community practice – 49.6% (Figure 1). Most providers (58.8%) perform between one and ten intravesical BoNT treatments per month; 9.2% perform between 10 to 20 treatments per month; 7.6% perform greater than 20 treatments per month; and 24.4% perform less than one treatment per month.
Funding
Most (49.6%) reported that intravesical BoNT is fully covered with pre-specified conditions by the province in which they practice (i.e., patient must be certain age, have a specific diagnosis, or have failed other treatments); full coverage without conditions was reported by 33.6%, partial coverage with or without conditions by 11.8%, and private payer only by 5.0%.

Pre-procedural assessment
Post-void residual (PVR) measurement was most commonly performed prior to treatment (61.0%). Other pre-procedure testing frequently performed included cystoscopy (51.3%), multi-channel urodynamics (42.9%), non-invasive uroflowmetry (38.7%), and ultrasound (10.9%). Fourteen percent do not routinely perform any investigations prior to treatment. The majority (67.2%) do not perform routine clean intermittent catheterization (CIC) teaching, whereas 29.4% perform CIC teaching for patients with an anticipated increased risk of retention, and 2.5% perform CIC teaching for all patients.

Infection prophylaxis
Thirty-seven percent of respondents perform pre-procedural urine cultures in all patients and 66.4% give routine antimicrobial prophylaxis. For those who provide routine prophylaxis, 61.4% use a single dose at the time of BoNT (Figure 2). The most common antimicrobial used for prophylaxis is cefalexin/cefazolin (39.7%), followed by ciprofloxacin (26.5%), and nitrofurantoin (10.3%).

Analgesia
A majority (62.2%) perform >=75% of BoNT treatments under local cystoscopy compared to 24% who perform all treatments in the operating room under sedation/general anesthetic. For those performing treatments under local cystoscopy, most (66%) use instillation of a lidocaine solution for analgesia (Table 1).

Technique
Most perform between 10 and 15 injections per treatment (44.5%) and over half (61.2%) administer 1mL of BoNT solution per injection. Almost three-quarters (74.0%) administer injections into the bladder body only (trigone sparing) and 84.0% perform intra-detrusor injections (Figure 3).

Followup
For the first follow-up visit, 34.4% of respondents will see patients back at 6 weeks, compared to 28.5% who see patients back at 4 weeks and 19.5% who see them back at 2 weeks. The remainder (17.6%) see patients back at intervals ranging between 3 days to 3 months. As part of the follow-up visit, 33.6% of respondents will always perform a PVR measurement, 14.3% perform PVRs only after the first treatment, 38.7% only if the patient reports voiding difficulties, and 13.4% do not routinely measure PVRs at follow-up.
Barriers to treatment for providers (n=119) and non-providers (n=29)
For respondents who are providers of intravesical BoNT, the most commonly identified barrier to administration was a lack of operating room/cystoscopy time (34.4%). A lack of funding for BoNT was identified as a barrier by 31.9% of providers (Figure 4). For respondents who do not perform intravesical BoNT, the most common reason for not providing treatment was little to no experience or training with intravesical BoNT injections (44.8%) followed by limited resources (31.0%) (Figure 4).

The COVID-19 pandemic was identified as a cause of increased wait times for treatment by 67.2% of providers, had resulted in a temporary cessation of treatment by 26.0%, and 26.0% reported no significant impact on their practice.

Impact of formal fellowship training
Respondents who have had formal fellowship training in functional urology performed more intravesical BoNT treatments per month and administered fewer injections per treatment compared to respondents without formal fellowship training in functional urology (p<0.05). There were no other differences in practice patterns based on level of training (Table 2).

DISCUSSION
To our knowledge, this study is the first to characterize both practice patterns as well as barriers to delivery for intravesical BoNT within the Canadian health care system. As hypothesized, there was a wide range of practices noted among providers of intravesical BoNT. Specifically, within the Canadian health care system, provincial differences in health care resources and funding may be contributing to some of the variability in practices, i.e., medication subsidy and access to treatment; however, further study would be required to confirm this. Of note, a majority of respondents who provide BoNT are community urologists with no formal fellowship training in functional urology.

There are no definite guidelines on pre-procedural investigations to be completed prior to intravesical BoNT injections. The results of this survey indicate that urologists most commonly perform a measurement of PVR before BoNT administration (61.3%); this is likely because of the risk of urinary retention that has been found to occur in 5 to 41% of patients, in a dose-dependent manner. Cystoscopy (51.3%) and urodynamics (42.9%) were also commonly performed. Although no formal recommendations on the use of urodynamics exists, initial clinical trials evaluating BoNT for idiopathic OAB did not routinely utilize pre-treatment urodynamics for patient selection. Furthermore, recent cohort studies have not demonstrated differences in outcomes for patients with and without detrusor overactivity on pre-treatment urodynamics. Given these findings, in the absence of clinical concern for neurogenic lower urinary tract dysfunction or impaired capacity/compliance, consideration towards patient reported outcomes of intravesical BoNT may be both an effective and practical means of monitoring treatment response. Urodynamics may be employed in patients with NLUTD,
suspected bladder outlet obstruction, mixed incontinence, or with risk factors for impaired compliance.

There is a lack of specific antimicrobial prophylaxis recommendations for intravesical BoNT injections. A recent American Urology Association – Best Practice Statement recommends a single dose of prophylaxis for any procedure with potential violation of the genitourinary tract but offers no procedure specific guidance. Although most respondents (66.4%) provide routine antimicrobial prophylaxis, antibiotic regimens and durations vary widely. A recent review on duration of prophylaxis noted a significant decrease in infection with three days of a fluoroquinolone compared to a single dose of ceftriaxone (20.8% vs 36%, p = 0.04). Another study found no difference in infection when comparing antimicrobial type or route of administration. Further study is required to champion antimicrobial stewardship and identify the optimal regimen and duration of prophylaxis for intravesical BoNT.

Only 34.4% of respondent providers perform routine pre-procedural urine cultures. The most recent guidelines from the Infectious Diseases Society of America recommend the screening and treatment of asymptomatic bacteriuria for procedures with anticipated mucosal trauma. A recent retrospective review demonstrated that patients with asymptomatic bacteriuria have an increased risk of UTI (OR 16.48) but not urosepsis or hospitalization. The overall risk of infection must be balanced against the recognized risk of antimicrobial overuse and the emergence of bacterial resistance. The routine identification of asymptomatic bacteriuria prior to intravesical BoNT may reduce antimicrobial exposure and procedure-related morbidity; however, further study is required.

The optimal analgesic for patients undergoing intravesical BoNT injections is also not well defined. Initial studies have utilized a wide array of analgesia ranging from no specific anesthesia to general anesthesia. A prior survey of functional and reconstructive urology experts revealed that pre-procedural instillation of intravesical lidocaine solution was the most common regimen used by respondents. Intravesical instillation of lidocaine solution requires additional time and personnel resources as well as an additional catheterization for patients. Interestingly, a randomized controlled trial found that alkalinized lidocaine solution was not superior to lidocaine gel for pain control during intravesical BoNT injections. Therefore, further study on the most effective and efficient means of analgesia in these patients is warranted.

A wide range of injection-specific patterns were noted, with respondents differing in the number, volume, location, and depth of injections. Most studies have used injection volumes of 0.5 to 1.0mL distributed into the detrusor muscle over 20 to 30 injections. A previous study using gadolinium-tagged BoNT found no difference in the distribution of injected BoNT when comparing 10 injections to 30. In terms of depth of injection, previous randomized studies have demonstrated similar efficacy between suburothelial and intra-detrusor injections. Previously, injections into the trigone have been avoided due to the theoretical risk of inducing
vesicoureteric reflux, however, several studies have disproven this concern\textsuperscript{13,24} Whether inclusion of the trigone into injection protocols provides any additional advantage is a matter of debate with some studies demonstrating a benefit to trigonal inclusion and others showing no difference in efficacy\textsuperscript{25–27}.

The optimal time frame for follow-up post-BoNT injection is also poorly defined. Based on initial trials, 2-week follow-up was initially recommended and differs from the results of our survey. Most respondents arrange follow-up in the 4 to 6 week range with some waiting up to three months\textsuperscript{21} The majority of respondents will perform a PVR measurement following treatment, either for all patients or just after the patient’s first treatment, however, the role of routine PVR assessment in the absence of voiding symptoms has not been evaluated. Only a small portion of respondents routinely perform CIC teaching for patients undergoing intravesical BoNT. The incidence of CIC after intravesical BoNT ranges widely from 5\% to 41\% with no specific recommendations on the need for routine teaching\textsuperscript{13}.

Unsurprisingly, respondents with formal training in functional urology provide more intravesical BoNT treatments per month compared to those without formal fellowship training in the field. Interestingly, providers with fellowship training perform less injections per treatment. The reason for this is not fully apparent but may be reflective of the non-significant trend towards providing more treatments under local cystoscopy (minimizing patient discomfort) or the failure to show a definite difference in BoNT efficacy by injection number\textsuperscript{28}.

A number of potential barriers to treatment delivery were identified. Predictably, operating room and cystoscopy resources were found to be the most limiting for BoNT providers. Although BoNT can be safely and effectively performed under local anesthetic, administration and anesthetic techniques may be unfamiliar to providers and further limit its delivery. Additionally, nearly half of non-providers expressed a lack of comfort with prescribing and administering BoNT treatment. Facilitating local cystoscopy intravesical BoNT administration through evidence-based recommendations, work-shops or comprehensive online videos has the potential to improve both patient and provider experience, resource utilization, and BoNT access. Finally, provincial BoNT funding needs to align with guideline recommendations for refractory OAB and NLUTD patients as it was identified as a barrier to delivery by 31.9\% of providers and 21.0\% of non-providers. Therefore, by improving and standardizing provincial funding of intravesical BoNT we likely improve universal healthcare equity and accessibility.

A limitation of this study includes its survey-based design. It is possible that respondents may not have accurately reported answers to the survey; however, we anticipate this risk to be minimal given its anonymous nature. Furthermore, the survey was voluntary, and not all urologists were captured, especially non-members of the CUA. Nonetheless, the response rate was over 25\% (>1 in 4 practicing CUA members), and therefore we feel that the results reflect practice patterns across Canada. This survey was also not distributed to Canadian urogynecologists, who perform a significant portion of intravesical botulinum toxin injections in
women. Only 19.6% of respondents do not provide BoNT which likely represents a selection bias towards providers of BoNT. The main purpose of distributing the survey to non-providers was to identify barriers to treatment delivery within this cohort.

CONCLUSIONS
Intravesical BoNT is a widely accepted and administered treatment for patients with refractory OAB and NLUTD. Due to an overall lack of high-quality evidence for proper assessment and administration, there remains a wide-variation in practice patterns amongst Canadian urologists. There is an urgent need for further study to optimize efficacy, efficiency, and safety of treatment. The results of our survey can be used as a guide by which further study can be established. In addition to a paucity of available evidence, formal guidelines or best practice statements are required to standardize assessment, administration, and follow-up amongst BoNT providers. Furthermore, addressing identified barriers to treatment delivery either through local or national initiatives may help to improve quality and access to care for patients with OAB and NLUTD in Canada.
References


Figures and Tables

Figure 1. Demographics and practice information for respondents who provide intravesical botulinum toxin (BoNT).

BoNT.

Figure 2. Infection prophylaxis patterns for respondents who provide intravesical botulinum toxin (BoNT).

Figure 3. Techniques for administration of intravesical botulinum toxin (BoNT).
Figure 4. Barriers to administration of treatment for both providers and non-providers of intravesical botulinum toxin (BoTA). OAB: overactive bladder; OR: operating room.

Table 1. Percentage of procedures performed under local anesthetic and type of analgesia used for providers of intravesical BoNT treatment
## Intravesical Botulinum Toxin Practice Patterns

### Table 2. Comparison of Practice Patterns between Respondents with Formal Fellowship Training in Functional and Reconstructive Urology Compared to Those Without

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fellowship-Trained in Functional Urology (n=41)</th>
<th>Non-Fellowship-Trained in Functional Urology (n=78)</th>
<th>p</th>
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</thead>
<tbody>
<tr>
<td><strong>Frequency of Treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1x/month</td>
<td>4 (9.8)</td>
<td>29 (37.3)</td>
<td>&lt;0.0001</td>
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<tr>
<td>1 to &lt;10x/month</td>
<td>20 (48.8)</td>
<td>45 (58.2)</td>
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<tr>
<td>10 to &lt;20x/month</td>
<td>9 (22.0)</td>
<td>3 (3.0)</td>
<td></td>
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<tr>
<td>≥0x/month</td>
<td>8 (19.5)</td>
<td>1 (1.5)</td>
<td></td>
</tr>
<tr>
<td><strong>% of Treatments under Local Cystoscopy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td>4 (9.8)</td>
<td>27 (34.2)</td>
<td>0.1195</td>
</tr>
<tr>
<td>&gt;0% to &lt;25%</td>
<td>1 (2.4)</td>
<td>6 (7.5)</td>
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</tr>
<tr>
<td>25% to &lt;50%</td>
<td>3 (7.3)</td>
<td>0 (0.0)</td>
<td></td>
</tr>
<tr>
<td>50% to &lt;75%</td>
<td>5 (12.2)</td>
<td>6 (7.5)</td>
<td></td>
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<tr>
<td>75% to &lt;100%</td>
<td>18 (43.9)</td>
<td>17 (22.4)</td>
<td></td>
</tr>
<tr>
<td>100%</td>
<td>10 (24.4)</td>
<td>22 (28.4)</td>
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<tr>
<td><strong>Anesthetic Type</strong></td>
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<tr>
<td>Lidocaine Solution</td>
<td>30 (73.2)</td>
<td>53 (68.2)</td>
<td>0.8508</td>
</tr>
<tr>
<td>Lidocaine Gel</td>
<td>9 (22.0)</td>
<td>22 (27.3)</td>
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<tr>
<td>Nothing</td>
<td>2 (4.9)</td>
<td>3 (4.6)</td>
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<tr>
<td><strong>Preprocedural Investigations</strong></td>
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IQR: interquartile range
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<tr>
<th>Procedure</th>
<th>&lt;10</th>
<th>10 to &lt;15</th>
<th>15 to &lt;20</th>
<th>≥20</th>
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<tbody>
<tr>
<td>Uroflow</td>
<td>18 (43.9)</td>
<td>26 (63.4)</td>
<td>24 (58.5)</td>
<td>4 (9.8)</td>
</tr>
<tr>
<td>PVR</td>
<td>33 (41.8)</td>
<td>55 (70.2)</td>
<td>31 (40.3)</td>
<td>10 (13.4)</td>
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<tr>
<td>Urodynamics</td>
<td>40 (51.2)</td>
<td>47 (59.7)</td>
<td>40 (51.2)</td>
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<tr>
<td>Ultrasound</td>
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<td>5 (6.0)</td>
<td>2 (4.9)</td>
<td>5 (6.0)</td>
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<tr>
<td>Cystoscopy</td>
<td>18 (43.9)</td>
<td>26 (63.4)</td>
<td>24 (58.5)</td>
<td>4 (9.8)</td>
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<tr>
<td>None</td>
<td>33 (41.8)</td>
<td>55 (70.2)</td>
<td>31 (40.3)</td>
<td>10 (13.4)</td>
</tr>
<tr>
<td>Number of injections</td>
<td>&lt;0.0001</td>
<td>0.4680</td>
<td>0.0654</td>
<td>0.5688</td>
</tr>
<tr>
<td>Distribution of injections</td>
<td>0.9192</td>
<td>0.3294</td>
<td></td>
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<tr>
<td>Bladder body</td>
<td>29 (70.7)</td>
<td>56 (71.6)</td>
<td>63 (80.6)</td>
<td>15 (19.4)</td>
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<tr>
<td>Bladder body and trigone</td>
<td>12 (29.3)</td>
<td>22 (28.4)</td>
<td>5 (12.2)</td>
<td>15 (19.4)</td>
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<tr>
<td>Depth of injections</td>
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<td>0.3882</td>
<td>0.8100</td>
<td>0.8100</td>
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<tr>
<td>Intra-detrusor</td>
<td>36 (87.8)</td>
<td>63 (80.6)</td>
<td>5 (12.2)</td>
<td>15 (19.4)</td>
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<tr>
<td>Sub-urothelial</td>
<td>0.8295</td>
<td>0.3882</td>
<td>0.8100</td>
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</table>

PVR: postvoid residual.