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ARTICLE

Clinical and urodynamic indicators of non-response to OnabotulinumtoxinA in idiopathic overactive bladder

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Background: *Onabotulinum toxin-A (BoNT/A) intradetrusor injection is an established, effective, and safe treatment for overactive bladder (OAB) refractory to anticholinergics. Although primary non-response to BoNT/A is infrequent, it remains clinically relevant. We investigated whether baseline clinical, demographic, or urodynamic characteristics could predict non-responders prior to treatment.*
Methods: *A Retrospective analysis of 65 consecutive refractory idiopathic OAB (I-OAB) male and female patients treated with 100 U BoNT/A at Jewish General Hospital between 2005 and 2015 was conducted. Response defined as >30% increase in maximum cystometric bladder capacity (MCBC) at 12 weeks, confirmed clinically and through urodynamic studies (UDS). Non-response was verified by lack of improvement after the second intradetrusor injection.*
Results: *A total of 13 men and 52 women with a mean age of 70 years (range 21 to 94) were studied. At 12 weeks, 63% (41/65) of patients demonstrated a significant response in both symptoms and UDS ($p < 0.05$), while 37% (24/65) were non-responders. Non-responders exhibited significantly higher baseline first desire to void volume (FDV) and postvoid residual urine (PVR) ($p < 0.05$), with a trend toward greater bladder compliance (18.8 ± 15.1 vs. 13.3 ± 9.4 cmH_2O, $p = 0.09$). Multivariate logistic regression identified no independent predictors of response.*
Conclusions: *Elevated baseline FDV and PVR are associated with poor response to 100 U BoNT/A in refractory I-OAB patients.*

Key Words: Botulinum toxin, Botox, idiopathic overactive bladder, predictors, urodynamic study

Introduction

Idiopathic overactive bladder (I-OAB) syndrome is defined as urgency, with or without urinary incontinence, that is usually accompanied by frequency and nocturia.[1] In the Canadian Urinary Bladder Survey published in 2008, OAB symptoms were reported by 13.9% of adults, compared with other Canadian population-based data confirming a similar prevalence between 11.8%–18.1%. Currently, OAB continues to impose a significant psychological and economic burden on the population.[2–4] Overactive bladder direct costs in Canada were estimated to be $175 million, and increased to $352 million when considering urinary incontinence.[5] Altogether, the annual direct cost of OAB to the Canadian healthcare system is estimated at approximately $11,329 per patient.[2] As concluded by Viste et al., there is a lack of Canadian-specific cost data for OAB treatments available in the literature.[6] To date, only one peer-reviewed study provides Canadian cost data for OAB treatments, limited to a handful of second-line therapies drawn from one province over 10 years ago.[7] This gap is

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particularly relevant for third-line therapies such as BoNT/A, where a systematic review of international cost-utility models suggests BoNT/A may be more cost-effective than sacral neuromodulation for refractory OAB, though Canadian-specific analyses remain needed.[8]

Onabotulinum toxin-A intradetrusor injection (BoNT/A) has been proven to be an effective and safe alternative therapy for treating overactive bladder (OAB) refractory to anticholinergics. Botox is a neurotoxin derived from the bacterium *Clostridium botulinum* that is injected into the detrusor muscle and acts by blocking the release of acetylcholine at the presynaptic neuromuscular junction, triggering temporary chemodenervation and assisting with muscle relaxation.[9] It is stipulated that its main effect is through the inhibition of involuntary detrusor contractions. There also might be an antinociceptive effect on afferent nervous transmission and decreased bladder sensory receptors expression, leading to a reduction in urgency symptoms and successful therapeutic outcomes.[10] Increasing evidence supports that the long-term effects of Botox is attributed to its action on bladder sensory rather than on motor receptors.[11] This could explain the high success rate of BoNT/A in patients with urgency symptoms with or without motor effects.[12]

Although success rates are promising, therapy with BoNT/A injections may still fail. In general, failure to therapy can be primary or secondary. Primary failure occurs if the patient has never had a positive clinical and urodynamic response to intradetrusor BoNT/A injections. Secondary failure is defined as resistance to treatment. Primary failure might be caused by reduced sensitivity to BoNT/A, technical problems, pre-existing BoNT/A antibodies, and abnormalities of BoNT/A receptors.[13]

There is also continuous debate in the literature on the definition of treatment response to BoNT/A. This can be defined based on clinical and urodynamic outcomes. Clinical response frequently used a threshold of 50%–100% improvement in general or specific symptoms; reduction in urinary frequency and urgency urinary incontinence episodes was commonly utilized in clinical trials. Urodynamic response can be defined as a reduction in mean detrusor pressure (MDP) inferior to 40 cmH_2O or an increase in maximum cystometric bladder capacity (MCBC) of more than 30%.[14]

Up to date, few studies have focused on treatment response and non-response in patients with I-OAB receiving BoNT/A therapy. Some have stipulated that vesical compliance dysfunction or higher maximal detrusor pressures might have some value in predicting response to treatment.[15,16] However, there have been relatively few reports on the ability to predict which patients will or will not respond to BoNT/A treatment. Therefore, we conducted a retrospective analysis of patients diagnosed with refractory I-OAB who underwent intradetrusor BoNT/A injections to determine whether certain pre-treatment urodynamic and demographic variables could be helpful in predicting which patients will respond to BoNT/A.

Methods

Population

We conducted a retrospective chart review of 65 consecutive patients with refractory I-OAB who had received intradetrusor injection of Onabotulinum toxin A 100 units (BOTOX®, Allergan Inc., Canada) at the Jewish General Hospital in Montreal, Canada, from January 2005 to December 2015. The study received approval from the Research Ethics Committee (REC) of the Jewish General Hospital (Date of approval: September 02, 2015; No. CR-15-47). Participant consent was waived by authorization of the Director of Professional Services. The patients were informed of the risks and benefits of the procedure and were aware of alternative therapies. Additionally, the risk of urinary retention with subsequent need for clean intermittent catheterization (CIC) as well as the possibility of treatment failure was explained. All patients were able and willing to perform CIC if necessary. Procedures were performed by two fellowship-trained, experienced surgeons.

Inclusion criteria were: (i) A clinical diagnosis of I-OAB according to the ICS definition. Additional diagnostic modalities were occasionally used, such as a urodynamic study or cystoscopy. (ii) Patients had a failure of conservative therapy with at least 2 anticholinergic medications for a period of at least 3 months or discontinued treatment due to intolerable side effects. (iii) Patients are able to initiate CIC post-treatment, if required. Exclusion criteria were: (i) high post-void residual (PVR) >100 mL, (ii) concomitant stress urinary incontinence, (iii) renal dysfunction, (iv) neurogenic bladder dysfunction, (v) disorders of the neuromuscular junction (vi) bladder or kidney tumor, (vii) concomitant bladder pathology (e.g., bladder pain syndrome or interstitial cystitis), (viii) serious medical comorbidity and (ix) pregnant or breastfeeding women.

Detailed preoperative assessment included baseline demographic characteristics, past medical history including previous pelvic irradiation,

previous treatments for OAB, physical examination, urodynamic evaluation, and baseline urinalysis and culture. All participants were instructed to complete validated questionnaires preoperatively and at the 3-month follow-up visit.

Baseline demographic parameters included age, gender, body mass index (BMI), and type of OAB (dry or wet). OAB-Dry was defined as patients with urinary urgency, urinary frequency (>8 voids per day), and no complaint of urge urinary incontinence (UUI). OAB-Wet was defined as patients with urgency and urinary frequency with at least one daily episode of UUI. The 3 validated questionnaires used were the Incontinence Impact Questionnaire (IIQ-7), scores range from 0 to 100, with higher scores indicating worse quality of life (QoL)[17]; the Overactive Bladder Symptom Score (OABSS), range from 0 to 28, with higher scores representing worse symptoms[18] and the International Consultation on Incontinence Questionnaire–Short Form (ICIQ-SF) which is measured over the range 0 (minimal symptoms) to 21 (maximum symptoms).[19]

Injection technique

Prior to the procedure, the urinary tract infection was screened, and if confirmed, treated with antibiotics, and sterile cultures were documented before injection. If taken, anticholinergic agents were stopped for two weeks or longer prior to the injection. With the patients under local anesthesia, a total of BoNT/A 100 units (BOTOX®, Allergan Inc., Canada) diluted in 10 mL of 0.9% normal saline solution were injected using a flexible cystoscope in an outpatient setting. The toxin was administered as 20 evenly distributed injections of 0.5 mL each (5 Units per injection site) into the detrusor muscle at approximately 1 cm intervals, with the trigone deliberately spared. The needle was advanced approximately 2 mm into the detrusor muscle to achieve proper depth, as confirmed by visualization of a bleb at each injection site. Following completion of the 20 injections, 1 mL of sterile saline was injected through the needle to flush the remaining toxin from the catheter. Bladder capacity was measured routinely. Patients were monitored until urinary recovery, and a single dose of antibiotics was administered as perioperative prophylaxis.

Follow-up assessment

The follow-up after BoNT/A treatment was at 4 and 12 weeks, and yearly thereafter. This includes assessment of incomplete bladder emptying, urodynamic evaluation, and self-reported questionnaires. Any adverse events considered possibly related to BoNT/A treatment were documented. Standard urodynamics were conducted and interpreted as recommended by the International Continence Society and by good urodynamic practice.[20]

Treatment response was based on clinical and urodynamic responses after the first BoNT/A injection, where patients were categorized using both subjective and objective parameters. Treatment success was defined as both urodynamic improvement and clinical benefit, specifically an increase in maximum cystometric bladder capacity (MCBC) of more than 30% from baseline, combined with patient-reported improvement in OAB symptoms.[14,15] This dual criterion approach aligns with established methodologies that recognize the importance of both objective urodynamic changes and subjective patient experience in evaluating treatment efficacy.[21] Patients who did not meet these criteria were qualified as non-responders (primary treatment failure). Failure was defined as neither urodynamic effectiveness (no 30% increase in MCBC) nor clinical effectiveness (persistence of symptoms) at the 12-week follow-up following the initial BoNT/A treatment. Non-responder status was confirmed by a second intradetrusor injection with neither clinical nor urodynamic improvement. Results after a second injection were not analyzed in this study. While both objective urodynamic parameters and subjective symptom improvement were assessed, the dual presence of both urodynamic improvement (≥30% increase in MCBC) and clinical benefit was prioritized for defining treatment success, as relying solely on continence status or urodynamic parameters may not capture the full therapeutic response.

Additional efficacy variables included changes from baseline in patient-reported outcomes, voiding diary parameters, and QoL measures. Baseline was defined as records collected prior to the first BoNT/A injection. Symptomatic patients with a residual volume > 150 mL were instructed to start CIC.

Statistical analysis

Continuous variables were reported as mean ± standard deviation (SD), while categorical data as was reported as frequencies. Paired pre- and post-treatment comparisons used two-tailed paired *t*-tests or Mann-Whitney U tests as appropriate. Group differences in gender and OAB subtype (wet vs. dry) were assessed via chi-square (χ^2) tests. Significance was set at $p < 0.05$. Cases with incomplete data were excluded from regression models. Multiple linear regression evaluated pre-treatment factors associated with BoNT/A response. Analyses were conducted using SAS® 9.3 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The cohort comprised 13 men and 52 women (mean age 70 years, range 21–94) with refractory I-OAB treated with 100 U BoNT/A intradetrusor injection. No acute urinary retention occurred post-catheter removal. OAB subtypes included 9 (14%) dry and 56 (86%) wet cases. Patients received a mean of 4.1 ± 2.8 injections (range 1 to 13), with 8.3 months (range 6 to 24 months) between injections.

Efficacy outcomes

At 12 weeks, 63% (41/65) exhibited significant symptom improvement and urodynamic changes ($p < 0.05$), while 24 (37%) were categorized as non-responders. Non-response was verified by persistent symptoms, unchanged QoL scores, and unaltered urodynamics despite a second injection. Baseline demographics (age, gender, BMI) and OAB subtype did not differ between groups (Table 1).

In the responder's group, significant increases for MCBC, first desire void volume (FDV), and bladder compliance (BC) with reductions in maximal detrusor pressure (MDP) and maximum vesical pressure (MVP) were observed throughout the study period (Table 2). Analysis of the poor responders group results showed non-significant increases in MCBC (191 ± 40.7 mL at baseline) along with a reduction in MDP (29.7 ± 16.5 at baseline vs. 24.1 ± 13.6 cmH_2O). No other significant changes were observed in this group in the other parameters investigated.

Further analyses of factors associated with the therapeutic efficacy of baseline demographic and urodynamic variables between groups are shown in Table 2. The FDV (141.2 ± 73.3 vs. 107.8 ± 52.8 mL) and PVR (50.1 ± 38.7 vs. 26.2 ± 26.4 mL) in the poor responders were significantly higher compared with the responder's group ($p = 0.0373$ vs. $p = 0.0218$), respectively. Non-responders tended to have higher baseline bladder compliance (18.8 ± 15.1 vs. 13.3 ± 9.4 cmH_2O, $p = 0.0887$). In a multivariate logistic regression model, no significant predictors for treatment response could be recognized. QoL, as assessed using the OABSS, ICIQ-SF, and IIQ-7, was not helpful for the prediction of postoperative clinical response; although responders tended to have higher baseline IIQ-7 score (68.2 ± 25.5 vs. 52.3 ± 29.9, $p = 0.0891$) (Table 1).

TABLE 1. **Baseline characteristics of responders vs. non-responders in refractory Idiopathic overactive bladder (I-OAB)**

Parameter (units)	Non-responders (Mean ± SD)	Responders (Mean ± SD)	Overall	*p*-value
N (%)	24 (37%)	41 (63%)	65	/
Age	70.6 ±14.9	70.9 ±15.8	70.8 ±15.4	0.8329 (Mann-Whitney test)
Gender (Male: Female)	3:21	10:31	13:52	0.5123 (Chi square)
OAB-Dry	2	7	9	0.6159 (Chi square)
OAB-Wet	22	34	56	
Body mass index	29.7± 4.5	29.3± 4.9	29.6 ± 4.3	0.9064 (two-tailed paired *t*-test)
FDV (mL)	141.2 ± 73.3	107.8 ± 52.8	120.1 ± 62.8	0.0373* (two-tailed paired *t*-test)
BC (mL/cmH_2O)	18.8 ± 15.1	13.3 ± 9.4	15.3 ± 11.9	0.0887 (Mann-Whitney test)
MDP (cmH_2O)	29.7 ± 16.5	26.9 ± 13.9	28.0 ± 14.8	0.4869 (two-tailed paired *t*-test)
MVP (cmH_2O)	51.9 ± 22.2	47.3 ± 15.6	49.0 ± 18.2	0.3337 (two-tailed paired *t*-test)
PVR (mL)	50.1 ± 38.7	26.2 ± 26.4	34.9 ± 33.2	0.0218* (Mann-Whitney test)
IIQ-7 score	68.2 ± 25.5	52.3 ± 29.9	57.9 ± 29.1	0.0891 (two-tailed paired *t*-test)
OABSS score	22.2 ± 4.1	22.0 ± 3.7	22.1 ± 3.8	0.9014 (two-tailed paired *t*-test)
ICIQ-SF score	15.2 ± 4.2	12.4 ± 6.3	13.4 ± 5.8	0.1693 (Mann-Whitney test)

Note. *$p < 0.05$ to show significance. Abbreviations: FDV, first desire void volume; BC, bladder compliance; MDP, maximal detrusor pressure; MVP, maximum vesical pressure; PVR, postvoid residual; IIQ-7, Incontinence Impact Questionnaire; OABSS, Overactive Bladder Symptom Score; ICIQ-SF, International Consultation on Incontinence Questionnaire—Short Form.

TABLE 2. **Urodynamic data and patient-reported outcomes for responders over the study period**

Parameter (units)	Baseline (Mean ± SD)	Post-treatment (Mean ± SD)	*p*-value
N	41	41	/
FDV (mL)	108.8 ± 53.9	229.2 ± 121.8	<0.0001**** (Mann-Whitney test)
BC (mL/cm H_2O)	13.3 ± 9.5	15.6 ± 7.0	<0.0001**** (Mann-Whitney test)
MDP (cmH_2O)	27.2 ± 14.0	20.2 ± 11.1	0.0314* (Mann-Whitney test)
MVP (cmH_2O)	47.8 ± 15.8	37.5 ± 16.6	0.0062** (two-tailed paired *t*-test)
PVR (mL)	26.3 ± 27.0	120.7 ± 100.9	<0.0001**** (Mann-Whitney test)
IIQ-7 score	53.6 ± 30.0	45.2 ± 27.7	0.2990 (two-tailed paired *t*-test)
OABSS score	22.1 ± 3.8	18.6 ± 6.5	0.0701 (Mann-Whitney test)
ICIQ-SF score	12.9 ± 6.1	10.0 ± 6.4	0.0852 (two-tailed paired *t*-test)

Note. *$p < 0.05$, **$p < 0.01$, and ****$p < 0.0001$ to show significance. Abbreviations: FDV, first desire void volume; BC, bladder compliance; MDP, maximal detrusor pressure; MVP, maximum vesical pressure; PVR, postvoid residual; IIQ-7, Incontinence Impact Questionnaire; OABSS, Overactive Bladder Symptom Score; ICIQ-SF, International Consultation on Incontinence Questionnaire—Short Form.

Safety

No major complications occurred. Transient incomplete emptying (PVR 150–300 mL) affected 4 responders (9.8%) and 2 non-responders (8.3%) 1–2 weeks post-injection, managed with temporary clean intermittent catheterization (CIC) until PVR normalized within 3 to 6 months. Four UTIs developed, all in CIC patients, resolving with antibiotics. No acute retention, muscle weakness, or hematuria requiring admission was observed. Baseline characteristics did not predict these events.

Discussion

Although existing experience with BoNT/A application for treatment of I-OAB is greater than ever before, the triggers of primary treatment failure of intradetrusor injections of botulinum toxin remain poorly understood. Therefore, a better understanding of the mechanism of treatment failure, as well as a patient's likelihood of responding to a given therapy, will improve patient care and reduce the burden of failing other costly therapies. In this regard, we have performed this secondary analysis of our data, evaluating the response to BoNT/A therapy in patients with refractory I-OAB in order to determine whether a poor response after BoNT/A treatment could be predicted based on clinical, demographic, or urodynamic parameters.

Given that poor response to BoNT/A therapy is relatively uncommon but still exists, at our institution, 24 of 65 (36%) patients with refractory OAB were categorized as poor responders. This proportion is similar with contemporary reviews summarizing predictors of poor response and adverse events after BoNT/A in I-OAB.[22] Several investigators have examined predictive factors for BoNT/A treatment success in OAB patients, with varying definitions of successful outcomes. Cohen et al.[16] evaluated demographic and urodynamic predictors in 47 I-OAB patients, defining response as ≥40% reduction in urinary frequency for OAB-dry patients and ≥50% reduction in urgency urinary incontinence episodes for OAB-wet patients. They found that younger patients with OAB-wet phenotype were more likely to respond, though this association lost significance on multivariate analysis. Importantly, they were unable to identify definitive UDS parameters predictive of response. Sahai et al.[23] evaluated 33 patients with I-OAB who were treated with 200 U of BoNT/A and reported that 5 patients (15%) had a poor response characterized by significantly higher maximal detrusor pressures during DO. Marcelissen et al.[24] reported a 70% discontinuation rate with BoNT/A after 5 years, with the majority (79%) discontinuing treatment following the first injection, of which 27% was attributed to lack of efficacy. Hsiao et al.[25] demonstrated that female gender, lower baseline OAB symptom scores, and OAB-wet phenotype were associated with better therapeutic efficacy, while low baseline voiding efficiency predicted larger PVR volumes. Their study utilized a subjective patient perception global response assessment (GRA) as the primary outcome measure, defining treatment success as GRA ≥ 2 at follow-up. Dmochowski et al.[26], in a phase 2 dose-ranging trial, demonstrated durable efficacy across multiple doses of BoNT/A (100-300 U), with the primary efficacy

variable being reduction in weekly UUI episodes. Their analysis suggested that doses greater than 150 U contributed minimal additional clinical benefit while increasing the risk of elevated PVR volumes and need for CIC. Rovner et al.[27] assessed both clinical and urodynamic outcomes, finding that successful idiopathic OAB treatment with BoNT/A did not appear related to pre-treatment detection of DO, as improvements occurred in both DO-positive and DO-negative patients. This finding emphasizes that urodynamic DO may not be an essential predictor of treatment response. Despite these investigations, a systematic review concluded that while multiple factors, including male gender, frailty, comorbidity, increasing age, and various urodynamic parameters, have been proposed as predictors of non-response or adverse events, the evidence remains predominantly level 3 with moderate quality.[16,22,23,25,28]

Although our analysis focused on overall responder vs. non-responder classification rather than age-stratified subgroups, the findings from Komesu et al.[29] underscore the potential importance of demographic and comorbidity factors in predicting treatment response. In their analysis of 364 women with refractory UUI treated with 200 U BoNT/A, younger women (<65 years) demonstrated 3.3-fold greater odds of achieving ≥75% reduction in urgency urinary incontinence episodes compared to older women. Additionally, they identified degenerative disc disease as a specific negative predictor for botulinum toxin efficacy, with affected patients showing significantly reduced odds of achieving ≥75% symptom resolution, an effect specific to botulinum toxin and not observed with sacral neuromodulation. Future prospective studies incorporating age stratification, systematic assessment of spinal pathology, and comprehensive comorbidity profiling may reveal patient subgroups at higher risk of treatment failure. The identification of degenerative disc disease as a botulinum toxin-specific negative predictor is particularly relevant for clinical practice, as it suggests that patients with documented spinal pathology may be better served by alternative third-line therapies such as sacral neuromodulation.

More recently, Lee and Kuo[30] identified that successful BoNT/A treatment outcomes could be predicted by lower baseline detrusor pressure, higher maximum flow rate, larger voided volume, and lower PVR in men, and by larger voided volume and lower PVR in women. Their comprehensive video UDS analysis revealed that patients with neurogenic DO due to central nervous system pathology and those with detrusor underactivity rarely achieved successful outcomes.

To address the heterogeneity in outcome definitions, Mailho et al.[31] recently established the first expert consensus definition of failure for intradetrusor botulinum toxin injection in neurogenic detrusor overactivity, defining failure as the persistence of detrusor overactivity with maximum detrusor pressures >40 cmH_2O and/or compliance issues and/or persistent urinary incontinence/urgency and/or >8 daily self-catheterizations and/or treatment efficacy <3 months. While this expert consensus was developed specifically for neurogenic bladder pathology, the framework emphasizes the need for standardized, multi-parametric outcome definitions incorporating both objective urodynamic criteria and clinically meaningful patient-centered endpoints. Applying such standardized definitions prospectively in future idiopathic OAB cohorts would substantially improve comparability of results and enable meta-analyses that adequately address the critical question of which patient characteristics predict treatment success.

While our study focused solely on outcomes after the first injection, Dowson et al.[32] provide an important perspective on the trajectory of treatment response with repeat injections. In their prospective series of 100 patients with refractory idiopathic OAB receiving up to 10 repeat injections, 37 patients discontinued treatment after the first two injections, predominantly due to poor efficacy (13%) or inability to perform clean intermittent self-catheterization (11%). These findings suggest that the majority of initial non-responders represent a true treatment failure phenotype rather than patients who might benefit from repeated attempts with dose adjustments or modified techniques.

In this study, patients presenting with elevated baseline FDV or PVR volumes exhibited limited therapeutic benefit following administration of 100 U BoNT/A. The observed changes in both clinical and urodynamic parameters were insufficient to achieve meaningful relief of OAB symptoms or to enhance health-related QoL. At 12 weeks post-treatment, FDV declined modestly from 141.2 to 132.8 mL, a difference that did not reach statistical significance ($p = 0.6826$). Conversely, PVR increased from 50.1 to 72.3 mL ($p = 0.1220$). Patients who responded favorably presented with substantially lower FDV and PVR values, accompanied by significant gains in MVP, MDP, MCBC, and BC, all contributing to superior QoL outcomes. Our findings are in line with the results of a study by Kuo et al.[33], who performed similar evaluations of their data, where approximately one-third of their participants (33.7%) experienced suboptimal clinical results. Consistent with prior

observations in the literature, elevated baseline PVR (>100 mL) was associated with increased likelihood of voiding strain following treatment, whereas patients demonstrating predominant sensory modulation, rather than motor effects, achieved higher response rates and longer therapeutic duration.[12] Therefore, our study supports the speculation that different mechanisms of action exist for intradetrusor Botox injection effects on I-OAB. The growing understanding of BoNT/A's dual mechanisms of action provides important context for interpreting our findings regarding high baseline FDV and PVR as predictors of poor response.

In the present study, we found a small subset of 6 patients requiring CIC due to elevated PVR volumes or symptomatic retention. The uniform dose eliminated dose-dependent effects, and the limited CIC sample size precluded statistical analysis of previously identified predictors such as male gender, older age, and higher baseline PVR.[21] The similar distribution of CIC patients within our cohort (9.75% responders, 8.33% non-responders) suggests that CIC does not directly correlate with treatment failure, consistent with findings from Abrar et al.[21], indicating that patients requiring CIC often achieve symptom improvement despite this adverse event. The small CIC subset limits statistical power and generalizability, requiring larger studies to explore predictors of CIC use.

Previous studies have reported that intradetrusor administration of BoNT/A not only enhances bladder storage capacity, but also attenuates bladder sensory perception.[10] This outcome is likely related to the suppression of afferent signaling, resulting in diminished detrusor contractile activity. These findings underscore the prominent modulatory effect of BoNT/A on sensory pathways, which has been proposed as a principal mechanism underlying its therapeutic efficacy.[34,35] An elevated baseline PVR combined with reduced sensation during bladder filling may therefore reflect dysfunction within these afferent nociceptive fibers, contributing to a less favorable treatment response.

Increasing evidence supports that changes in afferent neurotransmission activity might impact the antinociceptive action of botulinum A toxin through both direct and indirect sensory effects.[12] Thus, impaired afferent nociceptive sensory fibers could result in short-term therapeutic sensory effects and unsatisfactory outcomes. Intradetrusor injection of BoNT/A modulates the sensitivity of sensory pathways by desensitizing unmyelinated C-fibers in the urothelium through reduction of key sensory receptors, particularly purinergic receptor P2X3 and transient receptor potential vanilloid 1 (TRPV1), which are directly linked to urgency symptom generation.[36] The highest concentration of sensory nerves expressing TRPV1, P2X3, substance P, and calcitonin gene-related peptide (CGRP) is localized in the suburothelial plexus and urothelium. This anatomic distribution explains why BoNT/A achieves clinical efficacy through sensory desensitization even in patients without detrusor overactivity on urodynamics.[37] This may suggest that the BoNT/A mechanism of action is more on the afferent pathway as opposed to the efferent arm of the micturition reflex. Nevertheless, further studies in this area are needed before any strong conclusions can be made.

Not surprisingly, data in this study suggest that patients with poor baseline bladder compliance seem to have a trend to therapeutic failure even though it did not reach statistical significance ($p = 0.08$). However, in a multivariate logistic regression model, no significant predictors for treatment response could be recognized. Several studies reported on poor response following BoNT/A injections, analysis revealed low baseline detrusor compliance, which was attributed to a pre-existing fibrotic alteration of the bladder wall.[38,39] Schmid et al.[40], in their series of 100 OAB patients injected with 100 U BoNT/A, reported that poor pre-treatment detrusor compliance, together with maximal cystometric capacity < 100 mL, and bladder wall fibrosis on biopsy, predisposed to therapeutic failure. Other investigators showed that poor responders had significantly higher baseline MDP, and all other studied parameters were similar.[23] In a study of 45 patients with neurogenic OAB treated with 300 U BoNT/A, clinical and urodynamic data were comparable between the responders and non-responders.[41]

Contemporary approaches to identifying predictive factors for OAB treatment response utilize urinary biomarkers[42], machine learning, genetic analysis, or both to evaluate complex data sets.[43,44] A recent study on female patients analyzed gene expression from buccal swab samples, finding that the ADRB3:rs4994 polymorphism may be associated with urodynamic response to intradetrusor BoNT/A injection, though further research in diverse ethnic groups is needed to confirm its predictive role.[32] Most existing urinary biomarker research in OAB has focused on diagnostic classification and predicting response to pharmacological agents, rather than specifically examining BoNT/A efficacy.[45–47] A notable exception is the recent metabolomics study by Tellechea et al.[48], which demonstrated that intravesical BoNT/A injection significantly alters the urinary metabolome in parallel with OAB symptom

improvement. Analysis of 61 urinary metabolites revealed three showing significant changes in treatment responders: adenosine levels decreased significantly in mild and moderate responders, N8-acetylspermidine increased most markedly in moderate responders, and guanidinoacetic acid showed elevated levels in moderate responders. These metabolic alterations provide mechanistic insight, suggesting that BoNT/A acts through multiple pathways beyond simple detrusor muscle denervation, specifically through modulation of urothelial purinergic signaling, cellular regeneration pathways, and nitric oxide-mediated afferent nerve desensitization.

Traditional urinary biomarkers have shown more limited predictive value for BoNT/A specifically. Nerve growth factor (NGF) reliably predicts anticholinergic treatment response but does not consistently predict BoNT/A treatment outcomes.[49] Conversely, the ROSETTA Trial Biomarker Analysis found that elevated baseline CGRP identifies patients at higher risk of BoNT/A treatment failure and may guide selection toward alternative therapies such as sacral neuromodulation.[42] Additionally, post-treatment increases in matrix metalloproteinase-9 (MMP-9) and interleukin-8 (IL-8) were observed following BoNT/A injection, suggesting that tissue remodeling and inflammatory responses may represent secondary mechanisms contributing to therapeutic efficacy beyond direct neurotoxin effects. The integration of multivariate biomarker panels, metabolomics signatures, and genetic polymorphisms represents a promising path forward for personalized OAB treatment selection. However, substantial prospective validation studies with adequately powered cohorts are required before these approaches can be meaningfully implemented in clinical practice.

The main limitations of this study were the small sample size and lack of subgroup analysis based on age stratification, particularly in the poor responder group. Although this study reveals interesting findings, further large-scale trials are warranted to confirm these results. Another limitation was its retrospective design, which is not the best way to examine the effect of predictive factors on an outcome and increases the risk of selection bias. Another potential confound in our retrospective analysis is inter-operator variability. However, all injections were performed by two experienced urologists using identical standardized protocols, minimizing operator experience as a factor contributing to treatment failure. Therefore, we could not obtain exact factors affecting treatment response via multivariate regression analysis. Furthermore, the records regarding outcomes after BoNT/A injection in this analysis were obtained at 12 weeks of follow-up only. The lack of a standardized definition of poor response, coupled with varied literature on treatment success or failure, introduced heterogeneity and constrained the accuracy of response classifications. The final limitation was the lack of baseline and post-treatment voiding diary data, critical for quantifying OAB symptom changes. Combined with validated OAB questionnaires with known minimally important difference (MID) values[21], diaries enable comprehensive treatment response assessment. Their absence limits the evaluation of BoNT/A efficacy.

Conclusions

In conclusion, treatment failure remains a significant challenge in idiopathic OAB patients receiving botulinum toxin A therapy. This study identified that high pre-treatment values of first desire to void volume and post-void residual were associated with poor therapeutic efficacy. However, the absence of additional robust predictive factors highlights the multifactorial and poorly understood nature of BoNT/A treatment response. Current heterogeneity in treatment efficacy definitions across clinical trials undermines both clinical decision-making and comparative effectiveness research. Implementation of standardized, multi-dimensional outcome criteria, incorporating urodynamic parameters, clinical symptoms, and patient-reported outcomes, would substantially strengthen clinical practice and enable rigorous cross-study comparisons. Expert consensus frameworks for OAB treatment evaluation represent an important step toward this standardization.

To advance the field and improve patient selection, we recommend prospective, adequately powered studies with diverse cohorts, including balanced gender representation, that systematically assess demographic, clinical, and urodynamic predictors using standardized outcome definitions. Such investigations would enhance our ability to identify treatment responders and non-responders a priori, ultimately optimizing clinical decision-making and reducing unnecessary treatment attempts in this patient population.

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Author Contributions

The authors confirm contribution to the paper as follows: Conceptualization, Lysanne Campeau, Jacques Corcos, and Samer Shamout; methodology, Lysanne Campeau and Samer Shamout; formal analysis, Samer Shamout and Hani Kabbara; investigation, Samer Shamout and Claudia Covarrubias; resources, Lysanne Campeau and Jacques Corcos; data curation, Samer Shamout and Hani Kabbara; writing—original draft preparation, Samer Shamout; writing—review and editing, Samer Shamout, Lysanne Campeau, and Claudia Covarrubias; visualization, Samer Shamout and Claudia Covarrubias; supervision, Lysanne Campeau and Jacques Corcos; project administration, Lysanne Campeau. All authors reviewed and approved the final version of the manuscript.

Availability of Data and Materials

The data that support the findings of this study are available from the Corresponding Author, Lysanne Campeau, upon reasonable request.

Ethics Approval

The study received approval from the Research Ethics Committee (REC) of the Jewish General Hospital (Date of approval: September 02, 2015; CR-15-47). Participant consent was waived by authorization of the Director of Professional Services.

Conflicts of Interest

The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript.

BC	Bladder compliance
BMI	Body mass index
BoNT/A	Onabotulinum toxin-A
CGRP	Calcitonin gene-related peptide
CIC	Clean intermittent catheterization
FDV	First desire void volume
GRA	Global response assessment
ICIQ-SF	International consultation on incontinence questionnaire—short form
I-OAB	Idiopathic overactive bladder
IIQ-7	Incontinence impact questionnaire
IL-8	Interleukin-8
MCBC	Maximum cytometric bladder capacity
MDP	Maximal detrusor pressure
MID	Minimally important difference
MMP-9	Matrix metalloproteinase-9
MVP	Maximum vesical pressure
NDO	Neurogenic detrusor overactivity
NGF	Nerve growth factor
OAB	Overactive bladder
OABSS	Overactive bladder symptom score
Pdet-max	Maximum detrusor pressure
PVR	Postvoid residual
QoL	Quality of life
REC	Research ethics committee
SD	Standard deviation
TRPV1	Transient receptor potential vanilloid 1
UDS	Urodynamic study
UUI	Urge urinary incontinence

References

1. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. *Neurourol Urodyn* 2002;21(2):167–178. doi:10.1002/nau.10052.
2. Herschorn S, Gajewski J, Schulz J, Corcos J. A population-based study of urinary symptoms and incontinence: the Canadian urinary bladder survey. *BJU Int* 2008;101(1):52–58. doi:10.1111/j.1464-410X.2007.07198.x.
3. Corcos J, Schick E. Prevalence of overactive bladder and incontinence in Canada. *Can J Urol* 2004;11(3):2278–2284.
4. Corcos J, Przydacz M, Campeau L et al. CUA guideline on adult overactive bladder. *Can Urol Assoc J* 2017;11(5):E142–E173. doi:10.5489/cuaj.4586.
5. Hassouna MM, Sadri H. Economic evaluation of sacral neuromodulation in overactive bladder: a Canadian perspective. *Can Urol Assoc J* 2015;9(7–8):242–247. doi:10.5489/cuaj.2711.
6. Viste D, Barton C, Carlson K, Baverstock R, Crump RT. Canadian cost data associated with treating overactive bladder is lacking. *Can Urol Assoc J* 2022;16(3):E137–E145. doi:10.5489/cuaj.7500.

7. Herschorn S, Vicente C, Piwko C. Canadian cost-effectiveness analysis of solifenacin compared to oxybutynin immediate-release in patients with overactive bladder. *J Med Econ* 2010;13(3):508–515. doi:10.3111/13696998.2010.509244.
8. Gerjevic KA, Ahmad S, Strohbehn K, Riblet N. Cost-effectiveness analysis between sacral neuromodulation and OnabotulinumtoxinA for the treatment of refractory overactive bladder in women: a systematic review. *Female Pelvic Med Reconstr Surg* 2021;27(8):481–487. doi:10.1097/SPV.0000000000001074.
9. Anger JT, Weinberg A, Suttorp MJ, Litwin MS, Shekelle PG. Outcomes of intravesical botulinum toxin for idiopathic overactive bladder symptoms: a systematic review of the literature. *J Urol* 2010;183(6):2258–2264. doi:10.1016/j.juro.2010.02.009.
10. Apostolidis A, Popat R, Yiangou Y et al. Decreased sensory receptors P2X3AND trpv1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol* 2005;174(3):977–983. doi:10.1097/01.ju.0000169481.42259.54.
11. Ibrahim H, Maignel J, Hornby F, Daly D, Beard M. BoNT/a in the urinary bladder-more to the story than silencing of cholinergic nerves. *Toxins* 2022;14(1):53. doi:10.3390/toxins14010053.
12. Kuo HC. Reduction of urgency severity is associated with long-term therapeutic effect after intravesical onabotulinumtoxin a injection for idiopathic detrusor overactivity. *Neurourol Urodyn* 2011;30(8):1497–1502. doi:10.1002/nau.21132.
13. Schulte-Baukloh H, Bigalke H, Miller K et al. Botulinum neurotoxin type a in urology: antibodies as a cause of therapy failure. *Int J Urology* 2008;15(5):407–415. doi:10.1111/j.1442-2042.2008.02016.x.
14. Goldman HB, Wyndaele JJ, Kaplan SA, Wang JT, Ntanios F. Defining response and non-response to treatment in patients with overactive bladder: a systematic review. *Curr Med Res Opin* 2014;30(3):509–526. doi:10.1185/03007995.2013.860021.
15. Gaillet S, Bardot P, Bernuz B et al. Five years follow-up study and failures analysis of Botulinum toxin repeated injections to treat neurogenic detrusor overactivity. *Prog Urol* 2012;22(17):1064–1070. doi:10.1016/j.purol.2012.10.006.
16. Cohen BL, Caruso DJ, Kanagarajah P, Gousse AE. Predictors of response to intradetrusor botulinum toxin-a injections in patients with idiopathic overactive bladder. *Adv Urol* 2009;2009:328364. doi:10.1155/2009/328364.
17. Uebersax JS, Wyman JF, Shumaker SA, McClish DK, Fantl JA. Short forms to assess life quality and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and the urogenital distress inventory. continence program for women research group. *Neurourol Urodyn* 1995;14(2):131–139. doi:10.1002/nau.1930140206.
18. Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C. Validation of the overactive bladder symptom score. *J Urol* 2007;178(2):543–547. doi:10.1016/j.juro.2007.03.133.
19. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: a brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn* 2004;23(4):322–330. doi:10.1002/nau.20041.
20. Rosier PFWM, Schaefer W, Lose G et al. International continence society good urodynamic practices and terms 2016: urodynamics, uroflowmetry, cystometry, and pressure-flow study. *Neurourol Urodyn* 2017;36(5):1243–1260. doi:10.1002/nau.23124.
21. Abrar M, Pindoria N, Malde S, Chancellor M, DeRidder D, Sahai A. Predictors of poor response and adverse events following botulinum toxin a for refractory idiopathic overactive bladder: a systematic review. *Eur Urol Focus* 2021;7(6):1448–1467. doi:10.1016/j.euf.2020.06.013.
22. Roman MP, Ciortea R, Doumouchtsis SK et al. Comparison of different treatment outcomes for refractory overactive bladder: a systematic review and meta-analysis. *Toxins* 2025;17(10):479. doi:10.3390/toxins17100479.
23. Sahai A, Khan MS, Le Gall N, Dasgupta P. Urodynamic assessment of poor responders after botulinum toxin-a treatment for overactive bladder. *Urology* 2008;71(3):455–459. doi:10.1016/j.urology.2007.11.039.
24. Marcelissen T, Cornu JN, Antunes-Lopes T et al. Management of idiopathic overactive bladder syndrome: what is the optimal strategy after failure of conservative treatment? *Eur Urol Focus* 2018;4(5):760–767. doi:10.1016/j.euf.2018.05.004.
25. Hsiao SM, Lin HH, Kuo HC. Factors associated with therapeutic efficacy of intravesical OnabotulinumtoxinA injection for overactive bladder syndrome. *PLoS One* 2016;11(1):e0147137. doi:10.1371/journal.pone.0147137.
26. Dmochowski R, Chapple C, Nitti VW et al. Efficacy and safety of onabotulinumtoxinA for idiopathic overactive bladder: a double-blind, placebo controlled, randomized, dose ranging trial. *J Urol* 2010;184(6):2416–2422. doi:10.1016/j.juro.2010.08.021.
27. Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn* 2011;30(4):556–562. doi:10.1002/nau.21021.
28. Owen RK, Abrams KR, Mayne C, Slack M, Tincello DG. Patient factors associated with onabotulinum toxin a treatment outcome in women with detrusor overactivity. *Neurourol Urodyn* 2017;36(2):426–431. doi:10.1002/nau.22948.
29. Komesu YM, Amundsen CL, Richter HE et al. Refractory urgency urinary incontinence treatment in women: impact of age on outcomes and complications. *Am J Obstet Gynecol* 2018;218(1):111.e1–111.e9. doi:10.1016/j.ajog.2017.10.006.
30. Lee YK, Kuo HC. Urodynamic predictive factors for successful treatment outcomes following intravesical botulinum toxin a injection in patients with detrusor overactivity. *Biomedicines* 2025;13(9):2147. doi:10.3390/biomedicines13092147.
31. Mailho C, Peyronnet B, De Seze M et al. How to define failure of intradetrusor injections of botulinum toxin A for neurogenic detrusor overactivity. *Neurourol Urodyn* 2024;43(4):811–817. doi:10.1002/nau.25427.
32. Dowson C, Watkins J, Khan MS, Dasgupta P, Sahai A. Repeated botulinum toxin type A injections for refractory overactive bladder: medium-term outcomes, safety profile, and discontinuation rates. *Eur Urol* 2012;61(4):834–839. doi:10.1016/j.eururo.2011.12.011.
33. Kuo HC, Liao CH, Chung SD. Adverse events of intravesical botulinum toxin a injections for idiopathic detrusor overactivity: risk factors and influence on treatment outcome. *Eur Urol* 2010;58(6):919–926. doi:10.1016/j.eururo.2010.09.007.
34. Aoki KR. Review of a proposed mechanism for the antinociceptive action of botulinum toxin type A. *NeuroToxicology* 2005;26(5):785–793. doi:10.1016/j.neuro.2005.01.017.
35. Apostolidis A, Dasgupta P, Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006;49(4):644–650. doi:10.1016/j.eururo.2005.12.010.

36. Li X, Hu J, Yin P, Liu L, Chen Y. Mechanotransduction in the urothelium: ATP signalling and mechanoreceptors. *Heliyon* 2023;9(9):e19427. doi:10.1016/j.heliyon.2023.e19427.
37. Alshammari D, Yadav P, Ahmad I et al. Intradetrusor versus suburothelial onabotulinum toxin a in adults with neurogenic and non-neurogenic overactive bladder syndrome: a meta-analysis. *Arch Esp Urol* 2024;77(4):368–377. doi:10.56434/j.arch.esp.urol.20247704.50.
38. Kennelly M, Kang J. Botulinum-a toxin injections as a treatment for refractory detrusor hyperreflexia. *Top Spinal Cord Inj Rehabil* 2003;8(3):46–53. doi:10.1310/1640-xepp-y33e-tmk8.
39. Horst M, Weber DM, Bodmer C, Gobet R. Repeated Botulinum-a toxin injection in the treatment of neuropathic bladder dysfunction and poor bladder compliance in children with myelomeningocele. *Neurourol Urodyn* 2011;30(8):1546–1549. doi:10.1002/nau.21124.
40. Schmid DM, Sauermann P, Werner M et al. Experience with 100 cases treated with botulinum-a toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. *J Urol* 2006;176(1):177–185. doi:10.1016/S0022-5347(06)00590-8.
41. Compérat E, Reitz A, Delcourt A, Capron F, Denys P, Chartier-Kastler E. Histologic features in the urinary bladder wall affected from neurogenic overactivity—A comparison of inflammation, oedema and fibrosis with and without injection of botulinum toxin type A. *Eur Urol* 2006;50(5):1058–1064. doi:10.1016/j.eururo.2006.01.025.
42. Richter HE, Moalli P, Amundsen CL et al. Urinary biomarkers in women with refractory urgency urinary incontinence randomized to sacral neuromodulation versus OnabotulinumtoxinA compared to controls. *J Urol* 2017;197(6):1487–1495. doi:10.1016/j.juro.2017.01.037.
43. Ciećwież S, Lewandowska K, Szylińska A et al. Association analysis of ADRB3: rs4994 with urodynamic outcome, six months after a single intra-detrusor injection of botulinum toxin, in women with overactive bladder. *Pharmacol Rep* 2024;76(6):1489–1500. doi:10.1007/s43440-024-00647-9.
44. Okui N, Ikegami T, Hashimoto T, Kouno Y, Nakano K, Okui MA. Predictive factors for high post-void residual volume in older females after OnabotulinumA treatment for severe overactive bladder using a machine learning model. *Cureus* 2023;15(7):e42668. doi:10.7759/cureus.42668.
45. Mossa AH, Shamout S, Cammisotto P, Campeau L. Urinary metabolomics predict the severity of overactive bladder syndrome in an aging female population. *Int Urogynecol J* 2020;31(5):1023–1031. doi:10.1007/s00192-019-04175-6.
46. Covarrubias C, Cammisotto PG, Campeau L. Neurotrophins and proneurotrophins as biomarkers for overactive bladder syndrome in aging females. *Metabolites* 2025;15(7):429. doi:10.3390/metabo15070429.
47. Beta A, Giannouli A, Rizos D, Mantzou A, Deligeoroglou E, Bakas P. Nerve growth factor and brain-derived neurotrophic factor as potential biomarkers of mirabegron efficacy in patients with overactive bladder syndrome. *Int Urogynecology J* 2024;35(6):1317–1322. doi:10.1007/s00192-024-05809-0.
48. Tellechea LM, Freeman S, Agalliu I, Laudano MA, Suadicani SO, Abraham N. A feasibility study to evaluate changes in urinary metabolites after OnabotulinumtoxinA injection for refractory overactive bladder. *Metabolites* 2022;12(9):880. doi:10.3390/metabo12090880.
49. Sağır S, Bayrak Ö, Şen H, Kul S, Erturhan S, Seçkiner İ. Correlation between the NGF levels and questionnaire forms in patients receiving antimuscarinic treatment and those receiving onabotulinum toxin-a injection. *Turk J Urol* 2021;47(3):223–228. doi:10.5152/tud.2020.20432.

