

## INTRADETRUSOR BOTULINUM TOXIN INJECTIONS FOR THE MANAGEMENT OF ANTICHOLINERGIC REFRACTORY, POORLY COMPLIANT NEUROGENIC BLADDERS

### Hypothesis / aims of study

Pharmacotherapy with anticholinergic medications plays an important role in improving bladder compliance and capacity in patients with neurogenic bladder dysfunction (NGB). Alpha-blockers and imipramine added to a daily protocol of anticholinergic drug therapy has been shown to reduce storage pressures in a subset of patients that failed anticholinergics alone (1). However, many patients fail to show objective or subjective success and require further treatment. Enterocystoplasty reliably improves bladder capacity and compliance but is invasive and may carry significant potential risks.

Intradetrusor onabotulinum toxin A (BTX-A) injections have become an important tool in management of neurogenic detrusor overactivity in patients when pharmacotherapy is non-efficacious or poorly tolerated. There is also some evidence that BTX-A injections can improve bladder compliance in NGB patients (2). The objective of this study is to evaluate the therapeutic effect of intradetrusor BTX-A injections in patients with poorly compliant NGB refractory to medical management.

### Study design, materials and methods

We retrospectively examined the medical records of all patients with NGB with impaired compliance due to spinal myelopathy treated with intradetrusor BTX-A injections from October 2005 to December 2014. Inclusion criteria included patients  $\geq 18$  years of age with medication refractory, poorly compliant (defined as  $< 20\text{mL/cmH}_2\text{O}$ ) NGB diagnosed on video-urodynamics (VUDS). All patients performed clean intermittent catheterization and were treated with BTX-A injections. Medical therapy consisted of one or more anticholinergic medications +/- imipramine and/or alpha blockers. Patients were considered refractory if urinary symptoms persisted despite maximal recommended dosage of oral medications. Patients with a history of pelvic radiotherapy or prior bladder augmentation were excluded. VUDS were performed according to International Continence Society guidelines with fluid-filled transducers at a medium fill rate (30mL/min). Impaired bladder compliance was defined as  $20\text{mL/cm H}_2\text{O}$  or less. End fill capacity was defined as capacity at which either sensation of need for emptying, urinary leakage or detrusor pressures of  $40\text{cm H}_2\text{O}$  were reached. Compliance was measured by comparing changes in volume and detrusor pressure at start of infusion and end-fill capacity.

Trigone-sparing BTX-A injections (300u) were performed under local anesthesia using either a rigid or flexible cystoscope. Patients were evaluated 2-4 weeks after injection. Urinary symptoms were assessed using bladder diaries obtained pre and post-injection with patients describing overall symptom improvement relating to urinary complaints. Patients reporting clinical symptomatic improvement with at least 50% reduction in daily incontinence episodes following BTX-A injection underwent repeat VUDS to reassess bladder compliance. An objective improvement in compliance was defined as an increase of  $\geq 5\text{mL/cmH}_2\text{O}$  following BTX-A injections.

Patients with symptomatic and objective improvement in compliance ( $> 5\text{mL/cm H}_2\text{O}$ ) were categorized as "BTX-A responders". Patients without symptomatic improvement or those who did not have objective improvement in compliance of VUDS were considered "BTX-A non-responders". We compared clinical and demographic variables between BTX-A responders and non-responders including: age, gender, etiology of NGB (spinal cord injury (SCI) or myelomeningocele (MM)), urinary symptoms, medication use and VUDS findings. Statistical significance, defined as a p-value  $< 0.05$ , was determined using Student's t, chi square and Fisher's exact tests where appropriate.

### Results

27 patients (13 SCI and 14 MM) with medical refractory, poorly compliant bladders managed with BTX-A injections fulfilled the inclusion criteria. Prior to treatment all patients experienced urinary incontinence with or without recurrent urinary tract infections. After BTX-A injection 14 patients (51.9%) reported symptomatic improvement defined as  $> 50\%$  reduction in daily urinary incontinence episodes. Repeat VUDS demonstrated a mean change in bladder capacity and compliance of 14.6mL (-150mL to 173mL) and 6.28 mL/cmH<sub>2</sub>O (-7.30 to 22.26mL/cmH<sub>2</sub>O), respectively. Eight of these 14 patients had improvement in compliance  $> 5\text{mL/cm H}_2\text{O}$  following BTX-A injection, with mean compliance improvement of 12.38 mL/cm H<sub>2</sub>O (5.24 to 22.26mL/cmH<sub>2</sub>O), resulting an overall BTX-A response rate of 8/27 (29.6%).

When comparing baseline patient characteristics, BTX-A responders had a statistically significant shorter duration of time between their neurologic injury and BTX-A injections (10.2 yrs vs 18.2 yrs,  $p=0.05$ ). BTX-A responders were more likely to have NDO detected on initial VUDS (75% vs 36.8%,  $p=0.07$ ) and were more likely to have SCI as opposed to MM (75% vs 36.8%,  $p=0.07$ ), but these trends did not reach statistical significance. BTX-A responders tended to be older than non-responders, but this association did not reach statistical significance (40.3 yrs vs 30.2 yrs,  $p=0.10$ ). There was no significant relation between preoperative bladder compliance and responsiveness to BTX-A. Patients with a history of MM had similar VUDS parameters compared to patients with SCI, both before and after BTX-A injections. However, MM patients were significantly younger (23.4 vs. 44.4 yrs,  $p < 0.01$ ) and had a longer duration of myelopathy (23.4 vs. 7.36 yrs,  $p < 0.01$ ) than SCI patients.

### Interpretation of results

Given that less than 1/3 of our patients had both symptomatic and urodynamic improvement in bladder compliance following BTX-A injections attests to the severity of NGB in this patient population. A longer duration of NGB was a negative predictor of BTX-A responsiveness suggesting that over time fibrosis may contribute to poor compliance. The expectation would be less responsiveness to medications and BTX-A injections which act via neuro-myogenic blockade. While not achieving statistical significance, BTX-A responders tended to be more likely to have NDO on UDS than non-responders which is consistent with the bladder fibrosis hypothesis.

### Concluding message

Intradetrusor BTX-A injections significantly improved symptoms and urodynamic outcomes in 30% of patients with poorly compliant NGB that is refractory medical therapy. A shorter duration of NGB was a predictor of BTX-A responsiveness. BTX-A injections may prevent the need for bladder augmentation in approximately 30% of patients with poor bladder compliance.

### References

1. Cameron AP, Clemens JQ, Latini JM, McGuire EJ. J Urol. 2009 Sep;182(3):1062-7
2. Rovner E, Dmochowski R, Chapple C, Thompson C, Lam W, Haag-Molkenteller C. NeuroUrol Urodyn. 2013 Nov;32(8):1109-15

### Disclosures

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