Intradetrusor onabotulinumtoxinA injection: how I do it

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Overactive bladder is a highly prevalent condition that may have significant impact on quality of life. This condition may be idiopathic or may have a neurogenic etiology. Antimuscarinics have long been the preferred agents for the treatment of this condition. OnabotulinumtoxinA, an injectible agent that prevents presynaptic release of acetylcholine at the neuromuscular junction, has emerged as an important option in the management of patients with urinary incontinence caused by refractory detrusor overactivity. This manuscript describes our technique for performing utilizing this therapy, describes key equipment needed and provides technical tips for avoiding common pitfalls.

Key Words: overactive bladder, urinary incontinence, onabotulinumtoxinA

Introduction

Patients with underlying neurologic disorders develop significant lower urinary tract dysfunction. These patients may present clinically with overactive bladder (OAB), a highly prevalent symptom complex of urinary urgency and frequency, with or without urge incontinence.[1] These lower urinary tract symptoms in patients with a known neurologic cause are frequently referred to as neurogenic overactive bladder (NOAB). Similarly, when the urodynamic observation of detrusor overactivity (DO) is caused by a particular neurologic condition, it is referred to as neurogenic detrusor overactivity (NDO).

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The management of neurogenic overactive bladder (NOAB) can be challenging for both the patient and the physician. Management options for NOAB are usually aimed at protecting the upper urinary tract (elevated bladder storage pressures secondary to decreased bladder compliance and/or high pressure detrusor overactivity) and managing lower urinary tract symptoms. Treatments options may include behavioral changes, anticholinergic therapy, neuromodulation, intermittent catheterization, external or indwelling catheters, augmentation cystoplasty, and urinary diversion.

Anticholinergic medications can provide measurable relief of symptoms in some patients, however these medications produce many undesirable side effects and are often not well tolerated. Intradetrusor injection of onabotulinumtoxinA (BOTOX, Allergan Inc. Irvine, CA, USA) has emerged as a safe and effective treatment for urinary incontinence and recently received FDA approval for use in patients with NDO.

TABLE 1. **Commercially available botulinum toxin preparations**

Generic name	**OnabotuliumntoxinA**	**RimabotulinumtoxinB**	**AbobotulinumtoinA**	**IcobotulinumtoxinA**
Brand Name	Botox	Myobloc, Neurobloc	Dysport	Xeonim
Manufacturer	Allergan Inc.	Solstice Neurosciences	Ipsen	Merz Pharmaceuticals GmbH
Serotype	A	B	A	A
Constituents and excipients	Hemagglutinin, human albumin, saccharose, sodium chloride	Hemagglutinin, human albumin solution 0.05%, sodium chloride, sodium succinate	Hemmagglutinin, human albumin, 20% solution, lactose	Human albumin, saccharose
Complex size, kDa	900	700	900	150
Storage of packaged product	-5˚C or 2˚C to 8˚C	2˚C to 8˚C	2˚C to 8˚C	Room temperature
Storage once reconstituted	2˚C to 8˚C for 24 h	For a few hours	2˚C to 8˚C for several hours	2˚C to 8˚C for 24 h

Mechanism of action

Botulinum toxin (BoNT) is a potent neurotoxin that irreversibly blocks the release of acetylcholine from presynaptic nerve terminals. There are seven serotypes, A through G, of BoNT produced by different strains of Clostridium botulinum.[2] Botulinum toxins type A (BoNT-A) and B (BoNT-B) have been the most widely investigated and developed for therapeutic applications. The most well-established mechanism of action of BoNT-A is its ability to presynaptically inhibit the release of acetylycholine from motor neurons. This effect is mediated by binding of BoNT-A to synaptic vesicle protein type 2 (SV2) on the surface of nerve terminals and inhibiting acetylcholine release through the cleavage of synaptosome-associated protein of 25 kDa (SNAP-25) or vesical-associated membrane protein.[3,4] While the inhibitory effect of BoNT-A on detrusor muscle is well-established, there may also be an afferent effect, possibly mediated by modulation of acetylcholine release by urothelial cells or by sensory inhibitory effects that are unrelated to acetylcholine release.

There are several commercially available botulinum toxin preparations. Each available brand contains toxin isolated by different processes with a proprietary unit of measurement. Because botulinum toxins are biological compounds, the type of formulation is clinically important. The biological receptor affinity, size of the toxin complex, formulation, and intracellular target will all effect the optimal dose, safety and efficacy profile, and duration of action. There has recently been changes to established botulinum toxin drug names to differentiate commercially available formulations, reinforce the lack of interchangeability among products, and reduce the risk of medical error, Table 1. The potency units are strictly specific to each botulinum toxin product, and the doses or units of biological activity cannot be compared or converted from one product to any other botulinum toxin product. OnabotulinumtoxinA (BOTOX) is the most widely studied and only approved commercially available botulinum toxin for urologic indications.

Indications and results

The first urologic application of botulinum toxin injection was for the treatment of detruso-external sphincter dyssynergia.[5] The only currently approved urologic indication for onabotulinumtoxinA (BOTOX) is for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition such as spinal cord injury or multiple sclerosis in adults who have an inadequate response to or are intolerant of an anticholinergic medication. Consistent improvement in clinical and urodynamic parameters have been demonstrated in several randomized placebo controlled trials, Table 2.[6-8] Non-approved urologic uses currently include injection for idiopathic overactive bladder, interstitial cystitis

TABLE 2. **Summary of RCT studies using onabotulinumtoxinA for treatment of refractory symptoms in adult patients with neurogenic detrusor overactivity**

Authors	No. patients	Patients type	Continence (%)/ leak episode (Δ%)	MCC (Δ%)	Pdetmax (Δ%)	Duration of benefit
Schurch et al[6]						
Placebo	21	53 SCI, 5 MS	24/-10	+18	-13	NA
OnabotulinumtoxinA200U	19		71/-58	+85	-59	> 24 weeks
OnabotulinumtoxinA300U	19		53/-54	+63	-56	> 24 weeks
Ginsberg et al[7]						
Placebo	149	SCI or MS	NR/-29	NA	NA	92 days
OnabotulinumtoxinA200U	135		NR/-69	Significant increase		256 days
OnabotulinumtoxinA300U	132		NR/-74	Significant increase		254 days
Cruz et al[8]						
Placebo	92	154 MS, 121 SCI	7.6/-36	+3	+15	13.1 weeks
OnabotulinumtoxinA200 U	92		38.0/-67	+64	-55	42.1 weeks (200 U and
OnabotulinumtoxinA300 U	91		39.6/-62	+64	-64	300 U groups combined)

MCC = maximum cystometric capacity; NA = not applicable; NR = not reported; Pdet max = maximum detrusor pressure; SCI = spinal cord injury; MS = multiple sclerosis

and chronic pelvic pain syndromes, benign prostatic hyperplasia and external sphincter dyssynergia. Based on convincing placebo-controlled trials, applications for approval of onabotulinumtoxinA for the treatment of urinary incontinence due to idiopathic detrusor overactivity have been filed with United States and European regulatory authorities.

Method and technique

Patient preparation

All patients submit a urine specimen for detection of infection, if present medication will be administered prior to onabotulinumtoxinA (BOTOX) injections. Patients having a history of recurrent UTI are given culture specific antibiotics; otherwise patients treated in the office usually receive a fluoroquinolone prior to the procedure. Aminoglycosides should be considered contraindicated in this procedure as they can potentiate the neuromuscular blockade effect of botulinum toxins. We do not routinely stop anti-platelet or anti-coagulation therapy for this procedure.

Most patients are treated using intravesical and intraurethral anesthesia in an office setting. Exceptions to this are patients who are not able to tolerate this procedure or those. Patients with neurogenic bladder dysfunction who are prone to autonomic dysreflexia should be carefully evaluated prior to this procedure. It is our experience that most patients with autonomic dysreflexia can be safely treated in an office setting. There are select patients with known severe dysreflexia who should be treated under general anesthesia. Careful attention to avoiding over distention of the bladder should minimize dysreflexia. Other patients sometimes elect completion of the procedure under conscious sedation.

Patients are premedicated with a flouroquinolone or culture specific antibiotic for antibiotic prophylaxis. The patient is placed in the supine position and 50 mL of 2% lidocaine solution is instilled into the bladder and 10 mL of 2% lidocaine gel is instilled into the urethra. The instillation catheter is capped and lidocaine is allowed to dwell for 15 to 20 minutes. The lidocaine solution is then drained prior to start of the procedure.

Drug preparation

OnabotulinumtoxinA (BOTOX) is kept refrigerated at 2˚C to 8˚C as recommended in the package insert. The typical (and only approved dose) of 200 Units of onabotulinumtoxinA is reconstituted in 30 mL of non-preserved, injectable 0.9% injectable saline. The currently recommended dose of onabotulinumtoxinA for the treatment of neurogenic detrusor overactivity is 200 Units, as 1 mL (~6.7 Units/mL) injections across 30 sites into the detrusor muscle. Prior to injection, reconstitute each vacuum-dried vial of onabotulinumtoxinA (BOTOX) with sterile, non-preserved injectable 0.9% saline. Reconstituted onabotulinum toxin should be stored in a refrigerator (2°C to 8°C). The drug should be administered within 24 hours after reconstitution.

Reconstitution of 200 Units of drug should yield three, 10 mL syringes (~6.7 Units in each). A separate syringe of injectable saline is prepared to use as a flush injection at the conclusion of the procedure to ensure utilization of all toxin left in the lumen of the injection needle at the completion of the procedure. We typically prepare a 3 mL syringe with injectable saline to allow easy differentiation from the 10 mL treatment syringes. There is concern that botulinum toxins may be denatured by vigorous shaking leading to the package insert recommendation that reconstitution be performed gently.

OnabotulinumtoxinA (BOTOX) is supplied in single-use 100 Units and 200 Units per vial. Although BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, they have different labeled indications. To prevent potential difficulties with third party reimbursement, we recommend only utilizing BOTOX for urologic indications.

Injection technique

We utilize both rigid and flexible instruments for this procedure, Figure 1. Rigid instruments allow faster completion of the procedure and require less expensive injection needles. For this reason, rigid endoscopes are preferred for use in patients under anesthesia and some, usually insensate, patients in the office setting. We typically utilize a 20 French injection cystourethroscope (Karl Storz, Tuttlingen, Germany), although most rigid cystoscopes may also be used. For procedures using rigid endoscopes we prefer to use the Cook Williams Cystoscopic Injection 25ga Needle (5.0 Fr/35 cm Tip length 4 mm).

Flexible cystoscopes are used for the majority of procedures completed in the office setting. The major advantage of using flexible endoscopy to guide injection is greater patient comfort. Disadvantages include a typically longer procedure time, greater cost for injection needles, and the potential for damage to the working channel during needle placement.

Patients receive 30 intradetrusor injections excluding the trigone and bladder dome. Each injection is made 2 mm deep and roughly 1 cm apart. Visible blood vessels are intentionally avoided. The injection needle is primed with reconstituted drug to remove air in the needle channel. One mL (~6.7 Units/mL) of onabotulinumtoxinA is then injected in a grid type pattern in 1 cm intervals for a total of 30 injections. After all three 10 mol treatment syringes are utilized, a 3 mol syringe with 0.9 % ingestible saline is used to inject an additional 1 mol to 2 mol of injectable saline. This insures that all active drug is utilized and not left in the needle channel. The trigone is traditionally

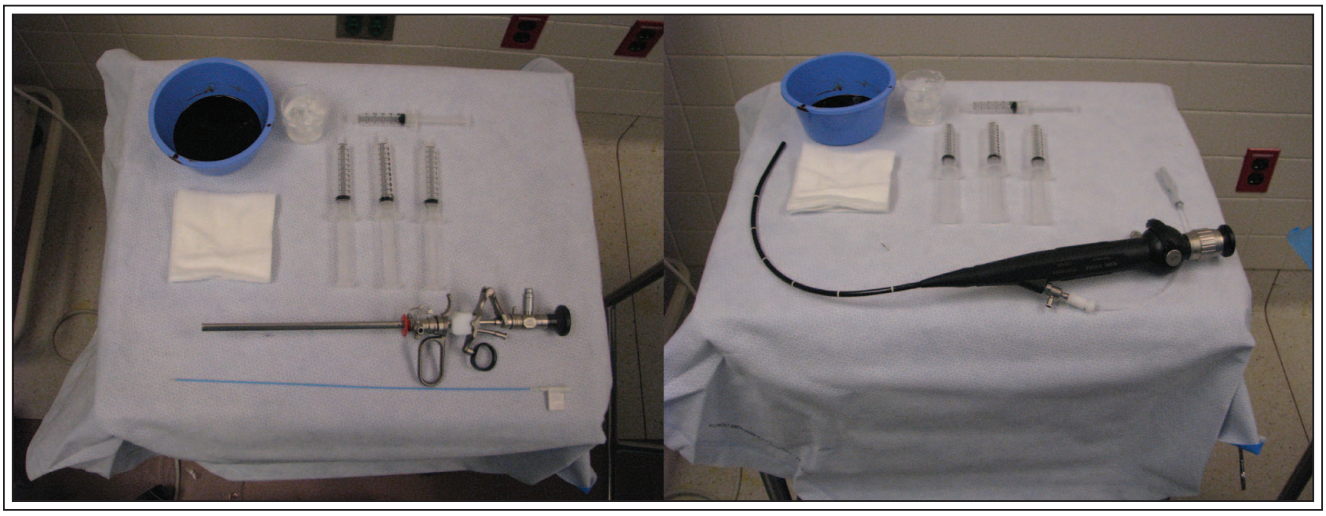

Figure 1. Procedure set up for onabotulinumtoxinA injection using rigid and flexible endoscopes. Three 10 mL treatment syringes and one 3 mL flush syringes are prepared.

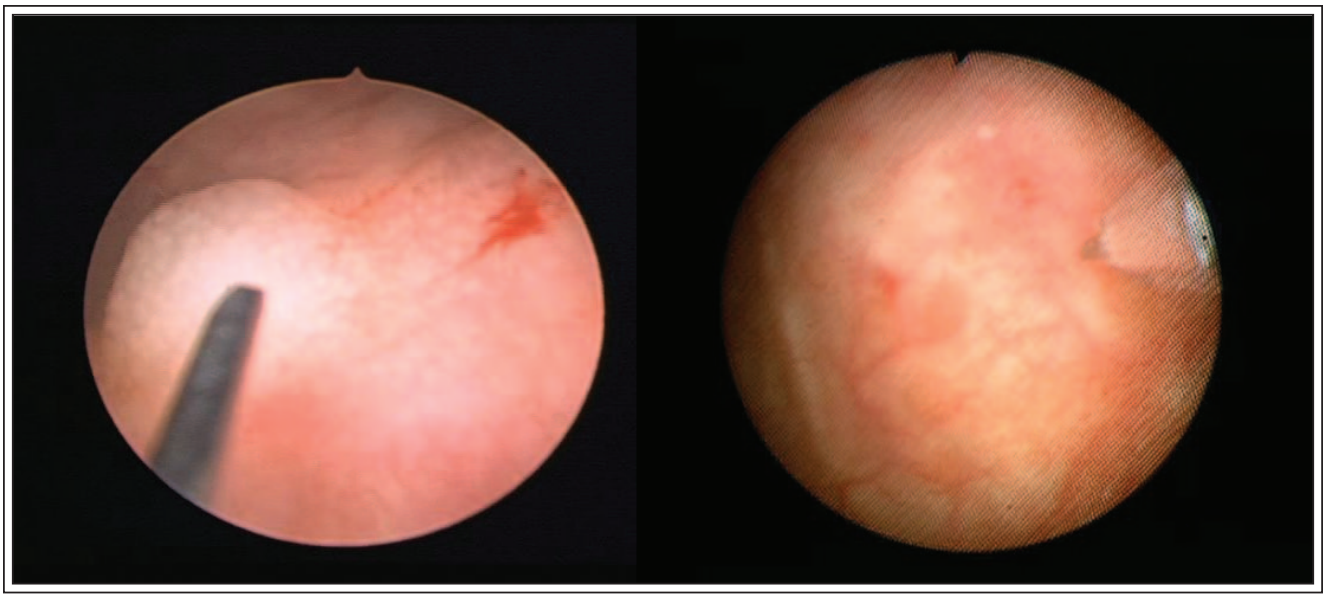

Figure 2. Improper injection technique showing raising of suburothelial bleb. Correct intradetrusor injection should result in a subtle rise in urothelium.

excluded to avoid the theoretical risk of causing vesicoureteric reflux. There is no evidence to date that trigonal injections result in reflux and injection at this site may actually improve clinical outcomes.[9] In most clinical trials, the bladder dome has also been avoided to minimize the risk of intraperitoneal injection.

It is important that proper technique be used when injecting the bladder. The needle should be placed a depth of 2 mm-3 mm in the detrusor muscle prior to injecting onabotulinumtoxinA. If the needle is placed too superficial, the injection will be into the suburothelium rather than the detrusor muscle itself, Figure 2. A superficial injection will raise a bleb. Although some toxin will likely diffuse into the detrusor, there may potentially be leakage of toxin through the puncture site.

Injection with flexible cystoscopic needles can easily depress rather than penetrate the bladder wall leading to intraluminal instillation of toxin rather than injection into the bladder wall. We have found that after an attempt to advance the needle into the detrusor, gentle retraction on the needle will tent the bladder wall to ensure that the needle does penetrate the urothelium. It is also important to remember that the angle of needle penetration will determine the depth of needle puncture. The bladder has a more or less spherical shape but a 90 degree deflection of the endoscope to allow perpendicular needle puncture is not always possible. Injections of the lateral walls often require oblique needle penetration and thus require the injection needle to be advanced deeper to allow injection into the detrusor.

A number of different injection needles may be utilized, Table 3. Needles designed to use through a flexible endoscope are generally much more expensive. When using a flexible cystoscope, it is important to either utilize a needle with an introducer sheath or preplace the needle with its tip just inside the working channel prior to introduction of the endoscope into the bladder. This prevents needle damage to the working channel. OnabotulinumtoxinA is then injected into the detrusor avoiding the trigone and bladder dome. Significant bleeding is exceedingly rare so we do not need to be routinely grounded for endoscopic fulguration.

Postoperative care

Patients have their vital signs checked following the procedure. Patients who do not routinely catheterize are discharged after voiding. We typically continue prophylactic oral antibiotics for 12 to 24 hours following the procedure. Patients treated under anesthesia are managed under ambulatory surgery facility guidelines. Patients should be counseled that minor hematuria is common and rarely requires intervention. Patients with potentially compromised respiratory mechanics, such as SCI and multiple sclerosis patients should be counseled to call for any breathing difficulties or muscular weakness. Because the therapeutic effect of onabotulinumtoxinA may not be seen for 1 to 2 weeks, we generally have the patient return 2 weeks following injection to check a post-void residual volume. Many patients with moderately increased post-void residual volume (150 mL-300 mL) are asymptomatic and

TABLE 3. **Commonly used injection needles**

Brand	Part #	Gauge	Tip length	Length	Price*
Rigid					
Coloplast	NB1035	22G	4 mm	35 cm	1-4: $100.00, 5-20: $58.00, > 21: $50.00
Cook	G15296	23G	8 mm	35 cm	$22.98, list $32.50
	G16684	23G	8 mm	35 cm	$22.98, list $32.50
	G15864	20G	7 mm	35 cm	$26.44, list $36.50
	G14220	23G	8 mm	35 cm	$17.68, list $32.50
	G16112	23G	8 mm	45 cm	$26.44, list $36.50
	G15276	25G	8 mm	35 cm	$22.98, list $32.50
Wolf	8652.775	22G	8 mm	31.3 cm	$432.00 for box of 5
Boston Scientific	M0068903040	21G		37 cm	$42.00 each
Laborie	DIS198	25G	Adjustable 2.5 mm-5 mm	35 cm	$390.00 box of 10, $250.00 > 2 boxes
Flexible					
Coloplast	NB1070	22G	4 mm	70 cm	1-4; $100.00, 5-20: $58.00, > 21: $50.00
Laborie	DIS200	25G	Adjustable 2.5 mm-5 mm	70 cm	$490.00 box of 10, $390.00 > 2 boxes
	DIS196	25G	Adjustable 2.5 mm-5mm	50 cm	$490.00 box of 10, $390.00 > 2 boxes
Olympus	NM-101C-0427	25G	4 mm	105 cm	$923.00 box of 6
	MAJ-656	25G	4 mm	105 cm	$868.00 box of 6

*as of 2/2012. All prices USD

can safely be observed. If retention is symptomatic, intermittent catheterization can be started.

Discussion

All marketed botulinum toxins, including onabotulinumtoxinA, currently have a boxed warning about the risk of distant toxin spread that may produce symptoms consistent with botulinum toxin effects. Symptoms of distant spread may occur hours to weeks after therapeutic injection. Major complications include swallowing and breathing difficulties that can be life threatening and even fatal. The risk of symptoms of distant spread is likely greatest in children treated for spasticity but symptoms can also occur in adults. Although distant spread after urologic use appears to be rare, great care should be taken in patients with underlying condition that would predispose them to these symptoms including cervical SCI and advanced multiple sclerosis patients who may have compromised respiratory mechanics. Because of the risk of cumulative effect, the currently recommended total dose is 360 Units administered in a 3 month interval. For urologic patients receiving onabotulinumtoxinA for other indications, such as spasticity, close coordination of care with other treating physicians is critical.

Patients need to be aware of this risk and be motivated to manage their bladder with intermittent catheterization. In many patients with neurogenic detrusor overactivity, this is an acceptable, even preferred, outcome. In our practice, less than 10% of treated patients with idiopathic OAB have required self-catheterization after treatment with BOTOX. Careful patient selection with pre-procedure screening of post-void residual volume is useful in predicting the risk of urinary retention. Additionally, patients need to be told to expect a delay in effect of roughly 2 weeks with further improvement until 6 weeks following injection. Patients can generally durable efficacy for 6 to 9 months.[7]

Conclusion

Intradetrusor onabotulinumtoxinA injections have become an increasingly important therapeutic option in the treatment of refractory urinary incontinence due to detrusor overactivity. OnabotulinumtoxinA acts

locally and avoids the typical bothersome side effects of antimuscarinic medications including dry mouth, constipation, and blurry vision.

The technique for this procedure employs endoscopes typically available in most urologic practices. It is technically simple to perform and is generally well tolerated by patients. Urinary retention remains the most concerning adverse reaction to this treatment for most patients and physicians. Patients should be well informed about their risk prior to consenting for onabotulinumtoxinA injections. An unwillingness to catheterize should be generally considered a contraindication to treatment. The risk of retention appears to be dose related.

Although it was initially approved for the treatment of incontinence caused by detrusor overactivity in patients with neurologic disease, it is increasingly be utilized for patients idiopathic OAB. Regulatory approval for this indication is currently pending given the high prevalence of overactive bladder. This option is expected to become an important tool in the armementarium for the treatment of medical refractory overactive bladder. □

EDITOR'S NOTE

As this article was being published the U.S. Food and Drug Administration (FDA) announced on January 18, 2013 the expanded approval of onabotulinumtoxinA. This approval now includes overactive bladder in adults who cannot use or do not adequately respond to anticholinergics.

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