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Urologic applications of botulinum toxin

ABSTRACT

The neuromuscular blocker botulinum toxin has a wide variety of medical applications, including overactive bladder and neurogenic detrusor overactivity in patients in whom drug therapy fails or is not well tolerated. Botulinum toxin therapy for these conditions has been shown to be safe and effective in several large multicenter randomized controlled trials. Off-label uses in urology include detrusor external sphincter dyssynergia and pelvic pain syndromes.

KEY POINTS

Anticholinergic drugs have been the first-line therapy for neurogenic detrusor overactivity. If drug therapy failed, the next option was reconstructive surgery such as cystoplasty. Botulinum toxin injection may be an option in select patients.

Urinary tract infection and urinary retention requiring intermittent self-catheterization are the most common adverse events of botulinum toxin injection in trials of patients with neurogenic detrusor overactivity or idiopathic overactive bladder.

Small studies have shown that botulinum toxin injection for painful bladder syndrome/interstitial cystitis can improve pain, urinary frequency, and quality of life. But larger randomized controlled trials are needed.

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PATIENTS WITH LOSS OF bladder control experience discomfort, embarrassment, personal care and health issues, and, often, significant pain, all with a decidedly negative impact on quality of life. Although some patients may find lifestyle modifications, drug therapy, and self-catheterization acceptable and effective, there is a clear need for more options.

Botulinum toxin, or onabotulinumtoxinA, is currently approved by the US Food and Drug Administration (FDA) for neurogenic detrusor overactivity and overactive bladder refractory to drug therapy. Studies so far have shown botulinum toxin injection to be safe and effective for these conditions, and these results have led to interest in off-label uses, eg, for detrusor external sphincter dyssynergia (DESD), motor and sensory urgency, and painful bladder syndrome/interstitial cystitis (Table 1).

Although more data from clinical trials are needed, botulinum toxin injection offers patients a much-needed treatment option.

■ HOW BOTULINUM TOXIN WORKS

Seven serotypes identified

Discovered in 1897, botulinum toxin is a neurotoxin produced by the gram-positive, rod-shaped anaerobic bacterium *Clostridium botulinum*¹ and is the most poisonous naturally occurring toxin known.² Seven immunologically distinct antigenic serotypes have been identified (A, B, C1, D, E, F, and G),¹ but only types A and B are available for clinical use.

Most research into potential therapeutic uses has focused on type A, which has the longest duration of action, a clinical advantage.³ Recently, work has been done to further characterize other serotypes and to isolate addition-

TABLE 1

Urologic applications of botulinum toxin

Diagnosis	Symptoms	Injection site	Efficacy	Alternative treatments
Neurogenic detrusor overactivity	Bladder spasms Urinary frequency Urinary urgency Nocturia Urinary incontinence	Intradetrusor	Studies show benefit	Anticholinergic therapy Neuromodulation Augmentation cystoplasty Urinary diversion
Idiopathic overactive bladder	Bladder spasms Urinary frequency Urinary urgency Nocturia Urinary incontinence	Intradetrusor	Studies show benefit	Anticholinergic therapy Neuromodulation
Detrusor external sphincter dyssynergia	Difficulty emptying, urinary retention Recurrent urinary tract infection Vesicoureteral reflux Elevated bladder pressure Renal damage (if untreated)	Intrasphincteric	Data are inconclusive	Medical management Catheterization Urethral stenting Sphincterotomy Reconstructive surgery
Painful bladder syndrome/interstitial cystitis	Unpleasant sensation associated with the urinary tract Pain with bladder filling Urinary frequency	Intradetrusor	Data are inconclusive	Stress management Physical therapy Pain management Medical management Intravesical therapies Cystoscopy with hydrodistention Neuromodulation Cyclosporine treatment Urinary diversion

al variants of botulinum toxin. For example, serotype E, the predominant serotype associated with foodborne botulism, is being studied in an effort to prevent future outbreaks.⁴

Our discussion focuses on clinical uses of the serotype A botulinum toxin preparation, which we will refer to simply as botulinum toxin.

Studies exploring how it works

Botulinum toxin exerts its effects by binding to peripheral cholinergic terminals, inhibiting release of acetylcholine at the neuromuscular junction. Flaccid paralysis ensues as a result.

Results of animal studies have shed additional light on the specific actions of botulinum toxin A:

- It may alter levels of nerve growth factor and transient receptor potential vanilloid

1 in rats, and this may provide an additional mechanism of reducing bladder detrusor overactivity.⁵

- In addition to blocking acetylcholine release from motor neurons, it inhibits the release of neurotransmitters involved in bladder sensory afferent pathways.⁶
- It inhibits the release of substance P and glutamate, neuropeptides involved in sensory and nociceptive pathways.^{6,7}
- It promotes apoptosis in prostatic tissue; however, this effect has not been shown in the bladder.³

The time necessary to recover function after botulinum toxin paralysis depends on the subtype of botulinum toxin as well as on the type of nerve terminal. Chemodenervation lasts from 3 to 6 months when the toxin is

injected into the neuromuscular junction of skeletal muscle, and considerably longer (up to 1 year) when injected into the autonomic neurons of smooth muscle.^{2,6}

■ TREATMENT OF NEUROGENIC DETRUSOR OVERACTIVITY

Neurogenic detrusor overactivity involves involuntary contractions of the bladder resulting from spinal cord injury, multiple sclerosis, and other neurologic conditions. An estimated 273,000 people in the United States have a spinal cord injury, and 81% of them have urologic symptoms ranging from areflexia to overactivity.⁸ From 75% to 100% of patients with multiple sclerosis have urologic symptoms, and detrusor overactivity is the most common.⁹

Detrusor overactivity can cause urinary urgency, urinary frequency, and urgency incontinence, significantly affecting quality of life and leading to skin breakdown, sacral ulcerations, and challenges with personal care.

Anticholinergic drugs have been the mainstay of therapy. If drug therapy failed, the next option was reconstructive surgery, often augmentation cystoplasty. Thus, botulinum toxin injection is an important advance in treatment options.

Studies that showed effectiveness

Botulinum toxin for neurogenic detrusor overactivity was first studied by Schurch et al.¹⁰ In their study, 200 U or 300 U was injected into the trigone of 21 patients with spinal cord injury and urgency incontinence managed with intermittent self-catheterization.¹⁰ At 6 weeks after injection, 17 of the 19 patients seen at follow-up visits were completely continent. Urodynamic evaluation revealed significant increases in maximum cystometric capacity and in volume at first involuntary detrusor contraction, and a decrease in detrusor voiding pressure. Of the 11 patients available for follow-up at 16 and 36 weeks, improvements in measures of incontinence and urodynamic function persisted.

In addition, two small randomized controlled trials^{11,12} showed significant increases in cystometric bladder capacity, significant improvement in quality-of-life measures, and reduction in episodes of urgency incontinence.

In 2011 and 2012, two multicenter double-blind randomized controlled trials reported on

patients with multiple sclerosis and spinal cord injury with neurogenic detrusor overactivity inadequately managed with drug therapy. The patients were randomized to botulinum toxin injection (200 U or 300 U) or placebo injection.^{13,14} The primary end point for both studies was the change from baseline in episodes of urinary incontinence per week at week 6. Secondary end points were maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction, and score on the Incontinence Quality of Life scale.¹⁵

In both studies, the mean number of urinary incontinence episodes per week was 33 at baseline. At week 6, Cruz et al¹⁴ found that patients who received botulinum toxin injection had significantly fewer episodes per week (21.8 fewer with 200 U, 19.4 fewer with 300 U) than those in the placebo group, who had 13.2 fewer episodes per week ($P < .01$). Ginsberg et al¹³ reported decreases in the mean number of episodes of urinary incontinence of 21, 23, and 9 episodes per week in the 200 U, 300 U, and placebo groups, respectively ($P < .001$). The patients who received botulinum toxin had statistically significant improvements in maximum cystometric capacity, maximum detrusor pressure during first involuntary detrusor contraction, and Incontinence Quality of Life scores compared with placebo ($P < .001$). Thirty-eight percent of patients in the treatment group were fully continent.^{13,14}

Safety and adverse effects

The most frequently reported adverse events were urinary tract infection (24% of patients)^{13,14} and urinary retention requiring initiation of clean intermittent catheterization. In the study by Cruz et al,¹⁴ these were reported in 30% with 200 U, 42% with 300 U, and 12% with placebo, while in the study by Ginsberg et al¹³ they were reported in 35% with 200 U, 42% with 300 U, and 10% with placebo.

In a study of long-term safety and efficacy of botulinum toxin injection in patients with neurogenic detrusor overactivity, Kennelly et al¹⁶ found that patients undergoing repeat injections had sustained reductions in episodes of incontinence and increases in the maximum cystometric capacity and quality of life scores, with no increase in adverse events over time.¹⁶

Botulinum toxin injection may be an option in select patients with neurogenic detrusor overactivity

But is it cost-effective?

While botulinum toxin injection may be safe and effective for neurogenic detrusor overactivity, is it cost-effective?

Carlson et al¹⁷ used a Markov State Transition model to assess the cost of refractory neurogenic detrusor overactivity in patients receiving botulinum toxin vs best supportive care (incontinence pads, medications, intermittent self-catheterization).¹⁷ They found that the injections were more expensive than supportive care but were cost-effective when considering the reduction in episodes of incontinence, the reduced need for incontinence products, and improvement in measures of quality of life.

What the evidence indicates

Trials of botulinum toxin injection for neurogenic detrusor overactivity have shown that it improves continence, maximum cystometric capacity, detrusor pressures, and quality of life. The main adverse effects are urinary tract infection and urinary retention requiring intermittent self-catheterization.

Although many patients with this condition are already self-catheterizing, the physician must discuss this before botulinum toxin therapy to ensure that the patient or a family member is able to perform catheterization. Studies have shown that patients have an increase in urinary tract infections after botulinum injections. But in these studies, a urinary tract infection was defined as 100,000 colony-forming units or the presence of leukocytosis with or without symptoms. It is important to remember that patients on intermittent catheterization have bacteriuria and should be treated only for symptomatic, not asymptomatic, bacteriuria.

■ TREATMENT OF IDIOPATHIC OVERACTIVE BLADDER

Patients with idiopathic overactive bladder have urinary urgency accompanied by urgency incontinence, nocturia, or urinary frequency.¹⁸ The prevalence of this condition has been reported to range from 1.7% to 13.3% in men age 30 and older and 7% to 30.3% in women of similar ages. About one-third of women with overactive bladder also have detrusor overactivity.¹⁹ Overactive blad-

der presents a significant economic and medical burden on the healthcare system, as well as having a negative impact on quality of life.

The FDA approved botulinum toxin injection for treatment of idiopathic overactive bladder in January 2013.

Evidence of effectiveness

Two multicenter randomized controlled trials^{20,21} of botulinum toxin 100 U enrolled patients age 18 and older who had more than three episodes of urinary urgency incontinence in a 3-day period or more than eight micturitions per day inadequately managed by anticholinergic drug therapy. Primary end points were the change from baseline in the number of episodes of urinary incontinence per day and the proportion of patients with a positive response on the Treatment Benefit Scale²² at week 12. Secondary end points included episodes of urinary urgency incontinence, micturition, urgency, and nocturia, and scores on health-related quality of life questionnaires (Incontinence Quality of Life scale, King's Health Questionnaire).

In both studies, patients receiving botulinum toxin had significantly fewer episodes of incontinence compared with placebo (-2.65 vs -0.87 ; $P < .001$ and -2.95 vs -1.03 ; $P < .001$).^{20,21} Reductions from baseline in all other symptoms of overactive bladder, a positive treatment response on the treatment benefit scale, and improvements in quality-of-life scores were also significantly greater with botulinum toxin injection than with placebo ($P \leq .01$).

As in the studies of neurogenic detrusor overactivity, the most common adverse effects were urinary tract infection (occurring in 15.5%²⁰ and 24.1%²¹ of patients) and urinary retention requiring self-catheterization (5.4%²⁰ and 6.9%²¹).

The largest study to date of anticholinergic therapy vs botulinum toxin injection²³ in women with urinary urgency incontinence, published in 2012, studied nearly 250 women who had five or more episodes of idiopathic urgency incontinence in a 3-day period. They were randomized either to daily oral therapy (solifenacin 5 mg with possible escalation to 10 mg and, if necessary, a subsequent switch

The FDA approved botulinum toxin injection for idiopathic overactive bladder in January 2013

to extended-release trosipium 60 mg) plus one intradetrusor injection of saline, or to a daily oral placebo plus one injection of botulinum toxin 100 U.²³

The dropout rate was low in both groups, with 93% of patients in both groups completing the 6-month protocol. Women experienced a mean reduction in urgency incontinence episodes of 3.4 per day (baseline 5) in the anticholinergic group vs 3.3 episodes in the botulinum toxin group ($P = .81$). However, more patients achieved complete resolution of urinary urgency incontinence in the botulinum toxin group than in the anticholinergic therapy group (27% vs 13%; $P = .003$). Quality of life improved in both groups without a significant difference between the groups. The botulinum toxin group had higher rates of initiation of self-catheterization (5% vs 0%, $P = .01$) and urinary tract infection (33% vs 13%, $P < .001$).²³

Botulinum toxin as a third-line therapy

In May 2014, the American Urological Association updated its guidelines on idiopathic overactive bladder²⁴ to include botulinum toxin injection as standard third-line therapy for patients in whom behavioral and medical management (ie, anticholinergics and beta-3-agonists) failed.

Interpreting the evidence to date

Overall, studies in idiopathic overactive bladder have shown a reduction in episodes of urgency incontinence and other symptoms, with some data also demonstrating a corresponding improvement in quality of life.

As in neurogenic detrusor overactivity, the main risks associated with botulinum toxin injection are urinary tract infection and the need to initiate self-catheterization. Although 94% of patients studied did not require self-catheterization after injection, the patient's ability to perform self-catheterization should be determined before proceeding with botulinum toxin injections.

■ DETRUSOR EXTERNAL SPHINCTER DYSSYNERGIA

Botulinum toxin has been used not only to improve bladder storage but also to facilitate bladder emptying, as in patients with DESD,

a lack of coordination between the bladder and the urinary sphincter. Normal voiding involves relaxation of the urinary sphincter and contraction of the bladder; in DESD the sphincter contracts and works against the bladder's ability to empty. This leads not only to difficulty emptying the bladder but also to elevated bladder pressure, which can cause renal damage if untreated.

DESD can be seen after injury between the pontine micturition center, which coordinates activity between the bladder and the sphincter, and the caudal spinal cord. This can occur in spinal cord injury, multiple sclerosis, myelomeningocele, and transverse myelitis and can cause significant morbidity for the patient.

Treatment options include drug therapy, injection of botulinum toxin into the sphincter, clean intermittent catheterization, indwelling catheterization, urethral stenting, sphincterotomy, and reconstructive surgery such as urinary diversion.²⁵

The goals of therapy are to avoid the need for clean intermittent catheterization in patients who have difficulty with manual dexterity, and to avoid the need for surgical procedures such as sphincterotomy and urinary diversion. The efficacy of urethral stenting is low, and medical management can be limited.²⁶

In the first published report on botulinum toxin for DESD (in 1988),²⁷ of 11 patients with spinal cord injury and DESD who received botulinum toxin injected into the external urethral sphincter, 10 showed signs of sphincter denervation on electromyography and reductions in urethral pressure profiles and postvoid residual volumes. Schurch et al²⁸ and de Sèze et al²⁹ also reported reductions in postvoid residual volume and maximal urethral pressures in patients with spinal cord injury and DESD.

In 2005, Gallien et al³⁰ reported what is still the largest multicenter randomized controlled trial of botulinum toxin injection in DESD. Eighty-six patients with multiple sclerosis, DESD, and chronic urinary retention were randomized to receive either a single transperineal botulinum toxin injection of 100 U plus the alpha-1-blocker alfuzosin, or a placebo injection plus alfuzosin. Botulinum toxin treatment was associated with signifi-

DESD leads to difficulty emptying the bladder, elevated bladder pressure, and, if untreated, renal damage

cantly increased voided volumes and reduced premicturition and maximal detrusor pressures, but no significant decrease in postvoid residual volume.³⁰

More study needed

Despite these findings, a Cochrane Review concluded that, given the limited experience with intrasphincteric injection of botulinum toxin, data from larger randomized controlled trials are needed before making definitive recommendations.²⁵ In the meantime, the clinician must weigh the low morbidity of the procedure against the limited options in the treatment of these patients.

■ OFF-LABEL UROLOGIC INDICATIONS

Botulinum toxin injection has been studied off-label for painful bladder syndrome/interstitial cystitis and for chronic prostatic pain. Patients with these conditions often describe pain with filling of the bladder, which leads to urinary frequency in an attempt to relieve the pain.

These pain syndromes can be difficult to treat and can have a devastating impact on quality of life. Treatment options include pain management, stress management, physical therapy, intravesical therapies, cystoscopy with hydrodistention, neuromodulation, cyclosporine, urinary diversion surgery, and botulinum toxin injection (an off-label use).³¹

In painful bladder syndrome/interstitial cystitis, botulinum toxin is thought to act on sensory afferent pathways, as well as to inhibit the release of substance P and glutamate, neuropeptides involved in sensory and nociceptive pathways.⁶ In animal studies,³² botulinum toxin was found to inhibit the afferent neural response by inhibiting mechanoreceptor-mediated release of adenosine triphosphate and by causing a decrease in calcitonin gene-related peptide, which helps regulate micturition and mediates painful bladder sensation.

Clinical studies to date in pelvic pain syndromes

Data from clinical studies of botulinum toxin injection for pelvic pain syndromes are limited. Zermann et al³³ performed transurethral perisphincteric injection in 11 men with chronic prostatic pain, 9 of whom reported subjective

pain relief, with an average decrease from 7.2 to 1.6 on a visual analogue scale. Postinjection urodynamic studies showed a decrease in functional urethral length, urethral closure pressure, and postvoid residual volume, and an increase in the peak and average flow rates.³³

Abbott et al³⁴ evaluated the effect of botulinum toxin injection into the levator ani in 12 women with chronic pelvic pain and pelvic floor hypertonicity. Pelvic floor manometry showed significant reduction in resting muscle pressures and improvements in dyspareunia and nonmenstrual pain. There were also improvements in quality of life and dyschezia, but these were not statistically significant.

Smith et al³⁵ injected botulinum toxin into the detrusor of 13 women with refractory painful bladder syndrome and interstitial cystitis,³⁵ and 9 women (69%) noted statistically significant improvements in the Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index, daytime frequency, nocturia, pain, and urodynamic parameters (volume at first desire to void, and maximum cystometric capacity).

In a prospective randomized study of patients with refractory painful bladder syndrome and interstitial cystitis, Kuo and Chancellor³⁶ compared suburothelial injection of 200 U or 100 U of botulinum toxin plus hydrodistention against hydrodistention alone. Patients who received botulinum toxin had increased bladder capacity and improved long-term pain relief, but no difference was noted between 200 U and 100 U, and more adverse effects were seen with the higher dose.³⁶

Pinto et al³⁷ treated 16 women with refractory painful bladder syndrome and interstitial cystitis with intratrigoal injections of botulinum toxin and reported improvements in pain scores, symptom scores, urinary frequency, and quality-of-life measures. The effect lasted 9.9 months (\pm 2.4 months) and persisted with successive injections.³⁷

More study needed

Although these studies show that botulinum toxin injection for pelvic pain syndromes has the potential to improve pain, urinary frequency, bladder sensation, bladder capacity, and quality of life, larger randomized controlled trials are needed.

Off-label applications for botulinum toxin injection include painful bladder syndrome/interstitial cystitis

What to tell patients

- 1. Does the procedure involve cystoscopy? What level of discomfort should they expect?**
Yes, it can be done with a flexible or rigid cystoscope. Lidocaine is instilled in the bladder to decrease patient discomfort.
- 2. Is the procedure done on an outpatient basis?**
It is usually done on an outpatient basis, either in the office or in an ambulatory surgery center.
- 3. What foods, drinks, and medications should the patient stop before the procedure, and for how long before the procedure?**
When the procedure is done in the outpatient setting, the patient can eat and drink up to the time of the procedure. If done under intravenous sedation, then the patient can have clear liquids up to 4 hours before the procedure. Aspirin (325 mg), antiplatelet medications, and warfarin are stopped 3 to 7 days before the procedure and are typically restarted 2 to 5 days after the procedure.
- 4. How long does the procedure take?**
The procedure usually takes 30 to 40 minutes.
- 5. How long until the injections take effect?**
Patients often note an improvement in their symptoms in 7 to 10 days after the procedure.
- 6. How many follow-up visits are usually needed?**
Patients are typically seen again at 3 weeks to check the postvoid residual volume.

Again, the treatment options are limited for refractory painful bladder syndrome and interstitial cystitis. Patients may be desperate for relief from their symptoms. Practitioners must manage expectations and properly inform patients of the potential risks of treatments, especially with patients who will easily agree to further treatment with the smallest hope of relief.

■ INJECTION TECHNIQUES

For general points about the procedure to discuss with patients, see “What to tell patients.”

Cystoscopic detrusor injection

This procedure is usually done on an outpatient basis (eg, office, ambulatory surgery center). With the patient in the lithotomy position, 100 mL of 2% lidocaine is instilled into the bladder and is allowed 15 to 20 minutes to take effect. A flexible or rigid cystoscope can be used. Depending on the indication, the bladder is injected with 100 U to 300 U of botulinum toxin. The ideal depth of injection is 2 mm in the detrusor muscle, with each injection spaced about 1 cm apart. The recommended administration for 100 U is to inject 20 sites with 0.5 U per mL of saline and, for 200 U, to inject 30 sites with about 0.67 U per mL of saline.³⁸ The location of the injections into the detrusor can vary, as long as adequate spacing is assured.

Injection sites vary. Proponents of injecting the trigone argue that as it is an area of greater nerve density, patients will have a better clinical response. Opponents argue that trigonal injection could result in distal ureteral paralysis and subsequent ureteral reflux. However, this theoretical concern has not been observed clinically.

Urethral injection (off-label use)

The urethra can be injected cystoscopically or periurethrally. Cystoscopic injection involves localization of the external sphincter using the rigid cystoscope and collagen needle; a total of 100 U is injected into the sphincter under direct vision, typically at the 3 o'clock and 9 o'clock positions.³⁵ The periurethral technique is an option in women and involves a spinal needle with 100 U to 200 U of botulinum toxin injected into the external sphincter muscle at the 2 o'clock and 10 o'clock positions.

■ ADVERSE EFFECTS AND CONTRAINDICATIONS

Adverse effects are rare for urologic applications. The injections are localized, with little systemic absorption, and the doses are 1/1,000th of the theorized lethal dose in a 70-kg male.² The maximum recommended dose for a 3-month period is 360 U.

Generalized muscle weakness has been reported in a paraplegic patient and in a tetraplegic patient after detrusor injections.² Interestingly, both patients had return of bladder

spasticity within 2 months, prompting speculation about diffusion of botulinum toxin through the bladder wall.²

Repeat injections can cause an immune response in up to 5% of patients.⁶ Patients undergoing repeat injections are at risk of forming neutralizing antibodies that can interfere with the efficacy of botulinum toxin.⁶ In a study by Schulte-Baukloh et al, all patients with antibodies to botulinum toxin had a history of recurrent urinary tract infection.³⁹

Botulinum toxin injection is contrain-

dicated in patients with preexisting neuromuscular disease, such as myasthenia gravis, Eaton-Lambert syndrome, and amyotrophic lateral sclerosis. It should also be avoided in patients who are breastfeeding, pregnant, or using agents that potentiate neuromuscular weakness, such as aminoglycosides.

Patients should be informed that some formulations of botulinum toxin include a stabilizer such as albumin derived from human blood, as this may be of religious or cultural significance. ■

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