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Review Article

Botulinun A toxin urethral sphincter injection for neurogenic or nonneurogenic voiding dysfunction

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ABSTRACT

Voiding dysfunction due to detrusor underactivity or urethral sphincter dysfunction is a treatment challenge for urologists. Recently, urologists have used botulinum toxin A (BoNT-A) injection into the urethral sphincter to treat voiding dysfunction. This treatment has been found to decrease urethral pressure and postvoid residual volume, and increase voiding efficiency in patients with neurogenic detrusor sphincter dyssynergia, nonneurogenic dysfunctional voiding, and detrusor underactivity. Although not all patients can achieve excellent therapeutic outcomes, patients with idiopathic detrusor underactivity might have recovery of detrusor contractility after urethral sphincter BoNT-A injection. However, urinary incontinence might be a *de novo* adverse event after treatment. Repeat urethral injection is necessary to maintain therapeutic efficacy. Patients should be fully informed of the limited therapeutic efficacy and possible adverse events prior to treatment. This article reviews recent studies of urethral sphincter BoNT-A treatment for voiding dysfunction.

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1. Introduction

Voiding dysfunction may result from bladder outlet obstruction, detrusor underactivity, or a poorly relaxed urethral sphincter during micturition. Voiding dysfunction may be neurogenic or nonneurogenic in origin, which causes difficulty in urination, a large postvoid residual urine (PVR) volume, and upper urinary tract deterioration. Treatment of voiding dysfunction with medication, abdominal straining to void, clean intermittent catheterization (CIC), or a cystostomy may help in some cases, but these techniques are ineffective in many others. Botulinum toxin A (BoNT-A) has been used for the treatment of lower urinary tract symptoms (LUTS) since the late 1980s. Dykstra and Sidi [1] injected BoNT-A into the external urethral sphincter of patients with spinal cord injury (SCI) to induce chemical sphincterotomy and to lower detrusor-sphincter dyssynergia.

BoNT-A has been used safely in the treatment of several types of neurogenic spasticity including that in patients with SCI or multiple sclerosis (MS) and detrusor sphincter dyssynergia. Schurch et al [2] reported that 21 of 24 patients with SCI benefited from BoNT-A injection. In patients with dysfunctional voiding due to urethral sphincter overactivity, nonbacterial prostatitis, and detrusor underactivity, BoNT-A has been shown to have therapeutic effects in improving voiding efficiency and recovering detrusor contractility in some patients with few adverse effects [3,4]. Phelan et al [4] found that after BoNT-A injection, 67% of patients were able to void smoothly with the PVR decreased by 71% and voiding pressure decreased by 38%.

2. Mechanism of BoNT-A in voiding dysfunction

Botulinum neurotoxin (BoNT), produced by *Clostridium botulinum*, a gram-positive, rod-shaped anaerobic bacterium, was originally thought to only act by inhibiting acetylcholine (ACh) release at the presynaptic cholinergic neuromuscular junction and has been used effectively for different conditions with muscular hypercontraction [5,6]. There are seven immunologically distinct neurotoxins designated as types A to G [7]. All serotypes of BoNT can block transmission at neuromuscular junctions; however, only type A BoNT (BoNT-A) has prolonged therapeutic effects. It is the most extensively studied, mainly in models of neurotransmission in striated muscle.

Conflict of interest: none.

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BoNT-A is initially synthesized as an inactive chain of 1285 amino acids. Activation occurs when the single chain is cleaved by an endogenous clostridial protease [5,8]. After the cleavage, a dichain polypeptide is formed, which contains a 50-kDa light chain and a 100-kDa heavy chain linked covalently by a weak disulfide bond [8]. BoNT-A inhibits signal transmission at the neuromuscular and neuroglandular junction through four discrete steps: (1) binding of the toxin heavy chain to a specific nerve terminal receptor; (2) internalization of the toxin within the nerve terminal; (3) translocation of the light-chain into the cytosol; and (4) cleaving of synaptosome-associated protein 25 (SNAP-25) and inhibiting signal transmission by disrupting the fusion of neurotransmitter-containing vesicles with the neuronal wall [9]. Each botulinum serotype cleaves a distinct protein site. BoNT-A cleaves SNAP-25, and type B cleaves synaptobrevin [5,6].

BoNT-A administration has the same clinical effect on both smooth and striated muscle. BoNT-A could reduce cholinergic nerve-induced bladder activity as well as impair adenosine triphosphate release in addition to ACh release from isolated bladder tissue [10,11]. In a study of structural changes in detrusor muscle, Haferkamp et al [12] observed no significant changes in muscle cell fascicles, intercellular collagen content, or muscle cell degeneration when comparing biopsies taken prior to and 3 months after BoNT-A administration. Unlike that in striated muscle, axonal sprouting in detrusor smooth muscle is limited following BoNT-A administration.

3. Rationale for BoNT-A in the treatment of voiding dysfunction

Voiding dysfunction might be caused by low detrusor contractility or high urethral sphincter resistance during voiding. Reduction of bladder outlet resistance could improve voiding efficiency in patients with either detrusor underactivity or urethral sphincter dysfunction. Injection of BoNT-A into the external sphincter blocks ACh release at the neuromuscular junction and essentially achieves chemical denervation of the external sphincter [1]. The goals of urethral treatment are to lower the urethral pressure, or detrusor leak point pressure, to below 40 cm of water and to promote bladder emptying such that the upper urinary tract is protected against the high bladder pressure. Based on previous clinical studies, the clinical effects begin within 2–3 days and are reversible as terminal nerve sprouting occurs 3–6 months later. In general, a significant decrease in the PVR and a significant reduction in urethral pressure could be observed [2,5]. However, appearance of *de novo* stress urinary incontinence and exacerbation of preexisting urinary incontinence due to sphincter denervation by BoNT-A have been reported as adverse events [4,13].

BoNT-A could have effects on both efferent and afferent nerve activity in the bladder wall, and might reduce the inflammatory reaction in some cases of cystitis [5,6,10]. Based on its therapeutic mechanism, BoNT-A can be used in the treatment of different lower urinary tract diseases (Table 1). It can bind to the nerve endings within muscles, blocking the release of ACh and perhaps other neurotransmitters, to modulate muscle contraction and reduce the sensitization of sensory nerve endings [10]. Selective injection permits specific paralysis of the detrusor muscle while leaving surrounding tissues and distant muscles unaffected [14]. Therapy with BoNT-A would appear to not only help alleviate muscle spasticity, but also promote antinociceptive properties and impact on sensory feedback loops to relieve hyperalagesia or hypersensitivity associated with a variety of LUTS. In BoNT-A treatment for detrusor overactivity, there was an increase in capacity with a reduction in urge incontinence episodes and symptoms of urgency [14]. However, a more complete neuromuscular blockade of the detrusor with larger doses of BoNT-A might result in impaired voiding and acute urinary retention [5,14]. Most patients not already performing CIC should be informed of the possibility of long-term catheterization. In patients with low detrusor contractility or a large PVR at baseline, a lower dose of BoNT-A might be given to avoid bladder paralysis and preserve voiding function [15].

Table 1
Indications of botulinum toxin injection for lower urinary tract dysfunction.

Injection	Disease	Dose of Botox (U)
Bladder	Neurogenic detrusor overactivity	200–300
	Idiopathic detrusor overactivity	100–200
	Interstitial cystitis	100–200
	Overactive bladder or hypersensitive bladder	100
	Low bladder compliance	200–300
Urethra	Detrusor sphincter dyssynergia	100
	Detrusor underactivity & nonrelaxing urethra	50–100
Prostate	Benign prostatic hyperplasia	200–400
	Chronic prostatitis	200
Pelvic floor	Chronic pelvic pain syndrome	100–200
	Poor relaxation of pelvic floor	100–200

4. Techniques for urethral sphincter injection of BoNT-A

Urethral sphincter BoNT-A injection can be performed in the operating room under light intravenous general anesthesia (in men) or in the outpatient department without anesthesia (in women) [13]. Each vial of 100 U BoNT-A (Allergan, Irvine, CA, USA) is reconstituted to 4 mL with normal saline, making the concentration equivalent to 25 U/mL. The dose of BTX-A can be 50–100 U for patients with detrusor underactivity who wish to void by abdominal pressure after treatment, or 100 U for patients with detrusor sphincter dyssynergia, dysfunctional voiding, or poor relaxation of the urethral sphincter [1,2,13]. A total of 50 U or 100 U of BoNT-A is injected into the urethral sphincter at the 3 o'clock, 6 o'clock, 9 o'clock, and 12 o'clock positions in approximately equal aliquots using a cystoscopic injection instrument in men. Cystoscopy is advised in women. The axis of the urethra is determined for proper injection positions and BoNT-A is injected into the urethral sphincter along the urethral lumen at the 3 o'clock, 6 o'clock, 9 o'clock, and 12 o'clock positions on the sides of urethral meatus using a 23-gauge 1-mL syringe. If 50 U of BoNT-A is injected, 0.5 mL is used for each injection. When 100 U of BoNT-A is injected, 1 mL is used for each injection.

During BoNT-A injection, patients are placed in the lithotomy position. After sterilization and draping, the BoNT-A solution is injected directly into the urethral sphincter under cystoscopic guidance in men and periurethrally in women. For urethral injections, it is essential to inject BoNT-A directly into the urethral sphincter. Too much solution might cause leaking of BoNT-A outside the urethral sphincter, resulting in an inadequate treatment dose. The injection needle should not be inserted too deeply to avoid injecting BoNT-A outside the sphincter muscle. With direct visualization of the tight sphincter, the needle is injected 0.5 cm deep at four or eight sites. The female urethra is about 3 cm long, and the maximal diameter is at the middle portion of the urethra. The injection needle should be inserted transcutaneously around the urethral lumen in a longitudinal direction with the lumen to a depth of 1.5 cm at four or eight sites. After the injections, a 14F Foley indwelling catheter is inserted in male patients who have general anesthesia, but a catheter is unnecessary in women.

The effect of BoNT-A usually appears about 2–3 days after injection, and the maximum effects are reached in about 2 weeks. Patients are instructed to void using the Crede maneuver or abdominal straining. When difficult urination persists, CIC is

advised instead of an indwelling Foley catheter until the PVR is less than 25% of the voided volume. Antibiotics may be given for 3 days to prevent urinary tract infection to form urethral instrumentation. Medications for reduction of urethral resistance may be discontinued if the patient can void efficiently after BoNT-A injections.

5. Urethral BoNT-A in treatment of neurogenic detrusor sphincter dyssynergia in patients with SCI or MS

OnabotulinumtoxinA was first applied in urethral sphincter injection to treat detrusor sphincter dyssynergia in patients with SCI who did not desire surgery or were unable to perform CIC [1,2]. After BoNT-A injection, the urethral sphincter showed decreased urethral pressure, decreased PVR, and reduction in episodes of autonomic dysreflexia [1,2,16]. Double-blind studies with BoNT-A injection performed transperineally or transurethrally confirmed the validity and durability of this treatment [2,17]. A dose of 100 U BoNT-A reduced the urethral resistance and achieved efficient voiding in patients with SCI and detrusor sphincter dyssynergia [1,14,16]. A systemic review also indicated a 50% reduction in urinary tract infections after urethral BoNT-A injections for detrusor sphincter dyssynergia in SCI patients [18]. Overall, 60.6% of patients reported satisfactory results after injection of BoNT-A 100 U with significant reductions in voiding detrusor pressure and PVR, and increases in the maximal urinary flow rate. However, the incontinence grade might increase after urethral BoNT-A injection, especially in patients with detrusor underactivity and low bladder compliance. Most urinary incontinence after BoNT-A injection occurs during sleep. [19]. Therefore, this procedure should be performed in well-chosen patients with their full consent.

6. BoNT-A urethral injection for treatment of nonneurogenic voiding dysfunction

As urethral BoNT-A injection had been successfully used in the treatment of detrusor sphincter dyssynergia in SCI patients, this treatment was further applied to adults with nonneurogenic voiding dysfunction [4,20]. Good therapeutic results were further confirmed by several small cohort studies with doses of 50 U and 100 U BoNT-A [4,19,21]. Other indications include voiding dysfunction due to urethral overactivity, dysfunctional voiding, idiopathic detrusor underactivity, detrusor areflexia caused by cauda equina lesions, and peripheral neuropathy [5,13,22]. In some patients with idiopathic detrusor underactivity, recovery of detrusor contractility was noted after urethral BoNT-A injections. Some patients had long-term effects for more than 1 year without repeat injection [23]. However, although urethral resistance is reduced by BoNT-A injection, patients still need to use abdominal pressure to empty their bladders. The main causes of failed BoNT-A injection are very low abdominal straining pressure, a tight urethral sphincter, psychological inhibition, and bladder neck obstruction [24].

Injections of BoNT-A at 50 U ($n = 48$) or 100 U ($n = 55$) were used in a large series of patients ($n = 103$) with voiding dysfunction. Forty (39%) patients had excellent results, 47 (46%) patients had significant improvement, and 16 (15%) patients had treatment failure [13]. Among the patients with excellent results, those with detrusor underactivity due to cauda equina lesions (62.5%) or idiopathic causes (61.5%) had the best results, whereas those with detrusor sphincter dyssynergia (27.6%) had the worst. The overall success rate was 84.5% (range, 75–100%). Indwelling catheters were removed or CIC was discontinued in 39 (87%) of the 45 patients with urinary retention (Table 2). Analysis of the patients with excellent or improved results showed that voiding pressure decreased significantly, as did maximal urethral closure pressure and PVR at 2 weeks or 4 weeks after treatment. The subjective maximum effect was achieved within 1–2 weeks. The mean voiding pressure decreased by 31.8%, maximum flow rate increased by 49.3%, PVR decreased by 60.8%, and maximal urethral closure pressure decreased by 28.1%.

7. BoNT-A treatment of urethral sphincter pseudodyssynergia in patients with cerebrovascular accidents or intracranial lesions

Patients with neurogenic lesions and voiding dysfunction often have mixed storage and voiding symptoms. Detrusor overactivity and urethral sphincter pseudodyssynergia may develop during recovery from cerebral vascular accident (CVA) or intracranial lesions, resulting in difficulty in urination, a large PVR, and recurrent urinary tract infections. Patients who are ambulatory and wish to urinate voluntarily without catheterization might prefer resumption of voiding ability. Urethral sphincter injections of 100–200 U BoNT-A in 4 mL divided in equal doses into four quadrants of the urethral sphincter have been shown effective in patients with MS, CVA, and SCI [5,20]. Patients with CVA and chronic urinary retention could also discontinue CIC after urethral injection of 100 U BoNT-A [5,25].

In a prospective study, 21 patients with chronic CVA or intracranial lesions and difficult urination were enrolled to evaluate the effectiveness of urethral injection of BoNT-A. Patients participating in the study elected to receive either 100 U of BoNT-A ($n = 11$) or served as medically treated controls ($n = 10$). An overall success rate of 91% was noted in the study group. The voiding pressure decreased (57.8 ± 35.2 cm vs. 33.8 ± 16.9 cm water, $p = 0.005$) and the maximum flow rate increased (7.2 ± 5.9 mL/s vs. 10.3 ± 5.2 mL/s, $p = 0.005$) significantly. In the control group, four patients (40%) had spontaneous voiding 6 months after medical treatment, whereas six others remained unchanged, requiring an indwelling Foley catheter ($n = 2$) or CIC ($n = 4$). The symptom score and the quality of life index showed significantly greater improvement in the study group than in the control group. Urethral injection of BoNT-A is effective and without adverse effects in the treatment of patients with urethral sphincter pseudodyssynergia after CVA or intractranial lesions.

Although urethral BoNT-A injection is effective in improving voiding efficiency, incomplete emptying remains a problem and mild stress urinary incontinence is another *de novo* issue after treatment, especially in women with SCI or MS [5,19,20,26]. Therefore, if they have not been well informed prior to BoNT-A injection, patients might not be satisfied with the therapeutic results of BoNT-A injection [19,27]. Large-scale randomized studies are needed to assess the true therapeutic efficacy and impact on quality of life in those with neurogenic voiding dysfunctions.

8. Effectiveness of BoNT-A urethral injection in treatment of voiding dysfunction after radical hysterectomy

After radical hysterectomy for cervical cancer, patients may have difficult urination owing to detrusor underactivity and a nonrelaxing urethral sphincter. One study evaluated the effectiveness of urethral injection of BoNT-A in treating voiding dysfunction in these patients [22]. Thirty patients with difficult urination after radical hysterectomy for cervical cancer received urethral injection of 100 U of BoNT-A ($n = 20$) or medical treatment as controls ($n = 10$). After urethral BoNT-A injections, eight patients had excellent results (40%) and eight had improvement (40%) in the study group. There were significant improvements in both voiding pressure (115.2 ± 63.7 mL vs. 90.2 ± 49.5 mL, $p = 0.025$) and PVR (330.9 ± 124.9 mL vs. 183.9 ± 183.4 mL, $p = 0.011$) after treatment.

Table 2
Therapeutic efficacy of urethral sphincter BoNT-A injection for neurogenic or nonneurogenic voiding dysfunction.

Disease	Patients	Excellent result	Improved result	Failure
DSD	29	8 (27.6)	15 (51.7)	6 (20.7)
Dysfunctional voiding	20	6 (30)	14 (70)	0
Nonrelaxing urethral sphincter	10	8 (42.1)	7 (36.8)	4 (21.1)
Cauda equine lesion	8	5 (62.5)	1 (12.5)	2 (25)
Peripheral neuropathy	14	5 (35.7)	6 (42.9)	3 (21.4)
Idiopathic detrusor underactivity	13	8 (61.5)	4 (30.8)	1 (7.7)
Totals	103	40 (38.8)	47 (45.7)	16 (15.5)

Data are presented as *n* (%).
Note. From "Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction," by H.C. Kuo, 2003, *J Urol*, *170*, p. 1908–12. Copyright 2003. *American Urological Association*. Reproduced with permission.
BoNT-A = botulinum toxin A; DSD = detrusor sphincter dyssynergia.

The obstructive symptom score decreased significantly (17.5 ± 4.7 points vs. 5.7 ± 2.3 points, $p = 0.000$), and the quality of life index also improved (4.5 ± 2.7 points vs. 2.3 ± 2.3 points, $p = 0.000$). The success rate was 80% in the study group. There were no significant changes in obstructive symptom scores or the quality of life index in the control group. The maximal effect appeared about 1 week after treatment. The duration of the therapeutic effect ranged from 3 months to 9 months. Mild stress urinary incontinence and nocturnal enuresis were noted in seven patients (35%). This study has shown that urethral injection of BoNT-A can be effectively used to treat patients with detrusor underactivity and nonrelaxing urethral sphincter after radical hysterectomy with few adverse effects.

9. Effect of BoNT-A in treatment of voiding dysfunction due to dysfunctional voiding

Nonneurogenic voiding dysfunction due to dysfunctional voiding is a therapeutic challenge for urologists. Dysregulated urethral function with a spastic or nonrelaxing external urethral sphincter is thought to be the possible cause of dysfunctional voiding, and results in voiding symptoms, a slow urinary flow, large PVR, and sometimes deterioration in upper urinary tract function. A large PVR develops because patients do not have adequate urethral sphincter relaxation during voiding, and CIC or an indwelling Foley catheter is necessary to empty the bladder.

BoNT-A injection has been licensed for use in patients with neurogenic detrusor overactivity or nonneurogenic overactive bladder [28]. However, its use for voiding dysfunction remains an off-label treatment. Nevertheless, BoNT-A injections to the lower urinary tract have been widely applied in various types of voiding dysfunction, including urethral sphincter injection for neurogenic or nonneurogenic dysfunctional voiding [29]. In 1997, Steinhardt et al [30] first used urethral sphincter BoNT-A injection to treat a neurologically normal child with refractory dysfunctional voiding. The patient had no more urinary tract infections or incontinence episodes after treatment. For pediatric dysfunctional voiding, urethral sphincter injection with BoNT-A 50–100 U resulted in 90% patients voiding without catheterization and with increased maximum flow rates and lower PVRs [30]. An increased dose of 200–300 U seems to increase the efficacy without increased morbidity [31]. BoNT-A injection can effectively improve the voiding condition in neurologically normal children with urodynamically proven dysfunctional voiding complicated by recurrent urinary tract infections or a large PVR [32]. For adults with dysfunctional voiding and poor relaxation of the urethral sphincter, overall subjective successful results of 86.7% and 95.7% have been reported, respectively, after urethral sphincter injection of 50–100 U BoNT-A [23]. Through the paralysis of the urethral sphincter and reduction of urethral resistance, BoNT-A injection therapy could facilitate bladder emptying, improve subjective symptoms and quality of life, and even reduce the frequency of CIC [4,13].

10. Recovery of detrusor contractility in patients with idiopathic detrusor underactivity after urethral BoNT-A injection

Twenty-seven patients with idiopathic low detrusor contractility received urethral injections of BoNT-A. Thirteen (48%) patients had recovery of detrusor contractility, defined as an increase in detrusor pressure and maximum flow rate and reduced PVR [23]. These 13 patients had baseline data characterized by normal bladder sensation during bladder filling combined with poor relaxation or hyperactive urethral sphincter activity. By contrast, patients without recovery of detrusor contractility had poor bladder sensation and a nonrelaxing urethral sphincter. Patients with low detrusor contractility combined with poorly relaxed or hyperactive urethral sphincter activity had better results than those with true detrusor underactivity. Five of the 13 patients with detrusor contractility recovery had long-term effects without the need for repeat urethral injection of BoNT-A for more than 1 year of follow-up.

Patients with detrusor underactivity with normal bladder sensation combined with poor relaxation or a hyperactive urethral sphincter were significantly more likely to recover normal detrusor function. Neuromodulation of the hyperactive urethral sphincter by urethral BoNT-A is the likely mechanism for this therapeutic effect. Through inhibition of the afferent input of the urethral sphincter, the inhibitory effect of the detrusor nucleus in the sacral cords may be reduced and patients can resume spontaneous and efficient voiding.

11. Possible causes of treatment failure after urethral BoNT-A injection

The possible causes of treatment failure included psychological inhibition of voiding, low generation of abdominal pressure, nonrelaxing urethral sphincter obstruction, complete denervation of the urethral sphincter, and bladder neck obstruction [24]. Identification of the underlying causes may indicate appropriate therapy. Urethral hyperactivity in patients with detrusor sphincter dyssynergia can be managed by repeat urethral injections of high doses (100–200 U) of BoNT-A, whereas patients with nonneurogenic dysfunctional voiding can be treated with lower doses (50–100 U). In patients with detrusor underactivity and voiding dysfunction, urethral sphincter BoNT-A may be tried if the bladder neck is open. If videourodynamic study shows a tight bladder neck, patients should be treated with transurethral incision of the bladder neck first. Urethral sphincter BoNT-A treatment will not be successful if the bladder neck is not open in patients with detrusor

underactivity. Patients with complete denervation of the urethral sphincter as demonstrated by electromyographic study should not have these injections. The cost-effectiveness of BoNT-A treatment should also be carefully considered.

12. Conclusion

BoNTA urethral sphincter injection is effective in treatment of voiding dysfunction due to neurogenic or nonneurogenic sphincter dysfunction as well as detrusor underactivity refractory to conventional medical treatment. Although not all patients can achieve excellent therapeutic outcomes, patients with idiopathic detrusor underactivity might have recovery of detrusor contractility after urethral sphincter BoNT-A injection. However, urinary incontinence might be a *de novo* adverse event. Patients who are planning urethral sphincter BoNT-A injection for voiding dysfunction should be fully informed of the limited therapeutic efficacy and possible adverse events prior to the treatment.

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