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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.

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