Botulinum-A Toxin Injections As a Treatment for Refractory Detrusor Hyperreflexia

Michael J. Kennelly and John Kang

Neurogenic urinary incontinence often results from loss of supraspinal inhibitory input that leads to involuntary bladder contractions (detrusor hyperreflexia). Recently, a novel approach has been used to "chemically" denervate the bladder. Botulinum-A toxin has been injected cystoscopically into neurogenic patients' bladder to treat refractory detrusor hyperreflexia and neurogenic incontinence. Reflex voided volumes, bladder capacities, and compliance increased while maximum detrusor pressures decreased. Continence was maintained for up to 6 months with anticholinergic agents eliminated or greatly reduced. Botulinum-A toxin detrusor injection appears to be a safe, minimally invasive, reversible, and effective treatment option for controlling detrusor hyperreflexia. Key words: *botulinum toxin, detrusor hyperreflexia, neurogenic incontinence*

Detrusor hyperreflexia coupled with a lack of higher cortical inhibition often leads to neurogenic urinary incontinence. This urinary leakage has obvious social and quality of life implications. Clinically, detrusor hyperreflexia can also lead to infection, high intravesical pressure, low bladder compliance, reduced capacity, and, at worst, deterioration of kidney function. Anticholinergic medications block efferent parasympathetic innervation to the detrusor muscle and, with clean intermittent catheterization, have been the mainstay of treatment since the 1970s.[1] These bladder-relaxant medications, however, often have untoward side effects including dry mouth, nausea, confusion, constipation, and gastroporesis. Side effects may precede or exceed effective detrusor suppression, which often limits therapy or causes withdrawal from anticholinergic treatment altogether.

Detrusor hyperreflexia that is refractory to anticholinergic medication has classically been treated with irreversible and aggressive surgical therapies such as sacral root rhizotomy, neurostimulation, and bladder augmentation. These therapies are major operative procedures, thereby carrying greater risks and complications. Current research has focused on less invasive, reversible treatments for detrusor hyperreflexia such as trigonal phenol injection, intravesical instillation of capsaicin or resiniferatoxin, and botulinum toxin injection. Phenol injection provides transient benefit but is unsuitable for repeat administration.[2] Capsaicin and its more potent analogue resiniferatoxin are

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neurotoxins that cause functional desensitization of sensory unmyelinated C and myelinated A-delta fibers. Preliminary results have been encouraging, but this technique remains controversial due to lack of consensus regarding protocol, side effect profile, and interpretation of results.[3–5]

Botulinum-A toxin blocks neuromuscular conduction by binding to receptor sites on motor nerve terminals and inhibiting the release of acetylcholine. When injected intramuscularly, a localized chemical denervation paralysis of the muscle is produced. Urologically, botulinum toxin urethral injections have been used to treat neurogenic detrusor-external sphincter dyssynergia, pelvic floor spasticity, pelvic pain, and voiding dysfunction.[6–10] Recently, Schurch et al. reported the feasibility and efficacy of intravesical botulinum-A toxin injections for neurogenic incontinence in patients with traumatic spinal cord injury (SCI).[10] Urinary continence was restored in 17/19 patients, and the mean duration of drug effect in regard to continence was 9 months. Apart from this study and the preliminary results we present, there are no other reports in the literature regarding this patient population.

To prove reproducibility of the reported beneficial effects of intravesical botulinum toxin injections, we prospectively treated 10 neurogenic incontinent patients refractory to high-dose anticholinergic medications. In addition to spinal cord–injured patients, we have expanded the study group to include multiple sclerosis patients. The results of our series are reported.

Method

Between November 2000 and June 2001, 10 patients with neurogenic incontinence refractory to high-dose anticholinergic medications were selected for prospective treatment. Data regarding basic demographics, neurologic deficit, and anticholinergic medication regimen were collected. All patients emptied their bladder by intermittent catheterization and had severe detrusor hyperreflexia documented on cystometrogram despite high-dose anticholinergic medication. All patients had incontinence between catheterizations noted on voiding diaries. Exclusion criteria included pregnancy, breast-feeding, active bladder infection, myasthenia gravis, significant bladder pathology, or vesicoureteral reflux. Patients with poor bladder compliance were allowed to participate.

Evaluation included a complete medical history, review of voiding diaries, physical examination, and cystometrogram on anticholinergic agents before botulinum injection using a Laborie Aquaris 120 machine (Laborie Medical Technologies, Williston, Vermont). Detrusor hyperreflexia was defined in accordance with the International Continence Society standards.[11] Urodynamic parameters measured included reflex volume, maximum detrusor pressure during voiding, bladder compliance, and maximum cystometric bladder capacity. Reflex volume is the infused volume that induced the first hyperreflexive detrusor contraction.[12] Bladder compliance is calculated by the change in volume divided by the change in detrusor pressure.[12] The maximum cystometric bladder capacity is defined as the volume at which involuntary voiding occurred and or filling was stopped (700 mL).[12]

All procedures were done on an outpatient basis using intravenous sedation anesthesia. Perioperative antibiotics were administered. Botulinum-A toxin was resuspended in ster-

Table 1. Patient demographics

No.	Sex	Age (years)	Neurologic injury level	Upper motor lesion	ASIA[a]
1	F	63	MS		
2	F	44	MS		
3	F	32	SCI – C6	Complete	A
4	M	53	SCI – C6	Complete	A
5	F	29	SCI – C6	Complete	A
6	M	42	SCI – C6	Complete	A
7	F	46	MS		
8	F	60	MS		
9	M	13	SCI – L1	Incomplete	B
10	M	70	SCI – L1	Incomplete	D

Note: F = female; M = male; MS = multiple sclerosis; SCI = spinal cord injury.
[a]American Spinal Injury Association (ASIA) criteria.

ile normal saline with final concentration of 10 units/mL normal saline. Using a Wolfe injection cystoscope and 21-gauge needle, a total of 300 units (30 mL) were injected at 30 detrusor muscle sites sparing the trigone as described by Schurch et al.[10] Patients were instructed to progressively taper and discontinue their anticholinergic medication within the first 3 weeks after the injections. Clinical and urodynamic follow-up was obtained at 6, 12, and 24 weeks after treatment.

Outcome parameters that were measured included reflex volume, maximum detrusor pressure during voiding, bladder compliance, maximum cystometric bladder capacity, patient satisfaction, and continence level. The patient satisfaction was based on a 3-point scale as 1 (*not satisfied*), 2 (*satisfied*), and 3 (*very satisfied*). The continence level was based on a 7-point scale as 1 (*worse incontinence than baseline*), 2 (*same incontinence as baseline*), 3 (*<25% improved continence*), 4 (*26%–50% improved continence*), 5 (*51%–75% improved continence*), 6 (*76%–99% improved continence*), and 7 (*dry*). Statistical significance was determined using the paired *t* test with significance at $p < .05$.

Results

Five men and five women who were 13 to 70 years old (mean age, 45 years) with refractory neurogenic incontinence participated in our study (**Table 1**). The reasons for neurogenic incontinence included multiple sclerosis (four women) and spinal cord injury (four persons with tetraplegia, two with paraplegia). All patients with tetraplegia were C6 complete SCI ASIA A; the two patients with paraplegia were L1 incomplete SCI (1 ASIA B, 1 ASIA D). Despite being on high doses of anticholinergic drugs, all patients were incontinent. Nine patients were on 20–40 mg oxybutynin chloride daily; however, two of those patients were also on 45 mg propantheline or 0.75 mg hyoscyamine. One patient was on 10 mg tolterodine daily.

All procedures were performed in an out-

patient setting and were well tolerated. There were no acute complications related to the injection procedure, such as gross hematuria, injury to adjacent structures, autonomic dysreflexia, or urinary tract infection. No complications possibly related to toxin, such as dysphagia, diplopia, or general paralysis of remote musculature, occurred. One multiple sclerosis patient had a postanesthesia seizure. Full neurological evaluation was negative, and there was no further sequelae.

At the 6-week follow-up, all patients had discontinued anticholinergic medication. Five of the 10 patients (50%) were completely continent. Of the remaining five incontinent patients, three (60%) needed to restart anticholinergic agents to achieve continence. However, the amount of anticholinergic medication they needed to become continent was less than 50% of their pre-botulinum dosage. Two of the 10 patients were incontinent despite baseline anticholinergic agents and were considered failures. The mean continence level was 5.9 (range, 3–7), and mean patient satisfaction was 2.5 (range, 2–3). Throughout the remainder of the study, all eight patients were continent (**Fig. 1**). At the 12-week follow-up, five patients (63%) remained continent off all anticholinergic medication, and three patients (37%) were on the same dose as needed at 6 weeks (<50% baseline doses). At the 24-week follow-up, four patients (50%) were continent off all anticholinergic medication. One patient (12%) was continent on the same dose as needed at 6 weeks (<50% baseline medications), and three patients (37%) were continent on baseline medication. The mean patient satisfaction for the procedure at 24 weeks was 2.6 (range, 2–3).

At the 6-week follow-up, urodynamic evaluation revealed significant increases in mean reflex volume and mean maximum cystometric bladder capacity from 241 mL to 415 mL ($p < .007$) and 270 mL to 418 mL ($p < .014$), respectively (**Fig. 2** and **Table 2**). There was significant increase in mean bladder compliance before and after treatment from 17.0 mL/cm H_2O to 53.4 mL/cm H_2O ($p < .023$). Posttreatment mean maximum de-

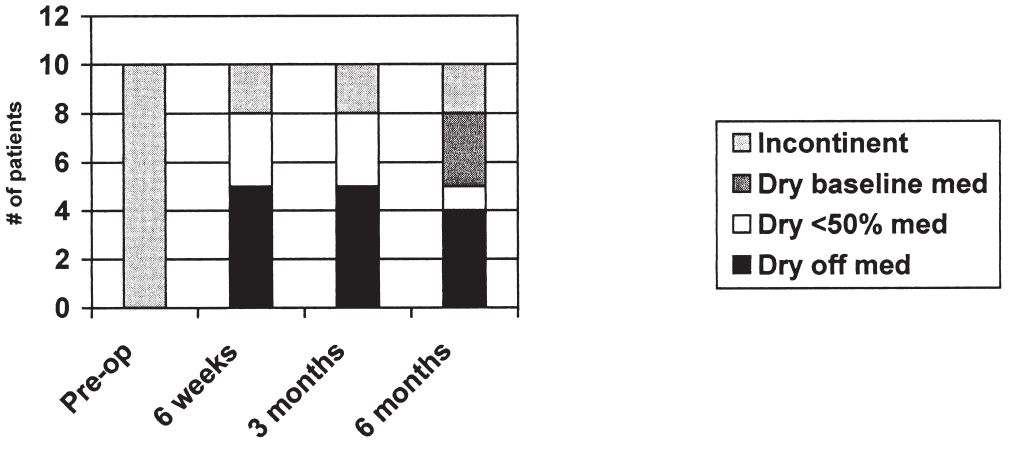

Figure 1. Continence status.

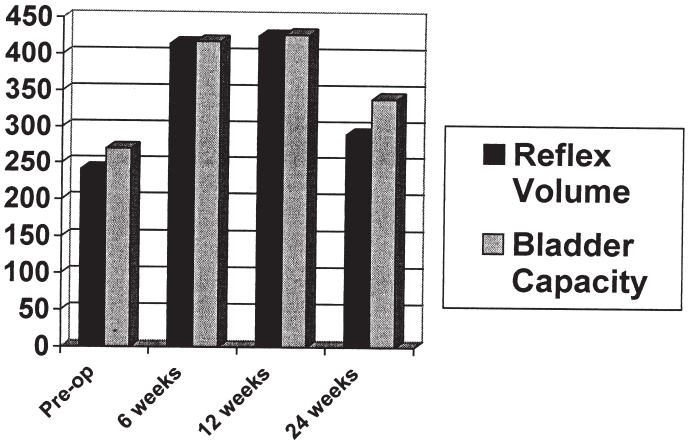

Figure 2. Mean reflex volume and mean bladder cystometric capacity.

trusor voiding pressure decreased from 41.8 cm H_2O to 27.3 cm H_2O ($p < .088$).

Urodynamic parameters remained statistically improved at the 12-week follow-up but, by the 24-week visit, began to deteriorate to levels below statistical significance (**Table 2**). At the 24-week follow-up, the mean reflex volume was 286 mL ($p < .471$) and mean maximum cystometric bladder capacity was 333 mL ($p < .231$), respectively. Compared to baseline parameters, mean bladder compliance remained improved at 25.3 mL/cm H_2O ($p < .596$), and mean maximum detrusor voiding pressure remained lowered at 30.9 cm H_2O ($p < .104$).

Discussion

Since its introduction and the Food and Drug Administration approval in the 1980s, botulinum-A toxin has been successfully used to treat focal dystonias, torticollis, strabismus, muscle spasm, and spasticity.[13,14] Autonomic parasympathetic disorders such as achalasia and hyperhidrosis have also been shown to benefit from treatment with

Table 2. Urodynamic parameters at baseline and follow-up

	Mean reflex volume (mL)	Mean maximum bladder capacity (mL)	Mean compliance (mL/cm H_2O)	Mean maximum detrusor pressure (cm H_2O)
Baseline	241	270	17.0	41.8
6 weeks	415	418	53.4	27.3
12 weeks	426	428	21.0	24.2
24 weeks	286	333	25.4	39.9

botulinum toxin.[15,16] Faced with limitations with currently available anticholinergic medication and surgeries, the urologic community has actively pursued studies with botulinum for a wide range of disorders including detrusor external sphincter dyssnergia, pelvic pain, pelvic spasticity, and voiding dysfunction.[7–9]

In their study of spinal cord–injured patients, Schurch et al. were the first to report the efficacy of botulinum toxin in neurogenic incontinence.[10] Our study finds a high level of patient satisfaction and validates the Schurch study with regard to safety, efficacy, durability of effect, and technique. By successfully treating patients with multiple sclerosis, we add another patient population that can safely benefit from therapy. Schulte-Baukloh et al.[17] and Corcos et al.[18] have recently reported the efficacy of botulinum toxin in children and adults with detrusor hyperreflexia due to myelomeningocele. These studies as well as our data strongly suggest that good results may be generalizable to all types of patients with neurogenic incontinence.

But, as with any therapy, patient selection is important. Our study included patients with poor bladder compliance. These patients often do not respond to other currently available conservative measures and are often treated surgically. Two of our patients were considered failures to botulinum injection, and these two patients had very poorly compliant bladders (0.9 mL/cm H_2O and 1.8 mL/cm H_2O) that were considerably less than the group mean (17 mL/cm H_2O). Though improved compliance after botulinum injection is reported in other studies[10,17,18] and confirmed by our findings, botulinum injection does not sufficiently overcome severely diminished, preexisting poor bladder compliance. This result would be expected given that the causes of poor compliance are most likely nonneurogenic (i.e., fibrosis and detrusor muscle changes). The level of minimum acceptable bladder compliance is not currently known.

Other differences in our data with the Schurch study highlight areas for further investigation. Using the same protocol, continence was maintained throughout our study in 80% of our patients who responded to treatment, comparable to the 89% reported by Schurch[10] and 80.5% reported by Cocros.[18] However, improvements in urodynamic parameters declined by 6 months in our study whereas Schurch et al.[10] report efficacy for greater than 9 months. Studies[6,8] involving striated sphincter botulinum toxin injection for detrusor sphincter dyssynergia report therapeutic effect for approximately 3–5 months before the need for retreatment. Differences in axonal regeneration between smooth and striated muscle have been cited as a possible explanation for this discrepancy in length of response.[10] Our study, however, used the same protocol, technique, and tissue target as the study by Schurch. Differences in our two study groups (i.e., patients with poor bladder compliance) may contribute to our earlier overall decline in urodynamic parameters. Ongoing larger clinical trials and basic science research into botulinum may further elucidate these discrepancies. Given the high cost of botulinum toxin (approximately $300/100 units), improved understanding of durable effect would be clinically as well as economically important.

The Schurch study[10] remains the standard with regard to not only clinical results but

also technique and protocol. As a confirmatory study, we hoped to and were able to closely replicate their technique and protocol. This, however, leaves questions regarding possibilities beyond the current "standard" and future modifications. It is not well known to what degree efficacy, durability of response, or side effects would be altered at higher doses of botulinum toxin. Furthermore, since it is established that botulinum toxin is reversible, repeat injection will be required. With subsequent treatments, antibody formation against the toxin may occur and neutralize the effect of the toxin.[19] To date, only one preliminary study has formally evaluated this question. Grosse et al. report that repeat injection with botulinum toxin (up to five) does not induce drug tolerance.[20] If additional studies and extended follow-up of these patients confirm this finding, the appeal of botulinum injection would be solidified. Finally, the current agent for treatment with botulinum toxin is the type A toxin. Six additional subtypes (subtypes B–F) have also been isolated and have been found to have different actions and properties.[21] Further experimentation and understanding of these subtypes may provide more synergistic options or a more effective single agent.

Conclusion

Botulinum-A toxin injection into the detrusor muscle is a safe, minimally invasive, reversible, and effective treatment option for controlling detrusor hyperreflexia in patients with neurogenic incontinence. Continence is maintained for up to 6 months. Anticholinergic medications can either be eliminated or greatly reduced. Patients with poor bladder compliance are not likely to respond to treatment. Further studies are ongoing to confirm these preliminary findings and refine the clinical applications.

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