Efficacy of botulinum-A toxin in adults with neurogenic overactive bladder: initial results

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Introduction and objectives: *To study the effects of intradetrusor botulinum-A toxin (BTA) (BOTOX®) injections in adult patients with detrusor overactivity who failed to respond to anticholinergic medications or developed intolerable side-effects.*

Materials and methods: *Ten patients (average age 41 years, range 19-76 years) with neurogenic bladder and detrusor overactivity who were using clean intermittent catheterization 4 to 7 times a day with anticholinergic therapy were included in our study. Their history, physical examination, abdominal ultrasound, urine analysis, serum creatinine and electrolytes, as well as multichannel urodynamic evaluation were documented before administration of BTA injections. Anticholinergic medication was stopped at the time of injection. Three hundred to 400 U of BTA were injected into 30 to 40 different sites in the detrusor muscle under cystoscopic guidance. Clinical assessment and urodynamic testing were repeated 3 months after injection.*

Results: *Five patients were tetraplegic and five were paraplegic at the thoracic or lumbar level. Three patients had incontinence episodes between catheterizations before treatment, and only one patient continued to have incontinence episodes between catheterizations after treatment. Reflex volume increased by 63.08% from 180 ± 44.99 ml to 293.7 ± 208.42 ml ($p<0.02$). Maximal bladder capacity was augmented by 73.63% from 290 ± 131.64 ml to 518.20 ± 273.35 ml ($p<0.03$). Maximal detrusor pressure decreased by 15.52% from 69.60 ± 39.19 cmH_2O to 58.80 ± 33.95 cmH_2O ($p<0.2$). No patients complained of side effects.*

Conclusion: *BTA appears to be an effective and safe therapeutic option for overactive bladder in patients with spinal cord injury failing anticholinergic therapy and delays more invasive treatments. These initial results confirm European literature reports.*

Key Words: paraplegia, spinal cord injury, neurogenic bladder, botulinium A toxin, intradetrusor injections, urodynamics

Introduction

In patients with spinal cord injury above the sacral level and after a period of spinal shock, disruption of voluntary voiding control results in detrusor overactivity often associated with incontinence episodes.[1,2] Incontinence has a tremendous impact on quality of life, physical and psychological well being.[3] The usual management of this bladder overactivity is based on anticholinergic medications and clean intermittent catheterization (CIC). The efficacy and tolerability of anticholinergics may be a problem for some patients requesting alternative treatments.[4]

Botulinum-A toxin (BTA) is a neurotoxin produced by *Clostridium botulinum*, a facultative anaerobe that blocks the release of acetylcholine from presynaptic cholinergic junctions into synaptic gaps, preventing neural transmission.[5] Injection of BTA into the detrusor muscle is followed by significant increases in maximal cystometric bladder capacity, and bladder reflex capacity. It has been proposed as a good alternative for patients who achieve insufficient results with anticholinergics and CIC or who cannot tolerate antimuscarinic therapy.[6-9] Dry mouth, blurred vision and constipation are commonly reported anticholinergic adverse events that

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have a significant impact on the long-term success of treatment.[4] In previous treatment algorithms of overactive bladder, if conservative therapy fails, surgical therapy (such as bladder augmentation) is the next option to consider.[10]

Botulinum-A toxin (BOTOX®) has been used successfully in urology since 1988 for the treatment of detrusor sphincter dyssynergia (DSD) in spinal cord injury patients.[11-17] More recent literature supports its application in the management of overactive bladder in children with myelomeningocele and adults with spinal cord injury.[6-9]

We report our results with BTA intradetrusor injections in the treatment of neurogenic bladder overactivity secondary to spinal cord injury. These data were generated by the first Canadian pilot study of BTA in adults.

Materials and methods

Ten adult patients (six males and four females; average age 41 years) were included in this prospective study. All subjects had detrusor overactivity secondary to spinal cord injury that occurred at least 1 year before entering the study. The inclusion criteria were the presence of detrusor overactivity defined as uninhibited contraction on cystometrogram, persistent incontinence despite CIC and no response to, or no tolerance to regular anticholinergic medications (Oxybutinin, Tolterodine, Imipramine, or combinations of these products). Incontinence was defined as any urinary leakage between CIC. The exclusion criteria were urinary tract infection (temporary exclusion), myasthenia, pregnancy, and uncontrolled blood coagulopathy.

All patients underwent complete history, physical examination, urine analysis and culture, ultrasonography of the upper urinary tract and multichannel urodynamic evaluation before entering the study. Anticholinergic medication was stopped on the day of botulinum-A toxin treatment.

For urodynamic evaluation, intravesical pressure, was recorded via a 6F micro tip catheter, and via balloon micro tip catheter. The bladder filling rate, using isotonic saline solution at room temperature, was 30 ml/min. The main parameters analyzed were maximal bladder capacity (MBC), maximal detrusor pressure (MDP), reflex volume at first uninhibited bladder contraction, uninhibited detrusor contraction, and detrusor leak point pressure.

BTA injections were given with or without general anesthesia, depending on the patient's bladder sensation or risk of severe autonomic dysreflexia at bladder distension. We injected 400 U botulinum-A toxin diluted (10/1) in isotonic saline solution at 40 sites on the bladder wall under cystoscopic guidance with the Storz injection system Figure 1 Patients were seen 3 months after injection for a clinical evaluation of their incontinence as well as a cystometrogram. If satisfactory result was not achieved at that visit, patient was rescheduled for a reinjection. If patient was satisfied with results and urodynamic studies were demonstrating a safe storage pressure (< 40 cmH_2O), patients were scheduled for a second visit 6 to 9 months later.

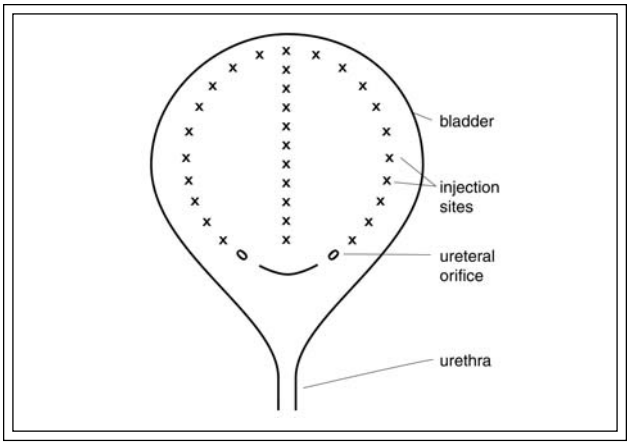

Figure 1. Injection sites following three vertical lines starting above the trigone.

Results

Four women and six men 19-76 years old (average age 41 years) entered our pilot study.

Three were tetraplegic, and seven were paraplegics at the thoracic or lumbar levels. All patients had passed the spinal shock period and were at least 1 year post- injury Table 1.

Seven patients had severe incontinence episodes between catheterizations before treatment while on high-dose anticholinergics; one patient continued to have incontinence episodes between catheterizations after treatment. After injection, average reflex capacity increased by 63.08% ($p<0.02$) from 180 ± 44.99 ml (range 99-208) to 293.7 ± 208.42 ml (range 50-647). Average MBC was augmented by 73.63% ($p<0.03$) from 290 ± 131.64 ml (range 100-501) to 518.20 ± 273.35 ml (range 84-1,000). Average MDP decreased by 15.52% ($p<0.2$) from 69.60 ± 39.19 cmH_2O (range 24-126) to 58.80 ± 33.95 cmH_2O (range 21-105) Table 2. No patients complained of any adverse effects after injection, and all were discharged immediately after treatment. A high satisfaction rate (90%), evaluated by interview, was reported by all except one patient.

TABLE 1. **Neurological level of spinal cord injury**

Neurological level	Upper motor neurons	ASIA classification
C5-6	Complete	A
C5-6	Complete	A
C6	Complete	A
T4-5	Complete	A
T5	Complete	A
T8-9	Incomplete	B
T10-11	Incomplete	C
T11-12	Incomplete	B
T10	Complete	A
L1	Incomplete	C

Discussion

BTA selectively blocked acetylcholine release from nerve endings and produced chemical denervation. Seven immunologically-distinct Botox neurotoxins are known: types A, B, C, D, E, F, and G. BTA received Canada Therapeutic Products Directorate (TPD) approval in 1990 for the treatment of strabismus and benign essential blepharospasm.

In urology BTA has been used to treat DSD and detrusor hyperreflexia.[6-9,11-17] Study of a rat model showed that the effect of BTA on the lower urinary tract may vary, depending on the site of injection; it exerts a significant inhibitory influence on bladder acetylcholine and urethral norepinephrine release that supports its clinical application to treat conditions such as bladder overactivity and DSD.[18] More recently, in a rat chemical cystitis model, BTA injection into the detrusor provided functional improvement, with cystometric recording showing that the increase in MBC and bladder compliance were significantly higher in the treatment than in the control group ($p=0.000$ and $p\leq0.025$, respectively). No morbidity and mortality were reported. The authors concluded that BTA intradetrusor injections may be an alternative treatment in chronic bladder inflammation such as interstitial cystitis.[19]

In neurogenic overactive bladder, BTA has been proposed as an alternative to oral or other intravesical medications. Schurch et al demonstrated a significant increase in mean MBC (296 to 480 ml, $p<0.016$) with a decrease in mean maximum detrusor voiding pressure (65 to 35 cmH_2O, $p<0.016$) after BTA injections in patients with detrusor hyperreflexia.[6] Employing the same approach in children with detrusor hyperreflexia due to myelomeningocele, Schulte-Baukloh et al reported MBC augmention from 137 to 215 ml, $p<0.005$) and decreased MDP from (58.9 to 39.7 cmH_2O, $p<0.005$).[7]

In another study of children with neurogenic bladder treated with BTA injection, Schulte-Baukloh et al observed significant improvement in MBC from 163 to 219 ml ($p<0.01$) after 4 weeks and to 200 ml, ($p<0.01$) after 3 months. MDP declined from 59 to 35 cmH_2O ($p<0.01$) after 4 weeks and to 46.7cm H_20 after

TABLE 2. **Pre- and post-botulinum-A toxin injection urodynamic data**

Patient no.	Age (year)	Pre-BC (cc)	Post-MBC (cc)	Pre-MDP (cmH_20)	Post-MDP (cmH_2o)	Pre-RC (cc)	Post-RC (cc)
1	19	217	647	96	21	199	647
2	26	325	233	24	62	200	400
3	67	501	1000	33	26	200	600
4	36	198	418	126	31	144	234
5	24	100	84	27	58	99	50
6	25	178	257	120	43	169	200
7	33	205	535	51	34	150	257
8	57	455	602	61	104	265	367
9	47	400	702	100	105	167	105
10	76	325	704	58	104	208	350
Average	41	290	518	69	58.8	180	293

MBC: maximal bladder capacity; MDP: maximal detrusor pressure; RC: reflex capacity

3 months; however, the result was not significant after 6 months and re-injections became necessary.[8] In our study, MBC increased significantly by 73.6%, and mean reflex volume, by 63.08% after BTA.

No side effects from botulinum-A toxin injection were reported by our patients. We believe that the delivery method used, the low injected dose and the relative lack of systemic reabsorption from quick local neural uptake may explain the innocuity of this treatment. However, two cases were reported recently in the literature with muscular weakness as a side effect of botulinum-A toxin injection for neurogenic detrusor overactivity. One of these patients was a 24 year-old treated with 300 U of botulinum-A toxin at 30 different sites, and the second received repeated injections of 300 and 1000 Units of Dysport® at 3-month intervals.

A previous study revealed that the outcome of BTA in nerve paralysis is a reversible process, as new axons re-sprout in 3-6 months.[20] In our study, we observed a long period of bladder paralysis up to 6-10 months in all except one patient. This finding is similar to that of previous investigations.[5,8] Consequently, repeated injections are required to maintain continence in these patients, and this might be a disadvantage of botulinum-A toxin mainly in patients who require anesthesia for their injections.

Schurch et al recently published a review on BTA, describing its indications and success rate in urology practice with possible side effects. They conclude that botulinum-A toxin is a new, promising treatment option for many different urological dysfunctions.[21]

If our preliminary results hold true, this simple and easy method may offer a viable alternative to more aggressive surgery, such as augmentation cystoplasty, if patients fail anticholinergic therapy or develop severe side effects.

However, long-term and controlled assessment with a larger patient sample is necessary to study not only the accuracy of dosage and injection site but also effectiveness, duration of paralysis, re-injection rate, possible immunization, local muscle histological changes and side effects of botulinium-A toxin.

Conclusion

BTA appears to be a safe therapeutic option for neurogenic overactive bladder in patients with spinal cord injury not improved enough by CIC and anticholinergic therapy to postpone or perhaps replace more invasive treatments. However, future controlled studies have to answer several important questions before this treatment becomes a standard. □

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