Neurourology and Urodynamics 27:311–314 (2008)

Trigonal Injection of Botulinum Toxin-A Does Not Cause Vesicoureteral Reflux in Neurogenic Patients

Frederico Mascarenhas,[1*,†] Marcello Cocuzza,[2‡] Cristiano Mendes Gomes,[2‡] and Nilo Leão[3¶]
[1]*Department of Urology, Hospital Santo Antonio das Obras Sociais Irmã Dulce, Bahia, Brazil*
[2]*Department of Urology, University of Sao Paulo (USP), Sao Paulo, Brazil*
[3]*Department of Urology, Federal University of Bahia (UFBA), Bahia, Brazil*

Aims: We evaluated the effect of botulinum toxin type A (BTX-A) injections in the trigone on the antireflux mechanism and evaluated its short-term efficacy. **Materials and Methods:** Between April and December 2006, 21 patients (10 men and 11 women) were prospectively evaluated. All were incontinent due to refractory NDO and underwent detrusor injection of 300 units of BTX-A, including 50 units into the trigone. Baseline and postoperative evaluation after eight weeks included cystogram, urinary tract ultrasound and urodynamics. **Results:** At baseline, 20 patients had no vesicoureteral (VUR) and one had grade II unilateral VUR. Postoperative evaluation revealed no cases of de novo VUR and the patient with preinjection VUR had complete resolution of the reflux. Ultrasound showed 5 (23.8%) patients with hydronephrosis before BTX-A injection and only one (4.8%) at the followup evaluation (p=0.066). After treatment, 9 (42.8%) patients became dry, 11 (52.4%) were improved and one (4.8%) had no improvement. Improved patients received antimuscarinic treatment and 8 (38.1%) became dry, with a final total continence rate of 80.1%. Cystometric capacity increased from 271 ± 92 to 390 ± 189 ml ($p = 0.002$), reflex volume varied from 241 ± 96 to 323 ± 201 ml ($p = 0.020$) and maximum detrusor pressure reduced from 66 ± 39 to 38 ± 37 cm H_2O ($p < 0.001$). **Conclusions:** Our results confirm the safety of trigone injections of BTX-A in terms of development of VUR and upper urinary tract damage. Whether they are beneficial for patients with NDO or other causes of voiding dysfunction will need further studies. *Neurourol. Urodynam. 27:311–314, 2008.* © 2007 Wiley-Liss, Inc.

Key words: bladder; botulinum toxin; detrusor overactivity; kidney; vesicoureteral reflux

INTRODUCTION

Urinary incontinence due to detrusor overactivity (DO) is a common problem in patients with neurological diseases, such as spinal cord injury (SCI), with significant impact on the quality of life (QOL). Moreover, in this population DO is frequently accompanied by high bladder pressures and may pose a risk for the upper urinary tract.[1,2]

The injection of *Clostridium botulinum* toxin type A (BTX-A) into the bladder has recently emerged as a safe and efficient treatment for refractory neurogenic DO, but controversy exists regarding the dose of BTX-A to be injected as well as the number and location of the injections.[3–5] Most investigators have spared the trigone when injecting BTX-A in the bladder mainly because of the potential of inducing vesicoureteral reflux (VUR), by disturbing the active trigonal antireflux mechanism.[6,7] However, BTX-A injections into the trigone might improve the effect on bladder afferent pathways which could be beneficial for patients with conditions related to bladder afferent disturbances such as idiopathic overactive bladder (OAB), interstitial cystitis and even neurogenic DO.[8–10]

In this study, we evaluated the presence and grade of VUR before and after the injection of 300 units of BTX-A throughout the bladder wall, including the trigone, to evaluate the safety of trigone injection.

MATERIALS AND METHODS

The study was done in accordance with the Ethics Committee regulations and written informed consent was obtained from all patients. Between April and December 2006, a total of 21 patients with neurogenic urinary dysfunction were enrolled, including 10 men and 11 women, with a mean age of 35.4 ± 15.9 years (range 15–78 years). All patients complained of urinary incontinence which was caused by neurogenic DO as demonstrated by urodynamics. The condition resulted from SCI in 12 (57%) patients, viral myelitis in 8 (38%), and multiple sclerosis in 1 (5%) patient. Except for one patient who did not tolerate the medication, all were taking oxybutynin during the preoperative evaluation.

Inclusion criteria were urinary incontinence for at least 6 months, failure of oral anticholinergics therapy and use of clean intermittent catheterization. Exclusion criteria included previous bladder surgeries, previous endovesical pharmacological agent treatment, symptomatic urinary tract infection (UTI) and a history of neurological disease of less than 6 months.

Preoperative evaluation included urine culture, urinary tract ultrasound to evaluate upper urinary tract dilation and a cystogram to evaluate VUR. A standard urodynamic study was performed in each patient. Cystometry was performed at a filling rate of 30 ml/min. All definitions conform to the standardized terminology of the International Continence Society.[11] The evaluated parameters were maximum cystometric capacity (MCC), reflex detrusor volume, maximum

No conflict of interest reported by the author(s).
Dirk De Ridder led the review process.
Abbreviation used: VUR, vesicoureteral reflux; SCI, spinal cord injury; QOL, quality of life; BTX-A, botulinum toxin type A; DO, detrusor overactivity; OAB, overactive bladder; UTI, urinary tract infection; MCC, maximum cystometric capacity; MDP, maximum detrusor pressure.
†Made substantial contributions to conception and design.
‡Drafted and revised the article critically for important intellectual content.
¶Had final approval of the version to be published.
*Correspondence to: Frederico Mascarenhas, MD, Department of Urology, Hospital Santo Antonio das Obras Sociais Irmã Dulce, Rua Clara Nunes, 310 SM AP 1102, Salvador, Bahia, Brazil. E-mail: fredericomascarenhas@ig.com.br
Received 6 May 2007; Accepted 17 August 2007
Published online 3 October 2007 in Wiley InterScience (www.interscience.wiley.com)
DOI 10.1002/nau.20515

detrusor pressure (MDP) during bladder contraction and compliance.

Injection Procedure

The BTX-A formulation used was BOTOX® (Allergan, Irvine, CA). A single dose of prophylactic antibiotic was administered during anesthesia. The 300 units of BTX-A were reconstituted with 0.9% saline to a total volume of 30 ml. Accordingly, the BTX-A solution concentration was 10 U/ml. The bladder was distended with 100 ml saline and 30 injections of 1.0 ml each were performed intramuscularly throughout the bladder wall, including the trigone, where five injections (50 units of BTX-A) were done in each patient. The procedure was performed under general anaesthesia using a rigid cystoscope and a 23-gauge flexible needle (Handle Cook®), yielding an injection depth of 3–5 mm. A Foley catheter was left overnight and patients were discharged in the following morning, after catheter removal, resuming clean intermittent catheterization. The antimuscarinic drug was withdrawn in the 7th post-operative day.

Safety evaluations included monitoring of vital signs and hematuria during the procedure and hospital stay and spontaneous reports of adverse events.

Follow-Up Evaluation

Patients were evaluated after 8 weeks of the injection with a clinical evaluation to assess continence, urodynamics, and cystogram. Patients were considered continent when they had no episodes of incontinence during the 7 days before evaluation.

Data Analysis

The primary outcome was the presence or absence of VUR at cystogram study before and 8 weeks after BTX-A injection. The secondary outcomes were the continence status and urodynamic parameters. Numerical data were reported as mean ± standard deviation and range. Categorical variables were reported as numbers and percentages. Changes from baseline in the urodynamic parameters, were analyzed using the paired *t*-test. The chi-squared (χ^2) test or the Fisher's exact test was used for categorical variables. Data were processed using SPSS 12.0 for Windows statistical software and $P < 0.05$ considered significant.

RESULTS

Twenty patients had no VUR and one patient (4.8%) had grade II unilateral VUR at baseline evaluation (Fig. 1a). At the cystogram performed after 8 weeks of BTX-A injection, no cases of de novo VUR were detected and the patient with pre-injection VUR had complete resolution of the reflux (Fig. 1b).

All patients underwent urinary tract sonography, which was normal at baseline in 16 (76.2%) patients. Four (19.0%) patients had mild hydronephrosis and one (4.8%) had moderate hydronephrosis. Postoperative ultrasound showed

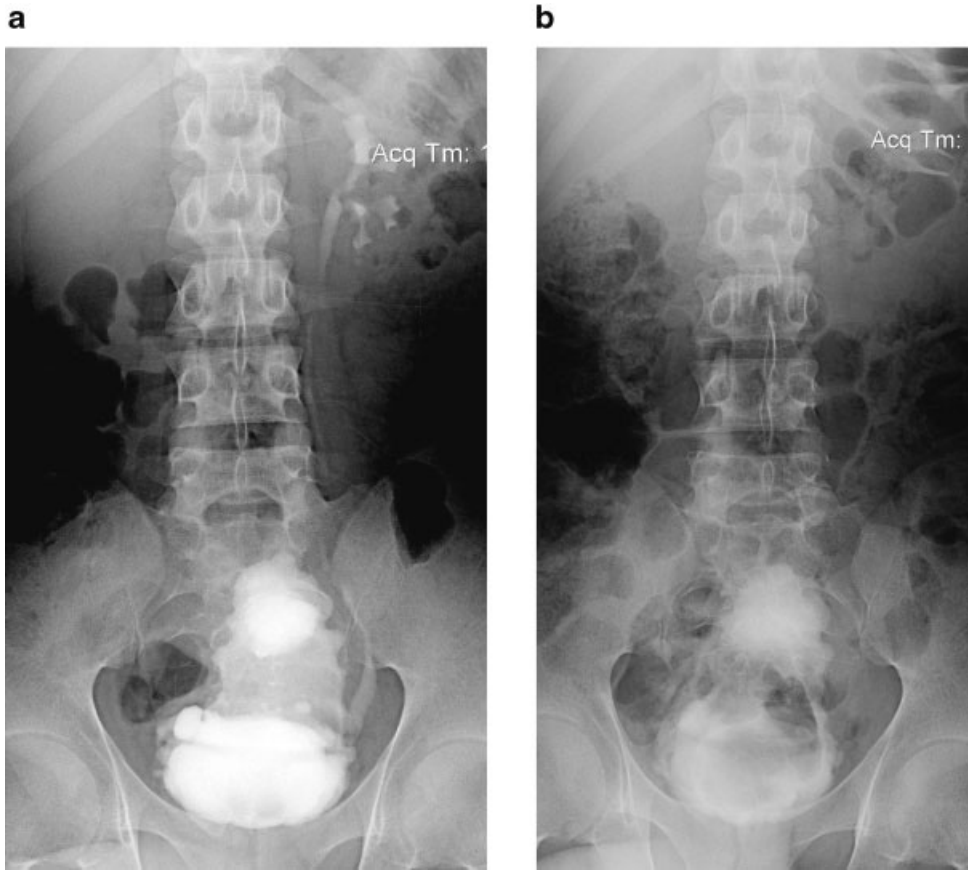

Fig. 1. **a**: Baseline cystogram demonstrates unilateral grade II VUR. **b**: Cystogram 8 weeks after BTX-A injection demonstrates resolution of VUR.

no hydronephrosis in 20 (95.2%) patients and mild hydronephrosis in 1 (4.8%, $P = 0.125$).

All patients were incontinent before BTX-A injection and after 8 weeks of injection 9 (42.8%) became completely dry, 11 (52.4%) had a significant improvement with occasional leaks, and 1 (4.8%) had no significant improvement. All of the improved patients received antimuscarinic treatment with oxybutynin 15 mg/day, and 8 (38.1%) became totally continent, with a final rate of total continence of 80.1% ($P = 0.013$).

Urodynamic Parameters

MCC increased 43.9%, varying from 271.1 ± 92.1 to 390.1 ± 189.3 ml ($P = 0.002$). Reflex detrusor volume increased from 241.0 ± 96.9 to 323.1 ± 201.9 ml (34.1% increase; $P = 0.020$). MDP was significantly reduced from 66.1 ± 39.8 to 38.5 ± 37 cmH_2O (41.8% decrease; $P < 0.001$). Compliance varied from 34.8 ± 19.9 to 43.3 ± 32.3 ml/cmH_2O (24.4% increase; $P = 0.380$). Urodynamic results are summarized in Table I.

Complications

The adverse events directly related to treatment were few, mild, and transient in nature. One patient had hematuria with blood clots at the fifth postoperative day that required evacuation. Three patients with cervical SCI experienced autonomic dysreflexia in the early postoperative period. All had history of previous episodes of dysreflexia and the condition was controlled with oral nifedipine. One patient experienced headache that resolved after 5 days with oral analgesics.

DISCUSSION

Our results confirm that BTX-A injection into the trigone is safe in terms of the possibility of causing VUR. It did not induce de novo or worsen preexisting VUR in any patient. In fact, the only patient in our series with VUR previous to the injection had it cured after BTX-A injection. Likewise, upper urinary tract was not adversely affected by the trigone injections of BTX-A. In fact, we observed improvement of the upper tracts in terms of hydronephrosis in most patients with baseline hydronephrosis. Both findings are probably explained by the decreased bladder pressures that are observed after treatment.

Since BTX-A may inhibit the release of many neurotransmitters, its injection in the trigone might induce VUR by interfering with the adrenergic control of the intramural part of the ureter and trigone, which are known to play important roles in the active antireflux mechanism.[12–14] Nevertheless, we did not observe de novo VUR after BTX-A injection, which indicates that the adrenergic control of the intramural part of the ureter and trigone smooth muscle is not affected by BTX-A at the dose used (50 units were injected in the trigone). Alternatively, it is possible that the active antireflux mechanism is not as important as the passive mechanism, which is based on the intramural submucosal traject of the ureter and is known to be sufficient to avoid reflux in patients submitted to ureteral reimplantation.[15,16]

TABLE I. Urodynamic Parameters Before and After BTX-A Injection

	Baseline	Eight weeks	*P*-value
Incontinence	21 (100%)	4 (19.1%)[a]	<0.001
CC_{max} (ml)	271.1 ± 92.1	390.1 ± 189.3	0.002
Reflex volume (ml)	241.0 ± 96.9	323.1 ± 201.9	0.020
P_{detmax} (cmH_2O)	66.1 ± 39.8	38.5 ± 37.1	<0.001
Compliance (ml/cmH_2O)	34.8 ± 19.9	43.3 ± 32.3	0.380

[a]Eight of the 17 continent patients required oxybutynin to become totally continent.

Recently, two studies have evaluated the effects of BTX-A injection into the trigone. Lucioni et al. evaluated the results of the injection of 300 units of BTX-A in the detrusor, of which 20 units were injected in the trigone in one group while the other group received the same dose, but without trigone injections.[17] They found no beneficial effects and no complications in the trigone injection group, but they did not evaluate the effect of trigone injection in terms of VUR. Karsenty et al. evaluated the effect of exclusive trigonal injection of 200 units of botulinum toxin in idiopathic OAB.[18] Their main goal was to evaluate the effect of BTX-A injection into the trigone in the antireflux mechanism. They found no cases of the novo VUR and one patient with preexisting VUR remained stable. Clinical improvement, however, was not satisfactory.

Since there was only one study evaluating the effect of BTX-A injection in the trigone in terms of the antireflux mechanism, we felt that this study could contribute for a better understanding of this issue. Moreover, in the present study we evaluated a different patient population, with refractory DO secondary to overt neurological diseases. Besides, we used a different injection protocol in comparison to the previous studies. Our primary goal was to evaluate the effect of BTX-A injections in the trigone on the antireflux mechanism as well as the upper tract. Therefore, we obtained a cystogram and an upper urinary tract ultrasound prior to as well as 8 weeks after BTX-A injection. There were no cases of de novo VUR and one patient with unilateral grade II VUR was cured after injection. Ultrasound evaluation of the upper urinary tract showed that the kidneys were also not affected by the procedure. As a matter of fact, the degree of hydronephrosis decreased with treatment in four of the five patients with baseline hydronephosis. It is possible that the injection of a higher dose of BTX-A might have a different effect in the antireflux mechanism. However, Karsenty et al.'s results with the injection of 200 units indicate that our findings were not significantly affected by the injected dose, since the suggested BTX-A dose for patients with refractory neurogenic DO is between 200 and 300 units, which are injected throughout the bladder walls.

We observed a significant improvement in the continence status of the patients after 8 weeks of BTX-A injection, with 9 (42.8%) becoming completely dry and 11 (52.4%) with significant improvement. Of these, 38.1% became totally continent after reintroduction of antimuscarinic treatment, with a final rate of total continence of 80.1%. Likewise, a significant improvement was observed in most evaluated urodynamic parameters, including a 44% improvement of the MCC, a 34% increase of the reflex detrusor volume, and a 42% reduction of the MDP.

Both the radiological and urodynamic results reflect a direct effect of BTX-A in the bladder, since the patients had discontinued antimuscarinic drugs for more than 1 month at the time of postoperative evaluation. As mentioned before, 11 (52.4%) patients needed reintroduction of antimuscarinic drugs to obtain maximal clinical improvement in terms of continence. However, most patients required a lower dose to be significantly improved. We chose to start with 5 mg of immediate-release oxybutynin twice a day and increase if needed.

In our series, the only adverse event that can be directly related to the BTX-A injection procedure was a case of hematuria with blood clots, at the fifth postoperative day, requiring evacuation with a large urethral catheter and bladder irrigation for 2 hr.

Injection of BTX-A into the detrusor has recently become part of the armamentarium of DO treatment and controversy still exists concerning the dose, number, and location of the injections. The risk of VUR due to trigonal injections has not been confirmed in this study. Further studies will be necessary to evaluate the effect of higher doses of BTX-A on the anti-reflux mechanism and, specially, the benefits of injecting BTX-A in the trigone in patients with different causes of voiding dysfunction.

CONCLUSIONS

Our study demonstrates that the injection of 50 units of BTX-A into the trigone does not induce VUR or upper urinary tract changes in patients with refractory neurogenic DO. Whether the injection of BTX-A in the trigone is beneficial for this population or for patients with other causes of voiding dysfunction remains unanswered and will need further studies.

REFERENCES

1. Weld KJ, Graney MJ, Dmochowski RR. Clinical significance of detrusor sphincter dyssynergia type in patients with post-traumatic spinal cord injury. Urology 2000;56:565.
2. Weld KJ, Graney MJ, Dmochowski RR. Differences in bladder compliance with time and associations of bladder management with compliance in spinal cord injured patients. J Urol 2000;163:1228.
3. Schurch B, Stohrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: A new alternative to anticholinergic drugs? Preliminary results. J Urol 2000;164:692.
4. Bagi P, Biering-Sorensen F. Botulinum toxin A for treatment of neurogenic detrusor overactivity and incontinence in patients with spinal cord lesions. Scand J Urol Nephrol 2004;38:495.
5. Smith CP, Chancellor MB. Simplified bladder botulinum-toxin delivery technique using flexible cystoscope and 10 sites of injection. J Endourol 2005;19:880.
6. Schurch B, Schmid DM, Stohrer M. Treatment of neurogenic incontinence with botulinum toxin A. N Engl J Med 2000;342:665.
7. Schurch B, de Seze M, Denys P, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: Results of a single treatment, randomized, placebo controlled 6-month study. J Urol 2005; 174:196.
8. Roppolo JR, Tai C, Booth AM, et al. Bladder Adelta afferent nerve activity in normal cats and cats with feline interstitial cystitis. J Urol 2005;173:1011.
9. Yokoyama O, Yusup A, Miwa Y, et al. Effects of tolterodine on an overactive bladder depend on suppression of C-fiber bladder afferent activity in rats. J Urol 2005;174:2032.
10. Yokoyama T, Nozaki K, Fujita O, et al. Role of C afferent fibers and monitoring of intravesical resiniferatoxin therapy for patients with idiopathic detrusor overactivity. J Urol 2004;172:596.
11. Abrams P, Cardozo L, Fall M, et al. The standardisation of terminology of lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21:167.
12. MacKenzie I, Burnstock G, Dolly JO. The effects of purified botulinum neurotoxin type A on cholinergic, adrenergic and non-adrenergic, atropine-resistant autonomic neuromuscular transmission. Neuroscience 1982;7:997.
13. Chuang YC, Huang CC, Kang HY, et al. Novel action of botulinum toxin on the stromal and epithelial components of the prostate gland. J Urol 2006;175: 1158.
14. Elbadawi A, Schenk EA. A new theory of the innervation of bladder musculature. 2. The innervation apparatus of the ureterovesical junction. J Urol 1971;105:368.
15. bol-Enein H, Ghoneim MA. Functional results of orthotopic ileal neobladder with serous-lined extramural ureteral reimplantation: Experience with 450 patients. J Urol 2001;165:1427.
16. Lapointe SP, Barrieras D, Leblanc B, et al. Modified Lich-Gregoir ureteral reimplantation: Experience of a Canadian center. J Urol 1998;159:1662.
17. Lucioni A, Rapp DE, Gong EM, et al. Intravesical botulinum type A toxin injection in patients with overactive bladder: Trigone versus trigone-sparing injection. Can J Urol 2006;13:3291.
18. Karsenty G, Elzayat E, Delapparent T, et al. Botulinum toxin type a injections into the trigone to treat idiopathic overactive bladder do not induce vesicoureteral reflux. J Urol 2007;177:1011.