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Intravesical botulinum type A toxin injection in patients with overactive bladder: trigone versus trigone-sparing injection

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LUCIONI A, RAPP DE, GONG EM, FEDUNOK P, BALES GT. Intravesical botulinum type A toxin injection in patients with overactive bladder: trigone versus trigone-sparing injection. The Canadian Journal of Urology. 2006;13(5):3291-3295.

Objective: *Botulinum toxin type A (BTX-A) has been successfully used in the treatment of patients with overactive bladder (OAB) symptoms refractory to anticholinergic therapy, with most studies performing trigone-sparing detrusor injections. Increasing evidence suggest that sensory nerve dysfunction contributes to the pathophysiology of OAB and, for this reason, targeting the afferent innervation of the bladder trigone during injection may provide clinical benefit.*

Materials and methods: *We conducted a pilot study to assess the benefit of trigonal-inclusion during BTX-A injection. A total of 40 patients with OAB refractory to anticholinergic treatment received trigone or trigone-sparing injection of BTX-A. Patients were evaluated using UDI-6 and IIQ-7 questionnaires prior to the BTX-A applications, at 3 weeks and 6 months after treatment.*

Results: *At 3-week follow-up, 15/24 (63%) and 10/16 (63%) patients showed improvement of symptoms in the trigone versus trigone-sparing groups, respectively. Combined 3-week UDI-6 and IIQ-7 scores improved from 37.3 prior to treatment to 27.4 ($p < 0.05$) and 35.5 to 27.2 ($p < 0.05$) in the trigone and trigone-sparing groups, respectively. Six-month follow-up demonstrated continued but diminished levels of symptom improvement when compared to pre-treatment and 3-week symptom scores. Improvement in symptom scores between the trigone and trigone-sparing groups was not significant.*

Conclusion: *No significant difference in symptom score or treatment response was noted between the trigone and trigone-sparing groups. Further study using pre- and post-operative urodynamic study is needed to evaluate possible benefit to trigonal injection in a select sensory urgency cohort, and to assess for urodynamic improvement following trigonal injection.*

Key Words: botulinum toxin, incontinence, sensory urgency

Introduction

Intravesical injection of botulinum toxin type A (BTX-A) has emerged as a promising treatment of overactive bladder (OAB). Recent study has demonstrated the efficacy of intra-detrusor injection of BTX-A in both reducing the negative symptomotology and improving the urodynamic parameters associated with neurogenic and idiopathic detrusor overactivity (IDO).[1-3] Even more promising is the fact that this benefit has been demonstrated in patients refractory to oral anticholinergic therapy.[2,3] However, despite this initial success, further improvement is necessary as a substantial number of patients treated with BTX-A fail to demonstrate significant improvement.

An important obstacle to the more successful widespread utilization of BTX-A in this patient cohort is the lack of a standardized technique for BTX administration. A variety of BTX doses, injection volumes, and injection sites have been used in these initial investigations, making definitive conclusions difficult. It is clear that before BTX-A may be offered as a more widespread therapy, standardized

Accepted for publication June 2006

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recommendations need to be made with respect to the administration protocol.

Specific to injection site, it is unclear whether the bladder trigone should be included in the injection distribution. Early investigation into the use of BTX-A utilized trigone-sparing injections. This protocol was adopted based mainly on concerns that injection of the trigone, which contains a complex efferent, afferent, and autonomic neuronal innervation, would complicate the analysis of treatment outcomes.[4] Subsequently, a significant amount of basic and clinical research has emerged to suggest that sensory neuron dysfunction may underlie the presentation in a significant number of patients with symptoms of overactivity (sensory urgency).[5-7] In addition, even in patients with urodynamic-proven detrusor overactivity, a significant component of sensory overactivity is often present.[8] Concurrently, several studies have recently demonstrated the inhibitory effect of BTX-A on the afferent neuron innervation to the bladder.[9] Combined, these data would suggest a potential benefit to targeting the dense sensory neuron supply of the trigone. For these reasons, we sought to conduct a focused pilot study to determine whether trigonal inclusion would result in superior symptom improvement when compared with trigone-sparing injection of BTX-A.

Material and methods

Patients with symptoms of frequency, urgency, and or/ urge incontinence that were refractory to a standard course of anti-cholinergic treatment were offered transurethral injection of BTX-A (Allergan Inc., Irvine, CA). Patients were determined to be refractory to anti-cholinergic treatment following a minimum of 4 weeks of anti-cholinergic therapy without improvement of symptoms. All patients were evaluated by complete history, physical examination, and urinalysis. Urine culture was performed as necessary based on symptoms consistent with infection and abnormalities on urinalysis. The investigational nature of these injections, including the implications of injecting the bladder trigone, was discussed with all patients and informed consent was obtained. Institutional review board approval was obtained for this study.

Patients with a history of urinary retention, surgical bladder reconstruction, or a history of bladder or urethral cancer were excluded from the study. Patients presenting with as history of treatment for, or symptoms suggestive of, interstitial cystitis (IC) were also excluded. Further, on subsequent cystoscopy, no patients were found to have findings suggestive of IC, such as glomerulations or Hunner's ulcers. A complete neurologic history and exam was performed during the initial assessment of each patient. However, a history of neurologic disease was not used as an exclusion criterion. Specific attention was placed on the evaluation of male patients to exclude those patients with symptoms of bladder overactivity resulting from bladder outlet obstruction. This evaluation included history, International Prostate Symptom Scores (I-PSS), post-void residual, and in some cases, urodynamic evaluation.

Pre-operative urinary symptoms were evaluated using a comprehensive urologic questionnaire. This questionnaire consisted of, in part, the validated Urogentital Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7).[10] Further questions were included to quantify daily pad use, frequency, nocturia, and to define prior treatment regimens. No minimum score on these questionnaires was required for entry into the study. Patients who were currently taking anti-cholinergic medication were required to stop medications at least 14 days prior to BTX-A injection.

BTX-A was injected under cystoscopic guidance as previously described.[3] Briefly, BTX-A injection was performed as an outpatient procedure under intravenous sedation. BTX-A was injected via collagen injection needle using a standard rigid 21F cystoscope. One hundred units of BTX-A toxin were diluted using 1 ml of preservative-free saline, yielding 10 units per 0.1 ml for injection at each site. A total of 300 units of toxin divided among thirty 0.1 ml intramural injections were used. The trigone-sparing technique comprised 30 evenly distributed injections of 10 IU each, placed throughout the posterior and lateral bladder walls. A 2-cm peri-trigonal margin was spared from injection. Patients undergoing trigonal injection also received 30 evenly distributed injections, with two injections being placed in the trigonal region. In all patients, care was taken to avoid injection in proximity to the ureteral orifices.

Patients were evaluated in the clinic at 3 weeks and 6 months post-operatively and underwent complete history, physical examination, urinalysis, and completion of the comprehensive urologic questionnaire. In addition to the previously described questions, the questionnaire also contained components to define how many days following BTX-A injection they first noted improvement in urinary symptoms, how many days following the procedure they experienced maximum improvement and to rate their degree of improvement (complete, slight or none). Further, post-operative complications, such as hematuria or dysuria, were assessed. Statistical analysis was performed using the student t test.

TABLE 1. **Changes in IIQ and UDI scores following trigone versus trigone-sparing injection of BTX-A (pre-treatment versus 3-week post-treatment)**

	Pre-treatment	3 weeks	p value
Trigone-sparing			
IIQ	18.2	13.9	0.02
UDI	17.3	13.3	0.005
Trigone			
IIQ	19.8	14.4	0.01
UDI	17.4	13.1	0.002

Results

Forty patients with symptoms of OAB were treated with BTX-A injection. The first 16 patients received trigone-sparing injections, while the following 24 patients received trigone injections. The average age for the trigone group and trigone-sparing group was 66 (range 48-85) and 67 (range 45-93), respectively. In the trigone group 18 (75%) of the patients were female and 6 (25%) were male. The no trigone group had a similar distribution with 12 (75%) of the patients being female and 4 (25%) being male. Four, two, and one patient had a history of multiple sclerosis, transient ischemic attack, and cerebral vascular accident, respectively.

Statistical analysis was performed to identify differences in treatment outcomes at post-injection week three. A significant improvement was seen in the mean individual IIQ-7 and UDI-6 questionnaire scores, as well as in the combined scores, at 3 weeks following treatment in both the trigone and trigone-sparing groups, Table 1. However, the difference in both individual and combined questionnaire scores before treatment and 3 weeks after treatment was not significant between the trigone and trigone-sparing groups. Overall, complete or partial resolution of symptoms was seen in 15/24 (63%) patients (10 complete, 5 partial) versus 10/16 (63%) patients (5 complete, 5 partial) in the trigone versus trigone-sparing groups, respectively. Time to first improvement in symptoms was 5.7 days (range 1-14) and 6.9 days (range 1-21) and time to maximum improvement of symptoms was 10.3 days (range 1-14) and 8.4 days (range 4-21) in the trigone and trigone-sparing groups, respectively (difference not statistically significant). Attention was then placed on analysis of treatment outcomes at 6 months. In a similar fashion, a mean improvement in both individual and combined symptom scores continues at 6 months post-operatively, Table 2. However, when compared with 3-week symptom scores, a decreased improvement was noted. Individually, both the trigone and trigone-sparing groups showed continued symptom improvement at 6 months. However, when these groups were compared, no statistically significant difference was seen.

No major side effects were noted following BTX-A. Mild hematuria not requiring catheterization, pelvic pain and dysuria were reported by 15 patients, seven in the trigone and eight in the no trigone group. No patient required hospitalization and all symptoms resolved within 4 days of the procedure. In addition, no patients experienced symptoms suggestive of vesicoureteral reflux such as flank pain or pyelonephritis.

Discussion

Although promising results have been reported following the administration of BTX-A for the treatment of OAB, significant obstacles to its widespread use in this patient population remain. Foremost, the optimal protocol for the intravesical administration of BTX-A has not been defined. Published studies to date have utilized varying doses, injection volumes, and injection site/numbers. This variation makes systematic assessment of the efficacy of intravesical BTX-A difficult. It is clear that before intravesical BTX-A may become a widespread treatment modality for OAB, a defined protocol for the optimal administration of BTX-A is needed.

Central to the issue of optimal injection site is the question of whether the trigone should be included in the injection distribution site. In one of the early experiences investigating the use of BTX-A in neurogenic

TABLE 2. **Changes in total IIQ and UDI score following trigone versus trigone-sparing injection of BTX-A (6-month follow-up)**

	Pre-treatment	3 weeks	p*	6 months	p*
No trigone	35.5	27.2	0.008	29.1	0.02
Trigone	37.3	27.4	0.002	31.2	0.04

*p-values are comparing 3 weeks and 6 months versus pre-treatment total scores

detrusor hyperreflexia, Schurch et al report a trigone-sparing injection distribution.[4] These investigators reported that the decision to avoid the trigone was multifactorial, including a desire to avoid inducing reflux to the upper tracts. Further, it was felt that injection of the trigone, containing dense innervation from both adrendergic, cholinergic and non-cholinergic excitatory pathways, might complicate the efficacy analysis of a cholinergic blockade. Finally, these authors felt that trigonal injection might include the suburothelial sensory plexus, resulting in possible impairment of the sensory nerve endings. Subsequent investigations have predominantly utilized trigone-sparing injections.[2,11] Whether these protocols were adapted based on similar concerns, simply a lack of other protocols to define trigonal inclusion, or for other reasons is unclear.

Given the concerns raised by Schurch et al, it was indeed reasonable for early investigators to spare the trigone in the absence of persuasive evidence to support trigonal inclusion. However, a significant amount of basic science research subsequent to this work has suggested a large role of sensory neurons in OAB.[5,9,12] From a clinical standpoint, it is commonly thought that the subset of patients diagnosed with sensory urgency is likely to have underlying sensory neuron dysfunction. This subset represents a large patient population, and is supported by the large number of OAB patients found to have no evidence of destrusor overactivity on urodynamic evaluation.[6,7] However, recent research has suggested that sensory neuron dysfunction may also underlie some of the functional lower urinary tract changes in spinal cord patients classically thought to originate from efferent neuron dysfunction.[13] Finally, it is possible that a significant number of patients even with demonstrable detrusor overactivity may have concurrent sensory neuron dysfunction contributing to symptomotology, but that is ill-defined on urodynamic evaluation.

Concurrently, recent investigation has demonstrated an inhibitory effect of BTX-A on bladder sensory neurons, as well as on the release of sensory neurotransmitter from non-neuronal bladder tissue.[9,13] Based on this investigation, and the emerging research to suggest a wider role of sensory neuron pathology in OAB patients, we sought to evaluate the clinical benefit of trigonal inclusion during BTX-A injection. We hypothesized that trigonal BTX-A injection might have therapeutic benefit in a generalized population of OAB patients, including not only patients with sensory urgency, but those with idiopathic and neurogenic overactivity as well.

Our investigation found no statistically significant difference in symptom improvement between the two study populations. Overall, 60% of the patients showed at least some degree of improvement of their urinary symptoms. The improvement in symptoms was found to be significant at both 3 weeks and 6 months after the BTX-A injection for both groups. Some deterioration of symptom scores was seen at 6 months as compared to 3 weeks post-injection, however, the improvement in symptom scores remained significant at all time points. These results are consistent with previously published findings.[3,11]

Additionally, we found no difference in the number of post-operative complications seen in the two study groups. Of note, a similar number of patients experienced mild post-operative hematuria in both groups. We felt that, due to the increased perfusion present in the region of the bladder neck, that it was possible that trigonal injection might be associated with a higher incidence of post-operative bleeding.[14] Further, although voiding cystourethrogram was not routinely performed post-operatively to rule out VUR, no patient presented with urinary tract infection based on urinalysis and symptom presentation.

Several limitations to this study should be addressed. Foremost, patients did not undergo routine urodynamic evaluation before and after receiving BTX-A injection, which may have several implications. First, it is likely that patients suffering from both sensory urgency and detrusor overactivity were included in our cohort. It is possible that urodynamic-based selection of only those patients with sensory urgency may improve the efficacy seen with trigonal injection of BTX-A. This possibility is suggested by recent investigation demonstrating a positive effect of BTX-A (administered in a trigonal inclusion pattern) on symptom improvement in patients with OAB without destrusor instability on urodynamic evaluation.[6] Second, the lack of post-operative urodynamic evaluation may have prevented our analysis from demonstrating therapeutic benefit of trigonal inclusion with respect to other endpoints. For example, it is possible that the effect of injecting the trigone may be so subtle that symptom questionnaires may not show significant difference, whereas post-operative urodynamic evaluation may have demonstrated differences in bladder capacity, compliance, or detrusor overactivity.

In addressing these limitations, it is important to note that our intent was to conduct a focused pilot study to determine whether symptomatic benefit could be augmented via trigonal inclusion. Given the number of questions that exist with respect to protocol administration, we felt that such a study was warranted prior to initiating a larger scale investigation for several reasons. First, while study demonstrating the effect of

BTX-A on urodynamic parameters is extremely important, we also believe that investigation focused on subjective patient outcomes is equally valuable. Foremost, such data is of direct clinical application in counseling the varied group of refractory OAB patients that present for treatment. Second, although the decision to include patients who likely had a variety of underlying pathologies may limit the outcomes seen in our study, we feel that investigating the role of injection in a broad group of patients provides important clinical data. This is supported by previously described research to suggest the potential involvement of sensory neuron pathology in patients with OAB of varied underlying etiologies.

Most importantly, we felt that a pilot study was warranted because the optimal protocol for overall dose, as well as the dose and number of injections applied to the trigone is unknown. We sought to determine if a positive effect could be demonstrated using our protocol before initiating the cost and effort of a large scale patient trial. With respect to overall dose, injection of 300 IU was based on previous investigation demonstrating efficacy with this dose.[3,6,15] Study to date has utilized 100 IU to 300 IU. Although the optimal dose for bladder neuronal inhibition is not defined, based on the success of other investigators within this dose range, we feel that further dose elevation is not likely to improve outcomes of trigonal injection. As well, it is likely that the risk of post-operative urinary retention would become greater with higher dosing. However, it is possible that a greater number of injections, or a higher dose, applied to the trigonal region would have improved patient outcome. Finally, it is unclear if the 2-cm margin used in the trigone-sparing group was sufficient to avoid BTX-A action on the trigonal innervation. Although the diffusion potential of BTX-A is generally limited due to its high molecular weight, it is possible that diffusion of BTX-A from other bladder regions to the trigone occurred in both groups, minimizing the distinction between the treatment arms. Based on these reasons, we feel that it is possible that altering the trigonal dose and/or number of injections, as well as the peri-trigonal margin, may help to increase symptom response and are the focus of continued investigation.

To conclude, in our pilot study we found no significant difference in symptom outcome between trigone and trigone-sparing injection of BTX-A toxin in the treatment of refractory OAB. Investigation is ongoing to optimize protocol administration with respect to trigonal injection dose and number. Further study is needed to determine if trigonal injection is associated with improved urodynamic outcomes. In addition, investigation is warranted to compare the efficacy of trigone versus trigone-sparing injection of BTX-A in select patients with sensory urgency. □

References

1. Smith CP, Chancellor MB. Emerging role of botulinum toxin in the management of voiding dysfunction. *J Urol* 2004;171:2128-2137.
2. Kuo HC. Urodynamic Evidence of effectiveness of Botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. *Urology* 2004;63:868-872.
3. Rapp DE, Lucioni A, Katz, EE, O'Connor CO, Gerber GS, Bales GT. The use of Botulinum-A toxin for the treatment of refractory overactive bladder symptoms: an initial experience. *Urology* 2004;63:1071-1075.
4. Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. *J Urol* 2000;164:692-697.
5. Ray FR, Moore KH, Hansen MA, Barden JA. Loss or purinergic P2X receptor innervation in human detrusor and subepithelium from adults with sensory urgency. *Cell Tissue Res* 2003;314:351-359.
6. Schulte-Baukloh, Weiss C, Stolze T, Sturzebecher B, Knispel HH. Botulinum-A toxin for treatment of overactive bladder without detrusor overactivity: urodynamic outcome and patient satisfaction. *Urology* 2005;66:82-87.
7. Apostolidis A, Popat R, Yiangou Y, Dasgupta P, Anand P, Fowler CJ. A possible explanation for the exceptional efficacy of botulinum toxin treatment for detrusor overactivity. *Neurourol Urodyn* 2004;23:608-609.
8. Clark B. The role of urodynamic assessment in the diagnosis of lower urinary tract disorders. *Int Urogynecol J Pelvic Floor Dysfunct* 1997;8:196-199.
9. Chuang Y, Yoshimura N, Huang C, Chiang PH, Chancellor MB. Intravesical botulinum toxin administration produces analgesia against acetic acid induced bladder pain responses in rats. *J Urol* 2004;172:1529-1532.
10. Uebersax JS, Wynman JF, Schumaker SA, McClish DK, Fantl JA. Short forms to assess quality of life and symptom distress for urinary incontinence in women: the incontinence impact questionnaire and urogenital distress inventory. *Neurourol Urodyn* 1995;14:131-139.
11. Werner M, Max Schmid DM, Schussler B. Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: a prospective nonrandomized study. *Am J Obs Gyn* 2005;192:1735-1740.
12. Chuang YC, Fraser MO, Yu Y, Chancellor MB, de Groat WC, Yoshimura N. The role of bladder afferent pathways in bladder hyperactivity induced by the intravesical administration of nerve growth factor. *J Urol* 2001;165:975-979.
13. Khera M, Somogyi GT, Kiss S, Boone TB, Smith CP. Botulinum toxin A inhibits ATP release from bladder urothelium after chronic spinal cord injury. *Neurochem Int* 2004;45:987-993.
14. Azadzoi KM, Pontari M, Vlachiotis J, Siroky MB. Canine bladder blood flow and oxygenation: changes induced by filling, contraction and outlet obstruction. *J Urol* 1996;155:1459-1465.
15. Frenkl TL, Rackley RR. Injectable neuromodulatory agents: botulinum toxin therapy. *Urol Clin N Am* 2005;32:82-99.