Botulinum A Toxin Treatment for Idiopathic Detrusor Overactivity

Satoshi Seki, M.D., Ph.D.

Department of Clinical Urologic & Pharmacological Research and School of Medicine, Shinshu University, Japan

INTRODUCTION

Antimuscarinic agents are used in the first line treatment of idiopathic detrusor overactivity. However, these medications have unfavorable side effects and often are not effective enough to improve incontinence. Botulinum A toxin (BoNT-A) treatment of neurogenic detrusor overactivity (NDO) has been reported to provide satisfactory results [1-6]. In recent years, BoNT-A has gained popularity as an off-label treatment of refractory overactive bladder, including idiopathic detrusor overactivity (IDO). In this report, recently presented data related to the therapeutic application of BoNT-A for IDO as well as adverse effects of the toxin injection will be discussed.

BONT-A TREATMENT FOR IDIOPATHIC DETRUSOR OVERACTIVITY

The first clinical study was reported by Radziszewski et al [7] who injected 300 U of Dysport® into 10-15 sites in the detrusor of 7 patients with IDO. One month after injection, no patient demonstrated DO during urodynamic study and all patients became continent. Radziszewski et al presented an abstract in 2002 [8] in which 12 patients with IDO underwent injection of 300 U of Dysport®. The maximal bladder capacity increased significantly and all patients gained continence. No side effects, such as acute retention, were reported.

In 2005, three papers that employed BoNT-A for treatment of IDO patients were published. Werner Schmid et al [9] performed a prospective, open-label, non-randomized study which targeted IDO with urge incontinence. In this study 100 units of Botox® were injected into the detrusor at 30 sites. Twenty-six women with urodynamically demonstrated detrusor overactivity were recruited. A majority of the patients had increased maximal cystometric bladder capacity. No detrusor contractions associated with urinary leakage were demonstrated in 14 of 26 patients after 4 weeks, in 13 of 20 after 12 weeks, and in 3 of 5 patients after 36 weeks. Fourteen of the 26 women were dry after 4 weeks, 13 of 20 after 12 weeks, and 3 of 5 after 36 weeks. No patient showed acute urinary retention after injection, but 2 patients developed a postvoid residual volume (PVR) after 4 weeks and temporarily required self clean intermittent catheterization (CIC) for 1 week. The authors concluded that BoNT-A treatment seems to be a safe and effective new treatment option for patients with IDO incontinence.

Rajkumar et al injected 300 U of BoNT-A into the detrusor at 30 sites of 15 women with IDO. Urodynamic studies performed 6 weeks after injection demonstrated that 6 patients had no evidence of detrusor overactivity and 6 showed an increase in the volume at first overactive contraction. Subjectively 14 patients noted an improvement in urgency and frequency immediately after treatment. Although no urodymanic evaluation was done after 6 weeks, the effects of treatment lasted at least 20-24 weeks. No major side effects, such as acute urinary retention, were reported in this study [10].

Kuo [11] used 200 units of Botox® (Allergan, Inc., Irvine, USA) in 20 patients to investigate its clinical and urodynamic effects in IDO. This unique study employed suburothelial injection of BoNT-A at 40 sites and demonstrated that 45% of patients regained continence, 40% had improvement, and 15% had no benefit at 3 months. Bladder capacity and the volume at the first sensation of bladder filling increased about two times from the baseline value. However, hesitancy in initiation and difficult urination were also noted in 75% of patients and the PVR was increased by seven times the baseline value at 2 weeks. In addition, 30% of patients required CIC transiently. Compared with the results of a study from the same institution in which Botox® was injected into the detrusor [12], the author concluded that the effect of suburothelial BoNT-A injection on detrusor contractility was greater than that of detrusor injection, and suggested that blockage of detrusor contractility through suburothelial sensory fibers was more pronounced than that at neuromuscular junctions. The author assumed that this phenomenon might have resulted from inhibition of sensory input which led to a reduction in detrusor contractility. Recently, Apostolidis et al [13] demonstrated that detrusor injection of BoNT-A directly acts on the afferent innervation of the bladder as evidenced by decreases in TRPV1 and/or $P2X_3$ immunoreactive (IR) suburothelial fibers after injection. In this study, decreases in $P2X_3$ IR fibers were significantly correlated with a reduction in urgency episodes, suggesting that decreased levels of sensory receptors may contribute to the clinical effect of BoNT-A injection for detrusor overactivity.

BONT-A TREATMENT FOR IDO VS NDO

Several lines of evidences have suggested that BoNT-A injection is a safe and effective therapeutic option for refractory IDO as well as NDO. However, fewer reports have demonstrated direct comparison of the response of patients with IDO to that of those with NDO.

Chancellor et al presented their experience with 10 patients who had refractory IDO and 11 patients with NDO to the American Urological Association in 2003 [14]. Initial urodynamic studies revealed involuntary detrusor contractions in all patients. The authors injected 100-300 U of BoNT-A cystoscopically into the bladder base and the trigone. Followup validation was done with bladder diaries only. None of the patients developed urinary retention, and 80% of patients in the IDO group and 73% in the NDO group indicated decreases in voiding frequency and incontinence episodes. The effects lasted about 6 months. Although statistical analysis was not done, the efficacy of BoNT-A seemed to be similar between the two groups.

Received: January 1, 2007 Accepted: February 14, 2007
Address correspondence to: Dr. Satoshi Seki, Department of Clinical Urologic & Pharmacological Research and School of Medicine, Shinshu University, 3-1-1, Asahi Matsumoto-city Nagano, 390-8621, Japan
E-mail: satoseki@hsp.md.shinshu-u.uc.jp

Kuo investigated the urodynamic changes after intra detrusor injection of Botox® in patients with detrusor overactivity [12]. Thirty patients (12 with NDO, 8 with IDO and 10 with detrusor overactivity related to bladder outlet obs-truction) were recruited in this study. Overall, 73.3% of patients became continent or showed decreased incontinence episodes. In the NDO and IDO groups, the success rates were 66.6% and 75% respectively. Although the author did not analyze statistical differences between the 2 groups, the therapeutic effects appeared to be comparable.

Two prospective, open-label studies, investigated the response of patients with NDO and IDO to BoNT-A treatment. Popat et al [15] assessed bladder BoNT-A injection in 31 patients with IDO and 44 with NDO. In this study patients with urgency and/or urgency incontinence due to detrusor overactivity received injections of 300 units (NDO) or 200 units (IDO) of Botox® into the bladder. At 16 weeks the maximum cystometric capacity increased from 229.1 ± 24.8 to 427.0 ± 26.9 mL in the NDO group and from 193.6 ± 24.0 to 327.1 ± 36.1 mL in the IDO group. Leak episodes decreased in a similar ratio in both groups. The 2 groups were comparable for baseline data but percent improvement in urgency was greater in the NDO group at 4 and 16 weeks. Sixty-nine percent of the patients in the NDO group required self-catheterization after treatment compared with 19.3% of the IDO group. This was not a randomized study and the 2 populations received different amounts of Botox®. However, these findings indicate that patients with IDO respond to BoNT-A with significant improvement equal to those with NDO. Kessler et al performed a prospective, open-label trial to assess and compare the effect of BoNT-A injections for IDO and NDO resistant to anticholinergic treatment [16]. In this study, 11 patients with IDO and 11 with NDO were injected with 300 U of Botox® into the detrusor. Median daytime frequency episodes decreased significantly from 11 to 4 and 12 to 5 in IDO and NDO patients respectively. Median nocturia episodes decreased from 3 to 1, and the median number of pads used from 5 to 0 in both groups. There was a significant increase in median maximum cystometric capacity, median bladder compliance and median PVR in both groups. The effect of BoNT-A injections lasted for a median time of 5 months in both groups. There was no significant difference between groups in clinical and urodynamic parameters assessed before and after BoNT-A injections.

BONT-A TREATMENT FOR CHILDREN

Verleyen et al reported BoNT-A treatment for children with detrusor overactivity in abstract form [17]. Five girls and six boys (mean age 10 years) were included in this study. All patients had therapy resistant daytime incontinence, detrusor overactivity and normal emptying. BoNT-A was injected cystoscopically under general anaesthesia; two patients received 125 units and nine received 250 units. The results were evaluated using frequency-volume charts and urodynamics. No patient had any general side effects. There was an increase in functional bladder capacity, and a decrease in overactive bladder (OAB) contractions and urgency symptoms. Residual urine was <25 mL in eight patients and <50 mL in two patients. The maximum urinary flow rate decreased in most patients and 1 girl needed to use intermittent catheterization for 2 weeks.

In a small study, Rao et al demonstrated that BoNT-A injection has positive effects in treating non-neurogenic bladder overactivity [18]. Six children with overactive bladder symptoms refractory to anticholinergics, bladder training and neuromodulation were investigated. Urodynamic studies confirmed idiopathic detrusor overactivity. A total of 300 U BoNT-A was injected into the dome of the bladder at 30 sites. For follow up a bladder diary and validated urgency and incontinence charts were assessed at 1, 3, and 6 months. Bladder diaries indicated reductions in daytime frequency and nocturia and decreases in pad use. Maximal voiding volume increased significantly. All 6 patients were dry after 6 months. No side effects such as urinary tract infections or retention occurred.

A few reports exist on the use of BoNT-A for children with idiopathic detrusor overactivity. Further investigation is needed to determine the optimum dose, sites and the long-term effects of BoNT-A treatment for children with IDO.

SIDE EFFECT - URINARY RETENTION

Voiding efficiency is frequently affected by BoNT-A injection into the bladder especially soon after treatment. Some patients require intermittent catheterization for a limited period. Sahai mentioned that paralyzing as much of the detrusor as possible in an attempt to "disable" any DO is often a desired outcome in patients with NDO who already use self-catheterization. However, the situation is more complex in those with IDO. Since the voiding function should not be affected by the treatment in this group, the right balance must be obtained in providing symptom relief without compromising bladder emptying [19].

CONCLUSIONS

The results of several studies have demonstrated that injection of botulinum A toxin is effective in the treatment of idiopathic detrusor overactivity refractory to anticholinergics. However, patients with detrusor overactivity and inadequate contractility should be carefully selected because increased postvoid residual urine volume may occur after treatment. Botulinum A toxin is a promising treatment for intractable urinary incontinence due to idiopathic detrusor overactivity.

REFERENCES

1. Reitz A, Stohrer M, Kramer G, et al: European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004; **45**:510-515.
2. 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**:196-200.
3. 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.
4. Schulte-Baukloh H, Schobert J, Stolze T, Sturzebecher B, Weiss C, Knispel HH: Efficacy of botulinum-A toxin bladder injections for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients: An objective and subjective analysis. Neurourol Urodyn 2006; **25**:110-115.
5. Smith CP, Chancellor MB: Emerging role of botulinum toxin in the management of voiding dysfunction. J Urol 2004; **171**: 2128-2137.

6. Ho MH, Lin LL, Haessler AL, Bhatia NN: Intravesical injection of botulinum toxin for the treatment of overactive bladder. Curr Opin Obstet Gynecol 2005; **17**:512-518.
7. Radziszewski P, Dobronski P, Borkowski A, et al: Treatment of the non-neurogenic storage and voiding disorders with the chemical denervation caused by botulinum toxin typeA - A pilot study. Neurourol Urodyn 2001; **20**:410.
8. Radziszewski P, Borkowski A: Botulinum toxin type A intravesical injections for intractable bladder overactivity. Eur Urol Suppl 2002; **1**:134.
9. Werner M, Schmid DM, Schussler B: Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: A prospective nonrandomized study. Am J Obstet Gynecol 2005; **192**:1735-1740.
10. Rajkumar GN, Small DR, Mustafa AW, Conn G: A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int 2005; **96**:848-852.
11. Kuo HC: Clinical effects of suburothelial injection of botulinum A toxin on patients with nonneurogenic detrusor overactivity refractory to anticholinergics. Urology 2005; **66**: 94-98.
12. 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.
13. Apostolidis A, Popat R, Yiangou Y, et al: Decreased sensory receptors P2X3 and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. J Urol 2005; **174**:977-983.
14. Chancellor MB, O'Leary M, Erickson J, et al: Successful use of bladder botulinum toxin injection to treat refractory overactive bladder. J Urol 2003; **169(Suppl 4)**:351.
15. Popat R, Apostolidis A, Kalsi V, Gonzales G, Fowler CJ, Dasgupta P: A comparison between the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin. J Urol 2005; **174**:984-989.
16. Kessler TM, Danuser H, Schumacher M, Studer UE, Burkhard FC: Botulinum A toxin injections into the detrusor: An effective treatment in idiopathic and neurogenic detrusor overactivity? Neurourol Urodyn 2005; **24**:231-236.
17. Verleyen P, Hoebeke P, Raes A, et al: The use of botulinum toxin A in children with a non-neurogenic overactive bladder: A pilot study. BJU Int 2004; **93(Suppl 2)**:69.
18. Rao R, Baker A: Botulinum toxin for treatment of non-neurogenic bladders in children - a case series. BJU Int 2006; **97(Suppl 1)**:23.
19. Sahai A: A prospective study to evaluate the safety, tolerability, efficacy and durability of response of intravesical injection of botulinum toxin type A into detrusor muscle in patients with refractory idiopathic detrusor overactivity. BJU Int 2006; **97**: 413.