

Botulinum A Toxin Treatment for Voiding Dysfunction

Hann-Chorng Kuo, M.D.

Department of Urology, Buddhist Tzu Chi General Hospital and Tzu Chi University, Hualien, Taiwan

Introduction

Voiding dysfunction may result from various etiologies and cause difficult urination, large postvoid residual urine (PVR) volume and upper urinary tract deterioration. Treatment of voiding dysfunction with medicine, abdominal straining to void, clean intermittent catheterization (CIC) or cystostomy may help in some cases but these techniques are ineffective in many others. Botulinum A toxin (BoNT-A) has been used safely in the treatment of several types of neurogenic spasticity including patients with spinal cord injuries (SCI) and detrusor sphincter dyssynergia (DSD). Schurch et al reported that 21 out of 24 patients with SCI benefited from BoNT-A injection [1,2]. In patients with dysfunctional voiding due to urethral sphincter overactivity, non-bacterial prostatitis and detrusor underactivity, BoNT-A has been shown to have a therapeutic effect in improving voiding efficiency and recovering detrusor contractility in a number of patients, with few reported adverse effects. Phelan et al found that, after BoNT-A injection, 67% of patients were able to void smoothly with PVR decreased by 71% and voiding pressure decreased by 38% [3-5].

Techniques of Urethral Sphincter Injections of BoNT-A

Urethral BoNT-A injection can be performed as day surgery with or without anesthesia [5]. Each vial of 100 U BoNT-A (BOTOX, Allergan, Irvine, California, U.S.A.) is reconstituted to 4 mL with normal saline, making the concentration equivalent to 25 U/mL. In men, a total of 50 U or 100 U of BoNT-A is injected into the urethral sphincter at 3, 6, 9 and 12 o'clock positions in approximately equal aliquots using a cystoscopic injection instrument. Cystoscopy is advised for women and the axis of the urethra is determined for proper injection positions. BoNT-A is injected into the urethral sphincter along the urethral lumen at 3, 6, 9 and 12 o'clock positions at the sides of the urethral meatus using a 23-gauge 1 mL syringe. If 50 U of BoNT-A is injected, 0.5 mL is used for each injection. When 100 U of BoNT-A is injected, 1 mL is used for each injection. After the BoNT-A injections, a 14 F Foley indwelling catheter is inserted in male patients who received general anesthesia but a catheter is unnecessary in women. The effect of BoNT-A usually appears about 2-3 days after the injections and the maximum effects are reached at about 2 weeks. The patients are instructed to void using the Crede maneuver or abdominal straining. When difficult urination persists, clean intermittent self-catheterization (CISC) is advised, instead of an indwelling Foley catheter, until the PVR is less than 25% of the voided volume. Antibiotics may be given for 3 days to prevent urinary tract infection due to urethral instrumentation. Medications for

reduction of urethral resistance may be discontinued after the BoNT-A injections.

Urethral BoNT-A Injection for the Treatment of Lower Urinary Tract Dysfunction

In a large series of patients (n=103) with voiding dysfunction, BoNT-A 50 U (n=48) or 100 U (n=55) were injected; 40 (39%) patients had an excellent result, 47 (46%) had significant improvement and 16 (15%) had treatment failure [6]. Among the patients with an excellent result, patients with detrusor underactivity due to cauda equina lesion (62.5%) or idiopathic cause (61.5%) had the greatest improvement, whereas those with DSD (27.6%) ranked last. The overall success rate was 84.5% (range 75% to 100%). Among the 45 patients with urinary retention, the indwelling catheters were removed or CIC was discontinued in 39 (87%) (Table 1).

Analysis of the patients with excellent or improved results showed voiding pressure decreased significantly, as did maximal urethral closure pressure and PVR, at 2 or 4 weeks after treatment. The subjective maximum effect was achieved within 1 to 2 weeks. The mean voiding pressure decreased by 31.8%, maximum flow rate increased by 49.3%, PVR decreased by 60.8% and maximal urethral closure pressure decreased by 28.1%.

Therapeutic Effect of Urethral BoNT-A Injection for Voiding Dysfunction - a Randomized Study Comparing 50 and 100 Units

Fifty-six patients with voiding dysfunction were randomly treated with urethral injection of 50 U (n=29) or 100 U (n=27) of BoNT-A [7]. The therapeutic results and changes of urodynamic parameters were compared between these two groups of patients. The overall therapeutic results in the 50 U and 100 U injection groups were excellent in 20 (69.0%) and 17 (63.0%) patients, improved in 5 (17.2%) and 9 (33.3%), and failed in 4 (13.8%) and 1 (3.7%), respectively. Significant reduction of voiding pressure, PVR volume and maximal urethral closure pressure, as well as improvement of quality of life (QOL) index and increase of maximum flow rate, were noted after treatment in both groups. No significant difference in the net changes between the groups was noted after treatment. An excellent result was noted in 59.1% of patients with detrusor underactivity and in 70.6% of patients with hyperactive urethral sphincter. This study concluded that urethral injection of 50 U of BoNT-A was as effective as 100 U for the treatment of voiding dysfunction of any etiology.

Effect of BoNT-A in the Treatment of Voiding Dysfunction due to Detrusor Underactivity

Twenty patients with chronic urinary retention (n=13) or severe

Received: January 29, 2007 Accepted: March 8, 2007
Address correspondence to: Dr. Hann-Chorng Kuo, Department of Urology, Buddhist Tzu Chi General Hospital, 707, Section 3, Chung Yang Road, Hualien, Taiwan
E-mail: hck@tzuchi.com.tw

dysuria (n=7) received 50 U of BoNT-A by urethral injection [5]. The clinical effects, obstructive symptom scores, QOL index and urodynamics were compared at baseline and after treatment. Of the 4 males and 15 females (age range 14 to 86 years) with voiding dysfunction, 18 (90%) were treated satisfactorily. Among these patients, the mean QOL score improved significantly from 5.68 ± 0.67 to 1.16 ± 1.61 . The median voiding pressure (56.5 ± 41.2 vs. 39.0 ± 32.1 cm water) and PVR (300 ± 189.1 vs 50 ± 153.6 mL) at 2 weeks after treatment remained stationary for 3 months. The subjective maximal effect was achieved within 1 to 2 weeks. In 7 patients, the indwelling catheters were removed. In 4 patients who performed CISC, the frequency decreased or it was discontinued. The other 7 patients with difficult urination had significant improvement in the obstructive symptom score (18 ± 3.3 vs. 7 ± 4.5 , $p=0.000$). BoNT-A at a dose of 50 U was effective in reducing urethral sphincter resistance among patients with detrusor underactivity and difficult urination.

Effectiveness of Urethral BoNT-A Injection Treatment for Voiding Dysfunction after Radical Hysterectomy

After radical hysterectomy for cervical cancer, patients may have difficult urination due to detrusor underactivity and non-relaxing urethral sphincter. This study evaluated the effectiveness of urethral injection of BoNT-A in treating voiding dysfunction in these patients [8]. Thirty patients with difficult urination after radical hysterectomy due to cervical cancer were enrolled to receive urethral injection of 100 U BoNT-A (n=20) or

medical treatment as controls (n=10). The clinical results and urodynamic parameters at baseline and after treatment were compared in the study group, and QOL index was compared between the study group and control group.

After urethral BoNT-A injection, 8 patients had excellent results (40%) and 8 had improved results (40%) in the study group. Both voiding pressure (115.2 ± 63.7 vs 90.2 ± 49.5 mL, $p=0.025$) and PVR volume (330.9 ± 124.9 vs. 183.9 ± 183.4 mL, $p=0.011$) showed significant improvement after treatment. The obstructive symptom score reduced significantly (17.5 ± 4.7 vs. 5.7 ± 2.3 points, $p=0.000$) and the QOL index also improved (4.5 ± 2.7 vs. 2.3 ± 2.3 points, $p=0.000$) after treatment. The success rate was 80% in the study group. There were no significant changes of obstructive symptom scores or QOL index in the control group. The maximal effect appeared about 1 week after treatment. The duration of therapeutic effect ranged from 3 to 9 months. Mild stress urinary incontinence and nocturnal enuresis were noted in 7 patients (35%). This study showed that urethral injection of BoNT-A can be effectively used to treat patients with detrusor underactivity and non-relaxing

urethral sphincter after radical hysterectomy with little adverse effects.

BoNT-A Treatment of Urethral Sphincter Pseudodysynergia in Patients with Cerebrovascular Accidents or Intracranial Lesions

Detrusor overactivity and urethral sphincter pseudodysynergia may develop during recovery from cerebral vascular accident (CVA) or intracranial lesions, resulting in difficulty in urination, a large PVR amount and recurrent urinary tract infection. Twenty-one patients with chronic CVA or intracranial lesions and difficult urination were enrolled in a prospective study to evaluate the effectiveness of urethral injection of BoNT-A for these lower urinary tract conditions [9]. Patients participating in the study elected to receive either 100 U of BoNT-A (n=11) or served as medically treated controls (n=10). An excellent result was obtained in 6 patients and an improved result in 4 patients, resulting in an overall success rate of 91% in the study group. The voiding pressure decreased (57.8 ± 35.2 vs. 33.8 ± 16.9 cm water, $p=0.005$) and the maximum flow rate increased (7.2 ± 5.9 vs. $10.3 \pm$

Table 1. Therapeutic Results of Urethral Sphincter Botulinum Toxin A Injections for Voiding Dysfunction

Disease	Number	No. excellent	No. improved	No. failure
DSD	29	8 (27.6%)	15 (51.7%)	6 (20.7%)
Dysfunctional voiding	20	6 (30.0%)	14 (70.0%)	0
Non-relaxing urethral sphincter	10	8 (42.1%)	7 (36.8%)	4 (21.1%)
Cauda equine lesion	8	5 (62.5%)	1 (12.5%)	2 (25.0%)
Peripheral neuropathy	14	5 (35.7%)	6 (42.9%)	3 (21.4%)
Idiopathic detrusor underactivity	13	8 (61.5%)	4 (30.8%)	1 (7.7%)
Totals	103	40 (38.8%)	47 (45.7%)	16 (15.5%)

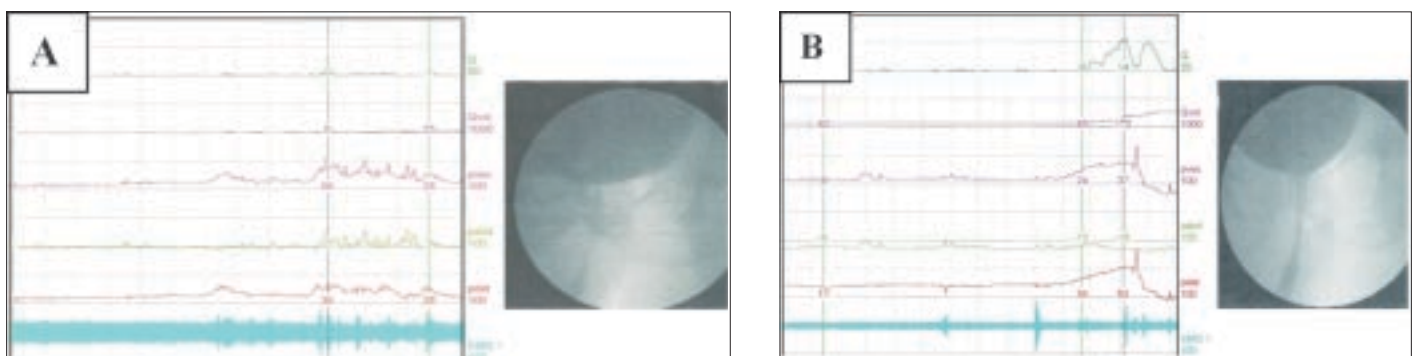


Fig. 1. Urodynamic tracings at (A) baseline and (B) after urethral Botulinum A toxin injection.

5.2 mL/s, $p = 0.005$) significantly. In the control group, 4 patients (40%) had spontaneous voiding 6 months after medical treatment, whereas 6 others remained unchanged and required an indwelling Foley catheter ($n=2$) or CIC ($n=4$). The symptom score and the QOL index showed significantly greater improvement in the study group than in the control group. Urethral injection of BoNT-A is effective and without adverse effects in the treatment of patients with urethral sphincter pseudo-dyssynergia after CVA or intracranial lesions.

Recovery of Detrusor Function after Urethral BoNT-A Injection in Patients with Idiopathic Low Detrusor Contractility and Voiding Dysfunction

Twenty-seven patients with idiopathic low detrusor contractility received urethral injection of BoNT-A [10]. Videourodynamic studies were performed at baseline and after treatment. Recovery of detrusor contractility was defined as an increase of detrusor pressure and maximum flow rate, and reduced PVR urine. The therapeutic results and changes in urodynamic parameters were compared between patients with and without recovery of detrusor contractility.

Recovery of detrusor contractility after urethral BoNT-A injection occurred in 13 (48%) patients. Patients with recovery of detrusor contractility had baseline data characterized by normal bladder sensation during bladder filling combined with poor relaxation or hyperactive urethral sphincter activity. In contrast, patients without recovery of detrusor contractility had poor bladder sensation and a non-relaxing urethral sphincter. Patients with baseline characteristics of low detrusor contractility combined with poorly relaxed or hyperactive urethral sphincter activity had better results than those with true detrusor underactivity. Among the 13 patients with recovery of detrusor contractility, 5 had a long-term effect without the need of repeat urethral injection of BoNT-A during more than 1 year follow-up.

Patients with detrusor underactivity with normal bladder sensation combined with poor relaxation or hyperactive urethral sphincter were significantly more likely to recover normal detrusor function. Neuromodulation of the hyperactive urethral sphincter by urethral BoNT-A is the likely mechanism for this therapeutic effect. Through inhibition of the afferent input of the urethral sphincter, the inhibitory effect of the detrusor nucleus in the sacral cords may be reduced and patients can resume spontaneous and efficient voiding.

Possible Causes of Urethral BoNT-A Injection Treatment Failure

The possible causes of treatment failure include psychological inhibition of voiding, low generation of abdominal pressure, non-relaxing urethral sphincter obstruction, complete denervation of the urethral sphincter and the presence of bladder neck obstruction. Identification of the underlying causes may indicate appropriate therapy. Urethral hyperactivity in DSD patients can be managed by repeat urethral injections of high dose BoNT-A, whereas bladder neck obstruction can be treated by transurethral incision of the bladder neck. Patients with a complete denervation of the urethral sphincter, as demonstrated by electromyographic study, should not be injected.

The cost-effectiveness of BoNT-A treatment should be carefully balanced.

References

- Schurch B, Hauri D, Rodic B, Curt A, Meyer M, Rossier AB: Botulinum-A toxin as a treatment of detrusor-sphincter dyssynergia: A prospective study in 24 spinal cord injury patients. *J Urol* 1996; **155**: 1023-1029.
- Dykstra DD, Sidi AA: Treatment of detrusor-sphincter dyssynergia with botulinum A toxin: A double-blind study. *Arch Phys Med Rehabil* 1990; **71**:24-26.
- Maria G, Destito A, Lacquaniti S, Bentivoglio AR, Brisinda G, Albanese A: Relief by botulinum toxin of voiding dysfunction due to prostatitis. *Lancet* 1998; **352**:625.
- Phelan MW, Franks M, Somogyi GT, et al: Botulinum toxin urethral sphincter injection to restore bladder emptying in men and women with voiding dysfunction. *J Urol* 2001; **165**:1107-1110.
- Kuo HC: Effect of botulinum A toxin in the treatment of voiding dysfunction due to detrusor underactivity. *Urology* 2003; **61**:550-554.
- Kuo HC: Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. *J Urol* 2003; **170**:1908-1912.
- Kuo HC: Comparison of the therapeutic effects of urethral injections of 50 and 100 units of Botulinum A Toxin for Voiding Dysfunction. *Tzu Chi Med J* 2007; **19**:134-138.
- Kuo HC: Effectiveness of urethral injection of botulinum A toxin in the treatment of voiding dysfunction after radical hysterectomy. *Urol Int* 2005; **75**:247-251.
- Chen YH, Kuo HC: Botulinum A toxin treatment of urethral sphincter pseudodyssynergia in patients with cerebrovascular accidents or intracranial lesions. *Urol Int* 2004; **73**:156-161.
- Kuo HC: Recovery of detrusor function after urethral botulinum A toxin injection in patients with idiopathic low detrusor contractility and voiding dysfunction. *Urology* 2007; **69**:57-62.