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Comparison of the Therapeutic Effects of Urethral Injections of 50 and 100 Units of Botulinum A Toxin for Voiding Dysfunction

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Abstract

Objectives: Urethral injection of botulinum A toxin (BoNT-A) has therapeutic effects on voiding dysfunction. However, the optimal dose remains to be determined. This study compared the therapeutic results of urethral injections of 50 U and 100 U of BoNT-A.

Materials and Methods: Sixty-six patients with voiding dysfunction were randomly treated with urethral injections of 50 U (n=33) or 100 U (n=33) of BoNT-A (BOTOX). The therapeutic results and changes in the urodynamic parameters were compared between these two groups of patients.

Results: The overall therapeutic results in the 100 U and 50 U injection groups were excellent in 20 (60.6%) and 23 (69.7%) patients, improved in 10 (30.3%) and 5 (15.2%), and failed in 3 (9%) and 5 (15.2%), respectively. Significant reductions in the voiding pressure, postvoid residual volume, and maximal urethral closure pressure as well as improvement in the quality of life index and increases in the maximum flow rate were noted after treatment in both groups. No significant between-group differences were noted in the net changes of the urodynamic parameters after treatment. Excellent results were noted in 68% and 33% of patients with detrusor underactivity, and in 71.4% and 70.8% of patients with hyperactive urethral sphincter who received injections of 50 U and 100 U, respectively. The mean durations of therapeutic effect were 6.4±3.6 months and 8.4±3.4 months in the 50 U and 100 U groups, respectively (p=0.022).

Conclusion: Urethral injection of 50 U of BOTOX is as effective as 100 U in the treatment of voiding dysfunction of any etiology, but the duration of therapeutic effect was significantly shorter in the group who received 50 U. (*Tzu Chi Med J* 2007;19(3):134–138)

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1. Introduction

Botulinum A toxin (BoNT-A) has been demonstrated to relieve urethral resistance by paralyzing the urethral sphincter [1]. A good therapeutic effect has been observed in patients with detrusor sphincter dyssynergia, spastic urethral sphincter, and isolated urethral sphincter obstruction [2,3]. Patients with spinal cord lesions, chronic stroke, and detrusor underactivity due to previous radical hysterectomy can also benefit from this treatment [4–6].

In previous studies, most treatments were single injections of 100 U of BoNT-A [1,2,4–6]. Only one reported study used 50 U to treat patients with detrusor underactivity and voiding dysfunction [7]. There is no consensus on the appropriate dose of BoNT-A for treating specific diseases or specific urethral conditions in patients with voiding dysfunction. In the treatment of anal fissure, a small dose of 20–50 U of BoNT-A has been adequate to achieve a successful result [8,9]. Repeat treatments with a dose of BoNT-A less than 1.5 U/kg have been shown to facilitate relief of contracture in extremities due to muscle spasm [10]. In the treatment of voiding dysfunction of various etiologies, the optimal dose of BoNT-A remains to be determined.

This randomized study was designed to compare the relative efficacy of the two most widely used doses of BoNT-A for the treatment of voiding dysfunction of different etiologies. The results of this study will provide clinical evidence to substantiate dose selection of BoNT-A in these patients.

2. Materials and methods

Sixty-six patients with voiding dysfunction who had failed treatment with conventional medications were enrolled in this randomized study. Patients were randomly assigned to receive either 50 U or 100 U of BoNT-A (BOTOX; Allergan, Inc., Irvan, CA, USA) regardless of the etiology of voiding dysfunction.

Upon enrolment, baseline screening was performed in all patients, including a videourodynamic study to confirm bladder and urethral dysfunction. The patients were then classified on the basis of videourodynamic results into the following categories: detrusor sphincter dyssynergia (DSD), dysfunctional voiding, poor relaxation of the urethral sphincter, or detrusor underactivity with non-relaxation of the urethral sphincter. Urethral pressure profilometry was also performed in all patients at the baseline screening. During urethral pressure profilometry, the infusion rate was 4 mL/min and the puller speed was set at 1 mm/sec. The maximal urethral closure pressure (MUCP) and functional profile length (FPL) were measured. Parameters assessed during videourodynamic study included the maximum flow rate (Qmax), detrusor pressure at Qmax (Pdet), voided volume and postvoid residual (PVR). The definitions of the terminology used to describe these urodynamic studies were in accordance with the recommendations of the International Continence Society [11]. The quality of life (QoL) index (scored from 0 to 6, representing excellent to bad) for voiding dysfunction was also assessed according to the international prostatic symptom score (IPSS) system [12].

This study was approved by the institutional review board of the hospital. Before treatment, each patient was thoroughly informed about the procedures, and written informed consent was obtained. Information conveyed to patients included possible complications associated with the injection of BoNT-A, such as anaphylaxis, hematuria, micturition pain, acute or chronic urinary retention, and urinary tract infections.

Urethral BoNT-A injection was performed in the operating room under light intravenous general anesthesia. Patients were placed in the lithotomy position. After sterilization and draping, the BoNT-A solution was injected directly into the urethral sphincter under cystoscopic guidance in men at the 3, 6, 9 and 12 o'clock positions at a depth of about 5 mm, and transcutaneously and periurethrally in women at an injection depth of 15 mm. Each vial of 100 U BoNT-A was diluted in 8 mL of normal saline. For patients who received 50 U of BoNT-A, the 4 mL BoNT-A solution was further diluted to a volume of 8 mL. Thus, both groups of patients received the same injection volume but different doses of BoNT-A.

After urethral injection, a 14-Fr Foley catheter was routinely placed overnight. Patients were discharged the next morning and then followed-up in the outpatient department 2 weeks later and monthly thereafter. Prophylactic antibiotics were prescribed for 1 week postoperatively. Other medications such as α-adrenergic blockers and skeletal muscle relaxants were not used concomitantly.

Qmax and PVR were routinely checked at each follow-up visit. Urethral pressure profilometry and videourodynamic study were repeated at the 1-month follow-up. Data for variables including the MUCP, FPL, Pdet, Qmax, and PVR were recorded.

The patient was interviewed to determine voiding conditions after BoNT-A injection and the QoL index was assessed by a questionnaire. An excellent result was defined as a $\geq$2 improvement in the QoL index in combination with a $\geq$50% reduction in PVR and a $\geq$25% reduction in MUCP. An improved result was defined as an improvement in the QoL of 1 combined with improvement in urodynamic parameters as shown by either a $\geq$50% reduction in PVR or a $\geq$25% reduction in MUCP. Treatment was defined as failed if there was no improvement in QoL regardless of the urodynamic improvement.

The primary endpoint was set at 1 month after treatment and the therapeutic outcomes were assessed. Patients were then followed-up at the outpatient clinic regularly. The duration of therapeutic effect was determined by the length of time between treatment and the return of voiding symptoms to baseline.

The therapeutic results in patients who received 50U and 100U injections of BoNT-A were compared. Urodynamic parameters at baseline were compared with those after urethral BoNT-A treatment in each group of patients. The net changes in these urodynamic parameters were also compared between the two groups of patients. The patients were further subgrouped according to voiding dysfunction etiology, and the therapeutic results in these subgroups were analyzed according to whether the patients received 50U or 100U of BoNT-A. Based on these results, the optimal dose of BoNT-A for urethral injection in specific voiding dysfunction categories was proposed for clinical reference.

Statistical analyses were performed using paired *t* test, non-parametric statistics by χ^2 test and ANOVA. A *p* value of less than 0.05 was considered statistically significant.

3. Results

A total of 66 patients were enrolled in this study, and received urethral BoNT-A injection at a dose of either 50 units (n=33) or 100 units (n=33). All patients had previously failed treatment with medications such as α-blockers and skeletal muscle relaxants.

In order to test the therapeutic effects of the doses, the initial 16 patients were not randomized in this study. Ten patients with detrusor underactivity were treated with 50U of BoNT-A, whereas 6 with dysfunctional voiding were treated with 100U of BoNT-A. After that, the remaining 50 patients were randomly assigned to receive 50U or 100U of BoNT-A irrespective of the etiology of voiding dysfunction. Five and 6 patients with poor relaxation of the urethral sphincter, 19 and 9 with detrusor underactivity, 6 and 15 with dysfunctional voiding, and 3 and 3 with DSD received 50U and 100U of BoNT-A, respectively. In the 50U treatment group, 18 patients were women and 15 were men, whereas in the 100U treatment group, 19 patients were women and 14 were men (p>0.05). The mean ages were 64.8±17.1 years and 60.0±14.6 years in the 50U and 100U treatment groups, respectively (p>0.05).

The overall therapeutic results in the 50U and 100U treatment groups showed that 23 (69.7%) and 20 (60.6%) patients had excellent results, 5 (15.2%) and 10 (30.3%) patients had improved results, and 5 (15.2%) and 3 (9.1%) patients had failed results, respectively (Fig. 1). The overall rates of successful treatment were 84.9% in the patients receiving 50U and 90.9% in the patients receiving 100U of BoNT-A (p=0.452).

Table 1 shows the urodynamic parameters at baseline and after BoNT-A treatment in all patients. A significant reduction in Pdet, PVR, MUCP and QoL index, and a significant increase in Qmax were noted in both groups. However, the net changes in these outcome parameters after BoNT-A treatment were not significantly different between groups.

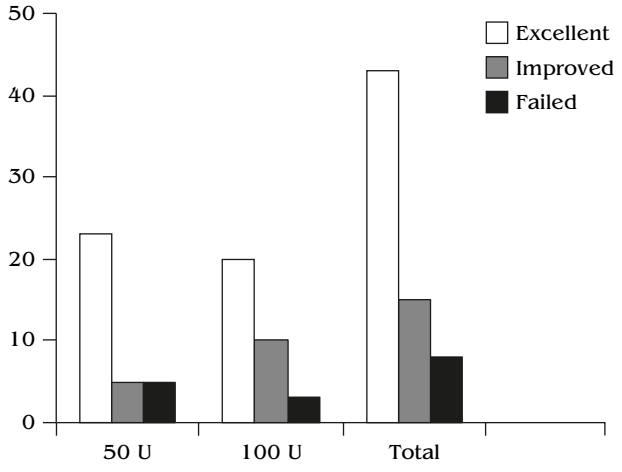

Fig. 1 — Therapeutic results of patients receiving urethral injection of 50 units or 100 units of botulinum A toxin.

Table 1 — Changes in urodynamic parameters and quality of life index in patients who received urethral injections of 50 units or 100 units of botulinum A toxin

	MUCP (cmH_2O)	FPL (cm)	Pdet (cmH_2O)	Qmax (mL/s)	PVR (mL)	QoL index
50U (n = 33)	66.6±34.4	3.3±0.5	51.6±40.7	5.6±5.3	285±154	4.1±0.9
	48.9±27.3	3.1±0.3	37.5±35.4	8.3±5.4	120±145	1.9±1.2
	p<0.001	p=0.186	p<0.001	p=0.016	p<0.001	p<0.001
100U (n = 33)	61.9±26.0	3.8±1.0	53.8±38.9	5.8±4.8	261±157	4.0±1.0
	49.5±21.5	4.1±1.0	33.0±31.7	10.5±5.9	114±107	2.2±1.2
	p=0.049	p=0.493	p=0.006	p<0.001	p<0.001	p<0.001

MUCP = maximal urethral closure pressure; FPL = functional profile length; Pdet = detrusor pressure at Qmax; Qmax = maximum flow rate; PVR = postvoid residual; QoL = quality of life.

Among the 28 patients with detrusor underactivity, an excellent result was noted in 13 (68.4%) patients after 50U injection compared to 3 (33%) patients in the 100U group (p=0.066). Among the 21 patients with dysfunctional voiding, excellent results were found in 5 (83.3%) patients in the 50U group and 8 (53.3%) in the 100U group (p=0.399). Among the 6 patients with DSD, 2 (66.77%) and 3 (100%) patients had excellent results in the 50U and 100U injection groups, respectively (p=0.273). Among the 11 patients with poor relaxation of the urethral sphincter, 3 (60%) and 6 (100%) patients had excellent results in the 50U and 100U groups, respectively (p=0.182). Combining the data from the latter three etiology groups, an excellent result was noted in 10/14 (71.4%) and 17/24 (70.8%) patients in the 50U and 100U groups, respectively (p>0.05). The overall rate of excellent results was 57.1% (16/28) and 71.1% (27/38) in patients with detrusor underactivity and hyperactive urethral sphincter, respectively (p=0.515) (Table 2).

Treatment was classified as failed in 8 patients, including 5 who received 50U and 3 who received 100U of BoNT-A. According to the patients, the maximum effect of urethral BoNT-A injection was reached at about 2 weeks after treatment and lasted from 5 months to more than 12 months. Five patients with detrusor underactivity had recovery of detrusor contractility after urethral BoNT-A injection and the effects lasted for more than 12 months without relapse of difficult urination. The mean duration of therapeutic effect was 6.4±3.6 months and 8.4±3.4 months in the 50U and 100U groups, respectively (p=0.022).

Table 2 — Therapeutic results of different doses of urethral botulinum A toxin injections in patients with different etiologies of voiding dysfunction

	Excellent	Improved	Failed	p
PRS (n=11)				0.182
50U (5)	3 (60%)	2 (40%)	0	
100U (6)	6 (100%)	0		
DU (n=28)				0.066
50U (19)	13 (68.4%)	2 (10.5%)	4 (21.1%)	
100U (9)	3 (33.3%)	5 (55.6%)	1 (11.1%)	
DV (n=21)				0.399
50U (6)	5 (83.3%)	1 (16.7%)	0	
100U (15)	8 (53.3%)	5 (33.3%)	2 (13.3%)	
DSD (n=6)				0.273
50U (3)	2 (66.7%)	0	1 (33.3%)	
100U (3)	3 (100%)	0	0	
Detrusor underactivity (n=28)	16 (57.1%)	7 (25%)	5 (17.9%)	0.515
Hyperactive sphincter (n=38)	27 (71.1%)	8 (21.1%)	3 (7.9%)	

PRS = poor relaxation of urethral sphincter; DU = detrusor underactivity; DV = dysfunctional voiding; DSD = detrusor sphincter dyssynergia.

4. Discussion

Urethral BoNT-A injection is effective in reducing urethral resistance and facilitating spontaneous voiding. This treatment allows patients with spinal cord lesions and DSD to resume spontaneous voiding and abolishes the complications of autonomic dysreflexia. In patients with dysfunctional voiding, BoNT-A injection can paralyze the spastic urethral sphincter and thereby improve voiding efficiency as well as irritative bladder symptoms after treatment [3]. Patients with detrusor underactivity and a fixed urethral resistance can also resume spontaneous voiding by abdominal straining after treatment [7]. These therapeutic effects of BoNT-A urethral injections can reduce the frequency of clean intermittent catheterization and even allow freedom from indwelling Foley catheter use [4,7]. The quality of life of patients treated with urethral BoNT-A injection can be significantly improved [3,4]. Although stress urinary incontinence may be a problem for women with detrusor underactivity and low bladder compliance, especially at night, most patients can enjoy a better quality of life with easy voiding after treatment.

Although urethral BoNT-A injection has been demonstrated to have good therapeutic effects, not all patients with voiding dysfunction benefit from this treatment. A small group of patients still cannot resume spontaneous voiding after treatment. The causes for failed treatment in these patients may include psychological inhibition, poor cortical facilitation, or severe urethral sphincter spasticity in patients with DSD or dysfunctional voiding [3]. Repeat urethral injections may achieve a better therapeutic result in these patients. However, the cost-effectiveness should also be considered.

Although there was a disproportional distribution of different etiologies of voiding dysfunction in the 50U and 100U treatment groups, this study demonstrated that urethral injection of 50U of BoNT-A is as effective as 100U in treating voiding dysfunction of various etiologies. The rate of excellent results in the 50U group (69.7%) was similar to that in the 100U group (60.6%).

In patients with detrusor underactivity, the rate of successful treatment as defined by an excellent result was significantly better in the 50U group than in the 100U group. This result might have been due to the greater percentage of women with detrusor underactivity in the 50U group. Women with detrusor underactivity in this study could all void with increased abdominal pressure after urethral BoNT-A injection, indicating excellent therapeutic results with a small dose of BoNT-A. On the contrary, a higher percentage of patients with hyperactive urethral sphincter (DSD, dysfunctional voiding, poor relaxation of urethral sphincter) were included in the 100U group and the therapeutic result was therefore slightly affected.

Nevertheless, the overall success rate in both groups of patients showed no significant difference.

There was a lower rate of excellent results and a higher rate of failed results in the patients with detrusor underactivity than in those with sphincter hyperactivity. Although the overall statistical analysis revealed no significant difference between these two groups, the result might have some clinical implications. Patients with detrusor underactivity and voiding dysfunction need abdominal straining to void even if their urethral sphincters have been paralyzed by injection of BoNT-A. Therefore, in patients who cannot properly use abdominal pressure to void, such as those with multiple strokes, general weakness, or those who are bedridden, spontaneous voiding might not be possible after urethral BoNT-A treatment.

Voiding dysfunction is a graded pathological condition. Mild to moderate improvement after urethral BoNT-A injection might not significantly improve quality of life. In this study, the QoL index was used to measure subjective improvement, and a ≥25% reduction in MUCP and a ≥50% reduction in PVR were used to measure objective improvement. If the QoL index improved by 1, the result was only considered improved. These results demonstrated that urethral BoNT-A injection with 50U is adequate for treating patients with voiding dysfunction resulting from poor relaxation of the urethral sphincter or dysfunctional voiding, and for some patients with DSD or detrusor underactivity. The use of 100U of BoNT-A did not result in a higher rate of success in treating voiding dysfunction of any etiology. However, the duration of therapeutic effect was significantly longer in the 100U treatment group than in the 50U treatment group, suggesting that a higher dose of BoNT-A might induce a greater denervation effect. For patients who have failed initial BoNT-A treatment, repeat treatment after the first month can be instituted. Although the patients in this study did not receive repeat treatment, it is reasonable to consider repeat treatment with an increased dose of BoNT-A for patients with severe urethral hyperactivity, such as patients with DSD or dysfunctional voiding, who fail the initial low-dose treatment.

This study has shown that BoNT-A urethral injection at a dose of 50U is as effective as 100U in the treatment of voiding dysfunction of any etiology. The duration of therapeutic effect was significantly shorter in the 50U group, suggesting that greater denervation is achieved with a larger dose of BoNT-A. A dose of 50U of BoNT-A is appropriate for urethral injection for initial treatment of voiding dysfunction refractory to conventional medication.

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