Clinical Application of Onabotulinum Toxin A in Overactive Bladder Syndrome/Detrusor Overactivity

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ABSTRACT

Overactive bladder/detrusor overactivtiy (OAB/DO) is a highly prevalent disease. Although antimuscarinics are used as first line therapy, many people cannot tolerate the side effects. Intravesical onabotulinum toxin-A (BoNT-A) injection, a minimally invasive procedure, is an alternative treatment used worldwide. However, there is no standard protocol to treat patients with OAB/DO, and no optimal dose is used. We reviewed the therapeutic results of intravesical BoNT-A injection for OAB/DO at Tzu Chi General Hospital in Hualien, Taiwan from 2004 to 2011. Injections of 200 U of BoNT-A provide good therapeutic results for a long duration, but the rate of side effects is high. There were similar success rates between intravesical BoNT-A 100 U and 200 U injections. Although a short therapeutic duration was noted in patients who received 100 U BoNT-A, the complication rate was obviously lower than with 150 U and 200 U injections. For patients at risk of urine retention after treatment, bladder base/trigone injection relieved the urgency sensation but did not increase the risk of urine retention. Common adverse effects, such as difficult urination and a large post-voided residual, did not affect the success rate at 3 months after administration and in long-term follow-up.

Key words: OAB, DO, botulinum toxin-A, intravesical injection

INTRODUCTION

Overactive bladder (OAB) is defined by the International Continence Society as a symptom syndrome suggestive of lower urinary tract dysfunction, including urinary urgency, with or without urge incontinence, usually with frequency and nocturia. Detrusor overactivity (DO) is a disease similar to OAB and it is defined as a urodynamic observation characterized by involuntary spontaneous or provoked detrusor contractions during the filling phase [1].

OAB is a highly prevalent disorder that affects millions of people worldwide, and significantly impacts their health-related quality of life (QoL) [2,3]. In Taiwan, the overall age-adjusted prevalence of OAB is 16.9%, including 4.5% with urge incontinence, and there is a higher prevalence rate in women (18.3%) than in men (16.0%) [4].

Although anticholinergics are known to be effective to most patients with OAB/DO, some patients are refractory or they cannot tolerate the side effects, such as dry mouth and constipation [5,6]. Intravesical injection of onabotulinum toxin-A (BoNT-A) is one of the alternative treatments [7]. BoNT-A injection was first successfully applied in patients with neurogenic detrusor overactivity (NDO) by Schurch et al [8], and it has also been considered an alternative treatment in patients with idiopathic detrusor overactivity (IDO) [8-13].

The mechanism of BoNT-A in treating OAB/DO is reversible and complicated. First, the light chain of BoNT-A can cleave synaptosome-associated protein 25 kDa and therefore the exocytosis of acetylcholine from the neuromuscular junction is inhibited. The release of adenosine triphosphate from urothelial cells is also inhibited by BoNT-A. BoNT-A can also reduce the expression of transient receptor potential vanilloid receptor 1 (TRPV1) and/or $P2X_3$ receptors in suburothelial nerve fibers. In addition, the release of calcitonin gene-related peptide (CGRP), substance P, and nerve growth factor are all inhibited by BoNT-A [14].

Herein, we review the results of intravesical BoNT-A injection therapy in patients with OAB syndrome at Buddhist Tzu Chi General Hospital, Hualien, Taiwan.

DOSES OF INTRAVESICAL BONT-A IN PATIENTS WITH OAB/DO AND NDO

A dose of 300 U intravescial BoNT-A was first applied in patients with NDO, which resulted in detrusor underactivity. The duration of action was about 9 months [8], and these patients sometimes needed clean intermittent catheterization (CIC) or clean intermittent self-catheterization to empty the bladder. However, in patients with IDO, the therapeutic goal was self voiding with a low residual urine, so a different dose was applied. In 2004, Kuo reported the therapeutic results of intravesical detrusor injections of BoNT-A 200 U in patients with DO refractory to anticholinergics at Buddhist Tzu Chi General Hospital, Hualien, Taiwan [15]. In this study, 30 patients with refractory DO, including 12 patients with NDO 8 patients with IDO, and 10 men with DO after transurethral resection of prostate (TUR-P) received detrusor injections of BoNT-A 200 U at 40 sites in bladder. The overall success rate was 73.4%, 8 patents (26.7%) regained urinary continence and lower urinary tract symptoms (LUTS), such as urinary frequency, urgency and urinary incontinence, significantly improved in 14 patients. The success rates were 75% in patients with IDO and 66.6% in those with NDO (Table 1). In addition, the scores for storage symptoms on the International Prostate Symptom Score, QoL index and incontinence grade improved significantly beginning 2 weeks after treatment, and the therapeutic effects lasted for at least 3 months. The maximal flow rate (Qmax) did not change significantly during the follow-up period and other parameters, such as capacity, bladder neck opening time, detrusor contractility, post-voided residual urine (PVR) and voiding efficiency, changed significantly beginning the second week after

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treatment. Side effects were common (33.3%) but no major complications were noted in this study. Four patients had transient urinary retention and needed the assistance of CIC and 6 patients had difficult urination during the follow-up period. The therapeutic results in this study were excellent. Several other studies also revealed that intravesical injection of 200 U BoNT-A is effective and safe [16-18].

DIFFERENCE BETWEEN INJECTIONS METHODS FOR BONT-A

The pathophysiology of OAB in unclear and many theories has been reported [19-22]. The lamina propia sensory fibers are considered to be associated with DO [23,24]. In addition, the nociceptive sensory fibers and stretching sensing fibers are abundant in the suburothelial space and are also considered to trigger DO [25,26]. BoNT-A can inhibit the release of acetylcholine from the neuromuscular junction, decrease the amount of neuropeptides such as substance P and CGRP from activated sensory neurons and decrease the expression of purinergic $P2X_3$ receptor immunoreactive suburothelial fibers and TRPV1-expressing fibers, leading to successful treatment of DO [14]. Kuo hypothesized that if BoNT-A delivered to the suburothelial space modulates the release of neurotransmitters from sensory fibers, it might have good therapeutic effects in patients with sensory urgency and DO. In 2005, he performed suburothelial injections of BoNT-A 200 U in 20 patients with refractory IDO and followed them for 6 months [27]. BoNT-A 200 U was injected into 40 sites in the bladder suburothelial space (Fig. 1). At 3 months after treatment, 45% of the patients (9 in 20) regained continence and 40% (8 in 20) had significant improvement in LUTS. At 6 months after treatment, 35% of the patients remained continent. Similar to patients who received intravesical detrusor injection of BoNT-A, these patients had improvement the second week after treatment, and no significantly change in the Qmax was noted during the follow-up period (Table 2). Side effects were still not uncommon, including 1 patient (5%) with hematuria, 7 (35%) with urinary tract infection (UTI), 6 (30%) with a large PVR who required catheterization, and 15 (75%) with hesitancy and difficult urination.

The high incidence of difficult urination and urine retention suggests that blockage of detrusor contractility through suburothelial sensory fibers was more pronounced than through the neuromuscular junction. This study revealed that suburothelial injection of BoNT-A is effective in the treatment of patients with nonneurogenic DO but the side effects should be carefully monitored.

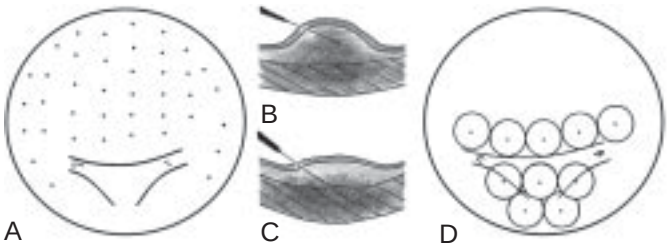

Fig. 1. Different methods of injecting intravesical BoNT-A. (A) Bladder body injection: the trigonal area is spared during injection. (B) Suburothlial injection: engorgement of the mucosa is characteristic after injection. (C) Detrusor injection: only mild engorgement of the mucosa is noted. (D) Bladder base/trigone injection: BoNT-A is injected only into the bladder base (5 shots) and trigone (5 shots).

THE EFFECTS OF DOSAGE AND INJECTION SITE ON THE INCIDENCE OF SIDE EFFECTS AND THE SUCCESS RATE

Side effects, such as a large PVR and difficult urination, were common in the above-mentioned and other studies [10,28]. Efforts have been made to decrease the incidence of impaired voiding efficiency and a large PVR. Different dosages of BoNT-A were injected into the bladder by Kuo in 2006 [29]. In this study, 75 patients including 40 with NDO and 35 with IDO were randomized to 3 groups receiving injections of intravesical suburothelial BoNT-A 100 U, 150 U or 200 U, Table 3 shows the results at 3 months after administration (p=0.813) and the therapeutic duration. In this study, significant urodynamic changes, including bladder capacity, detrusor pressure, PVR and voiding efficiency, were noted the first month after treatment in each subgroup, but at 3 months after treatment, the therapeutic effects remained significant only in the 150 U and 200 U groups. A significantly decreased Qmax at 1 month was noted only in patients who received 150 U (10.8±5.4 mL/s decreased to 8.2±3.6 mL/s) and 200 U (10.0 ±8.0 mL/s decreased to 8.2±5.6 mL/s). In addition, the voiding efficiency was impaired significantly until 3 months after treatment in these 3 subgroups. The complication rate in the 100 U group was much lower than in the other 2 groups (Table 4). Hesitancy and a large PVR were still common in patients with suburothelial BoNT-A 100 U injection but no urine retention occurred in this group. It is suggested that although suburothelial BoNT-A 100 U injection has a shorter therapeutic duration, the success rate is similar to other groups with significantly fewer adverse effects.

Because of the short therapeutic duration, patients need frequent injections. Other injection procedures have been tried with better results. Starting in 2007, bladder base/trigone BoNT-A injections were used to reduce sensation from the trigone. The hypothesis is that the bladder trigone is rich in sensory fibers and sensitive to small changes in pressure, and may function as an early warning system in bladder filling [30]. Phenol injections into the trigone and transvaginal denerva-

Table 1. Therapeutic Results of Detrusor BoNT-A Injection in Patients with Various Etiologies

Etiology	Excellent (%)	Improved (%)	Failure (%)
Previous bladder outlet obstruction (n=10)	6 (60.0)	2 (20.0)	2 (20.0)
Neurogenic voiding dysfunction (n=12)	1 (8.3)	7 (58.3)	4 (33.3)
Idiopathic detrusor overactivity (n=8)	1 (12.5)	5 (62.5)	2 (25.0)
Total (n=30)	8 (26.7)	14 (46.7)	8 (26.7)

Excellent=patient became continent without voiding difficulty; Improved=the International Prostate Symptom Score improved by 50% or more

Table 2. Changes of Urodynamic Parameters at Baseline and after Suburothelial BoNT-A Injection

Parameters	Baseline	2 wk	3 mo	6 mo	*p*-value
First sensation of bladder filling (mL)	139.8±78.2	349.4±145.1	212.0±104.3	208.2±90.9	<0.001
Bladder capacoty (mL)	224.4±124.8	412.6±179.2	314.9±135.9	307.6±120.0	<0.001
Detrusor pressure (cmH_2O)	29.8±11.5	17.3±10.4	21.5±10.1	24.1±11.8	0.022
Maximal flow rate (mL/s)	12.4±7.8	9.4±4.6	11.1±5.9	11.9±5.6	0.347
Bladder neck opening time (s)	14.5±13.3	31.9±45.2	18.4±12.6	17.6±8.6	0.152
Voiding efficiency (%)	87.1±16.9	45.4±28.3	69.9±23.4	73.2±22.8	<0.001
Post-void residual urine volume (mL)	29.8±43.8	221.0±158.3	97.6±87.4	85.8±82.9	0.001
Detrusor overactivity (%)	100	100	35	55	

Table 3. Therapeutic Results and Duration after Intravesical BoNT-A Injection with Different Dosage

Result	100 U (n=23)	150 U (n=25)	200 U (n=27)
Excellent	34.8%	36.0%	40.7%
Improved	47.8%	56.0%	48.2%
Duration (mos)	3.5	5.5	6.7

Self-reported urinary incontinence gragde=0-3, representing continent, mild, moderate and severe; Voiding difficulty score=0-3, representing no difficulty, mild, moderate and severe difficulty; Excellent=patient became continent with voiding difficulty score increase by less than 2; Improved=incontinence grade improved by 1 or more points with voiding difficulty score increase by less than 2

Table 4. Adverse Effects after Intravesical BoNT-A Injection with Different Dose

Adverse effects	Dose		
	100 U (n=23)	150 U (n=25)	200 U (n=27)
Difficult urination	56.5%	76.0%	70.0%
Large PVR	30.4%	72.0%	52.0%
Transient urine retention	0	8.0%	22.2%
UTI	0	8.0%	14.8%

PVR=post-voided residual urine; UTI=urinary tract infection

tion surgery have both been performed in patients with urge incontinence [31,32]. In 2007, 45 paitents with IDO refractory to antimuscarinics for at least 3 months were enrolled in a study of intravesial base/trigone BoNT-A injection [33]. They were categorized randomly into 3 subgroups of 15 patients each, receiving 100 U BoNT-A injected into the detursor layer, suburothelial space or bladder base/trigone (Fig. 1). The patients were followed for at least 9 months and Table 5 reveals the success rate in each subgroup. Compared with baseline, the urgency severity score improved significantly at 3 months in all 3 subgroups (2.2 ± 1.0 vs 1.1 ± 1.2, 2.1 ± 1.0 vs 1.2 ± 0.9, and 2.3 ± 1.0 vs 1.3 ± 1.4 in the suburothelial, detrusor and bladder base subgroups, respectively) with no significant changes in cystometric bladder capacity and PVR in the bladder base/trigone injection subgroup. The cumulative success rate of bladder body injection was significantly better than that for bladder base/trigone injection (Fig. 2) but there were significantly fewer complications and no urine retention in the bladder base/trigone subgroup (2 patients with dysuria, 1 with

Table 5. Success Rate during Follow-up with Different Injection Method

Time	Injection method (n)		
	Detrusor (n=15)	Suburothelium (n=15)	Bladder base (n=15)
3 mos	93.0%	80.0%	67.0%
6 mos	67.0%	47.0%	13.0%
9 mos	20.0%	20.0%	6.7%

General satisfaction rating=excellent, moderate, mild, stationary, measured by symptomatic improvement of more than 75%, 50%-75%, 25%-50%, or less than 25% compared to baseline; Successful result=excellent or moderately improved

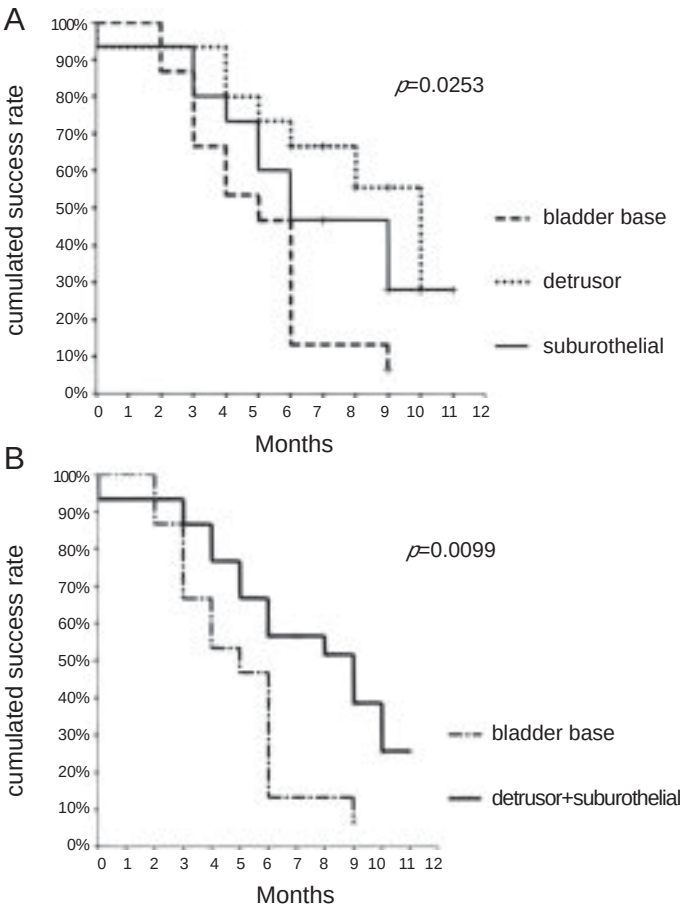

Fig. 2. Cumulative success rates of patients receiving intravesical BoNT-A injection. (A) Suburothelial, detrusor and bladder base injections. (B) Bladder body (suburothelial and detrusor) and bladder base injections.

UTI, 1 with gross hematuria and 1 with bladder/urethral pain). A longer therapeutic duration was noted in patients receiving detrusor and suburothelial BoNT-A injections. Bladder base/trigone injection caused fewer complications.

In the past, bladder base/trigone injection of BoNT-A was considered as effective as intravesical trigone-sparing injection [34]. In the above-mentioned study, a lower long-term success rate was noted in patients receiving base/trigone injections. Therefore, a single blind, randomized, paralleled, actively controlled trial was designed to investigate the safety and efficacy of bladder base/trigone BoNT-A injection in 2010 [35]. Thirty-seven patients had bladder body injections, 35 had bladder body/trigone injections and 33 had bladder base/trigone injections of 100 U BoNT-A. The long-term success rates over 12 months are shown in Table 6 and complications are listed in Table 7. No acute urinary retention (AUR) occurred and the PVR was not significantly increased after bladder base/trigone BoNT-A injection during follow-up. Changes in other urodynamic parameters, such as bladder capacity, detrusor pressure, Qmax and voiding efficiency, were similar in these 3 groups. There were no significant differences in the long-term success rate and incidence of side effects between these 3 groups. Intravesical BoNT-A injection is an effective treatment regardless of injection site, and bladder base/trigone injection is safe and may be suitable for patients with a large PVR before treatment.

THE RELATIONSHIPS BETWEEN THERAPEUTIC RESULTS AND ADVERSE EFFECTS

Intravesical BoNT-A injection for OAB patients is not widely used because many patients and doctors are afraid of side effects. Previous studies revealed high success rates for intravesical BoNT-A injection, but high rates of a large PVR, dysuria and even urine retention seem to be inevitable. The relationships between long-term therapeutic effects for at least 24 months and adverse effects of intravescial BoNT-A injection for patients with IDO were evaluated by Kuo. A total of 174 patients (85 women, 89 men including 79 men over 50 years old and 41 men who had a TURP) with refractory DO and urinary incontinence were enrolled from 2005 to 2009. They received intravesical BoNT-A 100 U injections, including detrusor suburothelial injection into the bladder base/trigone or bladder body. The treatment outcomes were assessed using the global response assessment and a successful outcome was defined as markedly or moderately improved results after treatment. During follow-up, the total success rate at 3 months was 79.3% (138 of 174 patients). The adverse effects were a PVR over 150 mL (81 patients, 46.6%), abdominal straining to void (73, 42%), UTI (15.5%), hematuria (17, 9.8%), AUR (12, 6.9%), and general weakness (6, 3.4%). AUR was more common in men, those with bladder body injections and those with a large PVR at baseline (baseline PVR≥ 100 mL). The success rate was notably different by gender, age and the voiding parameters. At 3 months after administration, the success rates were compared in patients with and without various adverse effects. Patients with a large PVR and those who needed to strain to void had significantly higher success rates than those without these adverse effects. In addition, the success rates were significantly lower in subgroups with hematuria and UTI (Fig. 3). The long-term cumula-

Table 6. Success Rate and Dry Rate after Intravesical BoNT-A Injection in Suburothelial, Detrusor and Bladder Base Subgroups

	Baseline	3 mos	6 mos	9 mos	12 mos
Bladder body (n=37)					
Success		26 (71.0%)	21 (56.0%)	18 (49.0%)	18 (49.0%)
Dry	8 (21.6%)	27 (73.0%)	22 (59.4%)	16 (43.2%)	13 (37.1%)
Bladder body/trigone (n=35)					
Success		26 (74.0%)	17 (50.0%)	17 (50.0%)	17 (50.0%)
Dry	8 (22.9%)	23 (65.7%)	19 (54.3%)	16 (45.7%)	15 (42.8%)
Bladder base/trigone (n=33)					
Success		24 (73.0%)	24 (72.0%)	15 (44.0%)	12 (37.0%)
Dry	7 (21.2%)	26 (78.8%)	21 (63.6%)	17 (51.5%)	12 (37.0%)
Total (n=105)					
Success		76 (72.4%)	62 (59.0%)	50 (47.6%)	47 (44.8%)
Dry	23 (21.9%)	76 (72.4%)	62 (59.0%)	49 (46.7%)	40 (38.1%)

Successful result=improved Perception of Bladder Condition scale by more than 2 points

Table 7. Occurrence of Adverse Effects in Different Injection Site Group

	Bladder body (n=37)	Bladder body/trigone (n=35)	Bladder base/trigone (n=33)	*p*-value
AUR	2 (5.4%)	4 (11.0%)	0 (0.0%)	0.127
Large PVR	16 (43.2%)	13 (37.1%)	16 (48.5%)	0.639
Straining to void	10 (27.0%)	11 (31.4%)	13 (39.4%)	0.538
UTI	8 (21.6%)	9 (25.7%)	5 (15.2%)	0.560
Hematuria	6 (16.2%)	4 (11.4%)	3 (9.1%)	0.833
General weakness	2 (5.4%)	3 (8.6%)	1 (3.0%)	0.672

AUR=acute urinary retention; PVR=post-voided residual urine; UTI: urinary tract infection

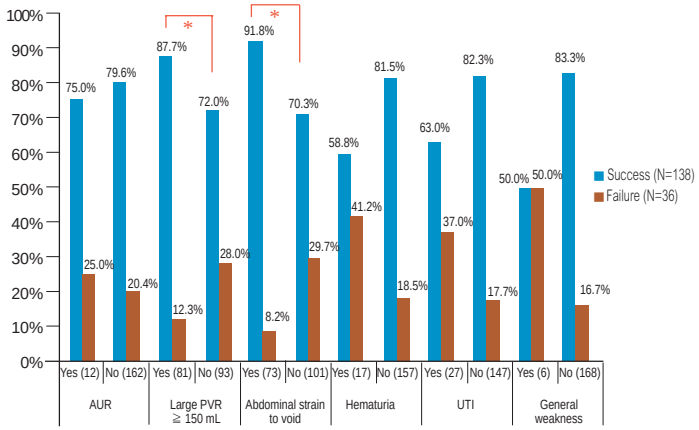

Fig. 3. Comparison of success rates in patients with and without various adverse effects 3 months after BoNT-A injection (*p<0.05). AUR=acute urinary retention; UTI=urinary tract infection.

tive success rates were also evaluated in these patients. Interestingly, there were no significant differences between patients with and without adverse effects such as AUR, large PVR, UTI and straining to void. But patients with hematuria and general weakness during the follow-up period had significantly lower success rates than those without these adverse effects. This suggests that the occurrence of a large PVR and straining to void does not affect the success rate at 3 months or long-term. Although patients with UTI after treatment had lower success rates at 3 months, the long-term success rate was not affected.

Other reports showed decreased voiding pressure at 1 month after treatment but this improved thereafter [30,36]. Although the voiding pressure improved, the voiding efficiency remained lower than at baseline, indicating detrusor contractility may need more time to recover, and difficult urination and increased PVR often occur during this period. However, patients usually tolerate difficult urination and increased PVR if there is a reduction of urgency or urge incontinence, which may be why a large PVR and straining to void does not affect the success rate after treatment.

CONCLUSION

Intravesical BoNT-A injection for patients with OAB/DO is safe and efficient. For patients with OAB/DO, 100 U of BoNT-A is sufficient and the therapeutic results are good. In patients at risk of AUR suburothelial injection in the bladder base/trigone could improve the urge sensation effectively without increasing bladder capacity after treatment. Although a large PVR and difficult urination are common, they do not affect the success rate at 3 months or long-term.

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