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Review Article

Intravesical Botulinum Toxin Injection for Overactive Bladder—What We Can Learn From Previous Clinical Trials

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Abstract

Intravesical botulinum toxin A (BoNT-A) injection is effective in treating overactive bladder (OAB) and detrusor overactivity (DO)-induced incontinence refractory to antimuscarinic treatment. In the past 5 years, there have been several clinical trials using BoNT-A targeting OAB and idiopathic DO (IDO), and the therapeutic results are promising. Recent investigations have shown that urothelial dysfunction and abnormality of sensory receptor expression or transmitter release in the suburothelial nerves might contribute to OAB refractory to antimuscarinics. Intravesical BoNT-A treatment to inhibit abnormal receptor expression or transmitter release in the sensory nerve terminals in the suburothelial space has shown to have a good therapeutic effect on OAB. Intradetrusor or suburothelial BoNT-A injections, with small or large doses of BoNT-A in the bladder body or bladder base, can achieve satisfactory results. However, BoNT-A impairs detrusor contractility and causes a large postvoid residual (PVR) urine volume after injection in some patients. This adverse effect induces acute urinary retention and it is difficult to empty the bladder in the early postoperative period. Urinary tract infections can occur in patients with a large PVR. Although adverse effects may not influence the therapeutic outcome, they might prohibit wide application of BoNT-A in the treatment of refractory OAB. Patients with a high risk of a large PVR or urinary retention should be taught clean intermittent catheterization. Analysis of patient characteristics and urodynamic variables has shown that patients who are elderly, have low detrusor contractility at baseline, and have chronic medical diseases are at risk of adverse effects. Therefore, careful adjustment of the dose, appropriate injection site and correct patient selection is mandatory to achieve satisfactory results with intravesical BoNT-A therapy. [*Tzu Chi Med J* 2009;21(4):277–284]

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1. Introduction

Overactive bladder (OAB) is a syndrome characterized by urgency frequency with or without urgency incontinence. Usually no metabolic or anatomical disorders can be found [1]. OAB symptoms have a significant impact on the emotional wellbeing and quality of life of those affected [2]. Although there are several new therapeutic options with promising treatment outcomes, antimuscarinic drugs remain the first-line treatment and clinical effects with good tolerability have been confirmed. However, not all OAB patients benefit from antimuscarinic agents [3], and adverse effects such as dizziness, dry mouth, blurred vision, and constipation, are intolerable for some patients [4]. Intravesical botulinum toxin (BoNT) injections provide an alternative treatment with favorable efficacy for these patients.

BoNT was first used in treating strabismus based on the mechanism that it can inhibit signal transmission at the neuromuscular and neuroglandular junctions by binding to the synaptic vesicle protein SV2 during neurotransmitter exocytosis when more active receptors are exposed [5]. The application of BoNT-A for the treatment of lower urinary tract symptoms was initiated in the late 1980s. Dykstra et al described injection of BoNT-A into the external urethral sphincter in spinal cord injured (SCI) patients to induce chemical sphincterotomy and to lower detrusor-sphincter dyssynergia [6]. Since the detrusor contraction is mediated by acetylcholine (ACh) parasympathetic innervation, Schurch et al successfully treated SCI patients with neurogenic overactivity incontinence using detrusor BoNT-A injections at multiple sites [7]. A large scale multicenter trial also confirmed that BoNT-A detrusor injection significantly improved urinary incontinence associated with health-related quality of life in patients with neurogenic urinary incontinence [8].

BoNT-A can cause muscle paralysis by blocking ACh release at the neuromuscular junction [9]. Reduction of expression of purinergic receptor $P2X_3$ and transient receptor potential vanilloid receptor subfamily 1 on suburothelial sensory fibers has been observed in patients receiving detrusor BoNT-A injections for detrusor overactivity (DO) and has been associated with reduction in the degree of urgency in patients with successful therapeutic results [10]. Nociceptive sensory fibers and stretch sensing fibers are abundant in the suburothelial space [11,12]. An antinociceptive effect through a direct decrease of neuropeptides, such as substance P and calcitonin gene-related peptide released from activated sensory neurons, accounts for the clinical effectiveness of BoNT-A in pain relief [13,14]. Based on the pathophysiology of OAB and DO, BoNT has been enthusiastically applied in treating urinary urgency or incontinence refractory to antimuscarinics in recent years [15–43] (Table 1). Although promising therapeutic effects have been confirmed in several case series and clinical trials, adverse events have been reported inconsistently. There is no consensus on the dose of BoNT-A or BoNT-B, injection sites, and the duration between repeat injections. This review attempts to analyze the clinical results of BoNT-A on OAB and idiopathic DO (IDO) and adverse effects that occur after BoNT-A injection. Doctors need to be aware of the adverse effects that might endanger the patient before injecting BoNT-A into the bladder.

2. Clinical effects of BoNT-A on DO

BoNT-A induces reduction of the urgency sensation in the first week after intravesical injection. In one study, significant improvement in urgency frequency, and nocturia were seen on day 2 and in urinary incontinence on day 3 in patients with neurogenic DO, with significant changes in OAB on day 4 in patients with IDO [35]. Clinical observation also found that acute urinary retention may occur as early as the first day after treatment [18]. A large postvoid residual (PVR) urine volume can develop during the first month and decrease slowly with time [31]. In one study, urinary incontinence disappeared within 1–2 weeks after injection [25].

At first, most investigators used detrusor injections of 200 U or 300 U of Botox (100 U/vial; Allergan, Irvine, CA, USA) to treat patients with IDO [15,16,18–20,22,23]. The therapeutic results varied greatly. Kessler et al treated 11 patients with IDO with detrusor injections of 300 U Botox and the maximal bladder capacity increased from 220 to 340 mL. However, four patients needed clean intermittent catheterization (CIC) due to a large PVR [16]. Rajkumar et al treated 15 IDO women with detrusor injections of 300 U Botox and 14 had improvement in urgency and frequency. The therapeutic effects lasted for 5–6 months [22]. Popat et al used 200 U for 31 IDO patients. Although significant improvement in bladder capacity was noted after treatment, 20% of the patients needed CIC [23]. Schulte-Baukloh et al used 300 U for detrusor and urethral injections in seven women with OAB without DO. The bladder capacity increased by 20% and all patients could void without the need for CIC [19]. The dose of BoNT-A seems to have an effect on the continence rate after injection, but the incidence of adverse effects also increases. In the author's previous study, detrusor injections of 200 U provided a 73.3% success rate in 30 IDO patients, with a mean therapeutic duration of 5.3 months [15]. Further studies using suburothelial injections of Botox at a dose of 200 U demonstrated better therapeutic results (85% success rate) similar to those

Table 1 — Occurrence of adverse events after intravesical BoNT injections in patients with IDO

Authors (yr) (ref.)	Patients, *n*	Dose & sites of injection	Dysuria, *n* (%)	Large PVR, *n* (%)	Required CIC, *n* (%)
Kuo (2004) (15)	18 IDO	200 U BTX-A Detrusor×40	6 (33)	6 (33)	4 (22)
Kessler et al (2005) (16)	11 IDO	300 U BTX-A Detrusor×30	4 (36)	4 (36)	4 (36)
Werner et al (2005) (17)	26 IDO women	100 U BTX-A Detrusor×30	1 (4)	2 (8)	2 (8)
Kuo (2005) (18)	20 IDO	200 U BTX-A Suburothelium×40	15 (75)	7 (35)	6 (30)
Schulte-Baukloh et al (2005) (19)	7 OAB	300 U BTX-A Detrusor×30 and/or urethral 50–75 U	NA	0	0
Schulte-Baukloh et al (2005) (20)	38 OAB	200–300 U BTX-A Detrusor×40–50	NA	0	0
Ghei et al (2005) (21)	20 IDO	5000 U BTX-B Detrusor×10	2 (10)	2 (10)	2 (10)
Rajkumar et al (2005) (22)	15 IDO	300 U BTX-A Detrusor×30	NA	7 (47)	0
Popat et al (2005) (23)	31 IDO	200 U BTX-A Detrusor×20	NA	2 (6.4)	6 (19.3)
Kuo (2006) (24)	35 IDO, 40 NDO	100 U BTX-A	13 (52)	8 (32)	0
		150 U BTX-A	19 (76)	13 (52)	2 (8)
		200 U BTX-A Suburothelium×40	19 (76)	18 (72)	6 (24)
Schmid et al (2006) (25)	100 IDO	100 U BTX-A Detrusor×30	NA	NA	4 (4)
Lucioni et al (2006) (26)	40 OAB	Trigone×24 Detrusor×16	NA	NA	NA
Hoebeke et al (2006) (27)	15 OAB children	100 U BTX-A Detrusor	4 (27)	1 (7)	0
Kalsi et al (2006) (28)	16 IDO	200 U BTX-A Detrusor×20	NA	NA	2 (12.5)
Hirst et al (2007) (29)	20 IDO	5000 U BTX-B Detrusor×20	NA	NA	1 (5)
Ghalayini & Al-Ghazo (2007) (30)	16 IDO	500 U Dysport Detrusor	NA	NA	3 (19)
Sahai et al (2007) (31)	16 IDO	200 U BTX-A Detrusor×20	NA	7 (44)	6 (37.5)
Kuo (2007) (32)	45 IDO	100 U BTX-A			
		Detrusor (n=15)	5 (33)	5 (33)	2 (13)
		Suburothelium (n=15)	7 (47)	7 (47)	2 (13)
		Bladder base (n=15)	2 (13)	2 (13)	0
Jeffery et al (2007) (33)	25 IDO	500 U Dysport Detrusor×20	NA	NA	8 (36)
Karsenty et al (2007) (34)	12 IDO	200 U BTX-A Trigone×10	0	0	0
Kalsi et al (2008) (35)	8 IDO	200 U BTX-A	NA	NA	0
Kuschel et al (2008) (36)	26 IDO	100 U BTX-A Detrusor	NA	1 (4)	1 (4)
Brubaker et al (2008) (37)	28 IDO	200 U BTX-A Detrusor×20	NA	12 (43)	12 (43)
White et al (2008) (38)	14 IDO>75 yr	200 U BTX-A Detrusor×20	NA	2 (10)	0
Khan et al (2009) (39)	81 IDO	200 U BTX-A Detrusor×20	NA	35 (43)	31 (38)
Cohen et al (2009) (40)	44 OAB	100 U BTX-A (n=20)	NA	NA	1 (5)
		150 U BTX-A (n=24) Detrusor×10–15			1 (4)
Sahai et al (2009) (41)	67 IDO	200 U BTX-A Detrusor×20	NA	NA	19 (29)
Flynn et al (2009) (42)	15 OAB	100 U BTX-A	NA	4 (26)	1 (7)
		200 U BTX-A			
Kessler et al (2009) (43)	67 OAB women	200 U BTX-A	NA	28 (43)	28 (43)

PVR=postvoid residual; CIC=clean intermittent catheterization; IDO=idiopathic detrusor overactivity; BTX-A=botulinum toxin type A; OAB=overactive bladder; NA=not available; NDO=neurogenic detrusor overactivity; BTX-B=botulinum toxin type B.

achieved with 300 U in other studies [16,19,22]. However, there was a higher incidence of adverse effects such as difficult urination (75%), a large PVR (35%) and need for CIC (30%) [18].

Ghei et al tested the efficacy and safety of BoNT-B for treatment of OAB in a randomized, double-blind, placebo-controlled crossover trial. There were statistically significant paired differences in the changes in average voided volume, urinary frequency and episodes of incontinence between active treatment and placebo as well as change in the quality of life evaluated by King's Health Questionnaire. However, autonomic side effects were observed in four patients [21].

Sahai et al performed a double-blind, placebo-controlled trial. They randomized participants to intradetrusor injections of 200 U Botox or a placebo. Significant increases in maximum cystometric capacity were observed at 4 weeks and 12 weeks in treated patients compared with those given the placebo. Botox reduced frequency and urgency urinary incontinence episodes at 4 and 12 weeks, respectively. Urgency was reduced at 4 weeks in the BoNT-A group. The PVR increased at 4 weeks in 44% of patients who received BoNT-A injections, but this was insignificant by 12 weeks. Of these patients, 37.5% required CIC. Significant improvement in the quality of life was observed following BoNT-A treatment. An extension study suggested that the beneficial effects of BoNT-A were maintained for at least 24 weeks [31].

Brubaker et al compared 200 U intradetrusor Botox versus a placebo in women with refractory idiopathic urge incontinence. Approximately 60% of the treated women had a clinical response based on the Patient Global Impression of Improvement [37]. The median duration of their responses was 373 days, significantly longer than the ≤62 days for the placebo group. However, in the BoNT-A group, 43% of patients had an increased PVR and 75% of those with large PVRs had urinary tract infections (UTI). Because these adverse effects exceeded expected ranges, further injections were stopped after 43 patients were randomized: 28 to the treatment group and 15 to the placebo group.

Based on these clinical trials, the efficacy of BoNT on OAB has been confirmed and BoNT-A has been recommended as an alternative for patients with OAB refractory to antimuscarinics or drug intolerance [44,45].

3. Dose of BoNT-A for OAB

Because of the high incidence of adverse events after BoNT-A injections, the dose of BoNT-A for IDO has been reduced to 100 U by many investigators and a satisfactory outcome can still be achieved. Werner et al treated 26 women with IDO with a 53% success rate [17]. Schmid et al treated 100 IDO patients with 100 U BoNT-A and an 88% success rate was achieved [25]. However, the duration of therapeutic effects and incidence of adverse effects with 100 U BoNT-A need further clarification. A dose-related increase in adverse events has been found with increasing doses of Botox [24]. In a recent report by the author, 35% of patients had UTI, 30% had a large PVR requiring CIC, and 75% had difficult urination after suburothelial injection of 200 U Botox [24]. This high incidence of adverse effects might prohibit patients receiving a second injection when OAB relapses. A dose of suburothelial Botox of 100 U can reduce the rates of UTI to 4.3%, a large PVR to 30.4%, and difficult urination to 56.5% [24]. Therefore, adjustment of the dose for IDO patients seems mandatory to minimize *de novo* adverse effects. A recent study comparing 100 U versus 150 U Botox in patients with IDO also showed that symptom reduction and improvement in quality of life were equivalent [39]. Patients with IDO can increase bladder capacity without reducing voiding pressure and maximum flow rate, although PVR might be increased after intravesical injection of 100 U BoNT-A [31].

4. Clinical effects of BoNT-A with different injection methods and sites

There is a consensus on the detrusor injection technique for neurogenic DO, but not for IDO or OAB [45]. Recently, studies of BoNT-A injection for OAB and IDO have used suburothelial instead of intradetrusor injections. The important point is to target the suburothelial sensory pathway rather than paralysis of detrusor muscle contractility in the treatment of OAB. However, because the bladder wall is thin, it is impossible to differentiate the suburothelium from the detrusor layer on cystoscopy [46]. With regard to injections into the bladder wall, it is difficult to inject solely into the suburothelium without affecting detrusor contractility. A randomized trial comparing the effects of detrusor, suburothelial and bladder base injections of BoNT-A in IDO showed no significant difference between detrusor and suburothelial injections [31].

Desensitization of the mechanoreceptors of suburothelial sensory fibers by BoNT-A can result in a decrease of bladder urgency sensation and reduced sensory neuropeptide-mediated DO. One important factor for a successful therapeutic outcome is an accurate injection depth and adequate distribution of toxin into the suburothelial space or detrusor muscle. Because the bladder wall is very thin, the injection needle should not be inserted more than 1 mm or the solution might leak outside the detrusor wall. In a recent study of the distribution of 300 U Botox for neurogenic DO, magnetic resonance imaging detected

approximately 17.6% of the solution outside the bladder dome, with a mean 25–33% of the detrusor volume covered [47]. Injection into the suburothelium might avoid the potential loss of BoNT-A through detrusor injections, especially in the bladder of patients with IDO. If the toxin is not adequately distributed into the bladder wall, or is injected outside the bladder wall, the desired effect might not be achieved. This might explain why some studies found that detrusor injections of large doses of BoNT-A had therapeutic effects similar to those of suburothelial injections of small doses. It is possible that some detrusor injections were too deep and were outside the bladder wall.

The trigone and bladder base have abundant sensory fibers. Injections of BoNT-A into these areas have therapeutic effects on idiopathic urgency frequency syndrome and interstitial cystitis [48]. Although the trigone is rich in sensory fibers, the role of these fibers in bladder urgency sensation and IDO has not yet been established. Most urologists use a "trigone sparing injection" technique, largely because of potential vesicoureteral reflux after BoNT-A. However, there has been no evidence of this to date [32,34]. An advantage of trigonal injections is that detrusor underactivity does not develop after treatment, so a large PVR and acute urinary retention may not develop [32]. Another study evaluating the effects of BoNT-A injections in the trigone on the antireflux mechanism confirmed the safety in terms of development of vesicoureteral reflux or upper urinary tract damage [49]. Whether trigone and bladder base injections have this effect on OAB-dry or bladder hypersensitivity deserves further clinical study.

4.1. Adverse effects of intravesical BoNT-A injections

The main adverse effects of intravesical BoNT A injection are acute urinary retention, and a large PVR and UTI, which occur in variable percentages of patients [15–43]. UTI is usually associated with a large PVR [37]. Other adverse effects such as hematuria, micturition pain and general weakness are transient and are easily overcome by conventional treatment [18]. Intravesical injections of BoNT-A usually will not cause bleeding if the vessels of the bladder wall are avoided under direct visualization. A Foley catheter can be placed overnight or until the urine turns clear. The effects of BoNT-A appear on the second or third day, with a gradual increase in difficult urination and incomplete emptying.

In a recent study, large PVRs requiring CIC occurred in 30% of patients treated with 200 U Botox. A lower Qmax, lower projected isovolumetric pressure and lower bladder contractility index are risk factors for incomplete emptying [41]. Although another study found injections of 200 U of Botox were safe in elderly patients, the detrimental effect of retention on quality of life can be considerable [38]. Therefore, patients should be fully counseled on the risks of urinary retention and trained in intermittent catheterization before the procedure [50]. If adverse effects occur, an indwelling Foley catheter or CIC should be used to avoid UTI or upper urinary tract damage. After the first month, difficult urination will resolve, with improvement in urinary incontinence, bladder pain and urgency symptoms [18,31]. Interestingly, the occurrence of acute urinary retention and a large PVR do not affect the success rate of BoNT-A for OAB. In an analysis of 65 women treated with 200 U BoNT-A detrusor injections, there was no significant difference in the success rate between those who did and those who did not use CIC for a large PVR. The institution of CIC for a large PVR does not impair the quality of life after BoNT-A injection [43].

The response rate of BoNT-A on DO is closely related to the dose. Detrusor injections of 200 U of BoNT-A yield a response duration of 12–15 months [31], whereas those of 100 U BoNT-A are approximately 6 months [32,33]. However, the incidence of adverse effects is closely related to the dose [32]. In a randomized trial of DO, the incidence of a large PVR was 30%, 52% and 72% for 100 U, 150 U and 200 U BoNT, respectively [24]. Another recent clinical trial also found that the therapeutic efficacy was equivalent for 100 U and 150 U BoNT-A detrusor injections for OAB. A dose as small as 100 U appears to be adequate for reducing OAB symptoms and avoiding adverse events [40]. Bladder base injection alone also results in a lower incidence of acute urinary retention, but this treatment modality has a significantly shorter therapeutic period than bladder body injection [32].

5. Risk factors for developing adverse events after BoNT-A injection

Although a large PVR, UTI and chronic urinary retention remain obstacles for the wide application of BoNT-A in treatment of refractory DO, no factors predicting these adverse effects have been found. Since major adverse effects are associated with decreased detrusor contractility after BoNT-A injection, it is rational to speculate that age, a large baseline PVR, presence of comorbidity and impaired baseline detrusor contractility might carry risks for large postoperative PVR. Elderly patients with comorbidity might have less whole body energy and reduced muscle power in the detrusor. Previous studies have shown that suburothelial injections increase the risks for a high incidence of adverse events, especially a large PVR and straining to void [18,32]. This may be attributed to

greatly impaired voiding efficiency because of impaired detrusor contractility through sensory denervation after BoNT-A suburothelial injection. Thus, the dose for suburothelial BoNT-A injection may be reduced in vulnerable patients to prevent urinary retention or a large PVR after treatment.

Eleven previous clinical trials and reports of BoNT-A for OAB and IDO reported a 24–43% incidence of transient urinary retention requiring CIC [15,16,18, 24,31,33,37,39,41,43] and 10 trials reported a 32–72% incidence of a large PVR and difficulty in urination [15,16,18,22,24,31,32,37,39,43]. Although not all patients develop a large PVR or urinary retention, difficult urination and voiding by abdominal straining may be under-reported and might be potential problems after BoNT-A injection. However, patients with OAB and urinary incontinence (OAB-wet) might prefer these adverse effects to refractory urinary incontinence.

Clinically, most patients with OAB are elderly and may have several other medical diseases. Although detrusor BoNT-A injection was found to be safe for elderly patients with refractory OAB [15], the high rate of adverse effects deserves special attention before this treatment is recommended for patients with OAB and for those who are refractory to antimuscarinics. The risk factors for adverse effects should be determined before this novel treatment is accepted as the first-line treatment for refractory OAB.

Another interesting finding is the higher rate of UTI in women after BoNT-A injection, even though fewer women have acute urinary retention. Women are prone to develop UTI if they have a large PVR [37]. After BoNT-A injection, half of women have to void by abdominal straining and have a large PVR, which are risk factors for UTI in women. Men with benign prostatic hyperplasia (BPH) also have a higher risk of UTI than men who have undergone transurethral resection of the prostate for BPH. This may be attributed to a high voiding pressure and large PVR after BoNT-A injection. BPH also carries the risk of hematuria after BoNT-A injection. Therefore, in men with BPH, the injection should be carefully carried out to avoid injury to the bladder base or prostatic urethra.

Treatment of idiopathic OAB is not similar to that for neurogenic DO. A good therapeutic result for neurogenic DO is no incontinence and patients can accept the need for CIC to empty the bladder instead of urinary incontinence. However, patients with OAB need to be continent and able to void spontaneously without CIC or difficulty in urination after BoNT-A injection. Patients with OAB might have unreasonably high expectations of the therapeutic results of BoNT-A treatment. Therefore, they may feel upset when a large PVR and difficulty in urination develop after BoNT-A injection. Thus, fully informed consent should be obtained preoperatively.

6. Conclusion

Intravesical BoNT-A injection has emerged as an effective treatment for DO incontinence refractory to antimuscarinic treatment. Reports from case series and clinical trials have demonstrated that BoNT-A can reduce urgency incontinence within 1–2 weeks and the effects can be maintained for 6–12 months, depending on the dose. However, increasing doses can result in *de novo* problems such as a large PVR, transient urinary retention and UTI. To reduce the risk of adverse effects, careful selection of patients and adjustment of the dose and sites of BoNT-A injection are important. Patients who are older than 75 years and have impaired detrusor contractility, a large PVR, or chronic medical diseases are at significant risk of postoperative adverse effects. Therefore, fully informed consent should be obtained and CIC should be taught in case adverse effects occur after BoNT-A injection. Nevertheless, institution of CIC within the first postoperative month does not impair the quality of life of patients after BoNT-A injection for OAB.

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