What should we learn in the era of onabotulinumtoxinA treatment for lower urinary tract dysfunction (LUTD)

W4, 15 October 2012 09:00 - 12:00

Start	End	Topic	Speakers
09:00	09:15	Opening and Introduction	• Hann-Chorng Kuo
09:15	09:30	Mechanism of action of onabotulinumtoxinA on LUTD	• Yao-Chi Chuang
09:30	09:45	Therapeutic effects on urinary incontinence and renal function in patients with neurogenic detrusor overactivity undergoing repeated detrusor onabotulinumtoxinA injections	• Hann-Chorng Kuo
09:45	10:00	Adverse events and safety concern of onabotulinumtoxinA injection in frail elderly patients with overactive bladder and medical comorbidities.	• Chun-Hou Liao
10:00	10:15	Can onabotulinumtoinA be effective in treatment of interstitial cystitis refractory to conventional therapy?	• Shiu-Dong Chung
10:15	10:30	Satisfaction and dissatisfaction and quality of life issues in patients receiving urethral or detrusor onabotulinumtoxinA injections for DSD	• Chung-Cheng Wang
10:30	11:00	Break	None
11:00	11:15	Does onabotulinumtoxin still play a role in treatment of BPH? How to select suitable patients with LUTS for BoNT-A injection?	• Yao-Chi Chuang
11:15	11:30	Injection technique, dose and injection sites of onabotulinumtoxinA and the influence on the effects and adverse events	• Hann-Chorng Kuo
11:30	11:45	Prevention and management of adverse events after detrusor onabotulinumtxinA injection for patients with OAB	• Chun-Hou Liao
11:45	12:00	Questions	All

Aims of course/workshop

Botulinum toxin injection has become a novel treatment for lower urinary tract dysfunction such as refractory overactive bladder, neurogenic detrusor overactivity and painful bladder syndrome. However, lack of sufficient knowledge of the pharmacology, injection technique, dose and therapeutic effects, or adverse events will lead to serious complications, such as large residual urine, acute urinary retention, or urinary tract infection, after inappropriate injection. This workshop helps participants to get the first hand experience from world-wide experts and will help them to select appropriate patients and suitable injection technique for botulinum toxin injection.

Educational Objectives

We have run a botulinum toxin workshop in the Christchurch ICS annual meeting. The response from the audience was excellent. Recently, FDA and EU all approved the clinical indication of botulinum toxin A on neurogenic detrusor overactivity. Clinical trial of botulinum toxin A on overactive bladder and interstitial cystitis are currently underway. We believe, in the future, botulinum toxin will become a hot topic and be widely applied for treatment of lower urinary tract dysfunction such as refractory overactive bladder, neurogenic detrusor overactivity and painful bladder syndrome. However, lack of sufficient knowledge of the pharmacology, injection technique, dose and therapeutic effects, or adverse events will lead to serious complications after inappropriate injection. This workshop helps participants to get the first hand experience from world-wide experts and will help them to select appropriate patients and suitable injection technique for botulinum toxin injection. This workshop is update and important for ICS members.

What Should We Know in the Era of OnabotulinumtoxinA Treatment for Lower Urinary Tract Dysfunction (LUTD)

000~010 Opening (Kuo, Hann-Chorng, Hualien, Taiwan)

010~030 (1) Mechanism of action of onabotulinumtoxinA on LUTD (Chuang, Yao-Chi, Kaohsiung, Taiwan)

030~050 (2) Therapeutic effects on urinary incontinence and renal function in patients with neurogenic detrusor overactivity undergoing repeated detrusor onabotulinumtoxinA injections (Kuo, Hann-Chorng, Hualien, Taiwan)

050~070 (3) Adverse events and safety concern of onabotulinumtoxinA injection in frail elderly patients with overactive bladder and medical comorbidities (Liao, Chun-Hou, New Taipei, Taiwan)

070~090 (4) Can onabotulinumtoxinA be effective in treatment of interstitial cystitis refractory to conventional therapy? (Chung, Shiu-Dong, New Taipei, Taiwan)

090~110 (5) Satisfaction and dissatisfaction and quality of life issues in patients receiving urethral or detrusor onabotulinumtoxinA injections for DSD (Wang, Chung-Cheng, New Taipei, Taiwan)

110~130 (6) Does onabotulinumtoxin still play a role in treatment of BPH? (Chuang, Yao-Chi, Kaohsiung, Taiwan)

130~150 (7) Injection technique, dose and injection sites of onabotulinumtoxinA and the influence on the effects and adverse events (Kuo, Hann-Chorng, Hualien, Taiwan)

150~170 (8) Prevention and management of adverse events after detrusor onabotulinumtoxinA injection for patients with OAB (Liao, Chun-Hou, New Taipei, Taiwan)

170~180 Round table discussion and Q & A

1. Mechanism of action of onabotulinumtoxinA on LUTD

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Abstract

Botulinum toxins (BoNT) are well known for their ability to potently and selectively disrupt and modulate neurotransmission and treat muscular hypercontractility. In addition, recent studies also suggest that BoNT has effects on modulation of sensory function, inflammation, and glandular function, like prostate. Although BoNT is currently not FDA approved for urological use, urologists have become interested in the potential use of Botulinum toxin in patients with detrusor and sphincter overactivity, bladder hypersensitivity, lower urinary tract symptoms suggestive of benign prostatic hyperplasia and other urological disorders in the recent decade. This paper is intended to provide a technical review of the mechanism by which it modulates acetylcholine and other biochemical messengers at presynaptic nerve terminals, as well as how botulinum toxin type A (BoNT-A) affects its biological function on lower urinary tract.

Introduction

Botulinum neurotoxin (BoNT), produced by clostridium botulinum, a gram-positive, rod-shaped anaerobic bacterium, was originally thought to only

act by inhibiting acetylcholine (ACh) release at the presynaptic cholinergic neuromuscular junction and has been used effectively for different conditions with muscular hypercontraction [1,2]. There are seven immunologically distinct neurotoxins designated as: types A, B, C, D, E, F and G [1-3]. All serotypes block transmission at neuromuscular junctions to varying degrees, but the effects of botulinum neurotoxin type A (BoNT-A) are the most prolonged and this serotype has been the most extensively studied, mainly in models of neurotransmission in striated muscle.

However, only botulinum neurotoxin types A (BoNT-A) and B (BoNT-B) are in clinical use. There are three commercially available BoNT worldwide. Botox (Allergan, Inc., Irvine, CA) and Dysport (Ipsen Ltd., Berkshire, UK) are BoNT-A and Myobloc (Elan Pharmaceuticals, Inc., Princeton, NJ) is a BoNT-B. The potency of each toxin is expressed in units of activity. Although there are similarities among the commercial preparations of BoNT, they have different doses, efficacy and safety profiles and should not be considered generic equivalents comparable by single dose ratios [3].

The application of BoNT-A for the treatment of lower urinary tract symptom (LUTS) has been initiated since the late 1980's. Dykstra et al. described injection of BoNT-A into the external urethral sphincter in spinal injured patients to induce chemical sphincterotomy and to lower detrusor-sphincter dyssynergia [6]. In the past few years a resurgence of interest in BoNT-A was led by Schurch et al, who reported successful treatment of spinal-cord-injured patients with neurogenic bladder hyperactivty using intravesical BoNT-A injection at multiple sites [5]. Furthermore, Maria et al. first published the therapeutic effects of BoNT-A in patients with BPH [7]. As the uses of BoNT-A continue to expand in the field of urology, it is important to

understand the mechanism and clinical effects by which the toxin works on different tissue types and disease entities.

Mechanisms on inhibition of neurotransmitters release

BoNT-A is initially synthesized as an inactive chain of 1285 amino acids, which activation occurs when the single chain is cleaved by an endogenous Clostridial protease [1,8].This creates a dichain polypeptide containing a 50 kDa light chain and a 100 kDa heavy chain linked covalently by a single disulphide bond [8]. BoNT-A inhibits signal transmission at the neuromuscular and neuroglandular junction in four discrete stages**:** 1. binding of the toxin heavy chain to a specific nerve terminal receptor; 2. internalization of the toxin within the nerve terminal; 3. translocation of the light-chain into the cytosol and; 4. inhibition of neurotransmitter release.

BoNT-A recognizes and enters neurons by binding to the synaptic vesicle protein SV2 during neurotransmitter exocytosis when more active receptors are exposed [9]. BoNT-A attaches itself to receptors located on the nerve terminal via its heavy chain binding domain, then BoNT-A was taken up in a neuron activity-dependent manner by utilizing SV2 as its protein receptor and attacking active neurons in a receptor-mediate endocytotic process. After the process of internalization, the heavy chain is instrumental and creates ion channels or pores in the vesicle wall and the light chain undergoes translocation into the cytosol.

In nerve terminals, synaptic vesicles fuse with the presynaptic membrane where they release the neurotransmitter into the neuromuscular or

neuroglandular junction. Vesicle fusion is mediated by a set of SNARE (Soluble *N*-ethylmaleimide-sensitive fusion Attachment protein REceptor) proteins. In nerve terminals affected by botulinum neurotoxin, light chain proteolytic fragments release into the cytosol and cleave specific peptide bonds presenting in the synaptic fusion complex, and prevent exocytosis of neurotransmitter containing vesicle at the nerve terminal [1,2,9]. Each botulinum serotype cleaves a distinct protein site. BoNT-A cleaves SNAP-25, and types B cleaves synaptobrevin [1,2].

Duration of BoNT effects

The varying lengths of time that each toxin effectively inhibits exocytosis depend on the differences in SNARE-binding profiles between the botulinum toxin serotypes. BoNT-A, when used clinically for the treatment of dystonias, has by far the longest duration of activity, inducing clinical effects on neuromuscular activity for greater than 4 months, as compared with a duration of effect of approximately 2 months for BoNT-B or less than 4 weeks for BoNT-E [2,3]. Recovery of neurotransmission is dependent upon the removal of the botulinum neurotoxin protease as well as the restoration of intact SNARE proteins. In addition, structure differences in the end organs will lead to different duration of effects even with the same toxin.

BoNT-A biological effects

BoNT-A has effects on the motor function, sensory function, glandular function, and anti-inflammation through the modulation of various

neurotransmitters release in different kinds of tissue.

Motor effects and muscle structure

Despite some apparent differences at the cellular level, BoNT-A administration has the same clinical effect on both smooth and striated muscle. They act as biochemical neuromodulators, temporarily inactivating cholinergic transmission at the neuromuscular junction. Smith et al. found significant decreases in the release of labeled acetylcholine in BoNT-A injected normal rat bladders suggesting that BoNT -A could reduce cholinergic nerve induced bladder activity. In addition, release of other transmitters can be inhibited, particularly if high enough concentrations are utilized. For example, contractile data suggests that BoNT-A may impair ATP release in addition to ACh release from isolated bladder tissue.

Morphological changes after BoNT-A injection include subsequent compensatory nerve sprouting and the creation of extra-junctional synapses [12]. The sprouts are retracted and endplate functioning returns to normal when exocytosis at the parent terminal eventually recovers [12,13].

Previous studies have shown that BoNT-A produces no persistent changes in muscle fiber internal architecture after recovery from paralysis. None of the clinically available Clostridial neurotoxins cause death of neurons or myocytes. Thus, these neurotoxins are not toxic to tissue.

In the study of structure change of detrusor muscle, Haferkamp et al. collected 30 biopsies from 24 patients with a diagnosis of neurogenic overactive bladder [16]. They observed no significant changes in muscle cell fascicles, intercellular collagen content or muscle cell degeneration when

comparing biopsies taken before and 3 months after BoNT-A administration. Unlike striated muscle, axonal sprouting in detrusor smooth muscle was limited following BoNT-A administration. In another study, bladder wall specimen obtained from cystectomy in 45 patients with neurogenic overactive bladders, revealed that patients who had received botulinum toxin injection showed significantly less fibrosis of the bladder wall than those who had not received the toxin injection. In addition, a trend was observed that responder to the toxin therapy had less fibrosis and oedema of the bladder wall than non-responder [17].

Sensory effects

Recent basic and clinical evidence suggests that BoNT-A may have sensory inhibitory effects unrelated to its actions on ACh release. There has been increasing evidence to support that BoNT-A might also inhibit afferent neurotransmission and have analgesic properties [20]. Changes in afferent activity may influence pain through both direct sensory effects and indirect central reorganization in the CNS. It has been shown that BoNT-A inhibit the release of CGRP, substance P, glutamate, NGF, and ATP, which are mediators of painful sensation. Furthermore, *in vivo* animal studies also support a role for BoNT-A in relieving nociceptive pain. In a model of somatic pain associated with formalin-induced inflammation, rats pretreated with BoNT-A displayed significantly reduced pain behaviors and glutamate release from 5 hours to 12 days post-injection [21]. The similar effects were observed in an acetic acid induced bladder pain model [22]. These results support clinical observations that BoNT-A has an antinociceptive effect that is independent of its effects on the neuromuscular junction [20].

Bladder urothelium plays an important role in the sensory transduction mechanisms modulating micturition, particularly in conditions of increased sensory nerve transmission following chronic inflammation and spinal cord injury [23]. BoNT-A was shown to inhibit ATP release from the urothelium in spinal cord injured rat bladders. BoNT-A's effects are not limited solely to inhibiting neurotransmitter release. For example, studies have shown that TRPV1 (i.e. capsaicin-sensitive) receptors are released by SNARE-dependent processes and can be inhibited by BoNT-A treatment during laboratory studies [20,21]. In addition, decreased sensory receptors $P2X_3$ and TRPV1 in suburothelial nerve fibers associated with decrease in urgency following intradetrusor injections of BoNT-A has been found in human detrusor overactivity [24]. Giannantoni reported that intravesical BoNT-A injection reduces NGF content in the bladder tissue of patients with neurogenic detrusor overactivity [25]. The reduction of NGF content leads to decrease the hyperexcitability of C-fiber bladder afferents, thereby reducing neurogenic detrusor overactivity. Thus, the inhibitory effects of BoNT on sensory function may relieve somatic and visceral irritative symptoms.

Anti-inflammation

Chronic nonbacterial prostatitis, interstitial cystitis (IC) or chronic pelvic pain syndrome are common but frustrating clinical entities characterized by prostate pain, bladder pain or pelvic pain in the absence of identifiable infection. Abnormal sensory function of the prostate or bladder has been claimed for the symptoms of chronic prostatitis or IC [26,27]. The afferent neurons that contain CGRP and substance P convey nociceptive information from the prostate or bladder and may contribute to the symptoms of prostatitis and IC.

Using a capsaicin-induced prostatitis model in rats, previous studies demonstrated that the painful behavioral changes, polymorphonuclear cells accumulation, and COX-2 expression in the prostate gland and in the L6 ventral and dorsal horn induced by capsaicin injection were inhibited in dose dependent fashion by BoNT-A [28,29]. BoNT-A pretreatment could inhibit the capsaicin induced COX-2 expression from the peripheral organ to L6 spinal cord and inhibit prostatic pain and inflammation. This finding suggests a potential clinical benefit of BoNT-A for the treatment of nonbacterial prostatitis. Furthermore, our recent studies also demonstrated that intravesical BoNT-A administration blocked the CYP-induced bladder inflammation and hyperactivity and inhibited COX-2 and EP4 expression in the bladder as well as the spinal cord [30]. Taken together, these findings suggest that a potential benefit of BoNT-A treatment for prostate and bladder inflammatory conditions.

References

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Mechanism of action of onabotulinumtoxinA on LUTD

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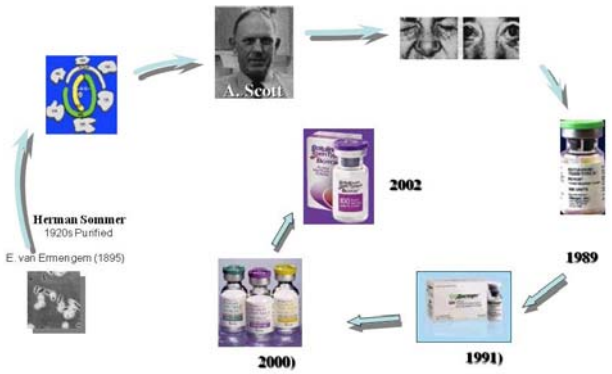
Botulinum Toxin Timeline



Botulinum Toxin Nomenclature

- Botulinum toxin as BoNT and BTX
- Other references in literature include:
  - BoNT
  - BoNT/A
  - BoNT-A
  - Btx-B
  - BTX-A is also the name of a botulinum product in China

FDA Recommended New Names

•AbobotulinumtoxinA
(Dysport; Ipsen Ltd., Berkshire, UK)

•IncobotulinumtoxinA
(Xeomin; Merz Pharmaceuticals GmbH. Germany)

•OnabotulinumtoxinA
(Botox and Botox Cosmetic, Allergan, Inc., Irvine, CA)

•RimabotulinumtoxinB
(Myobloc/Neurobloc; US WorldMeds, Louisville, KY)

Commercial preparations of BoNT have different doses, efficacy and safety profiles and should not be considered generic equivalents

Botulinum Toxins In Clinical Use

Serotype	A	A	A	B
Generic Name	Onabotulinum toxinA	Abobotulinumt oxinA	Incobotulinumto xinA	Rimabotulinum toxinB
Brand name	Botox	Dysport	Xeomin	Myobloc/Neuro bloc[1]
Manufacturer	Allergan Inc (United States)	Ipsen (France)	Merz Pharmaceuticals GmbH (Germany)	US WorldMeds (United States)
Packaging, U/vial	100	500	100	2500, 5000, or 10000
Specific activity, U/ng	20	40	167	75-125

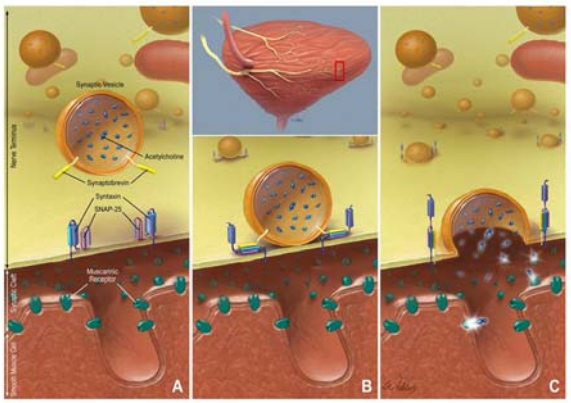
•Adopted from Albanese, JAMA 305:89, 2011. 1Myobloc is the brand name in the USA, Canada and Korea. Neurobioc is the brand name in the European Union, Iceland and Norway.

Key History of Botulinum Toxin (BoNT)- Clinical Urology

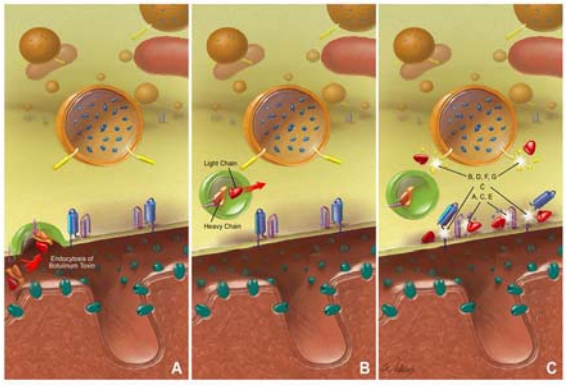
- Dykstra et al. published injection of BoNT in the urethral sphincter for DESD patients (J Urol, 1989)
- Schurch et al. published injection of BoNT in the bladder for neurogenic urge incontinence (New Eng J Med, 2000)
- Maria et al. published injection of BoNT in the prostate (Urology, 2003)

Key History of Botulinum Toxin (BoNT)- Basic Science in Urology

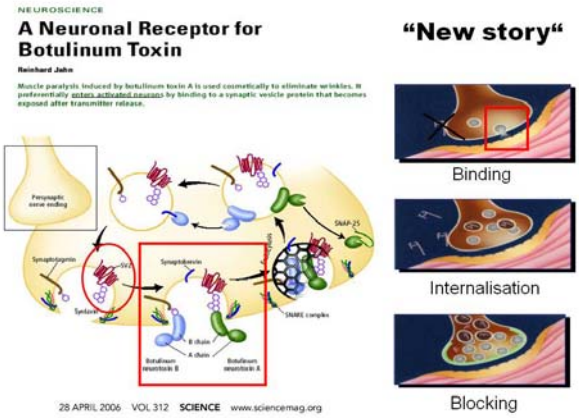
- Dogweiler et al. proved BoNT induced apoptosis in rat prostate (Prostate, 1998)
- Smith et al. proved BoNT inhibited Norepinephrine and Acetylcholine release in rat urethra and bladder (J Urol, 2003)
- Chuang et al. proved sensory effects on rat bladder (J Urol, 2004); effects on dynamic component and static component of rat prostate (J Urol, 2006); anti-inflammatory effect on rat prostate and bladder (Eur Urol, 2007, 2009; J Urol 2008, 2009)



- **Schematic diagram demonstrating normal fusion and release of acetylcholine from nerve terminals via interaction of SNARE proteins.**
- *Smith and Chancellor, JU 2004*

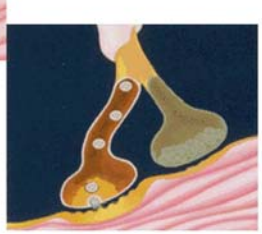


- **A) Binding of toxin heavy chain to nerve terminal receptor and internalization of the toxin; B) translocation of the light-chain into the cytosol and; C) Inhibition of neurotransmitter release by cleavage of specific SNARE proteins.**
- *Smith and Chancellor, JU 2004*



Mechanism of Action

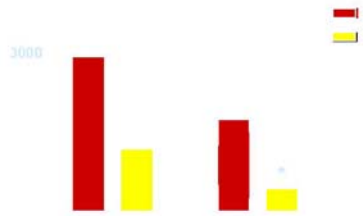
Re-establishment of nerve to muscle transmission



Botulinum toxin Injections wear off

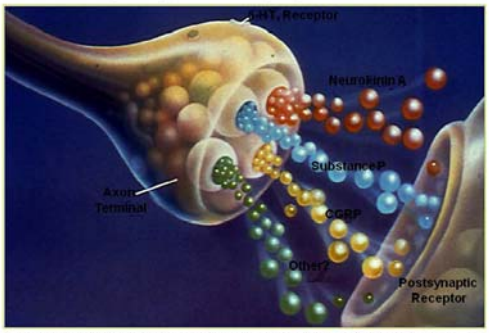
Mechanism of action of onabotulinumtoxinA on bladder

Bladder Neurotransmitter Release



(Smith and Chancellor *et al., J Urol, 2003)

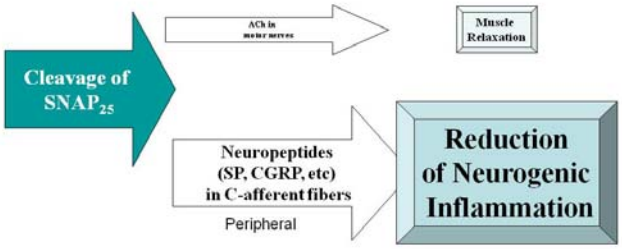
BoNT may inhibit release of peripheral peptides



Reproduced with permission from: Silberstein SD, et al. *Headache in Clinical Practice*. Isis Medical Media; 1998:41-55.

Reduction of Neurotransmission and Neurogenic Inflammation

Biochemical **Neurotransmitter Inhibited** **Clinical Benefit**



Intravesical Botulinum Toxin A Administration Produces Analgesia Against Acetic Acid Induced Bladder Pain Responses In Rats (Chuang et al., J Urol, 2004)

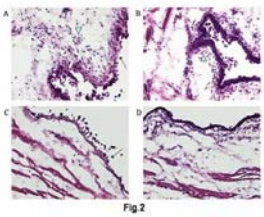


Fig.2

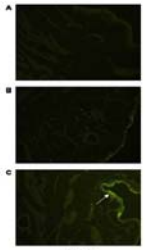


Fig.3

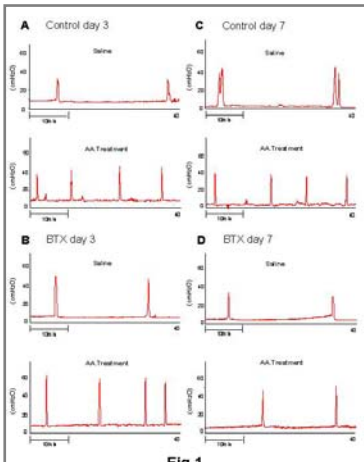


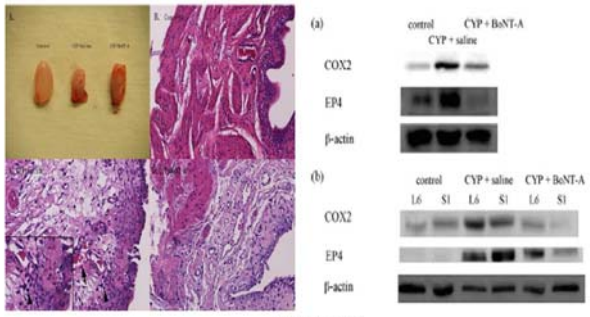
Fig.1

Fig. 1
Representative traces of in vivo continuous cystometrograms (CMG) in urethane anesthetized rats. CMG was performed in control rat at day 3 (A) and day 7 (C) after PS/saline instillation, and PS/BTX-A treated rat at day 3 (B) and day 7 (D). After acetic acid infusion, both control rat and BTX-A pretreated rat showed reduction in ICI, however, the reduction in ICI was significantly smaller (anti-nociceptive effect) in BTX-A pretreated rat at day 7.

(Chuang et al., J Urol, 2004)

Intravesical Botulinum Toxin A Administration Inhibits COX-2 and EP4 Expression and Suppresses Bladder Hyperactivity in Cyclophosphamide-Induced Cystitis in Rats

Yao-Chi Chuang [a,], Naoki Yoshimura [b], Chao-Cheng Huang [c], Moya Wu [a], Po-Hui Chiang [a], Michael B. Chancellor [d]*



(Eur Urol., 2009)

DECREASED SENSORY RECEPTORS $P2X_3$ AND TRPV1 IN SUBUROTHELIAL NERVE FIBERS FOLLOWING INTRADETRUSOR INJECTIONS OF BOTULINUM TOXIN FOR HUMAN DETRUSOR OVERACTIVITY

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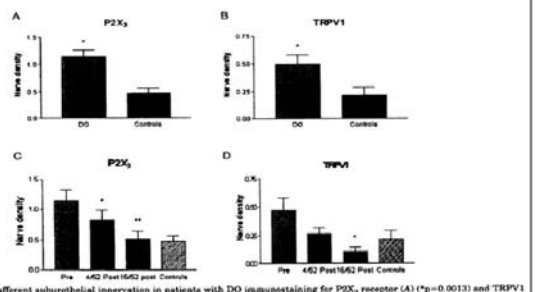
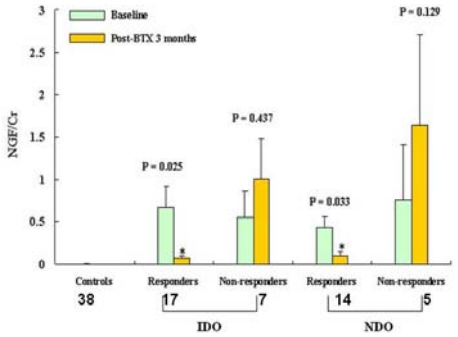


FIG. 3. Increased afferent suburothelial innervation in patients with DO immunostaining for $P2X_3$ receptor (A) (*p=0.0013) and TRPV1 receptor (B) (*p=0.018) compared with controls. Reduction of $P2X_3$ (C) and TRPV1-IR suburothelial fibers (D) was noted in successive followup after treatment with intradetrusor BoNT/A. Decrease at 4 weeks (*p=0.009) (C) was followed by more significant decrease at 16 weeks (**p =0.0004, fig. 3, C; *p=0.0008, fig. 3, D), achieving normalization of $P2X_3$ and TRPV1 values.

(J Urol, 2005)

Urine NGF Levels After BoNT-A



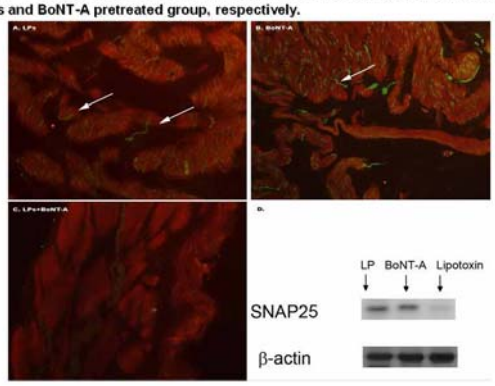
(Liu and Kuo * et al. Eur Urol 2008)

Urodynamic and Immunohistochemical Evaluation of Intravesical Botulinum Toxin A Delivery Using Liposomes

- Liposomes are stable self assembled phospholipid BUBBLES filled with water which adhere to a surface
- Liposomes have long history of safe clinical use for drug delivery

Chuang et al., J.Urology 182:786, 2009

SNAP-25 positive neuronal fibers were detected in the bladder samples of LPs and BoNT-A pretreated animals. However, SNAP-25 positive neuronal fibers were rarely seen in the Lipotoxin pretreated animals. Western blotting demonstrated that mean SNAP-25 protein level was 66.4% decrease and 58.1% decrease compared to the LPs and BoNT-A pretreated group, respectively.

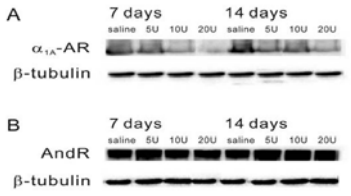


Liposome-BoNT Conclusions

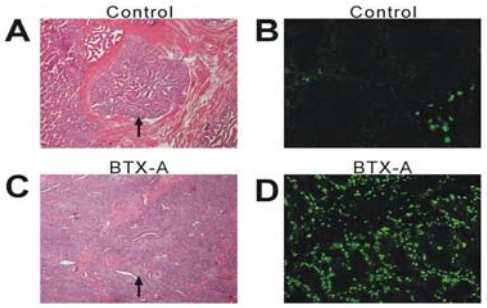
- Intravesical Lipotoxin cleaved SNAP-25 in bladder and inhibited CGRP release from afferent nerve terminals, and blocked the cystometric changes induced by AA induced irritation
- Intravesical instillation of Lipotoxin might provide a simpler and effective method for the treatment of OAB without the need for injection and with lower risk of urinary retention

Mechanism of action of onabotulinumtoxinA on prostate

Fig. 5 Western blotting for detecting α1A adrenoceptor (AR) and androgen receptor (AndR). A. The protein amount of α1A adrenoceptor was reduced by BTX-A treatment at 1 week, which effect was reduced at 2 week. B. No significant difference in the amount of androgen receptor in the saline and BTX-A treated animals



(Chuang et al., J Urol, 2006)



Canine prostate after saline (A,B) and BoNT-A (C,D) injection at 1 month
Significant glandular proliferation with papillary infolding in control (A)
Glandular atrophy with flattening of the lining epithelium in BoNT-A group (C)
Few apoptotic nuclei are recognizable in control (B)
Strong fluorescence of apoptotic nuclei was seen in BoNT-A treated animal

Chuang et al., BMC Urol., 6:12, 2006

Effects of Botulinum Toxin A on the Contractile Function of Dog Prostate

Alex Tong Long Lin [a,*], *An Hang Yang* [a,b], *Kuang-Kuo Chen* [a]

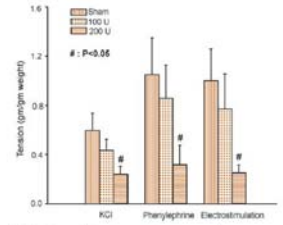


Fig. 4 – Contractile responses of prostate strips to 120 mmol/l potassium chloride (KCl), phenylephrine (10^{-5} mol/l), and electrostimulation (50 V, 1 ms, 64 Hz). Each bar represents the mean ± SEM of 5 to 7 animals. # indicates a significant difference compared with sham group.

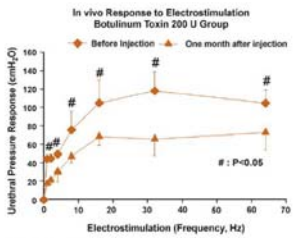


Fig. 3 – Prostate urethral pressure response to electrostimulation 1 mo after injection of 200 units botulinum toxin A (BoNT/A). # indicates a significant difference as compared with before BoNT/A injection.

(Eur Urol, 2007)

Intraprostatic Capsaicin Injection As A Novel Model For Non-bacteria Prostatitis

A: Severe prostatic pain induced by capsaicin (1000 uM) injection, most frequently characterized by closing of the eyes and hypolocomotion.
B: Less pain, eyes opening and good motion, one week pretreatment with BoNT-A 20 U.
C: More edematous change of prostate in rat without BoNT-A (right) than with BoNT-A 20 U (left).

Chuang et al., European Urology, 2007; J Urol, 2008

2. Therapeutic Effects on Urinary Incontinence and renal Function in Patients with Neurogenic Detrusor Overactivity Undergoing Repeated Detrusor OnabotulinumtoxinA Injections

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Abstract

Objective: To investigate the effect of repeated detrusor onabotulinumtoxinA injections on restoration of urinary continence and renal function in patients with chronic spinal cord injuries (SCI).

Methods: A total of 33 patients with chronic suprasacral cord injuries were enrolled. OnabotulinumtoxinA 200U was administered to 40 sites of the detrusor every 6 months for 2 years. Patients were instructed to perform clean intermittent catheterization during the treatment and follow-up periods. Videourodynamic study and 99mTc-DTPA renal scanning for glomerular filtration rate (GFR) were performed at screening and repeated every 6 months to assess the therapeutic effects on bladder and renal function. Quality of life was measured by the UDI-6, IIQ-7, and self-assessed QoL indices. Adverse events such as difficult urination, urinary tract infection, and hematuria were also recorded.

Results: Among the 33 patients, 30 had improvement in incontinence grade (n=18) or became completely dry (n=12) after initial and subsequent onabotulinumtoxinA injections. Mean bladder capacity increased from 207±111 to 412±33 ml, mean detrusor pressure decreased from 39.8±21.7 to 20.6±19.1 cm H_2O, mean end-filling intravesical pressure decreased from 31.5±20.1 to 22.5±14.0 cm H_2O (all $p<0.05$), and mean GFR decreased from 93.4±20.4 to 83.5±24 ml/min ($p=0.028$) at the end of the study. UDI-6, IIQ-7, and QoL-I scores revealed that quality of life improved significantly after repeated onabotulinumtoxinA injections.

Conclusion: Repeated detrusor injections of 200U onabotulinumtoxinA can reduce incontinence grade, increase bladder capacity, and decrease intravesical pressure but do not improve renal function over a 24-month period in patients with chronic SCI.

Introduction

Spinal cord injury (SCI) results in neurogenic voiding dysfunction and urinary symptoms. In patients with chronic suprasacral cord injury, detrusor sphincter dyssynergia (DSD) can result in increased intravesical pressure, urinary incontinence, and large postvoid residual (PVR) urine volume. [1] High intravesical pressure can also damage upper urinary tract function and cause renal scarring or chronic renal insufficiency. Indwelling Foley catheterization or clean intermittent catheterization (CIC) is frequently introduced for bladder management in patients with DSD and large PVR volumes. [1,2] Although some patients can void spontaneously by abdominal tapping or genital stimulation, high voiding pressure can jeopardize the function of the upper urinary tract in patients with chronic SCI. [3]

Antimuscarinics and CIC have been found to lower the risk of renal function deterioration. However, the high incidence of intolerable adverse events (dry mouth, constipation, blurred vision) and the need to frequently carry out CIC often result in patients abandoning CIC and instead relying on spontaneous reflex voiding. Those patients, therefore, are at high risk of incontinence and chronic renal insufficiency, conditions that can result in frequent urinary tract infection (UTI) and end-stage renal failure. [1-3] Although CIC has been shown to prevent renal damage in patients with chronic SCI, long-term renal insufficiency remains a problem.

Studies have shown that 200 to 300U of onabotulinumtoxinA injected into the detrusor can restore urinary continence, lower the rate of UTI, decrease intravesical pressure, and increase bladder compliance in up to 80% of SCI patients. [4-10] Although repeated injections of onabotulinumtoxinA are necessary to achieve the desired effects, most patients tolerate the procedure in exchange for a better quality of life (QoL). [4-6]

Repeated detrusor injections of onabotulinumtoxinA have been shown to be effective in treating neurogenic detrusor overactivity (NDO) and urinary incontinence. [9,10] Repeated injections of onabotulinumtoxinA lower the intravesical pressure, thereby reducing the intrapelvic pressure. If low-pressure status of the urinary bladder can be maintained over the long-term by repeated detrusor onabotulinumtoxinA injections, then the treatment may be able to restore renal function in patients with SCI.

In this study, we investigated the long-term therapeutic effects of repeated detrusor onabotulinumtoxinA injections on improvement of urinary continence and recovery of impaired renal function in patients with chronic spinal cord injuries.

Materials and Methods

A total of 38 patients aged > 18 years with more than a one-year history of chronic suprasacral cord injury were enrolled during the period January 2006 to October 2008 and followed until October 2010. In all patients, a diagnosis of DSD was made based on videourodynamic study. In addition, all patients voided by reflex or abdominal stimulation with or without CIC, were free of indwelling catheter or cystostomy, and were free of UTI on enrollment. During the screening period, total glomerular filtration rate (GFR) was measured by 99mTc-labelled diethylenetriamine pentaacetic acid (99mTc-DTPA) clearance renal scanning. [11] Exclusion criteria included patients with detrusor underactivity and large bladder compliance, patients proven to have intrinsic sphincteric deficiency, patients with grade 2 or higher vesicoureteral reflux, and patients who had hypersensitivity to onabotulinumtoxinA or any type of Botulinum toxin.

This study was approved by the Institutional Review Board and Ethics Committee of the Buddhist Tzu Chi General Hospital. Informed consent was obtained before the screening and all patients were informed about the possible complications related to onabotulinumtoxinA injection.

OnabotulinumtoxinA injection was performed in the operating room under light intravenous general anesthesia. A total of 200U onabotulinumtoxinA (Allergan Co., Irvine, USA) dissolved in 20ml normal saline was injected into 40 sites of the detrusor including the lateral and posterior walls and the dome, sparing the trigone. The injection sites were widely distributed to cover the bladder wall. A 14 Fr Foley catheter was routinely inserted after onabotulinumtoxinA injection and patients were discharged the next morning and followed up at the outpatient clinic. All patients were instructed to continue CIC or abdominal stimulation. OnabotulinumtoxinA injections were repeated every 6 months. Before each subsequent onabotulinumtoxinA injection, a videourodynamic study and GFR test were performed.

After onabotulinumtoxinA injection, antimuscarinics were discontinued. Patients were requested to return every 3 months to gauge improvements in continence and GFR. The Urogenital Distress Inventory (UDI-6) and the Incontinence Impact Questionnaire (IIQ-7) [12] were used to assess incontinence distress and impact of urinary incontinence on daily life, respectively. Quality of life was also evaluated with the self-assessed QoL index adapted from the International Prostatic Symptom Score (IPSS) [13]. The Patient Perception of Bladder Condition (PPBC) questionnaire, a

patient-reported measure of bladder condition, was used to assess patient satisfaction with treatment outcome. Patient satisfaction was based on change in PPBC score after onabotulinumtoxinA injection. No change in score was defined as not satisfied; a change of +1 was defined as mildly satisfied; a change of +2 was defined as moderately satisfied; and a change of +3 was defined as very satisfied with treatment outcome. [14]

Patients were regularly followed up every 3 months for up to 24 months. There were two primary end-points: (1) the net change in incontinence grade assessed by the sum of incontinence scores of the UDI-6 questionnaire from baseline to 24 months, and (2) the net change in GFR from baseline to 24 months. Secondary end-points included the net change in scores of the UDI-6, IIQ-7, QoL-I, and PPBC measures as well as changes in urodynamic variables including cystometric bladder capacity, detrusor pressure at Qmax (Pdet.Qmax), PVR, and bladder compliance from baseline to 24 months. The duration of the therapeutic effect was recorded and Kaplan-Meier survival curve was used for analysis.

Results

A total of 21 men and 17 women were enrolled in this study. Two patients withdrew from the study before treatment and 3 patients dropped out after the first treatment because they could not return for regular visits. The mean age of the remaining 33 patients who completed the study was 37 ± 23 years (range, 18 to 63 years). Seven patients had complete cervical SCI, 15 had complete thoracic or lumbar SCI, and 11 patients had incomplete suprasacral SCI. All had DSD on videourodynamic study and none of them had vesicoureteral reflux.

Among the 33 patients, 12 (36.4%) became completely dry, 18 (54.5%) had improvement, and 3 (9.1%) did not have any change in incontinence grade after initial and subsequent onabotulinumtoxinA injections. Summation of two incontinence-related items in the UDI-6 revealed persistent decreases in mean incontinence scores after repeated injections (4.76 ± 1.57 at baseline, 2.92 ± 2.11 at 6 months, 2.13 ± 1.96 at 12 months, 2.32 ± 1.91 at 18 months, and 2.56 ± 2.26 at 24 months) (all $p<0.05$ compared to baseline). The UDI-6, IIQ-7, and QoL-I scores significantly improved at all time points after repeated onabotulinumtoxinA injections. (Table 1) All three scores showed persistent and cumulative improvements throughout the treatment course. (Fig.1)

The mean urodynamic parameters at baseline and after onabotulinumtoxinA injections are shown in Table 2. Mean cystometric bladder

capacity significantly increased at 6 months and continued to increase at all time points. Mean bladder capacity increased from 207 ± 111 to 412 ± 33 ml, mean detrusor pressure decreased from 39.8 ± 21.7 to 20.6 ± 19.1 cm H_2O, and end-filling intravesical pressure decreased from 31.5 ± 20.1 to 22.5 ± 14.0 cm H_2O (all $p<0.05$). Bladder compliance also increased significantly after repeated onabotulinumtoxinA injections at 24 months (26.9 ± 26.8 v 40.1 ± 24.1, $p=0.035$). Interestingly, the urodynamic variables showed greater improvement at 3 months than at 6 months after each onabotulinumtoxinA injection. There was also a persistent and cumulative improvement in urodynamic variables after serial onabotulinumtoxinA injections. (Fig.2)

At baseline, 30 patients used CIC combined with reflex voiding and all patients required diaper protection to prevent urine soiling. After onabotulinumtoxinA injections, CIC was necessary in all 33 patients; however, the frequency of daily CIC decreased from 6.5 ± 2.7 times per day to 4.3 ± 2.1 times per day ($p<0.001$) and the number of diapers used daily decreased from 7.1 ± 2.3 to 3.5 ± 2.5 ($p<0.001$).

GFR significantly decreased throughout the treatment course (96.27 ± 22.50 at baseline v 83.51 ± 23.96 at 24 months, $p=0.028$) (Fig. 3). However, there was no significant change in mean serum Cr levels during the same period (0.623 ± 0.183 v 0.675 ± 0.175, $p=0.802$). The change in GFR from baseline to 24 months was not significant in patients with a baseline compliance of <10 ml/cm H_2O, but was significant in patients with a baseline compliance of $\geq$10 ml/cm H_2O. There was a significant reduction in GFR in patients with bladder compliance that increased by < 10 cm H_2O after repeated onabotulinumtoxinA injections ($p=0.002$), and in patients in whom Pdet decreased by < 10 cm H_2O after treatment ($p=0.036$), (Table 3).

Among the 132 BTX-A injections, there were 9 (6.8%) episodes of febrile UTI, 4 (3%) episodes of hematuria, and 37 (28%) episodes of pyuria (white blood cell count >10/HPF). No autonomic dysreflexia, urosepsis, respiratory distress, or gastroenteric distress was noted after any of the injections.

The therapeutic effect of onabotulinumtoxinA lasted from 6 to 26 months (mean, 14 months), and the effect lasted for more than 12 months in 18 (60%) patients. (Fig.4) All 30 of the patients with improvements in incontinence grade reported that the treatment effect was satisfactory and that they wished to continue onabotulinumtoxinA treatment.

Discussion

The results from this study demonstrate that detrusor injections of onabotulinumtoxinA can improve urinary incontinence grade but do not improve impaired renal function over a 24-month period in patients with chronic SCI. OnabotulinumtoxinA injections resulted in a marked increase in cystometric bladder capacity soon after the first injection and further increases in bladder capacity after the 4th injection. The therapeutic effect was maintained for one year in 60% of patients after four injections.

Impaired renal function used to be the leading cause of death in patients with chronic SCI. [15] Although bladder management methods have evolved in recent decades, chronic renal insufficiency remains a significant cause of morbidity in this population. [16] Detrusor hyperreflexia and low bladder compliance are the major risk factors for renal damage in SCI patients. [17,18] However, intermittent catheterization, antimuscarinic therapy, and regular urodynamic monitoring have been reported to reduce the risk of renal failure. [19-21]

Patients with suprasacral cord injuries may void by reflex or abdominal tapping with adjuvant CIC. [22] Many of those patients, however, might not perceive the presence of large PVR volumes and high intravesical pressure during bladder filling. Frequent detrusor contractions with persistent high intravesical pressure during the filling phase may jeopardize the function of the upper urinary tract over time. [17, 23] Serum creatinine levels are routinely used to monitor renal function; however, patients with impaired renal function might have normal serum creatinine levels in the early stage of renal failure. Therefore, early detection and management of impaired renal function is mandatory to prevent the development of end-stage renal disease in patients with chronic SCI.

Previously, SCI patients were encouraged to periodically perform CIC in order to evacuate residual urine and reduce the intravesical pressure. [19, 22] The cause of progressive renal insufficiency might be related to low bladder compliance or high detrusor contraction pressure. [17] Linsenmeyer et al. reported that the duration of uninhibited detrusor contractions was significantly associated with upper urinary tract stasis in patients with suprasacral SCI. [23] Oral or intravesical antimuscarinic therapy provides an effective treatment for detrusor hyperreflexia; however, those therapies are not acceptable to all SCI patients because of the long-term adverse effects and low level of tolerability. [24] On the other hand, SCI patients with detrusor overactivity incontinence might not perceive large PVR volumes and, therefore, might not perform regular CIC, resulting in the gradual impairment of renal function.

In recent decades, treatment of DSD with onabotulinumtoxinA has emerged as an alternative method for the management of urological complications due to SCI. Intravesical injection of 200 to 300 units of onabotulinumtoxinA has been shown to reduce detrusor contractility, improve bladder compliance, and restore urinary continence. [4,5] Urethral sphincter injection of onabotulinumtoxinA has also been shown to reduce urethral resistance and facilitate bladder emptying. [25,26] The former treatment usually induces detrusor underactivity and urinary retention, and about 70% of patients require periodic CIC, which increases the risk of developing UTI. [7] Although the latter treatment might cause undesired exacerbation of urinary incontinence, the treatment can lead to a reduction in PVR volume as well as a reduction in the number of episodes of UTI. [25,26] Both routes of onabotulinumtoxinA injection can lead to a reduction in intravesical pressure or detrusor leak-point pressure, and therefore, might have a protective effect against upper urinary tract damage and might be able to restore renal function.

Single-shot 99mTc-labelled diethylenetriamine pentaacetic acid (99mTc-DTPA) clearance has been shown to be an accurate and practical method of determining GFR in patients with SCI. [11] However, this study did not demonstrate that detrusor onabotulinumtoxinA injections lead to improvement in GFR after repeated injections over a 24-month period. Although the GFR decreased progressively during the follow-up visits, there was no significant difference in mean GFR values between baseline and the most recent follow-up. We found that a persistently high intravesical pressure at the end of bladder filling and poor improvement in bladder compliance were risk factors for impaired GFR. These patients, therefore, might be better managed with a treatment modality other than detrusor onabotulinumtoxinA injection.

The dose of onabotulinumtoxinA used in this study was 200U, which was different from that used in previous studies. Although the QoL after onabotulinumtoxinA injection has been noted to be comparable between patients that received 200U and those that received 300U onabotulinumtoxinA, [9] the effect of the agent on detrusor pressure or bladder compliance differed. Our finding that renal function decreased progressively in patients without an increase in bladder compliance as well as in those without a decrease in Pdet after repeated onabotulinumtoxinA injection further revealed the importance of administering an adequate dose of onabotuluinumtoxinA when treating SCI patients. The differences in dosage of onabotulinumtoxinA between our study and previous studies might explain why renal function failed to improve in our

patients.

The goals of bladder management in chronic SCI patients are (1) to ensure social continence; (2) to reduce pressure storage and improve bladder emptying at low detrusor pressure; (3) to avoid overdistention of the bladder; (4) to prevent upper urinary tract complications caused by high intravesical pressure; and (5) to prevent urinary tract infection. [27] This study has shown that detrusor onabotulinumtoxinA injections can improve incontinence episodes and improve QoL for patients with chronic SCI. However, 200U onabotulinumtoxinA appears to be insufficient to improve renal function. SCI patients might encounter progressive deterioration of renal function over time if their bladder condition does not improve.

Conclusion

Repeated detrusor injections with 200U onabotulinumtoxinA can increase bladder capacity, decrease intravesical pressure, reduce incontinence grade, and improve QoL but do not restore renal function in patients with chronic spinal cord injuries.

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Table 1. Changes in UDI-6 and IIQ-7 scores and Quality of life indexes at baseline and after onabotulinumtoxinA injections in patients with chronic spinal cord injury

	UDI-6	IIQ-7	QoL-I
Baseline	11.39±3.39	13.35±6.70	4.51±1.34
3 months	7.65±3.91 *	7.06±6.27 *	2.31±1.28 *
6 months	8.46±4.29 *	8.84±6.76 *	2.31±1.28 *
9 months	7.19±3.67 *	6.19±6.31 *	1.97±1.36 *
12 months	7.61±3.75 *	6.71±6.25 *	2.29±1.49 *
15 months	6.35±2.83 *	5.16±5.23 *	1.90±1.30 *
18 months	7.33±3.93 *	6.00±5.71 *	2.30±1.23 *
21 months	5.85±3.23 *	4.37±5.76 *	1.59±1.22 *
24 months	7.78±4.11*	6.00±6.78 *	2.26±1.68 *

p<0.05 compared to baseline

Table 2. Changes in urodynamic parameters at baseline and after onabotulinumtoxinA injections in patients with chronic spinal cord injury

	Cystometric capacity(ml)	Pdet.Qmax (cmH2O)	Qmax (ml/s)	PVR (ml)	Compliance (ml/cmH2O)	End-filling pressure
Baseline	207.1±111	39.8±21.68	5.46±5.83	131.1±100	26.9±26.8	31.5±20.1
3 months	370.5±181 *	25.6±17.02*	3.49±4.80*	288±209*		
6 months	306.4±186 *	29.4±25.54*	1.97±2.94*	263.±183*	29.0±31.6	24.7±18.8
9 months	371.3±152 *	19.1±16.3 *	2.81±4.01*	306±173*		
12 months	376.9±180 *	23.1±17.62*	2.00±4.01*	346±195*	31.8±27.1	24.9±17.8 *
15 months	386.7±112 *	17.6±16.12*	2.42±4.25*	342±148*		
18 months	369.7±129 *	22.5±20.14*	2.44±4.46*	324±150*	38.5±29.6	25.5±18.5 *
21 months	463.3±137 *	16.1±17.82*	1.96±4.00*	431±148*		
24 months	411.7±32.9*	20.6±19.08*	2.37±3.71*	364±189*	40.1±24.1 *	22.5±14.0 *

* p<0.05 compared to baseline

Table 3. Changes in GFR in patients with good or fair GFR at baseline

	Baseline GFR	24-M GFR	P value
Baseline			
Compliance ≤10 (n=14)	86.3 ± 20.4	84.9 ± 28.5	0.990
Compliance >10 (n=24)	98.9 ± 22.1	83.2 ± 21.8	0.003
BL - 24M Compliance			
Increased ≥10 (n= 17)	93.5 ± 20.4	86.2 ± 26.4	0.284
Increased <10 (n= 9)	92.3 ± 22.6	77.0 ± 19.9	0.002
BL - 24M Pdet change			
Decreased ≥10 (n= 23)	96.0 ± 21.1	89.2 ± 24.3	0.087
Decreased <10 (n=4)	78.5 ± 4.4 *	64.7 ± 13.9 *	0.036

GFR: glomerular filtration rate, Pdet: detrusor pressure

Fig 1. Changes in UDI-6 and IIQ-7 scores and QoL index at different time points in patients treated with detrusor onabotulinumtoxinA injections

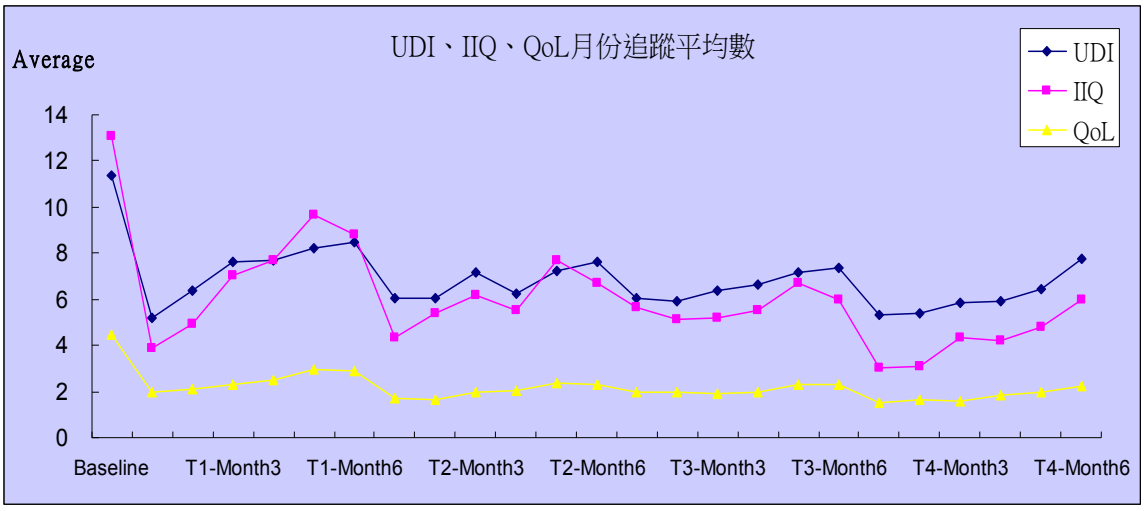


Fig.2. Changes in urodynamic parameters (CBC, Pdet, Qmax, PVR) from baseline to 24 months after repeated onabotulinumtoxinA injections

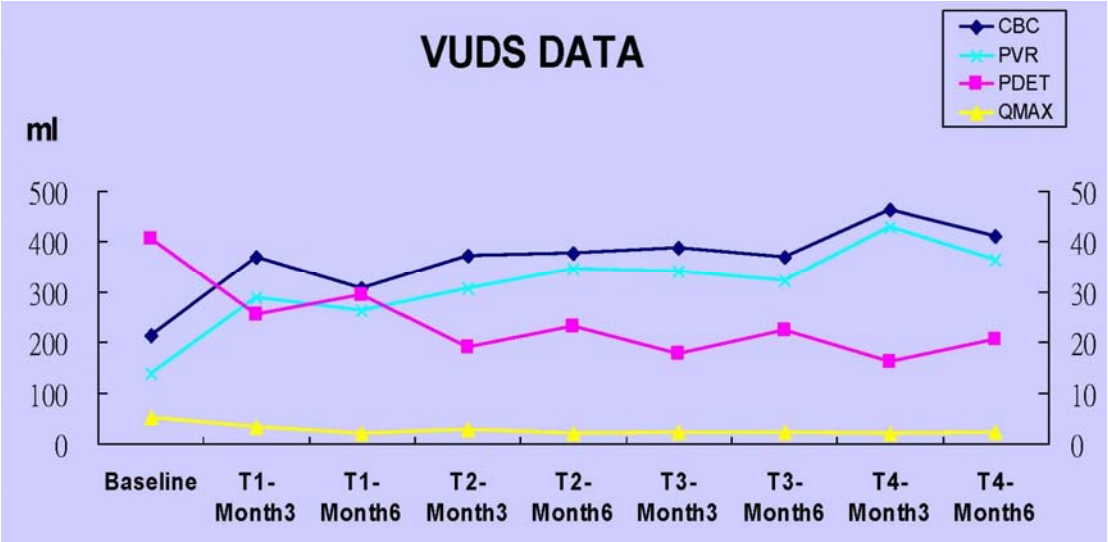
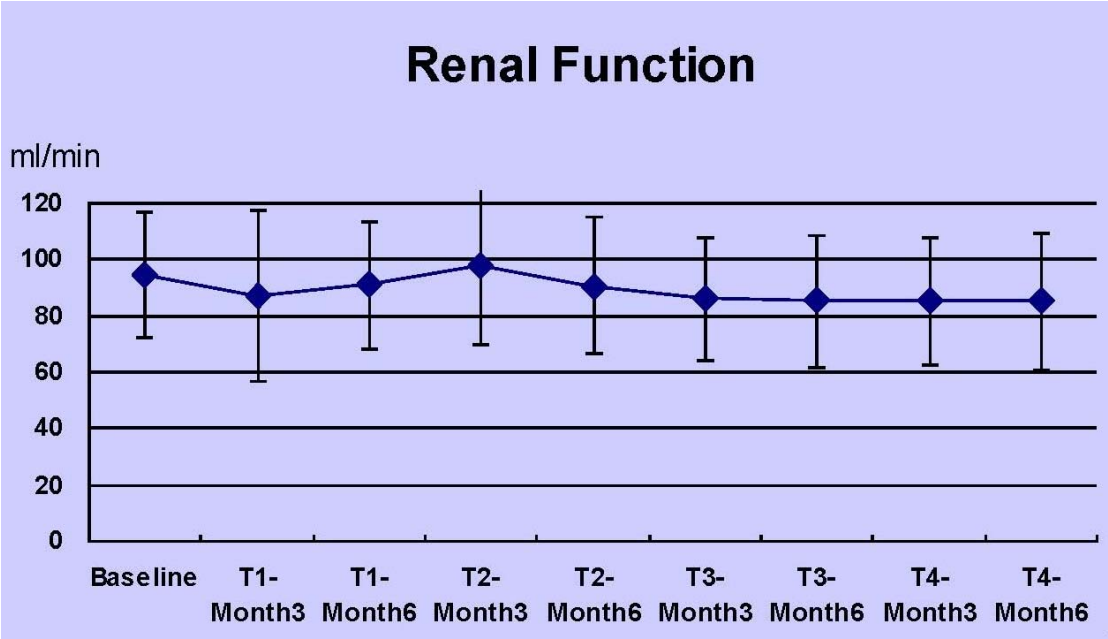
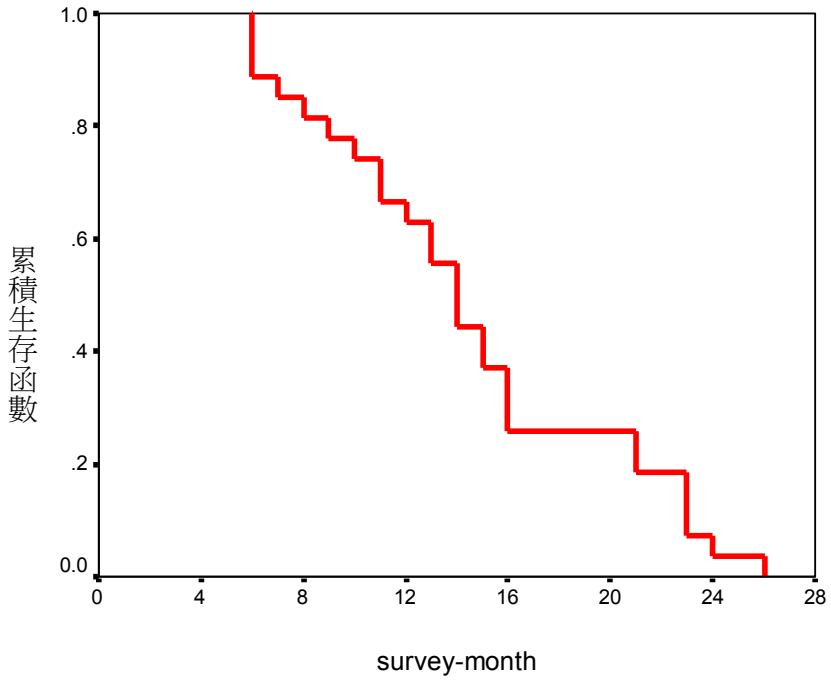


Fig. 3. Changes in glomerular filtration rate from baseline to 24 months in patients with chronic spinal cord injury



Data are expressed as mean ± standard deviation

Fig.4 Duration of therapeutic effect after the 4th onabotulinumtoxinA injection



3. Adverse Events and Safety Concern of OnabotulinumtoxinA Injection in Frail Elderly Patients with Overactive Bladder and Medical Comorbidities

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Introduction

Intravesical injection of onabotulinumtoxin A (BoNT-A) is effective for overactive bladder (OAB) and idiopathic detrusor overactivity (IDO) refractory to antimuscarinics. However, safety is a major concern and the high incidence of adverse events (AEs) remains problem to be solved, especially for the frail elderly patients or patients with comorbidities.

AEs and safety concern of intravesical BoNT-A injection in Frail Elderly

“Frail elderly” is usually defined as elderly with a clinical presentation or phenotype combining impaired physical abilities, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance (including feelings of fatigue and exhaustion). These patients are more vulnerable to experiencing complications. White et al. had report the short-term efficacy of intravesical 200 U BoNT-A injection for refractory OAB in the elderly population. We further investigated the efficacy and safety of intravesical 100 U BoNT-A injections for refractory IDO in frail elderly patients.

Our results show that the frail elderly patients can attain the same treatment results such as significant improvement of urgency urinary incontinence (UUI) and quality of life (QoL) as younger and older patients without frailty. However, an increased risk of large postvoid residual urine (PVR)

and lower long-term success rate were noted in the frail elderly patients. Around 60% of the frail older patients had PVR > 150 ml; 11% had acute urinary retention (AUR) after treatment. Catheter indwelling or clean intermittent catheterization (CIC) may be needed more frequently in the frail elderly patients. In addition, the frail elderly required longer time to recover from AUR although the incidence of AUR was similar among groups. This unfavorable outcome may cause suffering for frail elderly patients.

AEs and safety concern of BoNT-A injection in patients with medical comorbidities

Diabetic mellitus (DM) is an independent risk factor for IDO and OAB. Diabetic patients have more OAB symptoms and may be more refractory to behavioral and pharmacological therapy. We compared the treatment results of 48 diabetic patients with refractory IDO receiving intravesical 100 U BoNT-A injection with 48 age-matched patients were randomly selected from non-diabetic groups. Our findings demonstrated that the efficacy and safety of intravesical 100 U BoNT-A injection on patients with IDO and DM. Previous studies have showed that impairment of efferent pathways of the bladder in DM is considered the cause of DO with impaired contractility. Thus, it is reasonable to worry whether improvement of IDO will carry worse contractility. However, our results are against the assumption because baseline detrusor pressure is not a poor prognostic factor for AEs and treatment failure.

We also found that intravesical BoNT-A injection provides similar therapeutic effects in OAB patients with and without minor cerebral events. Although OAB patients with intracerebral lesions tend to have large PVR after intravesical BoNT-A injection, there was no significant increasing risk of urinary

tract infection (UTI), nor the increasing risk of AUR. However, effects of BoNT-A lasts significantly shorter in the OAB patients combined with intracerebral lesions.

Conclusions

After intravesical BoNT-A injection for patients with refractory OAB/IDO, an increased risk of large PVR and lower long-term success rate were noted in the frail elderly patients. Frail elderly patients who developed AUR had longer recovery time. Though the incidence of large PVR and general weakness increased in diabetic patients, DM itself did not influence the treatment outcomes and other AEs. A shorter treatment effective period was found in patients with minor cerebral events. Patients and their families should be informed of the risks.

Adverse events and safety concern of onabotulinumtoxinA injection in frail elderly patients with overactive bladder and medical comorbidities

Chun-Hou Liao

Outline

- Introduction
- Adverse events (AEs) and safety concern of intravesical onabotulinumtoxinA (BoNT-A) injection in Frail Elderly with overactive bladder (OAB)
- AEs and safety concern of BoNT-A injection in patients with medical comorbidities

Frail Elderly -- Definition

- "Frail elderly" is usually defined as
  - People over the age of 65 years
  - With a clinical presentation or phenotype combining impaired physical abilities, mobility, balance, muscle strength, motor processing, cognition, nutrition, and endurance (including feelings of fatigue and exhaustion
    - Fried LP et al. J Gerontol A Biol Sci Med Sci. 2001;56:M146-56.
  - More vulnerable to experiencing complications

Treatment for OAB in Frail Elderly

- Behavior therapies are often ineffective or difficult to implement
- Antimuscarinics can likewise be ineffective or they are relatively contraindicated in geriatric patients due to underlying cognitive issues
- Sacral nerve stimulation is also largely contraindicated due to the comorbidities inherent in this population
- There is still controversy about whether elderly would be more or less sensitive to intravesical BoNT-A injection based in inherent and unknown neurological changes that accompany aging

Short-tem Efficacy of botulinum toxin A for refractory OAB in the elderly population.

White WM et al. J Urol 2008;180:2522-6.

- 18 females and 3 males
  - mean age of 81.2 years (range 75 to 92)
  - DO was confirmed on urodynamics
  - refractory to or intolerant of antimuscarinics
  - treated with intravesical 200 U botulinum toxin A
- One month after treatment 16 of the 21 patients (76%) reported greater than 50% improvement in symptoms after 1 injection
- Two of the remaining 5 patients demonstrated greater than 50% improvement following repeat injection
- Mean time to deterioration was 7.12 months
- There were no treatment related complications

- ***Objective***: To investigate the efficacy and safety of intravesical BoNT-A injections for refractory IDO in frail elderly patients.
- ***Design, setting, and participants***: From 2004–2009, 157 patients with urodynamic IDO refractory to previous antimuscarinics for more than 3 months were enrolled. "Frail elderly" was defined as those older than 65 with medical comorbidities and low physical activity.
- ***Intervention***: One intravesical 100 U BoNT-A injection.
- ***Outcome measurements and statistical analysis***: Incontinence severity and treatment results were assessed as patients' perception of bladder condition (PPBC) and voiding diary. A 2-point decrease in PPBC was considered successful. Urodynamic parameters at baseline and 3 months were compared, and adverse events were recorded. Kaplan–Meier estimates of survival plots were constructed, and the log-rank test was carried out to compare long-term success rates.

Baseline parameters

	Frail Elderly (N=61)	Elderly without frailty (N=63)	Younger than 70 years without failty (N=42)	P value
Age (years)	75.8 ± 5.3	75.7 ± 6.8	44.6 ± 12.5	<0.001
Male gender	34 (55.7%)	44 (69.8%)	15 (35.7%)	<0.001
OAB wet	57 (93.4%)	48 (76.2%)	31 (73.8%)	0.013

Changes of outcome measures after intravesical BoNT-A injection

		Frail Elderly (N=61)	Elderly without frailty (N=63)	Younger than 70 years without failty (N=42)	P values
7-day urgency /UUI	BL	62.4 ± 25.3	64.9 ± 21.1	80.9 ± 30.0	0.288 *
	3M	53.8 ± 21.3	61.1 ± 24.9	62.0 ± 22.7**	0.073 #
7-day UUI	BL	20.3 ± 27.3	16.3 ± 18.2	12.7 ± 23.2	0.071 *
	3M	8.0 ± 16.0**	11.7 ± 31.4	6.5 ± 17.8**	0.558 #
QoL-I	BL	5.35 ± 0.77	5.06 ± 1.07	5.38 ± 0.77	0.265 *
	3M	3.18 ± 1.68**	2.09 ± 1.08	2.42 ± 1.74**	0.094 #
Success rate	BL	83.4 %	91.2 %	88.9 %	
	3M	44.9 %	52.1 %	49.4 %	0.0415
	6M	6.82 %	22.3 %	23.1 %	

**p<0.05 comparisons within group using Wilcoxon sign-rank test
*comparisons among groups at baseline; # comparison of the changes at 3 months among groups using ANOVA

		Frail Elderly (N=61)	Elderly without frailty (N=63)	Younger than 70 years without failty (N=42)	P values
CBC	BL	247 ± 105	266 ± 124	254 ± 113	0.816 *
	3M	309 ± 133**	309 ± 154**	342 ± 103**	0.272 #
Pdet	BL	26.5 ± 13.8	26.0 ± 16.4	23.9 ± 11.9	0.518 *
	3M	26.1 ± 14.8	21.0 ± 12.9**	20.4 ± 10.7**	0.124 #
Qmax	BL	13.0 ± 6.20	11.3 ± 5.47	14.2 ± 6.70	0.012 *
	3M	12.0 ± 6.53	11.0 ± 6.18	14.6 ± 6.38	0.402 #
PVR	BL	44.9 ± 49.0	32.8 ± 44.8	15.4 ± 31.2	0.004 *
	3M	129 ± 92.2**	101 ± 109**	95.3 ± 106**	0.690 #
VE	BL	82.9 ± 18.4	86.1 ± 22.0	93.0 ± 13.5	0.039 *
	3M	62.1 ± 21.9**	70.0 ± 24.0**	78.4 ± 21.0**	0.393 #
BCI	BL	90.4 ± 30.4	85.5 ± 30.0	97.2 ± 34.3	0.014 *
	3M	82.2 ± 27.6**	77.4 ± 33.5**	94.2 ± 32.3	0.631 #

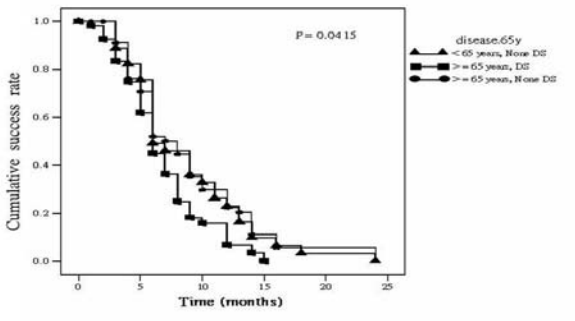
BCI: bladder contractility index, BL: baseline; CBC: cystometric bladder capacity; Pdet: voiding detrusor pressure; PVR: postvoid residual; Qmax: maximum flow rate; QoL-I: quality of life index; UUI: urgency urinary incontinence

AEs after intravesical BoNT-A injection

	Frail Elderly (N=61)	Elderly without frailty (N=63)	Younger than 70 years without failty (N=42)	P value
AUR	7 (11.5%)	4 (6.3%)	1 (2.4%)	0.203
Large PVR	37 (60.7%)	25 (39.7%)	15 (35.7%)	0.018
Straining to void	28 (45.9%)	26 (41.3%)	16 (23.8%)	0.721
Hematuria	8 (13.1%)	7 (11.1%)	2 (4.8%)	0.373
UTI	8 (13.1%)	6 (9.5%)	12 (28.6%)	0.025
General weakness	4 (6.6%)	0 (0%)	0 (0%)	0.029

All AEs are grade 1, *comparisons using ANOVA test
The recovery period (from AUR to spontaneous voiding without catheterization) was significantly longer in frail elderly group (median 3.5 months) than elderly without frailty (1 months) and younger group (0.5 months) (p=0.01).

Cumulative success rates among 3 group



Diabetes mellitus (DM)

- DM is an independent risk factor for IDO and OAB
- Diabetic patients have more OAB symptoms and may be more refractory to behavioral and pharmacological therapy
- 48 patients have DM and refractory IDO received intravesical injection of 100 U BoNT-A were compared with 48 age-matched patients were randomly selected from non-diabetic groups

Compared between DM and non-DM

	DM (n=48)	Non-DM (n=48)	P value
Age (years)	73.08±8.80	71.98±9.33	0.552
AUR	5 (10.4%)	3 (6.3%)	0.357
Large PVR	29 (60.4%)	16 (33.3%)	0.007
Straining to void	26 (54.2%)	20 (41.7%)	0.154
Hematuria	4 (8.3%)	5 (10.4%)	0.500
UTI	6 (12.5%)	6 (12.5%)	0.621
General weakness	10.4%	0%	0.028

Minor Cerebral Events (CVA, parkinsonism, early dementia)

	With Intracerebral lesions(n=28)	Without Intracerebral lesions(n=153)	P value
AUR	4 (14.3%)	9 (6%)	0.133
Large PVR	19 (67.9%)	60 (39.1%)	0.005
Straining to void	15 (53.6%)	65 (42.9%)	0.204
UTI	2 (7.1%)	23 (15.0%)	0.217
General weakness	1 (3.6%)	0 (0%)	0.174

Summary

- Although the safety and efficacy between elderly without frailty and younger patients were similar, an increased risk of lower long-term success rate were noted in the frail elderly after intravesical 100 U BoNT-A injection for refractory IDO.
- Frail elderly patients who developed AUR had longer recovery time
- Higher rate of large PVR after intravesical BoNT-A injection noted in frail elderly and patients with DM or intracerebral lesions

4. Can onabotulinumtoinA be effective in treatment of interstitial cystitis refractory to conventional therapy?

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Abstract

Botulinum toxins (BoNT) are well known for their ability to potently and noxious inputs by decreasing neuropeptide release including glutamate, substance P, and calcitonin gene-related peptides from the central endings of bladder sensory nerve. Bladder pain associated with interstitial cystitis and painful bladder syndrome (IC/PBS) is frequently excruciating and intractable. The use of onabotulinumtoxinA (BoNT-A) for relief of this type of bladder pain has not been well described. This article is intended to review the procedure and efficacy of intravesical onabotulinumtoxin-A injection for IC/PBS refractory to conventional therapy.

Introduction

The pathophysiology of interstitial cystitis/painful bladder syndrome (IC/PBS) has not been fully understood. Associated clinical features of IC/PBS included chronic bladder pain, which is aggravated by bladder distesion, frequency and urgency. This syndrome complex usually results in severely pain and impaired the quality of life of these patients. However, current treatments are usually unsuccessful in completely eradicating bladder pain and increasing bladder capacity [1].

It is known that the suburothelial space is well supplied with sensory nerves which transmit the sensation of bladder fullness and response to bladder inflammation [2, 3]. One hypothesis to explain the pathology of IC/PBS is that an initial insult such as urinary tract infection of chemical irritation to the bladder occurs will excite sensory nerves located in the bladder wall. This excitation triggers an inflammatory response, or neurogenic inflammation, which induced releases of the neuropeptide substance P, causing the release of mast–cell mediators, histamines, cytokines, cell and tissue damage, and fibrosis. These conditions result in the nervous system with neuroplasticity via c–fibers and pain beyond the bladder develops [4]. In an animal model of chemical cystitis, detrusor injection of BoNT-A has been shown to have effects on increasing bladder capacity and compliance [5]. Inhibition of neuroplasticity of the sensory fibers in the suburothelial space by intravesical BoNT-A injections might have good therapeutic targeting on pain and sensory urgency in patients with IC/PBS [6]. Several investigators evaluated the efficacy of different BoNT-A injections for IC/PBS and the results are positive in selected patients. We will introduce our injection technique and protocol and report the results of our experience in this handout.

Injection Techniques and followup

A total of 100 units of onabotulinumtoxinA (Allergan, Irvine, CA, USA) diluted in 10-30 ml of preservative saline (i.e. 10 units/ml, 1ml/injection) are injected submucosally throughout the bladder using an endoscopic injection needle followed by cystoscopic hydrodistention under intravenous general anesthesia in the operation room. 40 sites of suburothelial injections were made. The injection needle was inserted into the urothelium at the posterior

and lateral walls of the bladder, using a 23 gauge needle and rigid cystoscopic injection instrument (22 Fr, Richard Wolf, Knittlingen, Germany). Cystoscopic hydrodistention was performed to an intravesical pressure of 80 cm water for 15 minutes and the maximal bladder capacity (MBC) under hydrodistention was recorded. After the injections, a 14 Fr urethral Foley catheter was remained for 1 day and patients were discharged on the next day. Oral antibiotics were prescribed for 7 days.

Urodynamic study

Videourodynamic study was performed by standard procedures using a 6 Fr dual channel catheter and an 8 Fr rectal balloon catheter. Cystometric study was performed with warmed normal saline at a filling rate of 20 mL/min. All descriptions and terminology in this report were in accordance with the recommendations of the International Continence Society [7]. After the videourodynamic study, 40 mL KCl solution of 0.4 M was infused slowly into the bladder and the test was regarded as positive when painful (of more than or equal to 2 VAS score) or urgency sensation was elicited compared to normal saline infusion during prior urodynamic study [8].

Clinical assessment

Patients were requested to record a 3-day voiding diary prior to treatment to record the bladder capacity and the episodes of urinary frequency and nocturia. The IC/PBS symptoms were assessed by the O'Leary-Sant symptom indexes (ICSI) and problem indexes (ICPI) [9]. The pain score was reported by self-assessment using a 10-point visual analog scale (VAS) system. Videourodynamic study and potassium chloride (KCl) sensitivity test were

performed and patients were informed of the possible complications associated with BoNT-A injection such as generalized muscle weakness, difficult urination, transient urinary retention, or urinary tract infections. Outcome measurements were the change of sum of ICSI and ICPI [10], and VAS from baseline to 6 months after the BoNT-A injection.

The treatment outcome was also assessed using the global response assessment (GRA). Patients were requested to rate their bladder symptoms compared with baseline on a 7-point centered scale from markedly (-3), moderately (-2) and slightly worse (-1), no change (0), to slightly (+1), moderately (+2) and markedly improved (+3). Patients with moderately and markedly improved results after treatment were considered to have a successful treatment outcome. Otherwise, the treatment was considered to have failed.

Efficacy

Our studies demonstrated that intravesical injection of BoNT-A significantly improved patients' symptoms especially in the items of bladder pain, urinary symptoms and quality of life. Based on our results, the injection of BoNT-A with cystoscopic hydrodistension significantly also reduced the urinary concentration of nerve growth factor. Besides, NGF mRNA production in bladder tissue is significantly in- creased in patients with IC compared with that in controls and that successful intravesical BoNT-A injection reduced NGF mRNA expression to normal levels [11]. It is well known that NGF is one of the most essential neurotrophic transmmiters for the growth and maintenance of multiple nociceptors. It could be expected that reduction of NGF in the urine can also contribute to a decrease in bladder pain. Pinto et al also found that

urinary NGF reduced after BoNT-A trigonal injecton [12]. On the other hand, they identified that brain-derived neurotrophic factor (BDNF), another ubiquitous neurothrophin with nociceptive activity [13], is also decreased upon BoNTA treatment. In the literature, one pilot study by Giannantoni [14] showed injection of 200 U of BoNTA in 20 sites reduced bladder pain in 73% of the patients at 5 months. Smith et al injected 100 or 200U BoNT-A submucosally in 13 patients, among whom near 70% patients experienced improved in clinical symptoms with a therapeutic duration of 9 months [15]. In our six months followup in 67 patients who are refractory to conventional therapy, we demonstrated that there was a significant decrease in bladder pain scores at 3 and 6 months after intravesical BoNT-A injections [16]. The incidences of serious adverse effects associated with this therapy were mild and reversible. In addition, our results demonstrated the BoNT-A has clinical effects to reduce bladder pain, increase functional bladder capacity, and quality of life. The only randomized controlled study reported by Gottsch et al failed to demonstrate the efficacy of BoNT-A injection for IC/PBS [17]. However, their injection method was periurethrally and the dose is smaller as only 50U [17].

Perspective

Currently the optimal injection techniques including dose, dilution, number and location of injections for IC/BPS remain not to be standarized. Further randomized clinical trials, which enrolled more patients are mandatory to validate the benefit of this specific procedure and to establish standard injection site and dose and technique.

Conclusion

Intravesical injections of onabotulinumtoxin-A in selected patients with refractory BPS who have failed to respond to conventional therapy will reduce bladder pain, urinary symptoms and improve quality of life. Since randomized trials that are methodologically sound and sufficiently powered with a large patient number and follow-up period are not available now. In addition, study design should include assessing the optimum dose and sites of onabotulinumtoxin-A injection.

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5. Satisfaction and Dissatisfaction and Quality of Life Issues in Patients Receiving Urethral or Detrusor OnabotulinumtoxinA Injection for Detrusor Sphincter Dyssynergia

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Introduction

Detrusor sphincter dyssynergia (DSD) occurs commonly in patients with spinal cord injury (SCI), multiple sclerosis and transverse myelitis. Patients with DSD often suffer from urinary incontinence, voiding difficulty and large postvoid residual urine (PVR) needing intermittent or long-term urethral catheterization. Long term complications include repeated urinary tract infection, upper urinary tract damage and vesical stone formation. These adverse events cause poor quality of life (QOL) and depression in SCI patients.

Recently onabotulinumtoxinA has been emerging as a novel treatment for DED refractory to conventional treatment. Many studies have showed that detrusor injection of onabotulinumtoxinA can reduce the episodes of urge urinary incontinence, decrease neurogenic bladder overactivity and improve bladder compliance. In addition, urethral injection of onabotulinumtoxinA can reduce urethral resistance and possibly resume bladder emptying. However, detrusor injection usually induces detrusor underactivity and urinary retention. Patients maybe need periodically clean intermittent catheterization (CIC) and repeated UTI could become a *de novo* problem. On the other hand, urethral injection will cause undesired exacerbation of urinary incontinence, though the PVR can be reduced.

Thus, our priority of managing neurogenic bladder dysfunction could be not only based on improved parameters of urodynamics, free of indwelling catheter and preservation of renal function, but also considering patient's need and will of management, hand function and capability of CIC, family support, etc. " To be continent and on CIC" or " Incontinent but spontaneous voiding" , that is a question.

Satisfaction, dissatisfaction and quality of life after onabotulinumtoxinA injection

Several studies evaluating the therapeutic satisfaction, dissatisfaction and quality of life in patients with DSD who receiving urethral or detrusor onabotulinumtoxinA injection were reviewed. One study showed after 200 U onabotulinumtoxinA detrusor injection, significant increased maximal bladder capacity and PVR, and decreased detrusor pressure were noted at 3 months after onabotulinumtoxinA treatment. Significant improvements in the Urogential Distress Inventory 6-item short form (UDI-6) and Incontinence Impact Questionaire (IIQ-7) scores were also reported at 3 months. Forty-five (90%) patients could be improved in decrease incontinence but 25 (50%) were dissatisfied with increased PVR (Table, 1).

Another study demonstrated that after 100 U onabotulinumtoxinA urethral sphincter injection, increased maximum flow rate and decreased PVR and maximal voiding pressure were noted at 3 months after onabotulinumtoxinA treatment. 78.8% patients could benefit with less difficult urination but 48% patients were dissatisfied with increased urinary incontinence (Table 2).

Recently, a level A evidence study showed that onabotulinumtoxinA significantly reduced urinary incontinence and improved urodynamics and QOL in patient with neurogenic bladder overactivity. During week 6, 7.6%, 38.0%, and 39.6% of patients in the placebo, 200U, and 300U onabotulinumtoxinA groups, respectively, were fully dry. Compare with placebo group (11.7), the mean change from baseline in Incontinence quality of life total score were significantly higher in 200U (24.4) and 300U (24.3) groups.

Conclusion

Both urethral and detrusor onabotulinumtoxinA injection were effective treatment for patients with detrusor sphincter dyssynergia. Physicians should discuss the main therapeutic effects and possible disadvantages with patients before treatment. A full understanding of patient's will of management modality, their hand function and capacity of self-care, social economic and family support can bring better quality of life for these patients.

Table 1: Satisfaction and dissatisfaction after onabotulinumtoxinA detrusor injection for patients with detrusor sphincter dyssynergia

Main therapeutic effect	Patients (%)	Causes of dissatisfaction	Patients (%)
Decrease incontinence	45 (90)	Increased PVR	25 (50)
Increase bladder capacity	36 (72)	Difficult urination	16 (32)
Less urgency episodes	31 (62)	Nocturnal incontinence	10 (20)
Complete dry	29 (58)	Severe incontinence	6 (12)
Less autonomic dysreflexia	5 (71)	Needing CIC	5 (10)

Table 2: Satisfaction and dissatisfaction after onabotulinumtoxinA urethral sphincter injection for patients with detrusor sphincter dyssynergia

Main therapeutic effect	Patients (%)	Causes of dissatisfaction	Patients (%)
Less difficult urination	26 (78.8)	Increase urinary incontinence	16 (48.5)
Decreased PVR	23 (69.7)	Persistent difficulty urination	7 (21.2)
Less CIC	7 (21.2)	Increassed urgency	5 (15.2)
Less autonomic dysreflexia	2 (50)	*De novo* frequency	3 (9.1)
Less UTI	10 (67)		

Suggested Reading

Brodie M, Sakakibara B, Miller WC et al: A systemic review of depression and anxiety measures with individuals with spinal cord injury. Spinal Cord 2009; 47: 841-851.

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6. Does OnabotulinumtoxinA still Play a Role in Treatment of BPH?

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Physical denervation of the prostate by sectioning the hypogastric nerve in a rat model induces prostatic atrophy. Similarly, Doggweiler and colleagues using chemical denervation by injection of BoNT-A into the rat prostate observed a generalized atrophy and apoptosis of glandular elements. Cholinergic innervation of the prostate gland has an important role in regulation of the functions of the prostate epithelium, with effects on growth and secretion, while the noradrenergic innervation has been implicated in the contraction of smooth muscle and etiology of outflow obstruction accompanying BPH. BoNT-A, inhibiting the release of acetylcholine at the nerve terminal, can suppress the secretomotor function of acetylcholine on the prostate and result in a decrease of the prostate weight. In rats as well as in dogs, BoNT -A induces prostatic gland atrophy, and apoptosis. In humans, increases in apoptotic activity at both epithelial and stromal components were noted after BoNT -A injection, and thus reduce the bulk or anatomic obstructive component of BPH in humans. In addition, Lin et al. reported that injection of 200 U BoNT-A into the canine prostate significantly reduced the prostate urethral pressure response to intravenous norepinephrine and electrostimulation. They concluded that BoNT-A reduces contractile function of the prostate and might also attenuate the dynamic component of BPH.

No matter the origin of chronic prostatitis is from the prostate or outside the prostate, clinical study has revealed that urethral, perisphincteric, or intraprostatic BoNT-A injection might have therapeutic benefits for the human non-bacteria prostatitis or chronic prostatic pain. Likely, intravesical BoNT-A injection also relieved IC symptoms in some clinical studies.

Available evidence suggests that intraprostatic BoNT-A injection has been shown to improve LUTS associated with various degrees of decrease of prostate volume and increase of flow rate. The duration of effect is reported to last 6 months or longer. These results imply that BoNT-A has dual inhibitory effects on cholinergic and adrenergic pathways innervating the prostate.

We perform BoNT prostate injections by mixing 100 to 200 units of BoNT-A with 4 ml of saline just prior to injection. For those with prostate larger than 60 ml, more than 200 units may be necessary. The preparation and positioning of the patient is identical to that used for tranrectal or transperineal ultrasound guided prostate biopsy. We used a 21-G 15 or 20 cm long needle under the guidance of transrectal ultrasound with the transverse and sagittal views to ensure proper placement of the needle as a bright spot in the center of each lateral lobe where 2 ml of BoNT is injected into each side. Diffusion of hyperechoic BoNT over the lateral lobe of the prostate can be easily seen with TRUS monitoring. Urethral catheter drainage was not performed postoperatively, except patients with chronic indwelling a urethral catheter.

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Does onabotulinumtoxin A still play a role in treatment of BPH? How to select suitable patients with LUTS for onabotulinumtoxin A injection?

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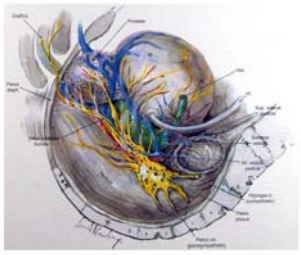
1

Human Prostate Innervation

- Cholinergic innervation- regulation of the functions of the prostate epithelium, with effects on growth and secretion
- Noradrenergic innervation- implicated in the contraction of smooth muscle and etiology of outflow obstruction accompanying BPH



Ventura et al., Pharmacol Ther, 2002
Ravindranath et al., J Androl, 2001

2

Autonomic nervous system overactivity in men with LUTS secondary to BPH

- Increased autonomic tone- in clinical BPH
- Spontaneous hypertensive rat- increased prostatic hyperplasia and OAB
- Increased sympathetic tone leads to BPH voiding symptoms, and possible BPH growth.

(McVary, J Urol, 2005)

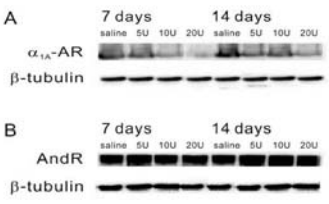
3

Laboratory Data of onabotulinumtoxin A (BoNT-A) Effects on the Prostate

4

Novel Action of Botulinum Toxin on the Stromal and Epithelial Components of the Prostate Gland

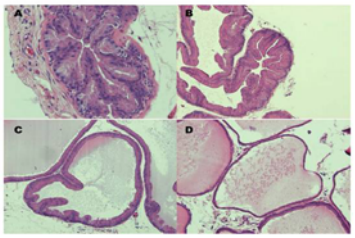
Yao-Chi Chuang,* Chao-Cheng Huang, Hong-Yo Kang, Po-Hui Chiang, Fernando Demiguel, Naoki Yoshimura and Michael B. Chancellor*,†



(J Urol 2006)

5

Fig. 1 Photomicrographs of prostate sections after the saline (A), 5 U BTX-A (B), 10 U BTX-A (C), and 20 U BTX-A (D) treatment at one week. Significant glandular proliferation with papillary infolding in the lumen was seen in the saline injected rat (A). Atrophy change of glandular component with flattening of the lining epithelium was seen in the BTX-A treated rat (B,C, D). magnification X 200.



6

BoNT-A effects in the Canine Prostate 1 M after injection

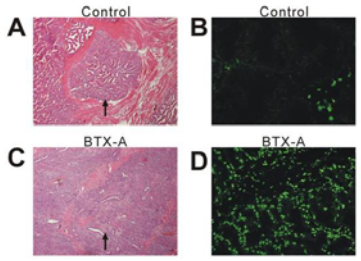
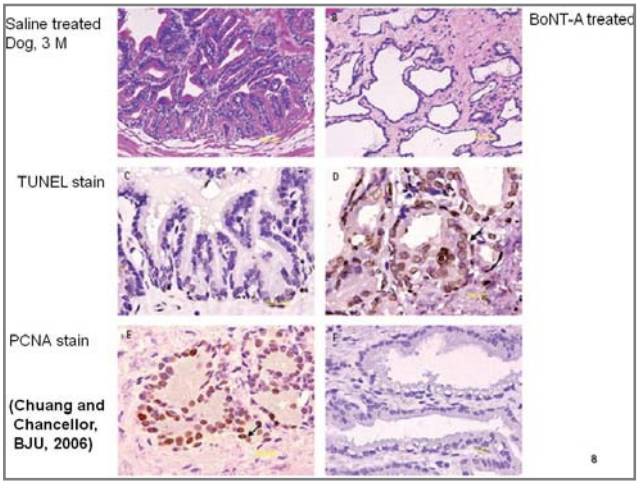


Fig. 4 Significant glandular proliferation with papillary infolding in the lumen was seen in the control canine (A). Atrophy change of glandular component with flattening of the lining epithelium was seen in the BTX-A treated canine (C). Very few apoptotic nuclei are recognizable in the control animal (B). Strong fluorescence of apoptotic nuclei was seen in the BTX-A treated animal at 1 month. A, C magnification X 40; B, D magnification X 100.

(Chuang et al., BMC Urology, 2006)

7



8

Effects of Botulinum Toxin A on the Contractile Function of Dog Prostate

Alex Tong Long Lin [a,], An Hang Yang [a,b], Kuang-Kuo Chen [a]*

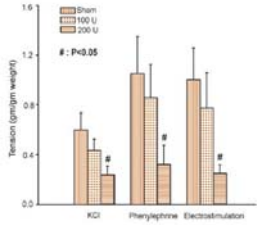


Fig. 4 – Contractile responses of prostate strips to 120 mmol/l potassium chloride (KCl), phenylephrine (10^{-3} mol/l), and electrostimulation (50 V, 1 ms, 64 Hz). Each bar represents the mean ± SEM of 5 to 7 animals. # indicates a significant difference compared with sham group.

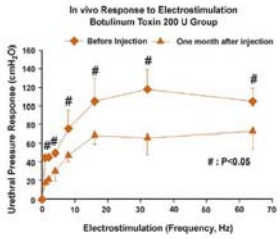
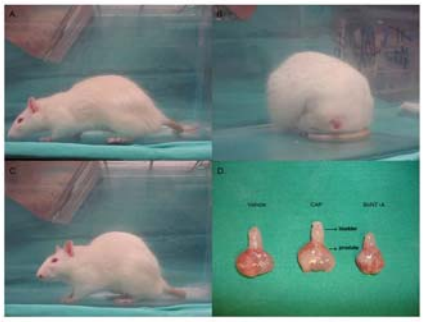


Fig. 3 – Prostate urethral pressure response to electrostimulation 1 mo after injection of 200 units botulinum toxin A (BoNT/A). # indicates a significant difference as compared with before BoNT/A injection.

(Eur Urol, 2007)

9

Intraprostatic Botulinum Toxin A Injection Inhibits COX-2 Expression in the Prostate and Spinal Cord and Suppresses Prostatic Pain on Capsaicin Induced Prostatitis Model In Rat (Chuang et al., Eur Urol 2007; J Urol 2008)



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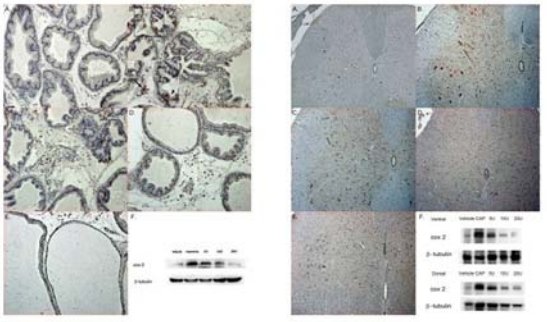


11

BoNT-A Effects in the Prostate

- BoNT-A suppress acetylcholine release and induce cellular apoptosis in the rat prostate (Doggweiler et al, Prostate, 1998)
- BoNT-A downregulates cellular dynamic and alpha 1A adrenergic receptor in rat prostate. BoNT-A appear unique in having dual actions on both the dynamic component and static component of BPH (Chuang et al, J Urol, 2006)
- BoNT-A induced apoptosis in canine prostate and decreased urethra pressure (Chuang et al., BJU Int. 2006; Lin et al., Eur Urol, 2007)

12

Prostate Applications-BPH Rational

- Botulinum toxin A (BoNT-A) blocks exocytosis of neurotransmitters including acetylcholine, noradrenalin, and sensory neuropeptides[1, 2]
- BoNT-A might inhibit the autonomic efferent effects on prostate growth and contraction[3]
- BoNT-A might inhibit the abnormal afferent sensation in the prostate[4]
- Intraprostatic injection of BoNT-A might relieve static and dynamic components of BPH and reduce lower urinary tract symptoms

[1]Smith and Chancellor, J Urol, 2003
[2]Chuang and Chancellor et al., J Urol, 2004
[3]Chuang and Chancellor et al., BJU, 2006
[4]Chuang and Chancellor et al., JU, 2008

Intraprostatic Injection Therapy for BPH

- The intraprostatic injection therapy for BPH has been used for more than 100 years with various results
- Most injectants will cause coagulative necrosis, followed by shrinkage of prostatic volume, and resulted in improvement of voiding dysfunction.

14

BoNT-A BPH Clinical Result

15

First Clinical Experience In BPH

- Randomized, double blind, placebo-controlled study
- Thirty symptomatic BPH patients were randomly assigned (1:1) to 200 U Botox in 4cc saline or placebo, 22 G needle
- Transperineal sono-guided, no anesthesia
- Results- TURP like great effects without any side effects or complications

	Baseline	1 M	12M
IPSS score	23.2	10.6	8.9
PSA (ng/ml)	3.7	2.1	2.3
Prostate volume (mL)	52.6	23.8	20.5
Peak flow (mL/sec)	8.1	14.9	15
Residual urine (mL)	126.3	49.6	24.2

(Maria et al., Urology, 2003) 16

Prostate Botulinum A Toxin Injection for BPH in Poor Surgical Candidates

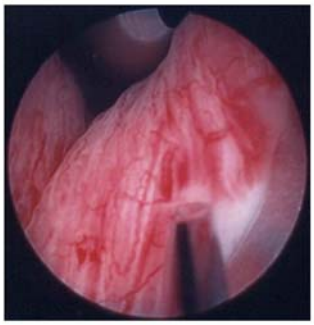
	Baseline	3 Months	6 Months
Voiding detrusor pressure(cm H_2O)	65.0 ± 54.1	54.1± 18.7*	
Maximum flow rate (ml/s)	7.6 ± 3.9	9.9 ± 3.2*	11.6 ± 3.5*
Abrams-Griffiths number	43.4 ± 21.5	34.0 ± 18.4	
Postvoid residual volume(ml)	243.0±133.9	53.9 ± 20.1*	36.8 ± 34.1*
Total prostate volume (ml)	65.5 ± 19.5	45.9 ± 17.2*	49.6 ± 17.6*
Transition zone index (%)	0.50 ± 0.14	0.50 ± 0.19	0.56 ± 0.15

*compared to baseline, p<0.05

(Kuo, Urology, 2005)

17

Botulinum A toxin Transurethral Prostate Injection



18

BOTULINUM TOXIN TYPE A IMPORVES BENIGN PROSTATIC HYPERPLASIA SYMPTOMS IN PATIENTS WITH SMALL PROSTATES

- Symptoms of BPH did not rigidly follow prostate size (Lepor, Br J Urol, 1998)
- We expand the clinical use of BoNT-A in treating patients with small prostates and symptomatic BPH

(Chuang, Chancellor et al., Urology, 2005)

19

Results

	Baseline (N=16)	1 M follow-up (N=16)	3 M follow-up (N=16)	6 M follow-up (N=16)	Last follow-up (mean: 10 M) (N=13)
Prostate (mL)	19.6±1.2	17.0±1.1*	16.7±1.2*	16.9±1.1*	16.4±2.5*
IPSS (0-35)	18.8±1.6	8.9±1.9*	7.9±1.7*	7.4±1.8*	9.0±2.2*
Peak flow (mL/s)	7.3±0.7	11.8±0.8*	11.9±1.1*	12.5±1.0*	12.6±0.9*
QOL (0-6)	3.8±0.3	2.1±0.3*	1.9±0.3*	1.8±0.3*	2.1±0.5*
RU (mL)	67.7±30.0	25.1±4.0	27.3±4.3	26.4±4.3	26.8±5.6

Values are mean ± S. E.
*p<0.05, in comparison with baseline
IPSS: international prostate symptom score
QOL: quality of life indices
RU: residual urine

20

SUSTAINED BENEFICIAL EFFECTS OF INTRAPROSTATIC BOTULINUM TOXIN TYPE A INJECTION ON LUTS AND QUALITY OF LIFE IN BPH PATIENTS

- 31 out of 41 patients (75.6%) have more than 30% improvement on LUTS and QOL indices.
- 4 out of 5 patients (80%) with urinary retention can void spontaneously from one week to 1 month after BoNT-A injection.
- 12 out of 41 patients (29.2%) did not have change of prosate volume, however, 7 out of the 12 patients (58.3%) still have more than 30% improvement in maximal flow rate, LUTS, and QOL.
- The efficacy is sustained at 12 months.

(Chuang and Chancellor, et al., BJU, 2006)

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2009 AUA 1964 abstract

VALIDATION OF SUBJECTIVE BENEFIT AFTER INTRAPROSTATIC BOTULINUS TOXIN A INJECTION IN PATIENTS WITH PROSTATIC HYPERTROPHY – AN EVIDENCE BY REAL-TIME TISSUE ELASTOGRAPHY

*Takeo Hiraoka MD *, Hiroaki Shiina MD, PhD, Shogo Inoue MD, Masahiro Sumura MD, Shinji Urakami MD, PhD, Satoshi Honda, Koji Wake and Mikio Igawa MD, PhD. Izumo Japan*

Real-time tissue elastography (RTE) can allow mapping tissue elasticity according to the difference in stiffness between hypertrophied lesions and normal tissues. Elasticity of the prostate was significantly reduced after BTX-A injection (2 weeks; 0.68, 1 month; 0.56, 3 months; 0.54, 6 months; 0.57), compared to the pre-treatment level of 0.77 ($p<0.05$, each).
Intraprostatic injection of BTX-A therapy affords excellent improvement in subjective symptoms, paralleling with the reduction of elasticity involved in the prostate.

22

BoNT in Men with Retention Unfit for Surgery

- 21 men with BPH and chronic indwelling catheter > 3mo
- Mean age 80 years old, unfit for surgery, volume 70 ml
- 200 U onaBoNTA TRUSP 2ml/4 sites

	Baseline	1 M	3M
Voiding		16 (76%)	17 (81%)
Qmax		9.0±1.2	10.3±1.4
RU		80±19	92±24
PSA	6±1.1		5.0±0.9*
Prostate	70±10	57±10*	47±7*

Silva et al: Eur Urol 53:153, 2008

23

Effect of 100 and 300 U OnaBoNTA on LUTS of BPH. NIH MIST Study Group

- Men ≥ 50 with BPH
  - AUA symptom index ≥ 8
  - Qmax<15 ml/sec
  - Voided volume ≥ 125 ml
  - PVR ≤ 350 ml
- 7 US sites and randomized to 100 or 300u onabotulinumtoxinA
- Treatment success: at least 30% improvement from baseline to 12 weeks in AUASI and/or Qmax
- 134 men, 68 received 100U and 66 received 300U

Crawford et al., J Urol 186:965, 2011

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Effect of 100 and 300 U OnaBoNTA on LUTS of BPH. NIH MIST Study Group

	AUASI		Qmax (ml/sec)	
	100 U	300 U	100 U	300 U
Baseline	18.8	19.5	10.0	9.6
1 Mo	12.0	12.5	12.6	12.1
3 M0	11.7	10.6	12.5	12.2
12 Mo	11.9	12.4	12.2	11.9

Crawford et al., J Urol 186:965, 2011

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Effect of 100 and 300 U OnaBoNTA on LUTS of BPH. NIH MIST Study Group

- No adverse effect on ejaculatory function
- No change in erectile function IIEF
- Conclusions: Intraprostatic injection of either 100 or 300 U of onaBoNTA passed both efficacy and safety at 3 months which was sustained at 12 months in a phase II randomized double-blind trial

Crawford et al., J Urol 186:965, 2011

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MIST2: BASELINE PSA AND TOTAL PROSTATE VOLUME PREDICTS CLINICAL RESPONSE TO INTRAPROSTATIC INJECTION OF BOTULINUM TOXIN FOR THE MANAGEMENT OF LUTS

- At 12 months we noted a significant change in AUASS (35.6% reduction from baseline), Qmax (27.6% increase from baseline) without change in volume or PSA.
- The greatest response in AUASS occurs in those with the lowest PSA and TPV. PSA and TPV significantly correlates with AUASS change and PSA with Qmax (absolute and %) change.

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Multi-regional injections of low dose Botulinum toxin A for men with chronic pelvic pain syndrome

- Shin et al. reported multi-regional injection of BoNT-A (including 4 intraprostatic injection) improved symptoms in 59% of CPPS patients

Shin et al., J Urol, 2006; 175 (supplement): 34

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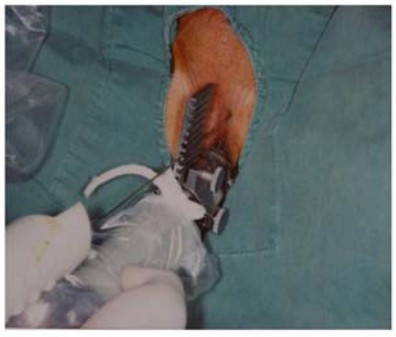
Transperineal Intraprostatic Injection Under Transrectal Ultrasound Guidance



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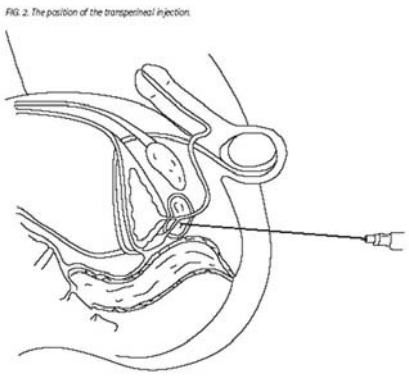

FIG. 2. The position of the transperineal injection.

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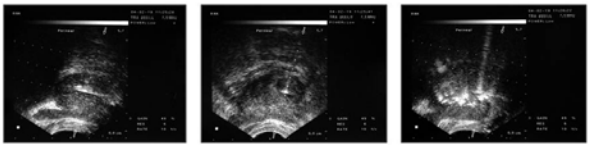
Clinical Prostate BoNT-A Injection Technique



A B C

A. Confirmation of needle (black arrow) within the prostate, longitudinal view. B. transverse view. C. Diffusion of hyperechoic BTX-A (black arrow) over the prostate immediate post injection. (Chuang and Chancellor, Urology, 2005)

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BoNT-A Prostate Injection: Technique and Dose

TABLE III. Techniques

	Technique	Dilution needle insertion point	Anesthesia	Dose	Drip feed post-treatment antibiotherapy
Mattia et al.[58]	Transperineal	4 ml/both lateral lobes	No	200 U	
Chuang et al.[51]	Transperineal	8 ml/both lateral lobes	Sedation	200 U	1 patient/cephazoline
Chuang et al.[50]	Transperineal	4 ml/both lateral lobes	Sedation	100 U	1 patient/cephazoline
Kuo et al.[57]	Transurethral	20 ml/both lateral lobes + median lobe	General	200 U	
Larsen et al.[47]	Transrectal	Base median prostate + both lateral lobes	No	100 U	
Guerrini et al.[59]	Transperineal			300 U	
Park et al.[53]	Transperineal	4–9 ml/both lateral lobes	No	<30 cm³: 100 U, 30–80 cm³: 200 U, >80 cm³: 300 U	
Chuang et al.[55]	Transperineal	4–8 ml/both lateral lobes	Sedation/no	<30 cm³: 100 U, >30 cm³: 200 U	5 patients with UR
Kuo et al.[60]					
Sowdar et al.[35]	Transrectal	Both lateral lobes	No	200 U	
Agrawal et al.[34]	Transperineal	Both lateral lobes	No	200 U	
Silva et al.[33]	Transrectal	8 ml/both lateral lobes	No	200 U	Yes/ciprofloxacin
Silva et al.[33]	Transrectal	8 ml/both lateral lobes	No	200 U	Yes/ciprofloxacin
Silva et al.[44]	Transrectal		No	200 U	
Jasinski et al.[36]	Transrectal	4 ml/both lateral lobes		100 U	
Crawford et al.[37]	Transrectal			100 U/300 U	
Brisinda et al.[38]	Transperineal	4 ml/both lateral lobes	No	200 U	
De Keet et al.[39]	Transrectal	Both lateral lobes		100 U	Unspecified antibiotic
Kuo et al.[54]	Transperineal	10 ml/both lateral lobes + median lobe	Local	200 U/600 U	Ciprofloxacin
McVary et al.[56]	Transrectal			100 U/300 U	
Nikoobakht et al.[61]	Transperineal			300 U/500 U	
Nikoobakht et al.[62]	Transperineal			300 U/500 U	
Gongal et al.[63]	Transrectal	Both lateral lobes + median lobe	No	200 U	Unspecified antibiotic
Mirkin et al.[45]	Schelin catheter	Both lateral lobes		150 U	

(Marchal et al., Neuro Urodyn, 2012)

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Conclusions

- BoNT injection improves flow rate, IPSS and QOL with a high degree of variability in the communication of results
- Different studies present considerable variations regarding the dose administered, inclusion criteria and follow-up time, as well as poorly defined retreatment, losses to follow up
- Intraprostatic BoNT injection may be a promising alternative for patients with refractory BPH , especially in elder patients with comorbidities, and unfit for surgery

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7. Injection Technical, Dose and Injection Sites of OnabotulinumtoxinA and the Influence on the Effects and Adverse Events

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Introduction

Recently botulinum toxin is emerging as a novel treatment for lower urinary tract dysfunctions refractory to conventional treatment. Review of the clinical trials in recent 5 years, botulinum toxin type A (BTX-A) has been widely used to treat incontinence due to neurogenic or idiopathic detrusor overactivity (NDO, IDO), [1,2] voiding dysfunction due to detrusor sphincter dyssynergia (DSD), [3,4] bladder sensory disorders such as overactive bladder (OAB), [5,6] interstitial cystitis (IC) and bladder hypersensitivity. [7,8] Currently BTX-A is also applied to treat benign prostatic hyperplasia (BPH) refractory to medical treatment [9, 10] and chronic prostatitis and chronic pelvic pain syndrome (CPPS). [11]

Indications of BTX-A injection

Although there are many new indications for intravesical and urethral injections of BTX-A, the key for a successful treatment is based on the

accurate diagnosis of lower urinary tract dysfunction and the optimal dose of BTX-A used as well as the correct and adequate sites of injections. Instrument can be any type of available injection needles or cystoscope. Patients can be treated either with local anesthesia or under intravenous general anesthesia depending on where to be injected. The adverse events which may occur after BTX-A injections such as gross hematuria, dysuria, miction pain, large postvoid residual and acute urinary retention (AUR) should be fully acknowledged to patients treated. (Table 1) For patients taking anticoagulant for their chronic stroke or cardiovascular disease, anticoagulant agent should be discontinued at least 1 week before the treatment to prevent bleeding after BTX-A injections.

Urethral sphincter injection of BoNT-A

Urethral BTX-A injection can be performed in the operation room under light intravenous general anesthesia (in men) or at OPD without anesthesia (in women). [12] The dose of BTX-A can be 50U for patients with detrusor underactivity who wish to void by abdominal pressure after treatment, or 100U for patients with DSD, dysfunctional voiding or poor relaxation of the urethral sphincter. [3,4,12] Patients are placed in lithotomy position, after sterilization and draping, BTX-A solution is injected directly into the urethral sphincter under cystoscopic guidance in men and periurethrally in women. Each vial of BTX-A can be diluted into 4- 8 ml of normal saline. For the patients who received 50 units of BTX-A the 2- 4 ml BTX-A solution is injected divided to 4 injections at equal volume.

While performing urethral injection, it is essential to inject BTX-A directly into the urethral sphincter. Too much the solution might force BTX-A to leak

outside the urethral sphincter and result in inadequate treatment dose. The injection needle should not be inserted too deep to avoid injecting BTX-A outside the sphincter muscle. The male urethral sphincter is about 1 cm in diameter and 2.5 cm in length, therefore, operator should identify the urethral sphincter and withdraw the cystoscope a little bit outer to the bulbous urethra. With direct visualization of the tight sphincter the needle is injected into 0.5 cm in depth at 4 sites or 8 sites. The female urethra is about 3 cm in length and the maximal diameter of female urethra is at the middle portion of the urethra. The injection needle should be inserted transcutaneously around the urethral lumen and in longitudinal direction with the lumen to the depth of 1.5 cm at 4 or 8 sites. More injection sites will ensure the percentage of leaking BTX-A to a minimum and to obtain the maximum drug effect on the urethral striated muscles.

After urethral injection, a 14 Fr Foley catheter is routinely placed overnight for male patients but not necessary in women. The patient can be discharged in the next morning and then followed-up at OPD until the recurrence of baseline voiding symptoms. Antibiotics are prescribed for 3 days after the procedure. Some patients with cauda equine syndrome or detrusor areflexia with high urethral resistance may need second urethral injection 2 to 4 weeks after the initial treatment to achieve a satisfactory result.

Intravesical (detrusor, suburothelial and trigonal) injections

Patients with symptoms of OAB, NDO, IDO, or IC refractory to conventional medical treatment are candidates for intravesical injections of BTX-A. There is no universal consensus for the optimal dose or sites of BTX-A injections in treatment of refractory OAB or DO. Injection of 300U of BTX-A is

the most commonly used dose for NDO, [6] whereas 200-300U of BTX-A have been applied in treating IDO. [5] Compared the therapeutic results from previous reports, the effects of BTX-A between 200U of suburothelial injection and 300U of detrusor injection on IDO are similar, possibly due to diffusion of the toxin occurs between the detrusor and the suburothelial space, as shown by a decrease in sensory fibers in the suburothelial space after detrusor injection of BTX-A. [13] However, patients receiving suburothelial injection of 200U of BTX-A have a higher rate of adverse events compared to those receiving detrusor injection of the same dose of BTX-A. [14]

Recently, the dose of BTX-A for IDO is further reduced to 100U by many investigators and still a satisfactory outcome can be achieved. Werner et al treated 26 women with IDO and 53% success rate was obtained. [15] Schmid et al treated 100 IDO patients and an 88% success rate was achieved. [16] The therapeutic effects of 100U BTX-A need further clarification, however, if we consider the adverse events occurring after BTX-A treatment, a dose related increase of adverse events is found with increasing dose of BTX-A. In the recent report by the author, urinary tract infection occurred in 35%, a large postvoid residual requiring CIC in 30%, difficult urination in 75% of patients who received 200U of BTX-A for IDO, [5] this high incidence of adverse events might prohibit patients to receive a second injection when their lower urinary tract symptoms relapse. If the dose of suburothelial BTX-A is reduced to 100U the rates of adverse events will also reduce to 4.3% of urinary tract infection, 30.4% of a large postvoid residual, and 56.5% of difficult urination. [14] Therefore, adjustment of the dose of BTX-A for IDO patients to minimize the de novo adverse events seems mandatory.

One important factor for a successful therapeutic outcome of BTX-A is

adequate distribution of toxin into the suburothelial space and detrusor muscles. Desensitization of the mechanoreceptors on suburothelial sensory fibers by BTX-A can result in decrease of bladder urgency sensation and reduce sensory neuropeptides-mediated detrusor overactivity. However, if the BTX-A is not adequately distributed into the bladder wall, or the toxin is injected outside the bladder wall, the desired effect might not achieve. This fact might explain why some investigators used large dose of BTX-A detrusor injections but the therapeutic effects are similar to the suburothelial BTX-A injections. It is possible that much BTX-A solution is injected too deep and outside the bladder wall while performing detrusor injections.

BTX-A 100U is usually reconstituted to 20ml by normal saline for detrusor injections and suburothelial injections while BTX-A 100U is reconstituted to 10ml by normal saline for trigonal injections. Detrusor injection will be performed by injecting BTX-A solution to 40 sites about 1- 2 mm in depth involving lateral walls, posterior wall and the dome of bladder. The injection sites will be equally distributed with 0.5ml for each injection. Suburothelial injection will be performed at a procedure identical to detrusor injections except the needle is inserted just into the suburothelial space and a ballooning formation is noted during infusion of BTX-A solution. When performing trigonal injection, BTX-A solution will be injected to 5 sites into the muscle layer with 2 injections in the first row near the bladder neck and 3 injections in the second row proximal to the interureteric ridge and about 0.5 cm away from the ureteral orifice.

All procedures can be performed transurethrally under local 2% lidocaine anesthesia at outpatient clinic or under intravenous general anesthesia in operation room. Twenty ml of 2% lidocaine will be instilled into the urinary

bladder and retained for 15 minutes during local anesthesia. Injection cystoscope is inserted into the bladder and injections are performed thereafter. The bladder volume will be kept at 100-150ml and the blood vessels are avoided during injections.

The intravesical injections of BTX-A usually will not cause bleeding if the vessels are avoided under direct visualization. A Foley catheter can be placed overnight or until the urine turns clear. The effect of BTX-A will appear at the second or the third day. Then patient will feel gradual increase of difficult urination and incomplete emptying. The patient should be informed of the possibility of large postvoid residual or the risk of acute urinary retention. If such adverse event occurs, an indwelling Foley catheter or institution of clean intermittent catheterization should be performed to avoid the subsequent urinary tract infection or upper urinary tract damage. After the first month, the adverse event of difficult urination will resolve and patient will feel improvement in urinary incontinence, bladder pain or urgency symptoms.

Prostate BTX-A injection

Patients with BPH, CPPS, or chronic prostatitis refractory to conventional treatment can be treated with BTX-A. Recent clinical trials have shown good therapeutic effects in these fields. [9,10] Prostatic injections of BTX-A can be carried out transperineally, transrectally or transurethrally. [9,10] Among these three ways, transperineal injection provides the best way of approach and free of risk of urinary tract infection. [9] During treatment, BTX-A 200U is reconstituted by normal saline to a volume of 20% of TPV and is injected transperineally to the transition zone and peripheral zone under 2% lidocaine local anesthesia at outpatient clinic or under intravenous general anesthesia in

the operation room. The injection needle should be inserted as deep as possible but not penetrating into the urinary bladder. Under transrectal sonography guidance, the prostatic gland is adequately distributed by the injecting solution with the volume. **(Fig.4)** BTX-A solution should be injected equally distributed to bilateral lobes including the median lobe. Broad spectrum antibiotics should be routinely prescribed for 3 days to prevent prostatic infection after injections.

After prostatic BTX-A injection, a certain percentage of patients might develop adverse events such as gross hematuria, difficult urination, perineal pain, or acute prostatitis. These adverse events are caused by inadvertent penetration of injection needle through the prostatic urethra in patients with asymmetry of the prostatic lobes, volume effect of the injected volume, or inadequate sterility procedure. Careful inserting the needle under sonographic guidance and small injecting volume, adequate sterility usually can reduce these adverse events to a minimum.

Conclusions

Treatment of lower urinary tract dysfunction by BTX-A injection is novel and usually effective. Although this procedure is not without any adverse effects, the therapeutic results are not impaired in those patients who had adverse events after BTX-A injections. Correct diagnosis and selection of adequate dose of BTX-A and injecting at the proper sites will determine the result of BTX-A injection.

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Table 1. Indications and injection site, route of injection, anesthesia, dose and adverse events of BTX-A injections

Indication	Injection route	Injection sites	Anesthesia	Dose of BTX-A	Adverse events
Voiding dysfunction	transurethral transperineal	urethral sphincter, 4-8	local or IVG	50U~ 100U	miction pain, AUR, hematuria
IDO	transurethral	detrusor suburothelium 30- 40	local or IVG	100U ~ 200U	UTI, miction pain, AUR, hematuria
NDO	transurethral	detrusor 30- 40	local or IVG	200U ~ 300U	UTI, miction pain, AUR, hematuria
IC	transurethral	detrusor suburothelium 30- 40	local or IVG	100U ~ 200U	UTI, miction pain, AUR, hematuria
OAB	transurethral	detrusor suburothelium 30- 40 Trigone 10	local or IVG	100U	UTI, miction pain, AUR, hematuria
BPH	transperineal transrectal transurethral	prostate 2	local or IVG	200U ~ 600U	UTI, miction pain, AUR, hematuria
CPPS	transperineal transrectal transurethral	prostate 2- 6	local or IVG	100U ~ 200U	UTI, miction pain, AUR, hematuria

8. Prevention and Management of Adverse Events after Intravesical OnabotulinumtxinA (BoNT-A) Injection for Patients with OAB

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Introduction

Intravesical injection of onabotulinumtoxin A (BoNT-A) is effective for overactive bladder (OAB) and idiopathic detrusor overactivity (IDO) refractory to antimuscarinics. The success rate has been reported to range from 50–80%. However, the high rates of treatment-related adverse events (AEs) prevent its more widespread use.

Common adverse events (AEs) after intravesical OnabotulinumtoxinA (BoNT-A) injection

The main AEs associated with intravesical BoNT-A injection include, increased postvoid residual (PVR), straining voiding, acute urinary retention (AUR), urinary tract infection (UTI), gross hematuria, and general weakness. Large PVR was clinically relevant and clean intermittent catheterization (CIC) was necessary. These AEs occurred in approximately 20–43% of patients.

Systemic reactions after local injections are rarely reported. Generalized paralysis after intravesical BoNT-A has never been reported, and this risk seems unlikely as treatment doses use only one-tenth of the lethal dose. Mangera A et al reported only 5 (0.005%) were reported to have developed muscular weakness of the 1025 patients who received onabotulinumtoxinA. The majority of cases of hypoasthenia are transient and self-limiting, and no reports of adults requiring hospitalization and intervention

Risk factors of AEs

In a retrospective analysis of AEs occurred after intravesical injections of 100 U BoNT-A, more than 40% of patients developed large PVR (>150 mL) and needed straining to void, and 6.9% of patients had AUR during the first 3 months after treatment. Male gender, baseline PVR≥100 mL, comorbidity and BoNT-A doses of more than 100 U are risk factors for increasing incidence of AEs. However, the occurrence of these BoNT-A related AEs did not affect the likelihood of successful outcome. Sahai et al reported that a projected

isovolumetric pressure (PIP1) of < or =50 in women and a bladder contractility index (BCI) of < or =120 might be predictive of a need for CIC in this setting, and might help when counseling patients.

Prevention and Management of AEs

Kuo found that UTI occurred in 35%, a large PVR requiring CIC in 30%, difficult urination in 75% of patients with IDO who received 200 U suburothelial onabotulinumtoxinA injections. If the dose of suburothelial onabotulinumtoxinA is reduced to 100 U the rates of adverse events will reduce to 4.3% of urinary tract infection, 30.4% of a large PVR, and 56.5% of difficult urination. Dose dependent adverse events was further confirmed by Dmochovski et al that doses of onabotulinumtoxinA greater than 150 U contributed minimal additional or clinical relevant improvement in symptoms whereas adverse events of large PVR needing CIC was greater than 100 U injection. Based on this multi-centric placebo control trial, a dose of 100 U onabotulinumtoxinA was recommended as optimal for treating refractory OAB.

Injection site seems to have little effect on therapeutic outcome. Bladder base and trigonal injections fare the same safety and efficacy as bladder body injections with or without trigone involvement. Although vesicoureteral refluex (VUR) might be a potential complication after BoNT-A injections in these areas, there is no evidence so far to prove it's presence in the recent studies. An advantage of trigonal injection of BoNT-A is free of detrusor underactivity developed after treatment. Another interesting finding in trigonal BoNT-A injection is the reduction of the incidence of autonomic dysreflexia in SCI patient with NDO and DSD. Trigonal BoNT-A injection might decrease sensory input from this area and reduce the bladder hypersensitivity in patients with dry OAB. Schulte-Baukloh et al demonstrated minimal PVR by simultaneous injection BoNT-A into the bladder and external urethral sphincter concurrently.

Conclusions

Intravesical BoNT-A injection for patients with refractory OAB is safe and efficient. Incomplete bladder empty with large PVR and UTI are the most common AEs. Careful patient selection, informed the risk of AEs and CICs is mandatory. Reduce dose and concurrent sphincter injection may decrease risk of large PVR.

Prevention and management of adverse events after intravesical onabotulinumtxinA (BoNT-A) injection for patients with OAB

Chun-Hou Liao

Outlines

- Introduction
- Common adverse events (AEs) after intravesical OnabotulinumtoxinA (BoNT-A) injection
- Risk factors of AEs
- Prevention and Management of AEs

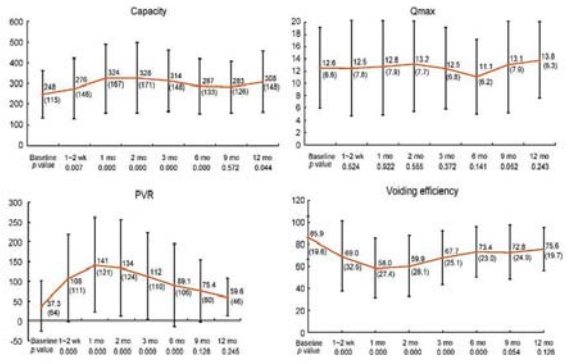
Introduction

- Intravesical injection of BoNT-A provides effective treatment for refractory detrusor overactivity (DO) and overactive bladder (OAB).
- The success rate has been reported to range from 50–80%
- However, the high rates of treatment-related adverse events (AEs) prevent its more widespread use

Common AEs

- The main AEs associated with BoNT-A injection
  - Increased postvoid residual (PVR)
  - Straining voiding
  - acute urinary retention (AUR)
  - urinary tract infection (UTI)
  - Gross hematuria
  - General weakness
- Occurred in approximately 20–43% of patients
- Large PVR was clinically relevant and clean intermittent catheterization (CIC) was necessary

Changes of parameters after BoNT-A injection



Risk of CIC after intravesical BoNT-A for IDO or OAB

Lead Author	Pts No.	Dose (U)	Trigone injected	PVR (ml) criteria to start CIC	CIC (% of pts)
Rapp, 2004	35	300	Yes	NA	0
Flynn, 2004	7	150	No	NA	0
Werner, 2005	26	100	No	>100	8
Kuo, 2005	20	200	No	>250	30-50
Schmid, 2006	100	100	No	>400	4
Sahai, 2007	16	200	No	>150	37.5
Brubaker, 2008	28	200	No	>200	43
Flynn, 2009	15	200-300	No	>100+symptomatic	7

Botulinum Toxin A Versus Placebo for Refractory Detrusor Overactivity in Women: A Randomised Blinded Placebo-Controlled Trial of 240 Women (the RELAX Study). Eur Urol (2012): 200U Botox

Table 4 – Adverse events during follow-up

Adverse events	At 6 wk				At 6 mo			
	Treatment (n = 118)	Placebo (n = 113)	OR (95% CI)	p	Treatment (n = 116)	Placebo (n = 110)	OR (95% CI)	p
Urinary tract infection, n (%)	35 (30)	10 (9)	4.34 (1.95–10.37)	0.0001	36 (31)	12 (11)	3.68 (1.72–8.25)	0.0003
Voiding difficulty, n (%)	19 (16)	5 (4)	4.1 (1.42–16.70)	0.004	10 (9)	1 (1)	10.28 (1.41–450.19)	0.01
ISC, n (%)	16 (14)	5 (4)	3.39 (1.13–12.20)	0.02	18 (16)	4 (4)	4.87 (1.52–20.33)	0.003
Use of additional treatment, n (%)	8 (7)	22 (20)	0.30 (0.11–0.75)	0.006	16 (14)*	35 (32)	0.34 (0.16–0.69)	0.001

OR = odds ratio; CI = confidence interval; ISC = intermittent self-catheterisation.
Reported events since discharge at each follow-up visit; urinary tract infection was reported by the patient (microbiological confirmation was not required). Routine ultrasound screening for retention was not part of the study protocol. Voiding difficulty was diagnosed, and ISC commenced on the basis of symptoms (voiding difficulty and/or incomplete emptying) and confirmed by ultrasound and/or catheterisation. Threshold volume for ISC was 100 ml (three centres) or 150 ml (four centres).
* Three patients in the active group had received two different drugs.

Risk factors of specific AEs

Table 4 – Univariable and multivariable logistic regression analyses for the risk of specific adverse events

	AUR		PVR ≥150 ml		Straining to void	
	OR (95% CI)	p value	OR (95% CI)	p value	OR (95% CI)	p value
Univariable analyses						
Male	9.0 (2.0–41.3)	0.001	1.2 (0.7–2.0)	0.058	1.3 (0.8–2.3)	0.292
Age >75 yr	3.2 (1.1–9.6)	0.014	1.6 (0.9–2.7)	0.039	1.2 (0.7–2.1)	0.435
Comorbidity	2.1 (0.8–5.6)	0.132	2.5 (1.4–4.4)	0.001	1.5 (0.9–2.5)	0.171
OAB-wet	1.1 (0.3–4.1)	0.857	2.4 (1.1–5.4)	0.024	1.4 (0.7–3.0)	0.373
Botox >100 U	1.9 (0.7–5.4)	0.216	1.2 (0.6–2.3)	0.577	2.0 (1.0–3.8)	0.007
Baseline PVR >100 ml	4.9 (1.7–13.9)	0.001	1.9 (0.9–4.0)	0.076	1.9 (0.8–4.5)	0.043
Baseline VE <70%	2.8 (1.0–8.1)	0.049	1.3 (0.6–2.7)	0.465	1.6 (0.8–3.2)	0.225
Multivariable analyses						
Male	9.2 (1.5–3.4)	0.013	–	–	–	–
Age >75 yr	2.1 (0.7–6.5)	0.221	1.5 (0.8–2.5)	0.191	–	–
Comorbidity	–	–	2.2 (1.2–3.8)	0.011	–	–
OAB-wet	–	–	1.7 (0.8–4.0)	0.195	–	–
Botox >100 U	–	–	–	–	2.1 (1.1–4.1)	0.029
Baseline PVR >100 ml	9.9 (7.2–44.7)	0.003	–	–	2.9 (1.3–6.9)	0.007
Baseline VE <70%	2.1 (0.4–10.5)	0.361	–	–	–	–

CI = confidence interval; AUR = acute urinary retention; PVR = postvoid residual; OR = odds ratio; OAB = overactive bladder; VE = voiding efficiency.

Kuo HC er al, EU 2010

Assessment of urodynamic and detrusor contractility variables in patients with overactive bladder syndrome treated with botulinum toxin-A: is incomplete bladder emptying predictable?

- S67 patients (mean age 50.3) with IDO received intravesical 200 U BoNT-A
- Detrusor contractility was assessed using the projected isovolumetric pressure (PIP1) in women and bladder contractility index (BCI) in men
- A PIP1 of < or =50 in women and a BCI of < or =120 might be predictive of a need for CISC in this setting, and might help when counseling patients.

– Sahai A et al. BJU Int 103(5):630-634

Suburothelial injection

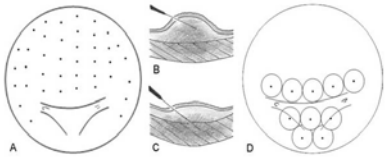


TABLE 2. *Adverse events after BTX-A injection in suburothelial, detrusor and bladder base injection groups*

	Suburothelial	Detrusor	Bladder Base
Dysuria	7	5	2
Acute urinary retention	2	2	0
Urinary tract infection	2	1	1
Gross hematuria	1	0	1
Bladder or urethral pain	1	1	1

Kuo HC, JU 2007;178, 1359-1363

Different Injection Site

TABLE V. Occurrence of Adverse Events by Different Injection Site Group

	Bladder body (n = 37)	Bladder body and trigone (n = 35)	Bladder base and trigone (n = 33)	*P*-value
AUR	2 (5.4%)	4 (11%)	0 (0%)	0.127
Large PVR	16 (43.2%)	13 (37.1%)	16 (48.5%)	0.639
Straining to void	10 (27%)	11 (31.4%)	13 (39.4%)	0.538
UTI	8 (21.6%)	9 (25.7%)	5 (15.2%)	0.56
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

Neurourology and Urodynamics DOI 10.1002/nau

Kuo HC, NAU 2011;30:1242–1248

Dose related effects and adverse effects in suburothelial Botox injections for DO

	Difficult urination	Urinary retention	Postvoid residual ≥150ml	Urinary tract infection (WBC≥8/HPF)	Hematuria
100 units (n=23)	13 (56.5%)	0	7 (30.4%)	1 (4.3%)	2 (8.7%)
150 units (n=25)	19 (76%)	2 (8%)	18 (72%)	2 (8%)	3 (12%)
200 units (n=27)	19 (70%)	6 (22%)	14 (52%)	4 (15%)	3 (11%)
p value	0.838	0.025	0.011	0.523	0.934

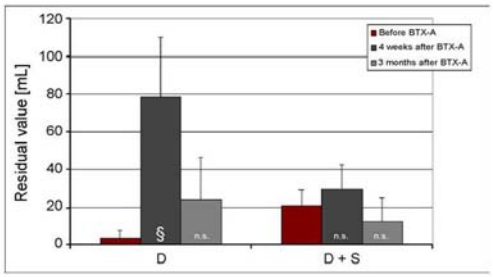
Kuo HC. Urology 2006; **68:993-998.**

AEs in different dose

	Placebo (N=44)	50 U (N=56)	100 U (N=55)	150 U (N=50)	200 U (N=52)	300 U (N=55)
AE UTI	16.3%	33.9%	36.4%	44.0%	48.1%	34.5%
AE urinary retention	2.3%	8.9%	18.2%	28.0%	23.1%	25.5%
PVR-related catheterization (CIC)	0.0%	5.4%	10.9%	16.0%	21.2%	14.5%

Dmochowski R et al. J Urol 2010 Dec;184(6):2416-22.

Concurrent sphincter injection (50-100U)



– Schulte-Baukloh H. Eur Urol 2005 ;48(6):984-90

Systemic AE

- Systemic reactions after local injections are rarely reported
- Generalized paralysis after intravesical BoNT-A has never been reported, and this risk seems unlikely as treatment doses use only one-tenth of the lethal dose.
- Of the 1025 patients who received onabotulinumtoxinA, only 5 (0.005%) were reported to have developed muscular weakness compared with 13 of 491 (0.026%) who received abobotulinumtoxinA.
  – Mangera A et al, EU 2011;64:784-795
- The majority of cases of hypoasthenia are transient and self-limiting, and no reports of adults requiring hospitalisation and intervention

Botulinum Toxin A Versus Placebo for Refractory Detrusor Overactivity in Women: A Randomised Blinded Placebo-Controlled Trial of 240 Women (the RELAX Study). Eur Urol (2012): 200U Botox

- Immediate AEs or reactions were uncommon
- During follow-up there were three drug-related serious adverse reactions.
  – Two patients reported generalised muscle weakness severe enough to interfere with daily activities (one in each allocation arm), and one patient who received onaBoNTA suffered a bronchopneumonia within 3 wk of injection.
  – One patient developed clot retention immediately after treatment, and her discharge was delayed by 48 h.

Summary

- Intravesical BoNT-A injection for patients with refractory OAB is safe and efficient
- Incomplete bladder empty with large PVR and UTI are the most common AEs
- Careful patient selection, informed the risk of AEs and CICs is mandatory
- Reduce dose and concurrent sphincter injection may decrease risk of large PVR

9. Round Table Discussion –
Botulinum toxin injection for lower urinary tract dysfunction

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Abstract

Botulinum toxin has been recently accepted as a novel treatment for lower urinary tract dysfunctions refractory to conventional treatment. Review of the clinical trials in recent years, BoNT type A has been widely used in the urethra or urinary bladder to treat voiding dysfunction due to detrusor sphincter dyssynergia, incontinence due to neurogenic or idiopathic detrusor overactivity, sensory disorders such as bladder hypersensitivity, overactive bladder, and interstitial cystitis/painful bladder syndrome. Intravesical BoNT-A injection is effective in treatment of urinary incontinence due to detrusor overactivity in men and women, as well as in children. Currently BoNT-A has also been applied to treat lower urinary tract symptoms due to benign prostatic hyperplasia in patients not suitable for surgery. This article reviewed the recent advances of BoNT-A on LUTD.

Keywords: painful bladder syndrome, lower urinary tract dysfunction, botulinum toxin, incontinence, voiding dysfunction

1. Mechanism of action of BoNT-A on LUTD

BoNT is one of the most potent natural toxin known in the world. Acute BoNT poisoning causes generalized paralysis and respiratory failure, which takes 3 to 6 months to recover after resprouting of the affected nerves.[1] BoNT is a protein with a 50 kd light chain and a 100 kd heavy chain. BoNT recognizes and enters neurons by binding to the synaptic vesicle protein SV2 during neurotransmitter exocytosis when more active receptors are exposed.[2] Through endocytosis of this toxin, the disulphide bond is cleaved. The light chain is the true active moiety of the molecule and can combine with the SNAP-25 protein to inhibit the exocytosis of neurotransmitter from the vesicles. The affected neuromuscular junctions become paralyzed after injection of BoNT.[3] Seven serotypes of BoNT have been identified, types A and B have been most widely used for medical purposes.[4] Type B BoNT has been shown effective in treating patients with cervical dystonia and refractory to repeated BoNT-A injections.[5]

The application of BoNT-A for the treatment of LUTD has been initiated since the late 1980's. Dykstra et al. described injections of BoNT-A into the external urethral sphincter in spinal cord injured patients to induce chemical sphincterotomy and treat DSD.[6] Schurch also reported successful results of urethral BoNT-A injections for treatment of DSD.[7] In the past few years, Schurch et al reported successful treatment of SCI patients with neurogenic DO using detrusor BoNT-A injections at multiple sites.[8] Later on, intravesical BoNT-A injections were successfully applied on patients with idiopathic DO or overactive bladder.[9,10] Furthermore, Maria et al. first published the therapeutic effects of BoNT-A in patients with BPH.[11] Because the mechanisms of action of

BoNT involve anti-inflammation, therefore, BoNT has currently been tried to treat IC/BPS refractory to medical treatment.[12] As the uses of BoNT-A continue to expand in the field of urology, it is important to understand the mechanisms and clinical effects by which the toxin works on different tissue types and disease entities.

There are three commercially available BoNT worldwide. Botox (onabotulinumtoxinA, Allergan, Inc., Irvine, CA) and Dysport (abobotulinumtoxinA, Ipsen Ltd., Berkshire, UK) are BoNT-A and Myobloc (Elan Pharmaceuticals, Inc., Princeton, NJ) is a BoNT-B. The potency of each toxin is expressed in units of activity. Although there are similarities among the commercial preparations of BoNT, they have different doses, efficacy and safety profiles and should not be considered generic equivalents comparable by single dose ratios. [13] Although the use of BoNTA in the treatment of LUTD has expanded recently, most of the clinical applications are off-licence except for NDO. A systemic review has revealed a high-level evidence for the use of onabotulinumtoxinA and abobotulinumtoxinA in adults with NDO but only for abobotulinumtoxinA in children with NDO. Only onabotulinumtoxinA has level 1 evidence supporting its use in IDO, BOO, DSD, and IC/PBS. [14]

2. BoNT-A Injections in Treatment of Voiding Dysfunction

Although urethral BoNT-A injections was first applied in treatment of voiding dysfunction due to DSD, very little has been added to the literature in the use of BoNT-A injections for neurogenic or non-neurogenic voiding

dysfunction in recent 5 years. Because urethral sphincter BoNT-A injections potentially have a side effect of increase urinary incontinence, urethral BoNT-A injection is seldom reported to be a standard procedure in treatment of voiding dysfunction.

Patients with voiding dysfunction due to SCI, pseudodyssynergia or non-relaxing urethral sphincter can be treated with 50 to 100 U urethral BoNT-A injection.[15] Urethral BoNT-A injections can be performed in the operation room under light intravenous general anesthesia (in men) or at out-patient clinic without anesthesia (in women). The dose of BoNT-A can be 50 U for patients with detrusor underactivity who wish to void by abdominal pressure after treatment,[16] or 100 U for patients with DSD, dysfunctional voiding or poor relaxation of the urethral sphincter.[15] Patients are placed in lithotomy position, after sterilization and draping, BoNT-A solution is injected directly into the urethral sphincter under cystoscopic guidance in men and periurethrally in women. Usually 4 to 8 injections at equal volume of BoNT-A solution is adequate. **(Fig.1A)** The injection needle should not be inserted too deep to avoid injecting BoNT-A outside the sphincter muscle. With direct visualization of the tight sphincter the needle is injected into 0.5 cm in depth at 4 to 8 sites in men. The injection needle should be inserted transcutaneously around the female urethral lumen and in longitudinal direction with the lumen to the depth of 1.5 cm at 4 or 8 sites. More injection sites will ensure the percentage of leaking BoNT-A to a minimum and to obtain the maximum drug effect on the urethral striated muscles.

BoNT-A has been used safely in the treatment of several types of neurogenic spasticity including patients with SCI and DSD.[6,7,15] Phelan et al found that after BoNT-A injection 67% of patients were able to void smoothly

with postvoid residual decreased by 71% and voiding pressure decreased by 38%.[17] In patients with dysfunctional voiding due to urethral sphincter overactivity,[18] urethral sphincter pseudodyssynergia in patients with cerebrovascular accidents or intracranial lesions,[19] non-relaxing urethra due to radical hysterectomy, [20] 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. [21]

In a large series of patients (n=103) with voiding dysfunction, 40 (39%) patients had an excellent result, 47 (46%) had significant improvement and 16 (15%) had treatment failure. The overall success rate was 84.5% (ranged 75% to 100%). Among the 45 patients with urinary retention the indwelling catheters could be removed or CIC was discontinued in 39 (87%).[15] (Table 1)

The actual pathophysiology of non-neurogenic voiding dysfunction has not been completely understood. The bladder neck, the prostatic smooth muscle as well as the urethral sphincter might play a role. Lim SK injected 100U of BoNT-A transurethrally into the bladder neck and proximal prostatic urethra laterally at 10 sites and found 87.5% of patients had a >50% reduction of IPSS from baseline.[22] Similarly, Chen JL, et al. also reported bladder neck and urethral BoNT-A injections improved LUTS and increased maximum flow rate in men with refractory LUTS and a small prostate.[23] It is necessary to perform clinical trial to clearly define the role of BoNT-A on urethral sphincter dysfunction and verify which voiding dysfunction can really benefit from urethral sphincter BoNT-A injections.[24.]

3. Botulinum Toxin A Injections for Overactive Bladder

OAB is a symptom syndrome characterized by urgency frequency with or without urge incontinence that may affect the patients' quality of life.[25] Recent investigations have demonstrated the urothelial release of neurotransmitters such as acetylcholine, adenosine triphosphate and neuropeptides substance P, and the expression of transient receptor potential vanilloid receptor subfamily-1 and purinergic receptors $P2X_3$ strongly imply a role for the urothelium in human bladder mechanosensation.[26-28] The urothelial release of ACh and ATP on bladder filling has been found to increase with ageing [29] and in spinal cord NDO,[30] implicating that an abnormal release of these neurotransmitters in the pathophysiology of DO. In treatment of IDO with intradetrusor injection of BoNT-A, a decreased immunoreactivity of $P2X_3$ expression in suburothelial fibers has been noted, which correlated with improvement in patients' sensation of urgency.[31] Recent study also showed detrusor wall BoNT-A injections can modulate the expression of nerve growth factor and TRPV1 on the urothelium in the rats of bladder outlet obstruction.[32] Established drug therapies also demonstrated the effect of BoNT-A on OAB may act partly through afferent mechanism.[33]

Intravesical BoNT-A injection has been well documented to be effective in treating adult patients with OAB and IDO refractory to antimuscarinic therapy.[9,10,34-40] The bladder capacity increases, intravesical pressure decreases, incontinence episode reduces after intravesical BoNT-A injection. [9] The pooled random effects estimate of effect across three randomized placebo controlled studies revealed that BoNT-A treatment had 3.88 fewer incontinence episodes per day, but a 9-fold increased odds of increased PVR after treatment were also noted.[41] Intravesical injections of BoNT-A improved

the health related quality of life in patients with IDO and NDO.[42] Patients received repeated doses do not seem to become refractory to BoNT-A.[43] Recent studies also revealed that BoNT-A is also effective in treatment of urinary incontinence in children.[44,45] However, the high rate of increased PVR which needs CIC after treatment remains a problem to be solved. Therefore, further robust data are required on long term outcomes, safety, and optimal dose of BoNT-A for OAB.[46]

3.1. What is the optimal dose of BoNT-A for OAB or IDO

Review of previous studies using BoNT-A for IDO, most investigators used 200 U or 300 U detrusor injections. Sahai A et al evaluated the efficacy of 200 U onabotulinumtoxinA detrusor injection for patients with IDO and found therapeutic effect lasted for 6 months, however, among the patients 33% required clean intermittent catheterization to evacuate PVR.[47] Jeffery S et al used 500 U abobotulinumtoxinA in treating patients with IDO and found that 32% remained continent at 6 months while 35% of patients required CIC at 3 months and 22% still needed CIC at 6 months.[48] Kessler et al treated 11 patients with IDO with 300 U onabotulinumtoxinA detrusor injections and the maximal bladder capacity increased from 220 to 340 mL, however, 4 of them needed CIC due to large PVR.[34] Rajkumar et al treated 15 IDO women with 300U onabotulinumtoxinA detrusor injections and 14 of them had an improvement in urgency and frequency, the therapeutic effects lasted for 5-6 months.[35] Popat et al used 200 U onabotulinumtoxinA for 31 IDO patients, although significant improvement of bladder capacity was noted after treatment, 20% of the patients needed CIC.[36] Schulte-Baukloh et al used 300

U of onabotulinumtoxinA detrusor and urethral injections for 7 women with OAB without DO, the bladder capacity increased by 20% and all patients could void without the need of CIC.[10] Kuo found that detrusor injections of 200 U onabotulinumtoxinA provided a 73.3% success rate in 30 IDO patients, the mean therapeutic duration was 5.3 months,[9] whereas suburothelial injections of 200 U onabotulinumtoxinA provided an 85% success rate for IDO patients.[37] **(Fig.1B)**

When comparing 200 U, 150 U and 100 U of onabotulinumtoxinA, Kuo found that 100 U can also have an excellent therapeutic effect on IDO (73.3%) comparing with the results of 200 U detrusor injections.[38] Recently, the dose of onabotulinumtoxinA for IDO is further reduced to 100 U by many investigators and still a satisfactory outcome around 53% to 88% was achieved.[38-40] Several recent multicenter placebo controlled studies also demonstrated that onabotulinumtoxinA at doses of 100 U was well tolerated and had durable efficacy in the management of IDO and UUI without increasing adverse events.[49,50] OnabotulinumtoxinA doses of more than 150 U were more commonly associated with PVR volume of more than 200 U.[51] Intravesical BoNT-A injections were also shown effective on patients with refractory OAB without DO.[10,52] However, although repeated 100 U onabotulinumtoxinA injections is safe and effective in treating patients with OAB, certain patients will benefit from dose optimization to improve efficacy or prevent voiding dysfunction.[53]

3.2. Adverse events after BoNT-A for OAB

Although clinical efficacy of BoNT-A on IDO has been largely confirmed,

the high incidence of adverse events remains problem to be solved. Kuo found that urinary tract infection occurred in 35%, a large PVR requiring CIC in 30%, difficult urination in 75% of patients with IDO who received 200 U suburothelial onabotulinumtoxinA injections.[37] Brubaker et al. found that approximately 60% of women had a clinical response but 43% developed increased PVR and 75% of whom developed UTI after detrusor injections of 200 U onabotulinumtoxinA.[54] This high incidence of adverse events might prohibit patients to receive a second injection when their LUTS relapse. If the dose of suburothelial onabotulinumtoxinA is reduced to 100 U the rates of adverse events will reduce to 4.3% of urinary tract infection, 30.4% of a large PVR, and 56.5% of difficult urination.[38] Dose dependent adverse events was further confirmed by Dmochovski et al that doses of onabotulinumtoxinA greater than 150 U contributed minimal additional or clinical relevant improvement in symptoms whereas adverse events of large PVR needing CIC was greater than 100 U injection. Based on this multi-centric placebo control trial, a dose of 100 U onabotulinumtoxinA was recommended as optimal for treating refractory OAB.[47]

In a retrospective analysis of adverse events occurred after intravesical injections of 100 U onabotulinumtoxinA, Kuo found that the occurrence of adverse events was high after BoNT-A injection for patients with IDO. **Fig. 2** shows the changes of bladder capacity, Qmax, PVR, Pdet and voiding efficiency from baseline to 12 months after 100 U onabotulinumtoxinA injection in patients with OAB. Bladder capacity and PVR increased to a maximum and voiding efficiency decreased to a minimum at 1 month, then slowly returned to baseline levels within 12 months.[55] More than 40% of patients developed large PVR (>150 mL) and needed straining to void, and 6.9% of patients had AUR

during the first 3 months after treatment. Male gender and baseline PVR≥100 mL, comorbidity and onabotulinumtoxinA doses of more than 100 U are risk factors for increasing incidence of adverse events.[55] However, the occurrence of these BoNT-A related adverse events did not affect the likelihood of successful outcome. Kuo et al also found that patients with occurrence of large PVR and straining to void after intravesical 100 U onabotulinumtoxinA injection had significantly higher success rates at 3 months and not significant at long-term compared with those without these adverse events.[56] However, patients usually could accept the adverse events of difficult urination and increased PVR in exchange of the reduction of urgency or UUI, suggesting a lower detrusor contractility is necessary for the therapeutic effect of BoNT-A injection.[55]

In fact, not all patients with OAB can benefit from BoNT-A injections. The overall success rate was found around 70%.[9,37,38,55,57] Patients might have both sensory and motor improvements or only sensory or motor effects. Reduction of urgency severity is associated with long-term therapeutic effect after intravesical BoNT-A injection for IDO.[58] Injection site seems to have little effect on therapeutic outcome. Bladder base and trigonal injections fare the same safety and efficacy as bladder body injections with or without trigone involvement.[59] Analysis of the baseline parameters, Kuo also found that baseline parameters of IDO patients, except subtype of DO, do not predict the treatment outcome.[60]

Whether trigone injections of BoNT-A can improve therapeutic effects of OAB has been discussed. The urinary bladder is rich in sensory fibers but their role in bladder urgency sensation and IDO have not been explored. Sensation from the trigone in these patients might be more closely related to early

bladder filling rather than bladder wall stretch at capacity. Hence, treatment aimed at reducing sensation from the trigone might not improve urgency sensation which occurs at phasic contractions during bladder filling. Significant increases in cystometric capacity and PVR compared to baseline were found in the bladder body injections but not in the bladder base and trigone group. Bladder base BoNT-A injection relieved urgency sensation but could not increase bladder capacity. Compared with bladder body injections, the bladder base and trigonal BoNT-A injections have been found to have a lower success rate at 6 months in patients with IDO.[61] However, another study showed if BoNT-A injections involved trigone and bladder body (trigone-including), injections of 500U abobotulinumtoxinA was found superior to trigone-sparing group for the treatment of refractory IDO and did not cause vesicoureteral reflux.[62]

Although VUR might be a potential complication after BoNT-A injections in these areas, there is no evidence so far to prove it's presence in the recent studies.[61-63] An advantage of trigonal injection of BoNT-A is free of detrusor underactivity developed after treatment.[60] Another interesting finding in trigonal BoNT-A injection is the reduction of the incidence of autonomic dysreflexia in SCI patient with NDO and DSD.[64] Trigonal BoNT-A injection might decrease sensory input from this area and reduce the bladder hypersensitivity in patients with dry OAB.

4. BoNT-A for Neurogenic Voiding Dysfunction

DO and DSD commonly occur in patients with suprasacral cord lesions, such as SCI, multiple sclerosis or transverse myelitis. The presence of DSD is

associated with complete injuries, elevated intravesical pressures and upper tract complications.[65] Patients with DSD usually suffer from urinary incontinence and large PVR needing CIC or indwelling a Foley catheter. These urological complications usually result in a low quality of life and might cause more serious complications such as AD, UTI or upper urinary tract deterioration.[66] In 2011, detrusor injections of 200 U onabotulinumtoxinA has been approved by Federal Drug Administration of USA for treatment f NDO due to SCI and MS.

4.1. Effects of BoNT-A on NDO

In recent decades, treatment of DO and DSD with BoNT-A has emerged as an alternative method for the management of urological complications due to spinal cord lesions. Detrusor injection of 200 U to 300 U of onabotulinumtoxinA can reduce detrusor contractility, improve bladder compliance and restore urinary continence in patients with NDO.[8,67] **(Fig.1C)** BoNT-A is found to modulate afferent activity of the bladder in association with reduced DO and OAB symptoms in NDO patients.[68] In a chronic SCI rat model, intravesical BoNT-A significantly inhibits the afferent response without impairing efferent bladder function.[69] However, clinically this treatment usually induces impaired detrusor contractility, large PVR or urinary retention in NDO, about 70% of patients require periodic CIC, and subsequent UTI could become a *de novo* problem.[70]

BoNT-A toxin treatment of DO due to spinal cord lesion has been reported to provide satisfactory results.[71,72] Detrusor underactivity will develop after detrusor injection of 300 U of onabotulinumtoxinA and the urodynamic and

QoL parameters improvement last for 9 months.[73] Seventy-three percent of patients with neurogenic bladder treated can resume a continent condition after treatment.[70] The results seem promising to achieve urinary continence and to increase bladder capacity. Repeated detrusor BoNT-A injections for refractory NDO in patients with SCI or MS have a consistent effect on bladder control.[72,74] Recent study further revealed 100 U onabotulinumtoxinA intradetrusor injection for MS seems to be effective and safe. Most patients can void voluntarily without compromising voiding efficiency.[73] In patients with Parkinson's disease and refractory DO, intradetrusor injection of 100U onabotulinumtoxinA also induced clinical and urodynamic improvement in OAB that lasts for 6 months.[76,77]

Schurch et al compared detrusor injections of 200 U and 300 U onabotulinumtoxinA to placebo in treating NDO in SCI patients. The QoL index showed no significant difference between 200 U and 300 U, but both doses showed significantly better therapeutic outcome than that in the placebo group.[71] Grosse et al compared the interval between repeated detrusor BoNT-A injections and found repeat BoNT-A injections are as effective as the first one. The intervals between repeated BoNT-A injections did not significantly different between 1-2 injections, 2-3 injections and 3-4 injections. However, the clinical and urodynamics parameters were significantly decreased at months 6 to 9, suggesting repeat injections were needed by this time point.[72]

Recent randomized, double-blind, placebo control trials of BoNT-A on NDO revealed that BoNT-A has benefit in both SCI and MS patients with NDO. BoNT-A significantly reduced UI and improved urodynamic parameters and QoL in MS and SCI patients with NDO. Both doses of 200 U and 300 U

onabotulinumtoxinA were well tolerated with no clinical relevant differences in efficacy or duration of effect.[78] Interestingly, the trigone-including BoNT-A injections was found to have significant superiority in both incontinence episodes and urodynamics parameters than trigone-sparing injections for NDO.[79]

4.2. Urethral or detrusor BoNT-A injections for DSD?

Patients with DSD usually have both storage and empty symptoms. Part of the patients with DSD has to perform CIC by themselves or care-giver in addition to voiding by abdominal tapping. However, some patients with DSD prefer spontaneous voiding without instituting CIC and some might prefer being dry after treatment although CIC is necessary. Therefore, management of voiding dysfunction and incontinence in patients with SCI and DSD is a challenge to physicians and should be considered an art-of-the-medicine. Although BoNT-A treatments have been demonstrated to be effective in reducing incontinence in patients with spinal cord lesion and DSD, patients might have too high expectations about the therapeutic effects of BoNT-A before treatment. Further, some patients might be disappointed by the development of *de novo* problems which they do not anticipate and are likely to have a low rate of satisfaction with BoNT-A treatment.

About 95% of patients with suprasacral lesions demonstrated DO with or without DSD.[80] The hand dexterity, abdominal muscle power, bladder sensation and the degree of urethral sphincter dyssynergia might affect the voiding efficiency and LUTD.[65] Treatment of DSD and improvement of QoL have many aspects, including medical or surgical procedures, however, most

types of management cannot achieve a high success rate. In the era of BoNT-A, it is possible to use detrusor injection to decrease detrusor contractility,[70, 71] urethral injection to reduce urethral resistance,[7,15] or to combine detrusor and urethral injections to achieve the desired goals.[81] Reduction of DO can decrease urinary incontinence whereas reduction of urethral resistance can decrease PVR.

Although intradetrusor BoNT-A injections for NDO can increase bladder capacity and achieve urinary continence, most patients still have to perform CISC or require a caregiver to perform CIC to empty their bladder periodically. This management is rationale but might not be widely adopted in developing countries where public services for CIC are lacking. Patients who cannot have facilities or resources for CIC would prefer spontaneous voiding and wearing an external appliance without needing CIC. In order to achieve improvement of incontinence, decrease urgency episodes, and retain spontaneous voiding function a lower dose of BoNT-A for detrusor injection could provide a satisfactory result to the majority of patients with spinal cord lesion and DSD.[82]

4.3. Satisfaction and dissatisfaction to detrusor BoNT-A injections for NDO

In a study evaluating the therapeutic satisfaction and dissatisfaction in patients with spinal cord lesion and DSD who received detrusor BoNT-A injections, complete dryness was welcome by 58% but 12% of patients were bothered by persistent incontinence and 10% still considered difficult bladder emptying and need for CIC as dissatisfaction of the treatment.[83] (Table 2) The dose of 200 U onabotulinumtoxinA in that study might not be adequate for

patients who wish to become completely dry as shown in the 12% of patients in this study possibly due to inadequate dose of BoNT-A for their DO. For these patients a dose of 300 U onabotulinumtoxinA or more might be necessary to achieve urinary continence. Nevertheless, with 200 U of onabotulinumtoxinA, most patients can achieve improvement in incontinence episodes and preserved spontaneous voiding.

Treatment of NDO and DSD might also be different between genders. Female patients with SCI and DSD usually have more severe urinary incontinence and need diaper protection. Because performing CIC needs more facility and resource in women, women with SCI and DSD would prefer to be dry and get rid of diaper. On the other hand, male SCI patients can use an external appliance to collect urine and prevent urine soiling, therefore, the desire to become dry is not as high as that in female SCI patients. On the other hand, male SCI patients might not appreciate being completely dry and needing CIC after detrusor BoNT-A injection, in that case, a small dose of BoNT-A, e.g. 200U of onabotulinumtoxinA would be an adequate dose to increase bladder capacity and allow patients to void by abdominal tapping.

5. Therapeutic effects of Botox on IC/PBS

IC/PBS is a debilitating chronic disease of unknown etiology characterized by urgency frequency and suprapubic pain at full bladder. Current treatments are usually unsuccessful in completely eradicating bladder pain and increasing bladder capacity in patients with IC/PBS.[84] Various therapy options including oral pentosan polysulphate, cyclosporine A, amitriptyline, and

intravesical heparin, hyaluronic acid, bacilli Calmette Guerin, resiniferatoxin have not demonstrated long-term effects.[85-88] Intravesical injection of BoNT-A has been introduced to treat IC/PBS although its use in LUTD remains unlicensed. Small scale studies suggested the short term efficacy of a single injection of BoNT-A seemed promising with acceptable adverse events. However, the long-term effects of repeated BoNT-A injection need to be elucidated. In addition, the method of administration (i.e. dose, volume and site of injection) still requires further determination.

5.1. Pathophysiology of IC/PBS

The unreliable effective therapy for IC/PBS is possibly a result of poorly understood pathophysiology. Recent findings suggest several pathophysiological mechanisms including epithelial dysfunction, activation of mast cells, neurogenic inflammation, autoimmunity and occult infection are involved in IC/PBS.[89] One of the most common findings in bladder mucosal biopsies from IC/PBS patients is denudation or thinning of the bladder epithelium, suggesting altered regulation of urothelial homeostasis.[90] Other bladder abnormalities include increased nerve fiber density and inflammatory cell infiltration.[91-94] Although investigations have been enthusiastically performed, the etiology of IC/PBS remains unknown. The loss of epithelial integrity is believed a predominant histopathologic finding. The epithelial damage may precede the other histopathologic findings in the bladder wall.[95] The suburothelial space immediately below the basal lamina is well supplied with sensory nerves which transmit the sensation of bladder fullness and response to bladder inflammation.[96,97] A local inflammatory process might be

induced through the afferent and efferent nerves in the suburothelial interstitial cellular network which integrate the transmission of signals from the urothelium to the detrusor muscles in the bladder wall.[98]

In a rat chemical cystitis model, a detrusor injection of BoNT-A increased bladder capacity and compliance.[99] In other basic researches, BoNT-A inhibited release of acetylcholine, norepinephrine, NGF, ATP, substance P and calcitonin gene-related peptide from the nerve fibers and urothelium.[30,100-102] Moreover, in a recent study using a cyclophosphamide induced cystitis model, Chuang et al demonstrated that intravesical BoNT-A administration could inhibit cyclooxygenase 2, and EP4 expression and suppress bladder hyperactivity in rats.[103] In clinical and animal experiments, BoNT-A has been shown to reduce DO, impair bladder sensation, and decrease visceral pain in chronic inflammatory diseases.[12,37,104] These results suggest that BoNT-A treatment can modulate sensory and motor transmission, as well as reduce bladder inflammatory conditions. It is also possible that the chronic symptomatology in bladder hypersensitivity is due to central sensitization and persisting abnormality or activation of the afferent sensory system.[105] In this regard, inhibition of neuroplasticity of the sensory fibers in the suburothelial space by intravesical BoNT-A injections might have good therapeutic targeting for pain and sensory urgency in patients with IC/PBS.[106]

5.2. Efficacy of BONT-A on IC/PBS

Pilot studies reporting the efficacy of BoNT-A for treating IC/PBS since 2004 have revealed controversial results.[12,107,108] However, most recent studies support the effects of BoNT-A in patients with chronic IC/PBS.[108-116] All

nine articles mentioned in Table 3 reporting the use of BoNT-A for IC/PBS utilised onabotulinumtoxinA. Of these, one study was level 1 and two were level 2. One of the level 2 studies compared 100 U or 200 U onabotulinumtoxinA with hydrodistention versus hydrodistention alone.[110] At 3 months, there was a significant decrease in symptom indices, symptoms recorded in a bladder diary, and urodynamic parameters with onabotulinumtoxinA compared with hydrodistention alone. The other level 2 study showed more improvement in frequency, nocturia, and global IC score with 300 U of onabotulinumtoxinA compared with instillation of bacillus Calmette-Guérin.[111] The level 1 study reported on quality of life outcomes utilising the Chronic Prostatitis Symptom Index (female modification) and American Urological Association indices as well as graded chronic pain and perceived stress scales and the visual analogue scale; outcomes were not found to be significantly different from a placebo.[109] The authors emphasized that adjustment of the administrated dose, dilution method and injection site may need further refinement.

5.3. Administration: technique, site, and volume of injection for IC/PBS

Different injection depths (i.e. superficial muscle versus suburothelial) and various injection sites (whole bladder, trigonal or periurethral) have been reported for application of BoNT-A. All nine studies in Table 3 used suburothelial injections for the treatment of IC/PBS. Of these, four included the trigone and one injected around the bladder neck. The volume varied from 2 mL to 30 mL in 10–40 injection sites. The method of administration clearly requires further study.

5.4. Adverse events of BONT-A treatment for IC/PBS

Gottsch et al. injected 50 U of onabotulinumtoxinA in to the bladder neck and found no systemic or local complications.[109] In contrast, Kuo and Chancellor reported 2 of 15 patients had hematuria, 7 had dysuria, and 5 with a large PVR after receiving 200 U of onabotulinumtoxinA.[110] It must also be noted that patients received hydrodistention with onabotulinumtoxinA, but the incidence of hematuria and large PVR was 0%, and 4% developed dysuria after hydrodistention alone.

5.5. Long-term efficacy of BoNT-A on IC/BPS

Although BoNT-A injection seems promising in treating symptoms of IC/PBS, long term results have not shown successful outcomes. Giannantoni et al reported a one-year follow-up of 15 IC/PBS patients receiving BoNT-A injection therapy. Thirteen of these patients (86.6%) reported subjective improvement at the 1 and 3-month follow-ups. At 5 months, the beneficial effects persisted in 26.6% of cases, but frequency, nocturia and the pain VAS had increased. At 12 months, pain had recurred in all patients.[112] Kuo et al demonstrated long term results with repeated BoNT-A injections every six months in 71 patients with refractory IC/PBS for up to 4 injections.[117] Among them, 71, 49, 32 and 19 patients completed one, two, three and four intravesical BoNT-A injections, respectively. As the number of treatments increased from one to four, the IC/PBS symptom score, pain VAS and daytime frequency significantly decreased. When the BoNT-A injection was repeated

up to four times, functional bladder capacity, volume at full sensation and cystometric bladder capacity significantly increased. In addition, a successful result (change of Global Response Assessment scores≧2) at 6 months after the first, second, third and fourth BoNT-A injection was reported in 24 (44%), 15 (44%), 9 (53%) and 7 (54%) patients. The overall incidences of adverse effects including UTI, dysuria, intermittent catheterization, acute urine retention and hematuria during the first, second, third and fourth treatments were 28%, 29%, 45% and 32%, respectively.

In comparison with studies of BoNT-A for treatment of other LUTD, the studies of this drug for treatment of IC/PBS were relatively fewer, smaller scaled, and lower evidence-based level. Intravesical injection (with or without trigone involvement) of BoNT-A seems effective in reducing daily frequency, nocturia, and pain VAS, and improving functional bladder capacity, maximum cystometric capacity and QoL in IC/PBS patients in the short term. The long term efficacy of repeated BoNT-A for treatment of IC/PBS and the optimal administration method require further confirmation.

6. BoNT-A on LUTS/BPH

BPH is a common cause of voiding dysfunction in men. Medical treatment by combining α_1 adrenergic antagonists and 5-α reductase inhibitors is currently effectively used to relax the urethral smooth muscle and shrink the prostatic glandular component.[118-120] Some patients who receive the combined 5ARI and α-blocker medical treatment still experience clinical BPH progression or have only limited improvement in the condition.[120,121] Such patients may have a low QoL due to bothersome LUTS which may lead

to surgical intervention.

6.1. Mechanism of action of BoNT-A on BPH

Previous studies established that the prostatic epithelium receives a cholinergic innervation while the stroma receives a predominantly noradrenergic innervation.[122,123] Recent investigations also suggest that BPH could originate from neural dysregulation of the prostate and alterations in local neuropeptides.[124] BoNT-A has been shown to block the release of neurotransmitters from the presynaptic nerve terminal including acetylcholine, norepinephrine, CGRP, substance P, and glutamate.[125,126] Injection of BoNT-A in the prostate provides an alternative treatment for patients with symptomatic BPH, especially those who are at high surgical risks.[127]

Previous studies using rat models provided direct evidence that intraprostatic injection of BoNT-A induces selective denervation and subsequent apoptosis and atrophy of the glands.[128,129] Injecting BoNT-A into dog prostate reduced contractile function while maintaining relaxation response of the prostate.[130] The prostate atrophy induced by BoNT-A injections in rat is likely the results of sympathetic nerve impairment and decrease of adrenergic stimulation of the gland.[131]

Previous clinical trials have shown that BoNT-A has durable therapeutic effects in relieving LUTS in patients with small BPH of smaller than 30 mL.[132] Another previous study showed that intraprostatic injection of 200U onabotulinumtoxinA reduced about 50% of the total prostate volume in BPH patients with large prostates and improved LUTS from 1 month after injection and the effect persisted at 12 month.[11] However, other studies failed to confirm

these therapeutic effects.[127,132] Silva et al. injected 200 U onabotulinumtoxinA into the prostate of patients with BPH and refractory urinary retention and found 81% of them could resume voiding at 3 months. The mean prostate volume decreased from 70ml to 57 mL at 1 month and to 47 mL at 3 months.[133] The duration of prostatic volume reduction was found lasting for a period of 18 months after a single intraprostatic injection of 200 U onabotulinumtoxinA.[134] Risinda et al. found 55 (71%) of 77 patients had subjective symptomatic improvement after intraprostatic injection of 200 U onabotulinumtoxinA, however, the prostatic volume reduced by only 12.7%.[135]

6.2. Injection technique of BoNT-A in prostate

Prostatic injections of BoNT-A can be carried out transperineally, transrectally or transurethrally.[127,132] Among these three ways, transperineal injection provides the best way of approach and free of risk of UTI.[132] However, transrectal prostatic injection is the procedure that urologists are most familiar. During treatment, onabotulinumtoxinA 200 U is reconstituted by normal saline to a volume of 20% of total prostate volume and is injected transperineally or transrectally to the transition zone and peripheral zone under 2% lidocaine local anesthesia at outpatient clinic or under intravenous general anesthesia in the operation room. The injection needle should be inserted as deep as possible but not penetrating into the urinary bladder. Under transrectal sonography guidance, the prostatic gland is adequately distributed by the injecting solution with the volume **(Fig.1D).** BoNT-A solution should be injected equally distributed to bilateral lobes including the median lobe. Broad spectrum antibiotics should be routinely prescribed for 3 days to prevent prostatic

infection after injections.

After prostatic BoNT-A injections, a certain percentage of patients might develop adverse events such as gross hematuria, difficult urination, perineal pain, or acute prostatitis. These adverse events are caused by inadvertent penetration of injection needle through the prostatic urethra in patients with asymmetry of the prostatic lobes, volume effect of the injected volume, or inadequate sterility procedure. Careful inserting the needle under sonographic guidance and small injecting volume, adequate sterility usually can reduce these adverse events to a minimum.

Although clinical results of intraprostatic BoNT-A injections for BPH seems promising, the report from large scale, randomized, placebo-controlled clinical trial has not come out. An enlarged prostate consists of variable proportion of the glandular component, fibrous tissue and smooth muscles.[136] The glandular component comprises only 20-40% of the total prostate volume.[137] Whether intraprostatic injection of BoNT-A can reduce the prostatic volume by more than 20% is still questionable. Using 5-ARI to reduce prostatic hyperplasia, the total prostatic volume reduction was estimated to be 15 to 20% in long-term treatment.[119] If BoNT-A has effect on glandular apoptosis, the volume reduction of total prostate volume will be at most the same extent of that by 5ARI.

Kuo et al conducted a clinical study of adding-on BoNT-A on patients with large BPH (>60 mL) and unsatisfactory to combined medical therapy.[138] They found that add-on BoNT-A prostatic injection provided no significant therapeutic benefit to patients. Although BoNT-A prostatic injections had a short-term effect in improvement of clinical BPH parameters, the long-term therapeutic effect was similar to the patients who continued medical treatment.

Nevertheless, BoNT-A prostatic injection treatment was safe but with minor adverse effects including hematuria, acute urinary retention and acute prostatitis. The results of this study did not support previous reports and showed add-on BoNT-A treatment provides limited clinical effect in patients with LUTS and BPH larger than 60 ml.

6.3. Controversy of BoNT-A treatment for BPH

Based on these clinical studies, patients receiving BoNT-A injections showed early decrease of prostate volume and improvement of flow rate, indicating that BoNT-A can be an effective and rapid treatment of BPH through the possible mechanisms of induction of glandular atrophy or smooth muscle degeneration. However, the therapeutic outcome of BoNT-A therapy might not maintain and the long-term result is similar to continuing medical therapy, suggesting BoNT-A might not produce durable effect of prostatic glandular atrophy in large BPH at long-term.

Previous studies of BoNT-A effect on men with small BPH have shown durable effect on LUTS improvement without remarkable decrease of prostate volume.[133] In fact, the prostatic volume is not well correlated with urethral resistance, ageing men with a small prostate might have a high bladder outlet resistance and LUTS.[139] On the other hand, LUTS in men are not solely caused by BPH obstruction. The causes for non-BPH LUTS in these patients could by increased bladder sensation, DO or urethral dysfunction.[140] In patients with total prostate volume of less than 40ml or 30ml, the incidence of BOO is only 75% or 50%, respectively.[141] In other words, LUTS might not be caused by BPH in a large scale of patients with small BPH. The enlarged

prostate could be an innocent bystander in patients with LUTS and a small BPH.

The main therapeutic effect of BoNT-A on LUTS of patients with small BPH might not from reduction of prostate volume but through urethral muscle paralysis or suburethral neuromodulation without actually decreasing the glandular component of the prostate. Urethral sphincter injection of BoNT-A has been demonstrated to reduce urethral resistance in patients with spastic urethral sphincter or isolated urethral sphincter obstruction.[15] The effect of BoNT-A on small BPH and LUTS might be due to reduced urethral resistance through affecting the urethral muscles rather than affecting the prostate glands. Therefore, in patients with large BPH receiving transperineal BoNT-A injections, the BoNT-A effect on the reduction of prostate volume was not remarkable and cannot have long-term effect.

Based on currently available data, BoNT-A might not be considered as the first line therapy for large BPH. However, because a short-term BoNT-A effect still can be achieved, prostatic BoNT-A injection can be used as an adjuvant therapy for patients who have unsatisfactory response to long-term medical treatment and need urgent treatment for refractory urinary retention, especially in elderly patients unfit for surgical intervention.

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Fig.1. Several different BoNT-A injections for lower urinary tract dysfunction: (A) transurethral urethral sphincter BoNT-A injections in man (asterisks indicate injection sites), (B) transperineal urethral sphincter injections in woman (asterisks indicate injection sites), (C) intravesical suburothelial BoNT-A injections for overactive bladder, (D) detrusor BoNT-A injections for neurogenic detrusor overactivity, and (E) transperineal prostate BoNT-A injections for benign prostatic hyperplasia (arrow heads indicate injection needle).

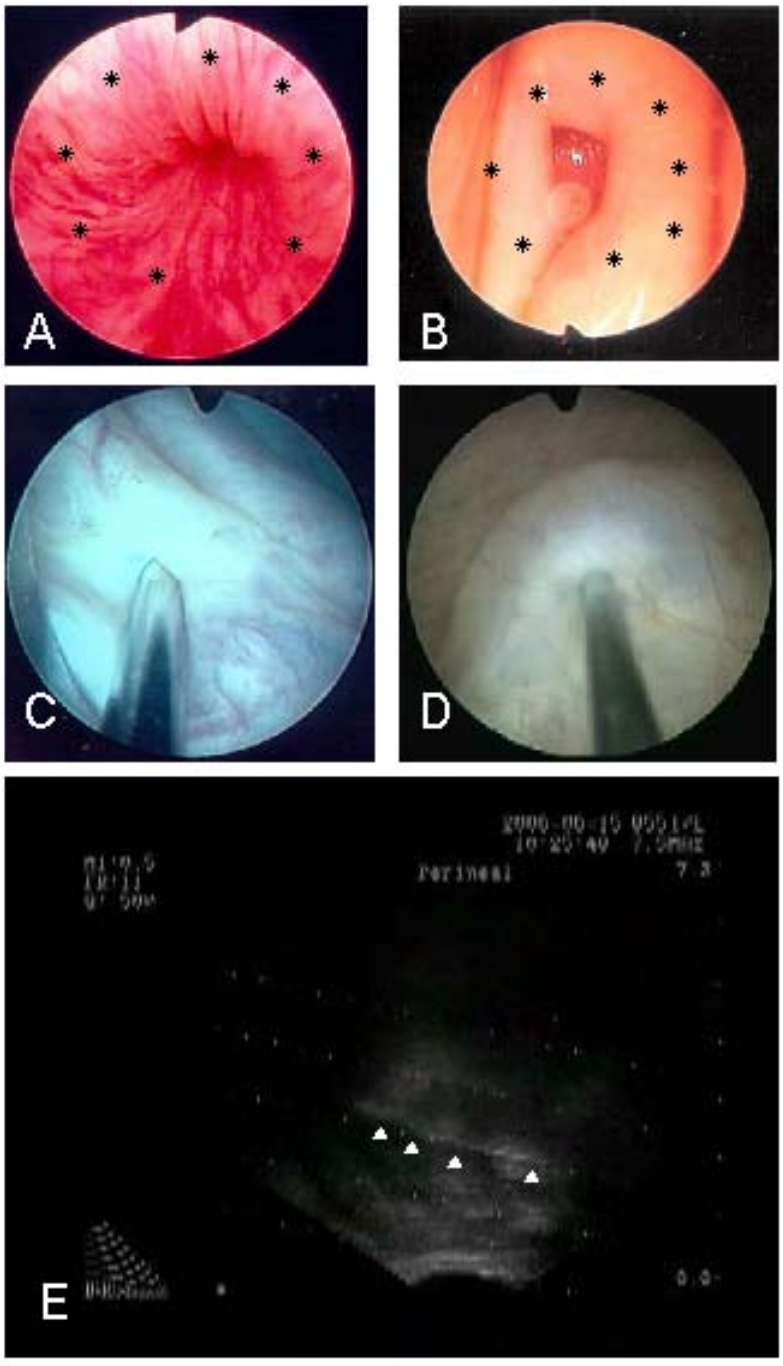
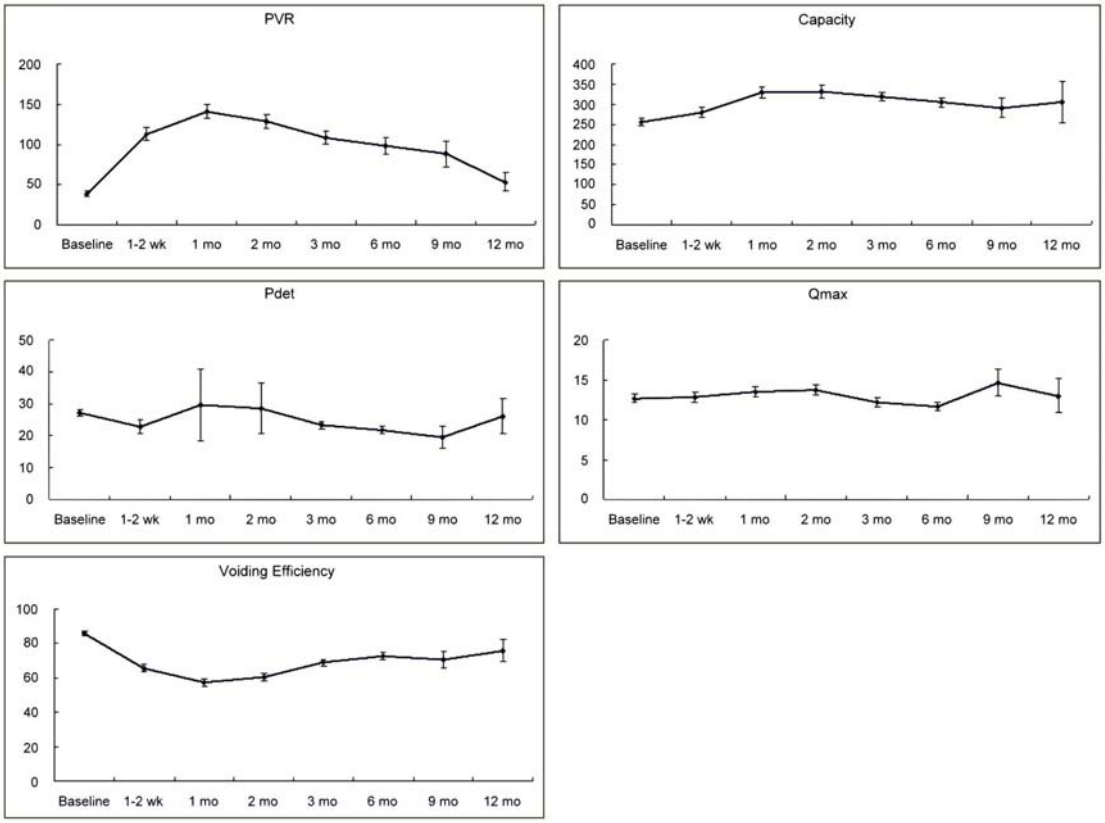


Fig.2 Effects of intravesical 100U onabotulinumtoxinA injection on voiding function from baseline to 12 months. Data are expressed as mean ± SEM



PVR: postvoid urine, Qmax: maximum flow rate, Pdet: detrusor pressure

Table1 Therapeutic effects of urethral sphincter BoNT-A injections of different 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%)	14 (70%)	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%)
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%)

DSD: detrusor sphincter dyssynergia

Table 2 Main therapeutic effects of lower urinary tract dysfunction and causes for dissatisfaction with detrusor BoNT-A treatment

Main therapeutic effects of LUTD	Patients	**Causes of dissatisfaction to treatment**	Patients
Complete dry	29 (58%)	Persistent severe	6 (12%)
Increase bladder	36 (72%)	incontinence	
capacity		Increased PVR	25 (50%)
Decrease incontinence	45 (90%)	Difficult urination or	16 (32%)
Less urgency episodes	31 (62%)	retention	
Less AD	5 (71%)*	Need CIC/CISC	5 (10%)
		Nocturnal incontinence	10 (20%)

* Only 7 patients presented with symptoms of autonomic dysreflexia at baseline BoNT-A: botulinum toxin A, LUTD: lower urinary tract dysfunction, CIC: clean intermittent catheterization; CISC: clean intermittent self-catheterization; PVR: postvoid residual; AD: autonomic dysreflexia

Table 3 Data for the use of botulinum toxin A in interstitial cystitis/painful bladder syndrome

Study	*N*=	Follow-up	Preparation, dose	injection sites, volume	Daytime frequency, %Δ	Nocturia, %Δ	FBC, %Δ	MCC, %Δ	VAS, %Δ	QoL, %Δ	LOE
Gottsch HP et al [107]	9	3 mo	Botox; 50 U	2 mL	–	–	–	–	–	CPSI-F: −11	1
	11		Placebo	–	–	–	–	–	–	CPSI-F: −4	–
Kuo HC and Chancellor [108]	15	3 mo	Botox and HD; 200 U	40; 20 mL	−34	−51	40	62	−55	–	2
	29		Botox and HD 100 U	–	−25	−24	17	26	−39	–	–
	23		HD	–	−14	−5	9	4	−18	–	–
El-Bahnasy AE, et al [109]	16	22 wk	BCG	–	−31	−54	–	–	–	GICS: −71	2
	16	23 wk	Botox; 300 U	–	−68	−100	–	–	–	GICS: −92	–
Giannantoni A, et al [106]	14	1 mo	Botox; 200 U	20; 20 mL	−41	−53	–	37	−38	–	3
Giannantoni A, et al [110]	15	1 mo	Botox; 200 U	20; 20 mL	−48	−67	–	41	−35	–	3

Giannantoni A, et al [111]	13	1 mo	Botox; 200 U	20; 20 mL	−50	−75	–	32	−36	–	3
Giannantoni A, et al [112]	14	3 mo	Botox; 200 U	20 mL	−56	−74	–	90	−46	SF-36, HAM-A, HAM-D	3
Pinto R, et al [113]	26	1 mo	Botox; 100 U	10; 10 mL	−52	−51	–	130	−64	–	3
Ramsay AK, et al [114]	11	6 wk	Botox; 200–300 U	20–30; 20–30 mL	–	–	–	29	–	BFLUTS /KHQ	3

BCG = bacillus Calmette-Guérin; CPSI-F = Chronic Prostatitis Symptom Index (female modification); FBC: unctional bladder capacity; GICS = Global Interstitial Cystitis Score; HAM-A = Hamilton Anxiety Rating Scale; HAM-D = Hamilton Depression Rating Scale; KHQ = King's Health Questionnaire; LOE = level of evidence; MCC = maximum cystometric capacity; VAS = visual analogue scale

Notes

Record your notes from the workshop here