Technical Points of Botulinum Toxin A Injections in the Treatment of Lower Urinary Tract Dysfunction

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INTRODUCTION

Recently, botulinum toxin has emerged as a novel treatment for lower urinary tract dysfunctions refractory to conventional treatment. Review of the clinical trials in the past 5 years shows that 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 used to treat benign prostatic hyperplasia (BPH) refractory to medical treatment [9,10], chronic prostatitis and chronic pelvic pain syndrome (CPPS) [11].

INDICATIONS FOR BTX-A INJECTION

Although there are many new indications for intravesical and urethral injections of BTX-A, the key for successful treatment is the accurate diagnosis of lower urinary tract dysfunction and the optimal dose of BTX-A, as well as correct and adequate sites of injection. The instrument can be any type of available injection needle or cystoscope. Patients can be treated either with local anesthesia or under intravenous general anesthesia, depending on where they are to be injected. The adverse events that may occur after BTX-A injections, such as gross hematuria, dysuria, miction pain, large postvoid residue and acute urinary retention (AUR), should be fully explained to the patients being treated (Table 1). For patients taking an anticoagulant for chronic stroke or cardiovascular disease, the anticoagulant agent should be discontinued at least 1 week before the BTX-A treatment to prevent bleeding after the injections.

URETHRAL SPHINCTER INJECTION OF BTX-A

Urethral BTX-A injection can be performed in the operating room under light intravenous general anesthesia (in men) or in the Outpatients Department (OPD) without anesthesia (in women) [12]. The dose of BTX-A can be 50 U for patients with detrusor underactivity who wish to void by abdominal pressure after treatment, or 100 U for patients with detrusor sphincter dyssynergia (DSD), dysfunctional voiding or poor relaxation of the urethral sphincter [3,4,12]. Patients are placed in the lithotomy position and, 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 by 4-8 mL of normal saline. For patients who receive 50 U BTX-A, 2-4 mL BTX-A solution is injected divided into 4 injections of equal volume.

While performing urethral injection, it is essential to inject the BTX-A directly into the urethral sphincter. Too much solution might force the BTX-A to leak outside the urethral sphincter and result in an inadequate treatment dose. The injection needle should not be inserted too deep to avoid injecting the BTX-A outside the sphincter muscle. The male urethral sphincter is about 1 cm in diameter and 2.5 cm in length; therefore, the operator should identify the urethral sphincter and withdraw the cystoscope a little bit from the bulbous urethra. With direct visualization of the tight sphincter, the needle is inserted 0.5 cm in depth at 4 or 8 sites. The female urethra is about 3 cm in length and the maximal diameter is at the middle portion of the urethra. The injection needle should be inserted transcutaneously around the urethral lumen and in a longitudinal direction with the lumen to a depth of 1.5 cm at 4 or 8 sites. More injection sites will ensure the percentage of BTX-A leakage is kept to a minimum, thus obtaining the maximum drug effect on the urethral striated muscles (Fig. 1).

After urethral injection, a 14 Fr Foley catheter is routinely placed overnight for male patients but is not necessary in women. The patient can be discharged the next morning and then followed up at the 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 a 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 the treatment of refractory OAB or DO. Injection of 300 U of BTX-A is the most commonly used dose for NDO [6], whereas 200-300 U of BTX-A have been applied in treating IDO [5]. Comparing the therapeutic results from previous reports, the effects of BTX-A 200 U of suburothelial injection and 300 U of detrusor injection for IDO are similar, possibly due to diffusion of the toxin 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 200 U of BTX-A have a higher rate of adverse events compared to those receiving detrusor injection of the same dose of BTX-A [14].

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Recently, the dose of BTX-A for IDO was further reduced to 100 U by many investigators and a satisfactory outcome was still achieved. Werner et al treated 26 women with IDO and a 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 100 U of 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 residue requiring clean intermittent catheterization (CIC) in 30% and difficulty in urination in 75% of patients who received 200 U of BTX-A for IDO [5]. This high incidence of adverse events might prohibit patients from receiving a second injection when their lower urinary tract symptoms relapse. If the dose of suburothelial BTX-A is reduced to 100 U the rates of adverse events will also reduce to 4.3% for urinary tract infection, 30.4% for a large postvoid residue and 56.5% for difficulty in 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 the suburothelial sensory fibers by BTX-A can result in decrease in bladder urgency sensation and reduction of 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 be achieved. This fact might explain why some investigators used large doses of BTX-A detrusor injections but the therapeutic effects were similar to suburothelial BTX-A injections. It is possible that much of the BTX-A solution is injected too deep and outside the bladder wall while performing detrusor injections.

BTX-A 100 U is usually reconstituted to 20 mL by normal saline for detrusor injections and suburothelial injections, while BTX-A 100 U is reconstituted to 10 mL by normal saline for trigonal injections. Detrusor injections are performed by injecting BTX-A solution into 40 sites about 1-2 mm in depth and involving the lateral walls, posterior wall and the dome of the bladder. The injection sites are equally distributed with 0.5 mL for each injection (Fig. 2A). Suburothelial injections are performed by a procedure identical to detrusor injections except that the needle is inserted just into the suburothelial space and a ballooning formation is noted during infusion of BTX-A solution (Fig. 2B). When performing trigonal injections, BTX-A solution is injected into 5 sites in 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 about 0.5 cm away from the ureteral orifice (Fig. 3).

All procedures can be performed transurethrally under 2% lidocaine local anesthesia in the OPD or under intravenous general anesthesia in the operating room. Twenty mL of 2% lidocaine is instilled into the urinary bladder and retained for 15 minutes for local anesthesia. An injection cystoscope is inserted into the bladder and injections are performed thereafter. The bladder volume is kept at 100-150 mL and the blood vessels are avoided during injections.

Intravesical injections of BTX-A usually do 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 be apparent on the second or third day. The

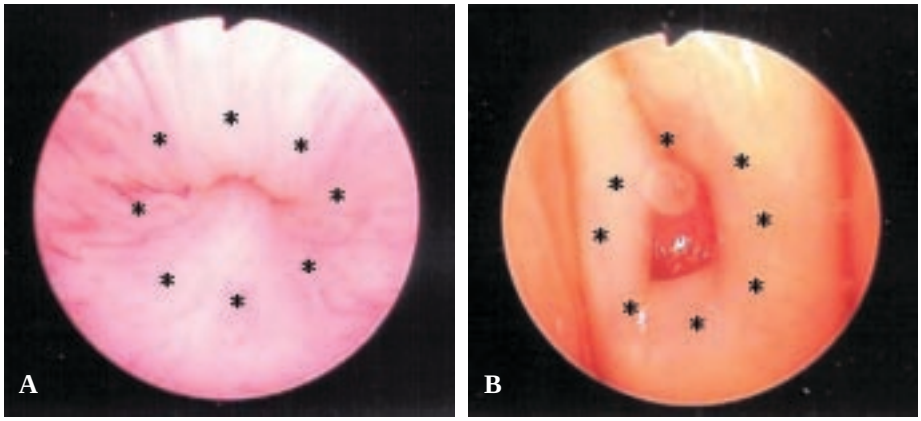

Fig. 1. Urethral sphincter injections of BTX-A (A) in a man and (B) in a woman.

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

patient will feel gradual increase of difficulty in urination and incomplete emptying. The patient should be informed of the possibility of large postvoid residue or the risk of acute urinary retention. If such adverse events occur, an indwelling Foley catheter or CIC should be used to avoid subsequent urinary tract infection or upper urinary tract damage.

After the first month, the adverse event of difficulty in urination will resolve and the patient will feel an improvement in urinary incontinence, bladder pain or urgency symptoms.

PROSTATE BTX-A INJECTION

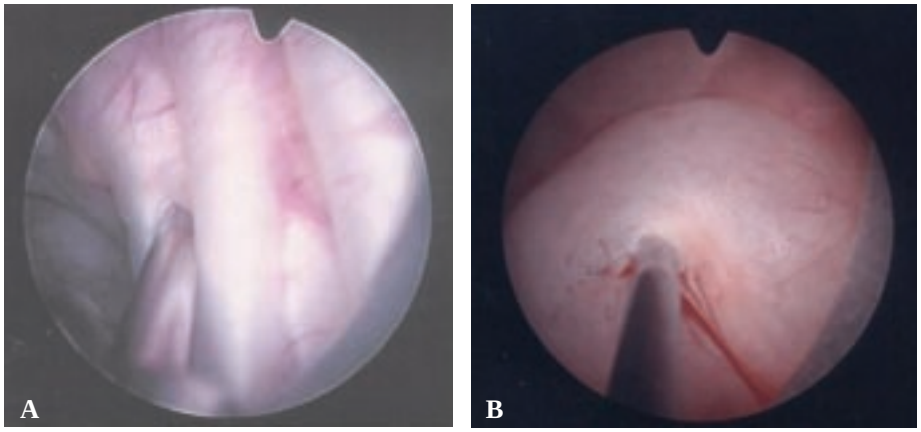

Fig. 2. BTX-A injections (A) into the detrusor muscle and (B) into the suburothelial space.

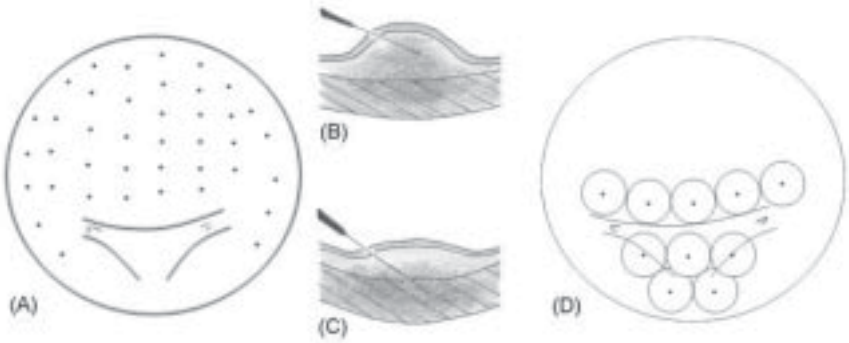

Fig. 3. BTX-A injection (A) at 40 sites in the lateral and posterior walls of the bladder, into (B) the suburothelial space, (C) the detrusor muscle, and (D) at the bladder base and trigone.

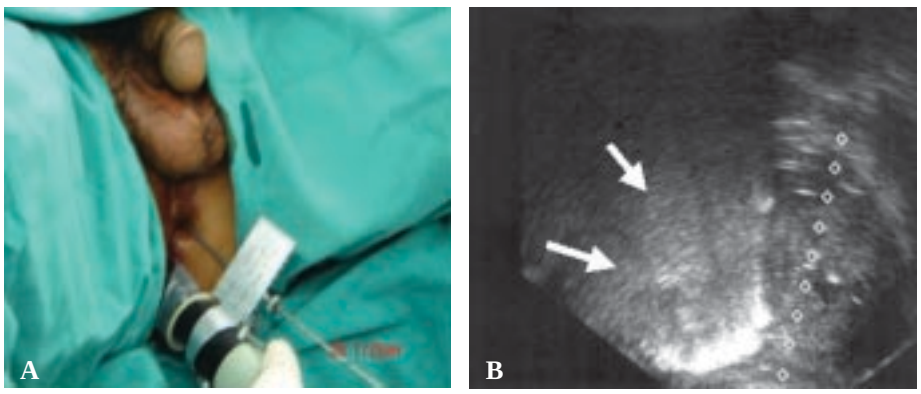

Fig. 4. Prostatic BTX-A injection (A) performed under transrectal sonographic guidance and (B) injected into the middle portion of the prostate with adequate distribution of BTX-A throughout the whole prostate.

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]. Of these three routes, transperineal injection provides the best approach and is free of risk of urinary tract infection [9]. During treatment, BTX-A 200 U is reconstituted by normal saline to 20% of the total prostate volume (TPV) and is injected transperineally to the transition zone and peripheral zone under 2% lidocaine local anesthesia in the OPD or under intravenous general anesthesia in the operating room. The injection needle should be inserted as deep as possible but should not penetrate into the urinary bladder. Under transrectal sonographic guidance, the volume of injecting solution is adequately distributed within the prostate gland (Fig. 4). The BTX-A solution should be equally distributed in the 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, difficulty in urination, perineal pain or acute prostatitis. These adverse events are caused by inadvertent penetration of the prostatic urethra by the injection needle in patients with asymmetry of the prostatic lobes, the volume effect of the injected BTX-A or an inadequately sterile procedure. Careful insertion of the needle under sonographic guidance, a small injecting volume and an adequately sterile procedure can usually 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 adverse effects, the therapeutic results are not impaired in those patients who suffer adverse events after BTX-A injections. Correct diagnosis, selection of an adequate dose of BTX-A and injecting at the proper sites will determine the result of BTX-A injections.

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