



## Review Article

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# Frontiers in the Clinical Applications of Botulinum Toxin A as Treatment for Neurogenic Lower Urinary Tract Dysfunction

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Patients with neurogenic lower urinary tract dysfunction (NLUTD) experience urinary incontinence with or without difficult urination, which might promote recurrent urinary tract infection (UTI) and exacerbate upper urinary tract function. Nonetheless, appropriate bladder management has been shown to reduce urological complications and improve quality of life. In addition to pharmacological therapy and surgical intervention, botulinum toxin A (BoNT-A) has been widely utilized in NLUTD. The therapeutic efficacy of detrusor BoNT-A injections for neurogenic detrusor overactivity due to spinal cord injury (SCI), multiple sclerosis, or other central nervous system lesions, such as cerebrovascular accident, Parkinson disease, early dementia, and pediatric NLUTD due to myelomeningocele, has been well established, with repeated BoNT-A injections every 6 to 9 months being necessary to maintain its therapeutic effects. Urethral BoNT-A injection can decrease urethral sphincter resistance and facilitate efficient voiding in patients with NLUTD who wish to preserve self-voiding. Detrusor BoNT-A injection can also decrease the occurrence of autonomic dysreflexia in patients with SCI, even after failed augmentation enterocystoplasty, with additional benefits including reduced UTI episodes and preserved renal function with repeated injections. However, this treatment does have some side effects. Complete informed consent for BoNT-A injection therapy with full disclosure of its potential complications should therefore be obtained before this procedure is undertaken.

**Keywords:** Botulinum toxins; Urinary bladder, Neurogenic; Detrusor; Urinary incontinence; Urodynamics

• **Conflict of Interest:** No potential conflict of interest relevant to this article was reported.

## INTRODUCTION

Neurogenic lower urinary tract dysfunction (NLUTD) causes various lower urinary tract dysfunctions following neurological diseases or injuries. Accordingly, patients may experience urine storage failure due to detrusor overactivity (DO) or urethral sphincter incompetence; bladder emptying failure due to detrusor areflexia, detrusor underactivity, bladder neck dysfunction, or detrusor external sphincter dyssynergia (DSD); or combined urine storage and emptying failure due to DSD or detrusor hyperreflexia and inadequate contractility. Botulinum toxin A (BoNT-A), which was initially utilized in urology as a treat-

ment for patients with NLUTD due to chronic spinal cord injuries (SCIs) [1-4], selectively modulates neurotransmission from motor nerve endings to cause muscular paralysis, acts on sensory receptors to decrease pain and sensory disorders, and promotes anti-inflammatory effects to improve chronic inflammation and related functional disorders. Moreover, studies have shown that BoNT-A injection into the urethral sphincter improves voiding efficiency in patients with DSD [5], while others have revealed that detrusor BoNT-A injection reduces DO and intravesical pressure and improves urinary incontinence [6,7]. The clinical applications of BoNT-A can be further extended to include the treatment of neurogenic DO (NDO) and urinary

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**Table 1.** Clinical applications of botulinum toxin A for neurogenic lower urinary tract dysfunction

NLUTD	Therapeutic effects	Target	Usual dose	References
SCI, DSD	Improved self-voiding, decreased PVR	Urethra	100 U	1–5, 18, 19, 22, 27
SCI, NDO	Improved continence, decreased detrusor pressure, increased bladder capacity, protected upper tract	Detrusor	200–300 U	6, 7, 16, 20, 23, 39, 40, 42, 43, 46, 47, 49, 53, 54, 55
SCI, AD	Decreased AD	Detrusor	200 U	28, 30
MS, PD, CVA, NDO	Improved continence, decreased detrusor pressure, increased bladder capacity, preserved self-voiding	Detrusor Detrusor	200–300 U 100 U	59, 60, 61, 65, 67, 62, 63, 64, 66, 68
MS, PD, CVA, DSD	Improved self-voiding, decreased PVR	Urethra	100 U	5
Pediatric MMC, NDO	Increased bladder capacity, decreased detrusor pressure, increased compliance, decreased VUR	Detrusor	5–10 U/kg	73, 74, 75
Pediatric MMC, DSD	Improved self-voiding and increased capacity	Urethra +detrusor	Total 10 U/kg	78, 80

NLUTD, neurogenic lower urinary tract dysfunction; SCI, spinal cord injury; DSD, detrusor sphincter dyssynergia; NDO, neurogenic detrusor overactivity; AD, autonomic dysreflexia; MS, multiple sclerosis; PD, Parkinson disease; CVA, cerebrovascular accident; PVR, postvoid residual; VUR, vesicoureteral reflux; MMC, myelomeningocele.

incontinence among pediatric patients with myelomeningocele and other types of NLUTD, as well as autonomic dysreflexia (AD) in patients with high-level SCI (Table 1). However, urinary tract infection (UTI) remains the most bothersome adverse event (AE) prohibiting its widespread use in actual clinical practice. The current review focuses on the frontiers in the clinical applications of BoNT-A for the treatment of NLUTD.

## MECHANISM OF ACTION OF BOTULINUM TOXIN A FOR NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

BoNT-A has been found to cleave N-ethylmaleimide-sensitive fusion attachment protein receptor complex (SNAP-25), thereby inhibiting neurotransmitter release at the neuromuscular and neuroglandular junctions [8]. The pharmacological mechanism of action of BoNT-A for lower urinary tract dysfunction in humans may involve not only efferent function, but also afferent nerve terminals and the urothelium [9–11].

Studies have shown that the detrusor injection of BoNT-A affects preganglionic parasympathetic and adrenergic nerves and sensory fibers, blocking acetylcholine (ACh) release and promoting paralysis of bladder motor neurons [9,10]. Moreover, other studies have found a reduction in human bladder muscarinic receptors M2 and M3 and purinergic receptors P2X2 and P2X3 after detrusor BoNT-A injections [12]. By inhibiting both sensory and motor nerves in the micturition reflex, BoNT-A injections can attenuate DO in the bladders of patients with SCI. BoNT-A has also been found to alter the re-

lease of adenosine triphosphate, neurotrophins, and nitric oxide (NO) in the urothelium, which can also reduce sensory urgency both in neurogenic and nonneurogenic bladder dysfunction [9,13–15]. One study showed that urethral sphincter BoNT-A injection can decrease urethral striated muscle tonicity, lower urethral resistance, and improve voiding efficiency in patients with detrusor sphincter dyssynergia [5]. Notably, BoNT-A has been found to have both motor and sensory inhibitory effects. However, considering that sensory inhibition is unrelated to ACh release, BoNT-A may have longer inhibitory effects on detrusor contractility than on the urethral sphincter [2,16].

## URETHRAL SPHINCTER BOTULINUM TOXIN A INJECTION FOR DETRUSOR EXTERNAL SPHINCTER DYSSYNERGIA

Urethral sphincter BoNT-A injection was initially used to treat DSD in patients with SCI to facilitate spontaneous urination without self-catheterization [1]. The therapeutic effect of urethral sphincter BoNT-A injection, which is typically dosed at 100 U, usually appears 1 week after injection and lasts for 3 to 6 months [1–5,17,18]. Accordingly, a decrease in postvoid residual (PVR) volume and maximal urethral closure pressure and an increase in maximum flow rate have been observed after BoNT-A injection [1,2]. Regardless of whether injections are performed transperineally or transurethrally, previous studies have confirmed treatment efficacy [3,4]. Notably, a 50% decrease in UTIs in NDO has been observed after BoNT-A injection, mainly due to the decrease in PVR and intravesical pres-

sure following treatment [18]. However, urethral sphincter BoNT-A injection has yet to be widely utilized among patients with SCI considering the emerging evidence on AEs after injection, which include increased urinary incontinence and persistent incomplete bladder emptying [5,19-21]. The exacerbation of urinary incontinence in patients with SCI generally prohibits the clinical use of urethral BoNT-A injections in treating DSD. As such, patients are usually switched to detrusor BoNT-A injections to promote urinary continence despite the need for clean intermittent self-catheterization (CISC) [19,22,23].

Although urethral BoNT-A injections have not been widely utilized for DSD treatment in patients with SCI, this treatment may likely benefit those who have neurogenic lesions and dis-coordinated urethral sphincter during urination, as well as those who are ambulatory and prefer to urinate voluntarily. Previous studies have revealed that 100- to 200-U injections of urethral sphincter BoNT-A were effective for patients with multiple sclerosis (MS), cerebrovascular accident (CVA), or SCI [5,20]. Meanwhile, a study showed that clean intermittent catheterization (CIC) can be avoided in patients with CVA and chronic urinary retention after urethral BoNT-A injection of 100 U [24]. However, repeat injections are necessary to maintain therapeutic efficacy.

## CURRENT ROLE OF BOTULINUM TOXIN A IN AUTONOMIC DYSREFLEXIA AMONG PATIENTS WITH SPINAL CORD INJURY

Patients with SCI who have high-level spinal cord lesions typically present with AD, a potentially life-threatening urological complication that results in hypertension, headaches, and even stroke when not treated appropriately [25]. AD is believed to be triggered by cutaneous or visceral afferent stimuli that originate below the level of the spinal cord lesion [26] and occurs most often in individuals with SCI above the T6 level [25]. Patients with chronic SCI may develop AD during bladder overdistention, stool impaction, or UTI [27]. Accordingly, studies have shown that BoNT-A injections into the detrusor or urethral sphincter abolished AD or decreased its severity in some patients with SCI [6,27] perhaps by decreasing intravesical pressure or inhibiting sensory afferent pathways. Our previous study demonstrated that AD may resolve, persist, or exacerbate after detrusor BoNT-A injections in patients with SCI who had NDO. Overall, 62% of patients exhibited improvement in AD severity after BoNT-A injections, whereas only 10 patients de-

veloped AD exacerbation after detrusor BoNT-A injections.

Patients with persistent AD after augmentation enterocystoplasty may also benefit from BoNT-A injections into the native bladder [28]. Although intravesical BoNT-A injection has been considered as a novel treatment to control AD in patients with high-level SCI, some may develop an acute AD response during detrusor BoNT-A injection. This is because detrusor BoNT-A injection causes bladder wall trauma, acute suburothelial nerve plexus inflammation, and autonomic nervous system activation, thereby exacerbating AD during the acute stage of BoNT-A injection. This discomforting experience often discourages patients from undergoing repeat BoNT-A injections for NDO and urinary incontinence [29,30]. Nevertheless, detrusor BoNT-A injections should be attempted in patients with high-level SCI whose AD is refractory to conventional medical treatment in order to alleviate AD severity and improve quality of life.

## BOTULINUM TOXIN A FOR NEUROGENIC DETRUSOR OVERACTIVITY

Less invasive and reversible treatment strategies, such as neurotoxin injection into the detrusor or urethral sphincter, should be utilized for bladder control and emptying in patients with NLUTD. Based on an understanding of its pharmacological mechanism, BoNT-A was enthusiastically utilized for the treatment of NDO by 2000. Intradetrusor BoNT-A injection has been demonstrated to be effective in restoring urinary continence for over 3 to 9 months [16,31,32]. Moreover, a BoNT-A dose of 200 to 300 U injected into the detrusor successfully increased the cystometric bladder capacity, decreased voiding detrusor pressure, and improved urinary continence in patients with SCI. However, CIC remains mandatory for periodic emptying of the bladder [6]. Other studies have noted that this treatment decreased AD and significantly improved quality of life among patients with who had DSD [27,33].

Earlier studies found that a BoNT-A dose of 300 U increased cystometric bladder capacity, decreased reflex volume, decreased detrusor voiding pressure, and increased bladder compliance [34-38]. Further clinical trials all confirmed that detrusor BoNT-A injection had superior therapeutic efficacy compared to placebo in patients with SCI or MS [16]. One study showed that a BoNT-A dose of 200 and 300 U had similar therapeutic effects on NDO, and a dose of 200 U was approved by the U.S. Food and Drug Administration (FDA) [39]. Moreover,

repeated detrusor BoNT-A injections seem to be as effective as the initial injection [40]. A pooled data analysis of the effects of detrusor BoNT-A injection on NDO in patients with SCI found a 63% decrease in daily incontinence, an 18% decrease in CIC episodes, a 68% increase in cystometric bladder capacity, a 61% increase in reflex volume, and a 42% decrease in maximal detrusor pressure [41]. A further analysis of treatment outcomes also revealed significant improvements in health-related quality of life indices [38,42] and a significant decrease in the incidence of symptomatic UTI after detrusor BoNT-A injections in patients with SCI [43]. Although AEs, such as UTI, bladder pain, temporary hematuria, and AD, can occur after BoNT-A injection, the satisfaction rate of BoNT-A therapy has remained high in patients with SCI [44]. Considering the high incidence of UTI after BoNT-A injection, prophylactic antibiotic treatment is recommended to prevent symptomatic UTI after injection [45].

Concomitant use of anticholinergics, SCI etiology, or SCI levels did not affect the therapeutic effects of BoNT-A on NDO due to SCI or MS [46,47]. Patients with SCI who received 200 U detrusor injections of BoNT-A for NDO exhibited significantly greater satisfaction in terms of improvements in urinary incontinence and quality of life than those who received injections of 100 U of BoNT-A into the urethral sphincter to improve bladder emptying [23].

To maintain the therapeutic efficacy of BoNT-A for NDO, repeated detrusor BoNT-A injections are mandatory. Among patients with SCI who received BoNT-A injections for NDO, 67% continued to receive repeated BoNT-A injections, of whom 90% had a high level of satisfaction and considered long-term BoNT-A treatment over the following 5 years [48]. Clinically, detrusor injections of both 200 and 300 U of BoNT-A promoted greater improvement in subjective patient satisfaction compared to placebo [49].

Several open-label studies have shown that detrusor BoNT-A injections improved clinical and urodynamic parameters and quality of life in patients with refractory NDO [7,16,50], while our previous study revealed that a single BoNT-A injection for NDO in SCI patients had a 73.3% success rate [51]. Furthermore, several phase 3 placebo-controlled multi-center clinical trials investigating the efficacy and safety of detrusor BoNT-A injections in patients with NDO due to SCI or MS revealed that 200 or 300 U of BoNT-A promoted significantly fewer urinary incontinence episodes compared to placebo. Moreover, the therapeutic efficacy of BoNT-A injections was similar in both

SCI and MS [39,52,53]. After BoNT-A treatment, 62.9% and 61.6% of patients in the 200 and 300 U groups achieved the subjective primary treatment goal of dryness, respectively [54]. Given the similar therapeutic efficacy, the regulatory dose of BoNT-A approved by the FDA of the United States, European Union, and Asian countries was 200 U for SCI or MS patients with NDO. However, in actual clinical practice, patients with SCI who received injections of 300 U of BoNT-A for NDO had lower detrusor pressure and fewer involuntary detrusor contractions (IDCs) than those receiving 200 U (44.1% vs. 89.5%,  $P=0.001$ ) during repeated injections [55]. The lower incidence of IDCs in the 300 U group than in the 200 U group after the second BoNT-A injection suggests that 300 U of BoNT-A could potentially have a longer therapeutic duration than 200 U. Hence, patients who experienced a short therapeutic duration with 200 U BoNT-A injection should be treated with 300 U BoNT-A when the initial treatment effect disappears [55].

## ADVERSE EVENTS OF BOTULINUM TOXIN A INJECTIONS FOR NEUROGENIC BLADDER

AEs related to BoNT-A injections have often been observed, with the most frequent being UTI and urinary retention requiring CIC [53]. Clinically, although detrusor BoNT-A injections effectively reduce urinary incontinence, they usually impair detrusor contractility, resulting in large PVR or urinary retention in NDO, with approximately 70% of patients requiring periodic CIC, and subsequent UTIs as *de novo* problems [7]. Considering the unrealistic expectations that patients receiving BoNT-A injections for urinary incontinence or difficulty in urination might have regarding treatment, some might be disappointed by the *de novo* AEs or complications occurring after BoNT-A treatment, promoting low satisfaction rates. Accordingly, increased incontinence was found to be the leading cause of dissatisfaction with urethral BoNT-A injections, while increased PVR volume requiring CIC was found to be the primary cause of dissatisfaction with detrusor injections [56].

One study found that more than 60% of patients with NDO due to SCI or MS receiving 200 or 300 U of BoNT-A injections had no IDCs by week 6 [35]. Apart from UTI and large PVR, detrusor BoNT-A injections were reported to cause *de novo* AD [52], which was related to the bladder injection, rather than to BoNT-A. Our previous study found that some patients with SCI developed *de novo* AD after detrusor onabotulinumtoxinA injections (23.7% and 17.6% in the 200 and 300 U groups, re-

spectively) [30,55]. *De novo* AD after onabotulinumtoxinA injection could have likely been triggered by noxious stimuli due to transient bladder wall inflammation after multiple detrusor injections.

The aforementioned intolerable AEs often discourage patients from repeat BoNT-A injections, despite the potential for achieving treatment goals after BoNT-A injection. Our small series of patients with SCI who received repeated BoNT-A injections for NDO reported improvements in the satisfaction rate from 25.4% at baseline to 74% at 3 months after the fourth injection, although a slight decrease was noted after the fourth injection [30]. The overall satisfaction rate after single or repeated injections was 59.3% (35 patients), the failure rate was 33.9% (20 patients), and discontinuation rate due to AEs (2 recurrent UTIs and 2 cases of AD) was 6.8% (4 patients). Among the 20 patients who reported treatment failure, 10 (16.9%) reported no significant improvement after 1 or repeated injections, 8 converted to augmentation enterocystoplasty, and only 20% of patients continued repeated treatment. Nevertheless, patients with NDO due to SCI who continued to receive detrusor BoNT-A injections exhibited sustained improvement in voided volume and quality of life with repeated treatment [34].

## **BOTULINUM TOXIN A INJECTIONS FOR NEUROGENIC DETRUSOR OVERACTIVITY DUE TO MULTIPLE SCLEROSIS, CEREBROVASCULAR ACCIDENT, PARKINSON DISEASE, AND DEMENTIA**

Patients with neurogenic lesions other than SCI, such as those with MS, CVA, Parkinson disease (PD), and early dementia, may also have DO and urinary incontinence. The incidence of overactive bladder (OAB) symptoms increases with age among patients with central nervous system (CNS) lesions. Accordingly, the incidence of urinary incontinence varied from 33% to 79% in patients with CVA [57], 33.1% in those with PD, and 50.9% in those with MS [58]. Most patients with CNS disorders and OAB exhibited NDO. Although such patients experience urinary incontinence due to NDO, they may still have ambulatory ability and bladder sensation. Therefore, spontaneous urination without CIC is usually requested when BoNT-A injection is suggested for the treatment of NDO.

Previously, a 200- or 300-U dose of BoNT-A was recommended for the treatment of urinary incontinence in patients with MS [59]. However, patients receiving the aforementioned

BoNT-A dose need CIC for bladder emptying, despite a continence rate of 76% after 300 U of BoNT-A injection [60]. Patients with MS might experience progression of disability, resulting in increased difficulty in CIC and discontinuation of repeated BoNT-A injections [61]. As such, a small BoNT-A dose of 100 U is recommended for patients with MS who wish to improve urinary incontinence and preserve bladder sensation and spontaneous voiding after treatment. Improvements in urodynamic and voiding diary variables have been noted after injecting 100 U of BoNT-A [62]. However, a high BoNT-A dose of 200 or 300 U followed by CIC would still be the treatment of choice to restore urinary continence among patients with severe disability and urinary incontinence.

For patients with urinary incontinence due to CNS lesions, such as CVA, PD, or early dementia, a BoNT-A dose of 100 U can effectively decrease urgency symptoms and improve clinical and urodynamic parameters for more than 6 months [63, 64]. A previous study using detrusor injections of 200 U of BoNT-A provided beneficial efficacy for patients with urinary incontinence due to PD and multiple system atrophy [65]. Another study confirmed that injecting 100 U of BoNT-A into the bladder of patients with PD promoted therapeutic effects without urinary retention [66]. However, not all patients with CNS lesions have similar treatment outcomes. Given that patients with CVA might not perceive urinary urgency until full bladder capacity is reached, such patients may not achieve complete urinary continence after treatment with 200 U of BoNT-A, with one study showing urodynamic improvements in only 50% of patients [67]. Our recent study also revealed the therapeutic efficacy and safety of 100 U of BoNT-A bladder injections in elderly patients with chronic CVA, PD, and early dementia [68]. However, longstanding urinary retention requiring chronic CIC might be unavoidable in exceedingly vulnerable elderly patients with CNS lesions and NDO. Moreover, most patients with CNS lesions are vulnerable and cannot handle bladder self-management. As the risk of UTI increases together with PVR after BoNT-A injection, the need for CIC/CISC also increases [41,69]. Moreover, patients who develop chronic urinary retention after BoNT-A injection also experience a significant increase in the recovery duration from chronic urinary retention [70]. Hence, patients with CNS lesions who request BoNT-A treatment should be informed of this potential consequence [68].

Patient selection for BoNT-A injection is important considering that those with CNS lesions usually have severe physical

or mental impairment. Given that bladder fullness and urinary urgency might be impaired after BoNT-A injection, chronic urinary retention and subsequent UTI might develop. As such, an indwelling Foley catheter may be necessary when urinary retention or large PVR volume occurs after BoNT-A injection to avoid bladder overdistention owing to an inappropriate CIC program and to restore adequate bladder perfusion. Quality of life and satisfaction are usually not affected by the need for CIC in patients who can achieve complete dryness after BoNT-A injection [71]. Thus, before injecting BoNT-A in patients with CNS lesions, health costs, the caregiver burden, and potential AEs should be thoroughly discussed with the patients' families [72].

## **BOTULINUM TOXIN A FOR THE TREATMENT OF PEDIATRIC NEUROGENIC LOWER URINARY TRACT DYSFUNCTION**

BoNT-A has been approved for use in the treatment of urinary incontinence due to NDO or nonneurogenic OAB with well-documented treatment outcomes. However, BoNT-A injections have currently not been officially approved for use in pediatric lower urinary tract dysfunction. Urinary incontinence among children is common and needs medical treatment with antimuscarinics or mirabegron. However, if medical treatment fails, BoNT-A injections could be used as an alternative, especially in children with dysfunctional voiding or NDO due to myelomeningocele.

Detrusor BoNT-A injections at a dose of 5 to 10 U/kg across 30 to 40 sites can increase cystometric bladder capacity, reduce detrusor pressure, and improve bladder compliance in children with myelomeningocele and NDO refractory to antimuscarinic treatment, with the therapeutic duration lasting for 8 months [73-75]. Repeated BoNT-A injections have been found to be as effective as the initial treatment, while patients with vesicoureteral reflux may also benefit from BoNT-A injections [76,77]. Moreover, urethral sphincter BoNT-A injections at a dose of 2 U/kg together with detrusor BoNT-A injections at a dose of 8 U/kg have been shown to decrease PVR volume, improve urinary incontinence, improve constipation, improve vesicoureteral reflux, and reduce serum creatinine levels among patients with myelomeningocele who had NDO and DSD [78].

Urethral sphincter discoordination during NDO or dysfunctional voiding are highly prevalent in pediatric patients with myelomeningocele or nonneurogenic OAB [79]. Accordingly,

urethral sphincter BoNT-A injections at a dose of 50 to 100 U can normalize the flow curve in uroflowmetry and decrease PVR volume among children incapable of emptying their bladder [80,81]. One study showed long-term therapeutic efficacy and durability for refractory dysfunctional voiding in children [82].

Current investigations have also demonstrated that detrusor BoNT-A injection is safe and effective for the treatment of pediatric urinary incontinence due to nonneurogenic OAB refractory to antimuscarinics [83,84]. Repeated BoNT-A injections 6 to 7 months after the initial treatment also provided equal clinical and urodynamic effects [85].

## **DETRUSOR BOTULINUM TOXIN A INJECTIONS AND RENAL FUNCTION IMPROVEMENT IN PATIENTS WITH NEUROGENIC LOWER URINARY TRACT DYSFUNCTION**

Chronic renal failure is a frequently encountered long-term complication in patients with SCI, especially in those with high intravesical pressure and large PVR [86]. Given that detrusor BoNT-A injections can decrease voiding pressure, reduce occurrence of IDCs, and increase bladder compliance, repeated detrusor BoNT-A injections may likely improve renal function in patients with NDO and upper tract function deterioration. A 6-year follow-up study of patients with SCI who had NDO and received repeated 300-U BoNT-A injections showed that renal pelvis dilatation and vesicoureteral reflux resolved in all patients [37]. However, our short-term study on renal function changes in 33 patients with SCI who received 4 repeated 200-U BoNT-A injections revealed no significant improvement in the glomerular filtration rate (GFR) after 2 years [87]. A further comparison of GFR changes between patients with SCI receiving repeated 200- and 300-U BoNT-A injections showed no significant changes between the 300 group and 200 U group at the end-point ( $P=0.197$ ). Similarly, no significant difference in GFR changes at the end-point following BoNT-A injections was noted between patients with SCI who had a baseline bladder compliance  $\geq 30$  and  $< 30$  mL/cm H<sub>2</sub>O in either the 200 or 300 U group [55].

Several reasons may explain why short-term repeated detrusor BoNT-A injections could only maintain renal function, but not improve GFR, in our previous studies, including high intravesical pressure and low renal plasma flow [88-90]. Although detrusor BoNT-A injections can reduce intravesical pressure

during bladder filling, they might not improve the reduced renal plasma flow in patients with high-level SCI. Therefore, repeated detrusor BoNT-A injections did not improve GFR. Moreover, our study found that IDCs were still present in 89.5% and 44.1% of patients with SCI receiving BoNT-A injections of 200 and 300 U 6 months after the initial injection, respectively. Thus, detrusor BoNT-A injections may have possibly reduced urinary incontinence, but did not adequately lower intravesical pressure during the storage phase [55]. Adding antimuscarinics or mirabegron might provide additional benefits in reducing detrusor pressure and improving renal function for the long-term bladder management of patients with SCI [91]. Renal function concerns could be an important indication for the long-term use of BoNT-A in patients with NDO who are at high risk for renal function impairment. Numerous modalities can be utilized for bladder management in patients with SCI at high risk for upper urinary tract deterioration. Repeated detrusor BoNT-A injections provide a safe therapeutic modality for not only improving incontinence symptoms, but also preserving renal function.

### QUALITY OF LIFE COMPARISON BETWEEN REPEATED DETRUSOR BOTULINUM TOXIN A INJECTIONS AND AUGMENTATION ENTEROCYSTOPLASTY IN PATIENTS WITH SPINAL CORD INJURY

The therapeutic efficacy of detrusor BoNT-A injections for NDO due to SCI or other CNS lesions has been well established. Repeated BoNT-A injections every 6 to 9 months are necessary for maintaining their therapeutic effects against NDO, especially in patients with chronic SCI. While treatment is generally safe and well tolerated, the most common AEs of detrusor BoNT-A injection include UTIs [35,45,43] and chronic urinary retention [39,40,56], with AD occasionally occurring during the injection process [7,29,30]. Therefore, preoperative antibiotic prophylaxis and postoperative CIC in patients who receive BoNT-A injection are mandatory. Patients with SCI may consider augmentation enterocystoplasty to obtain lifelong therapeutic effects rather than periodical BoNT-A injections, especially when AEs occur after each BoNT-A injection. Augmentation enterocystoplasty is indicated in patients with reduced bladder capacity and compliance due to NLUTD or other chronic inflammatory bladder diseases [92,93]. The procedure has been used to treat bladder dysfunction in adults and

pediatric patients with myelomeningocele [94] and can effectively decrease intravesical pressure during bladder storage and increase bladder capacity in patients with end-stage bladder diseases or refractory DO [95]. Although augmentation enterocystoplasty has long-term durability and high satisfaction, discomforting complications still exist [96]. Our recent study of a large cohort of patients with SCI who underwent augmentation enterocystoplasty revealed that 86.9% of the 76 patients were very satisfied or moderately satisfied with the treatment outcome, while the postoperative incontinence rate was only 16.5%. However, although some patients were able to void spontaneously with the Crede maneuver, 76% of the patients were completely dependent on CIC. Thus, patients might ultimately opt for an indwelling urethral catheter or cystostomy for convenience of bladder emptying [97].

Considering the high complication rates, augmentation enterocystoplasty is usually reserved as the final treatment modality for NDO in patients with SCI. Currently, urologists suggest detrusor BoNT-A injections for patients with SCI who have NDO or lower bladder compliance, subsequently recommending augmentation enterocystoplasty to reconstruct the diseased bladder and increase bladder capacity only when the NDO is refractory to repeat BoNT-A injections. A previous prospective study that compared the quality of life between a small group of patients who underwent augmentation enterocystoplasty (n = 16) or repeated BoNT-A injections (n = 14) found that the BoNT-A group had a significantly lower continence rate (87.5% vs. 42.3%,  $P = 0.0187$ ), whereas the augmentation enterocystoplasty group had a significantly higher quality of life index using the Qualiveen-30 instrument (1.625 vs. 1.077,  $P = 0.037$ ). None of the patients receiving augmentation enterocystoplasty had low bladder compliance or a higher detrusor pressure at bladder capacity [33].

While detrusor BoNT-A injections can be considered as a medical procedure for bladder augmentation, augmentation enterocystoplasty can be rationally recommended as the final form of bladder management when treatment is ineffective or frequent detrusor injections are intolerable.

### PATIENT SATISFACTION WITH DETRUSOR OR URETHRAL BOTULINUM TOXIN A INJECTION FOR NEUROGENIC LOWER URINARY TRACT DYSFUNCTION

Appropriate management of lower urinary tract dysfunction in

patients with SCI can be challenging to urologists. One study showed that most patients with suprasacral SCI exhibited NDO with or without DSD [98]. Bladder self-management by patients relies on good hand dexterity, strong abdominal muscles, intact bladder sensation, and urethral sphincter coordination during voiding stimulation [98]. Currently, detrusor BoNT-A injections to decrease detrusor contractility [6,7], urethral sphincter BoNT-A injections to reduce urethral resistance [2,5], or combined detrusor and urethral BoNT-A injections to simultaneously improve bladder storage and emptying can be utilized [99].

Repeated BoNT-A injections for the treatment of NDO were strongly recommended by a European consensus report [72]. Another study recommended that BoNT-A retreatment be administered over an interval of 6 to 9 months [16]. As such, patients who do not respond well to the first BoNT-A injection still need adequate time for retreatment. The feasibility of BoNT-A injection into the detrusor or urethral sphincter of patients with SCI exhibiting NDO and DSD depends on the patients' will and bladder condition. Accordingly, detrusor BoNT-A injection should be performed in patients who have a contracted bladder with low compliance to protect the upper urinary tract function. After detrusor BoNT-A injection, most patients expressed satisfaction with quality of life despite the need for CIC. However, patients who opted for urethral BoNT-A injections for DSD treatment might experience bothersome incontinence, while still exhibiting incomplete bladder emptying, prompting the need for CIC for periodic bladder emptying. Our previous study showed that patients with NDO and DSD who received detrusor BoNT-A injections had greater quality of life improvements than those receiving urethral BoNT-A injections [23]. However, a discrepancy was observed between objective urodynamic outcomes and actual patient satisfaction in the treatment of DSD by urethral or detrusor BoNT-A injections.

The adherence rates in patients with SCI receiving detrusor BoNT-A injections depend on treatment outcomes, with those receiving BoNT-A injections for NDO generally having high satisfaction rates [48]. Recurrent UTI, AD during injection, CIC-related issues, and persistent urinary incontinence are the primary causes for discontinuation of BoNT-A. Some patients have been converted to augmentation enterocystoplasty following repeated detrusor BoNT-A injections after expressing their desire to have a permanent correction without periodic injections. Nonetheless, patients with SCI who have minor compli-

cations after BoNT-A injections can usually tolerate complications and continue with detrusor BoNT-A injections when the therapeutic efficacy satisfies their expectations.

## CONCLUSIONS

BoNT-A injections have been widely utilized for the treatment of NLUTD and LUTD in patients with SCI and those with other neurogenic lesions, such as MS, CVA, PD, dementia, and pediatric NLUTD. Treatment outcomes have been associated with the patients' lower urinary tract condition and their preference for bladder management. However, some AEs after BoNT-A injections, such as UTI, large PVR volume, and urinary retention requiring CIC, are still important concerns that need careful management. As such, complete informed consent for BoNT-A injection therapy with full disclosure of its potential complications should be obtained before this procedure is undertaken for any patient with NLUTD.

## AUTHOR CONTRIBUTION STATEMENT

- Conceptualization: *HCK*
- Writing-original draft: *YHJ, SFC, HCK*
- Writing-review & editing: *HCK*

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