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ORIGINAL REPORT

CONCOMITANT DETRUSOR AND EXTERNAL URETHRAL SPHINCTER BOTULINUM TOXIN-A INJECTIONS IN MALE SPINAL CORD INJURY PATIENTS WITH DETRUSOR OVERACTIVITY AND DETRUSOR SPHINCTER DYSSYNERGIA

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Objective: **To investigate the effects of concomitant injections of botulinum toxin-A (BoNT-A) into the detrusor and external urethral sphincter muscles in suprasacral spinal cord injured patients with detrusor overactivity and detrusor sphincter dyssynergia.**
Design: **An open treatment trial with pre- and post-treatment evaluations.**
Subjects: **Male suprasacral spinal cord injury patients ($n = 20$) with neurogenic detrusor overactivity and detrusor sphincter dyssynergia who emptied their bladder by reflex voiding and were unwilling to increase the frequency of intermittent catheterization.**
Methods: **Cystoscopic guidance of 200 U BoNT-A injections into the detrusor muscle and 100 U into external urethral sphincter muscles were applied. The urodynamic parameters, voiding diaries and quality of life scores using Urinary Distress Inventory, Short Form (UDI-6) and Incontinence Impact Questionnaire, Short Form (IIQ-7) were compared.**
Results: **All participants experienced a significant mean reduction in maximal detrusor pressure and maximal urethral pressure profile, and a mean significant increase in maximal cystometric bladder capacity 12 weeks after concomitant injections. Bladder diaries demonstrated persistently increased spontaneous voided volume, but no increase in post-void residual ratio, daily clean intermittent catheterization (CIC) frequency and diaper pad use from baseline to 24 weeks. UDI-6 scores were significantly improved at 4 and 12 weeks and IIQ-7 scores improved only at 12 weeks.**
Conclusion: **Concomitant detrusor and external urethral sphincter BoNT-A injections may decrease detrusor and urethral pressure without increasing post-void residual ratio and diaper pad use. For spinal cord injury patients with neurogenic detrusor overactivity and detrusor sphincter dyssynergia who are unwilling, or for whom it is inconvenient, to increase CIC frequency and who want to preserve spontaneous voiding, this treatment may provide an optional alternative.**

Key words: detrusor; urethra sphincter; Botulinum toxin; urodynamics; catheterization; spinal cord injury.

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LAY ABSTRACT

Detrusor botulinum toxin type A (BoNT-A) injection has become the standard of care for bladder overactivity associated with neurological pathology in recent years. However, increased post-void residual and even acute urinary retention make it difficult for patients to accept this treatment. Our study demonstrates that a combination of detrusor and urethra sphincter BoNT-A injections may relieve detrusor and urethral pressures without increasing intermittent catheterization (IC) frequency. Life quality associated with voiding is also improved after combined injections. Physicians should take into account the patient's expectation and ability to manage his bladder when planning BoNT-A injection in treatment of neurogenic lower urinary tract dysfunction (NLUTD) in spinal cord injury (SCI) patients. For male SCI patients with NLUTD who are unwilling or inconvenient to increase IC frequency and want to preserve spontaneous voiding, this treatment may provide optional alternative.

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Approximately 81% of patients with spinal cord injury (SCI) will experience some form of urinary dysfunction within 1 year of their injury (1). Only approximately 1% of these patients will recover fully. In another cross-sectional study, only 21% of patients with SCI reported having normal voiding (2). Overall, 95% of suprasacral SCI patients with neurogenic lower urinary tract dysfunction (NLUTD) experience neurogenic detrusor overactivity (NDO) and/or detrusor sphincter dyssynergia (DSD) (3).

NLUTD is a dynamic condition with its own natural history, and it can cause functional and morphological changes in both the lower and upper urinary tracts (4, 5). NDO is caused by spontaneous, involuntary contractions of the bladder wall during urinary filling. DSD occurs when the internal or external urethral sphincter (EUS) contracts inappropriately or

fails to relax during detrusor contraction. NDO and DSD both have the potential to reduce bladder wall compliance and elevated filling pressure, possibly resulting in vesicoureteral reflux and even renal failure (6).

Dykstra et al. first described the injection of botulinum toxin type A (BoNT-A) into the EUS in patients with SCI to induce chemical sphincterotomy and treat DSD (7). The following studies, including our 2 previous reports, have also demonstrated the efficacy of BoNT-A in DSD (8–10). Several researchers, including Schurch et al., reported that injecting BoNT-A into the detrusor significantly increased storage capacity and decreased bladder pressure to treat NDO (11–13). Both DSD and NDO have been reported to be triggers of autonomic dysreflexia (AD), as obstruction of the bladder outlet during detrusor muscle contractions increases intravesical pressure, resulting in the transmission of noxious bladder sensations. According to the literature, injecting BoNT-A into the detrusor or EUS prevented AD (14, 15). These findings demonstrate that injecting BoNT-A into the detrusor is the standard method for treating NDO in patients with SCI who are intolerant of, or resistant to, oral anticholinergic medications. In 2011, the US Food and Drug Administration (FDA) approved BoNT-A for medical use in the treatment of NDO, particularly in cases of urinary incontinence, because detrusor overactivity is associated with neurological pathology refractory to anticholinergic therapy (16, 17). In 2013, the Taiwan FDA also approved 200 U BoNT-A for NDO treatment, and the National Health Insurance Administration granted reimbursement. However, detrusor BoNT-A injections usually cause impaired detrusor contractility, large post-void residual (PVR), or urinary retention in NDO treatment, necessitating periodic clean intermittent catheterization (CIC) for approximately 70% of patients (18). Frequent CICs are required for increased PVR and even acute urine retention (AUR). These de novo problems may cause physical and environmental inconvenience to patients, making it difficult for them to accept this treatment.

Concomitant detrusor and EUS injections in SCI patients with NDO and DSD may be an alternative for those who want to preserve spontaneous voiding. Until now, only a few clinical studies have investigated the effects of the combination of detrusor and EUS injections. The aim of this study was to determine the feasibility and efficacy of injecting BoNT-A into both the detrusor and the EUS in male suprasacral SCI patients with NDO and DSD.

METHODS

Participants

The participants were males over the age of 18 years who had suprasacral SCI and were from the rehabilitation department ward. All the enrolled patients were neurologically stable (i.e. their neurological symptoms had not progressed in the previous 3 months). The inclusion criteria were: *(i)* presence of NDO and DSD, as defined by the International Continence Society (19), *(ii)* bladder emptying by adjunct intermittent catheterization (IC) with reflex voiding and unwillingness to increase frequency of IC for personnel reasons, and *(iii)* inadequate response or intolerance to oral anticholinergic agents (oxybutynin, trospium, tolterodine, propiverine, and solifenacin), spasmolytic agents (hyoscine butylbromide), skeletal muscle relaxants (baclofen), and alpha-blockers (doxazosin mesylate, terazosin, tamsulosin, and silodosin). Exclusion criteria were: *(i)* BoNT-A allergy, *(ii)* coagulopathy disease and myasthenia gravis, *(iii)* acute urinary tract infection (UTI), *(iv)* other causes of bladder outlet obstruction (such as urethral stricture and benign prostatic hyperplasia), and *(v)* prior sphincterotomy. Before each injection, patients were informed about the potential side-effects of the toxin. This prospective study was approved by the ethics committee and the Institutional Review Board of Chung Shan Medical University Hospital (IRB approval number: CS1-16065). Each patient was fully informed about the procedure, and written consent was obtained before treatment. All enrolled patients had to stop taking alpha-blockers, spasmolytic agents, and anticholinergic agents 1 week before toxin injection and during the follow-up period.

Injection procedure

Injections were performed in the operating room using a 22.5 FR cystoscope (Olympus, Tokyo, Japan). The equipment for vital sign monitoring was set up as part of the routine general anaesthesia, and an intravenous sedative was administered to all the patients. The bladder was instilled with 100–150 mL sterile saline to achieve adequate visualization and avoid the blood vessels during injections. A 23-gauge injection needle (Cook Urological Incorporated, Bloomington, IN, USA) was inserted 2 mm into the detrusor. Two vials of Botox (Allergan, Irvine, CA, USA), each containing 100 U BoNT-A, were reconstituted in a total of 20 mL sterile saline. A total of 20 1-mL injections were administered, evenly distributed approximately 1 cm apart across the bladder wall. For EUS injection, 100 U BoNT-A was diluted with 2 mL sterile saline. Subsequently, equal aliquots of the diluted toxin were

injected into the EUS approximately 1–1.5 cm deep at 3, 6, 9, and 12 o'clock positions. An additional 0.2 mL normal saline was then injected to ensure that the maximum amount of toxin left in the needle was delivered. Oral prophylactic antibiotics were administered on the day of treatment, and a Foley catheter was routinely indwelled for 1 day.

Outcome measures

Each participant underwent a video-urodynamic (VUD) study, which was performed with a Urodyn 5500 apparatus (Dantec Inc., Skovlunde, Denmark) before and 12 weeks after the BoNT-A injection. This examination was performed using filling cystourethrometrography (CUMG), sphincter electromyography (EMG), and static urethral pressure profilometry (UPP). CUMG was performed using a triple lumen catheter, which measured the intravesical and urethral pressures at the same time while continuously bladder filling isotonic saline at a rate of 30 mL/min. The measuring point of the urethral pressure was at the maximum urethral pressure. Trans-perineal EMG of the external urethral sphincter was performed using disposable concentric needle electrodes. The needle was inserted into the perineum midline approximately 1.5–2 cm anterior to the anus. While the electrode was directed toward the apex of the prostate, its position was monitored using a gloved finger in the rectum. The final localization was determined by EMG monitoring of the motor unit activity and fluoroscopic examination of the needle position. A VUD study was conducted at baseline and 12 weeks after toxin injections.

The PVR was measured using catheterization. The bladder diary and diaper pad usage were recorded at baseline, and 4, 12, and 24 weeks after injections. The symptom distress and the impact of urinary incontinence on daily life were assessed using a validated Chinese version of the Urogenital Distress Inventory (UDI-6) short form and Incontinence Impact Questionnaire (IIQ-7) short form, respectively (20). The UDI-6 questionnaire has 6 questions with possible answers of "no", "a little", "moderately" and "very much", whereas the IIQ-7 questionnaire has 7 questions with the same ordinal scale. For the total scores of both the IIQ-7 and UDI-6 questionnaires, the answers "no", "a little", "moderately" and "very much" were assigned values of 0, 1, 2, and 3, respectively. Thus, when the values from each of the questions were summed, the total scores ranged from 0 to 21 for IIQ-7 and from 0 to 18 for UDI-6. The scores at baseline were compared with the scores at 4, 12, and 24 weeks after treatment. According to our previous study and the Consortium for Spinal Cord Medicine, an increase of more than 20 mmHg in systolic blood pressure (SBP) was considered an AD reaction (21, 22). Related adverse events were also recorded throughout the study.

Statistical analysis

The urodynamic parameters before and after BoNT-A injection were compared using the Wilcoxon signed-rank test. The longitudinal data were analysed using the Friedman test, and the post hoc analysis was conducted using the Wilcoxon signed-ranks test with Bonferroni correction. All tests had a significance level of $p<0.05$. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS for Windows Version 16.0, SPSS Inc., Chicago, IL, USA).

RESULTS

The mean age of the enrolled participants was 38.6 (standard deviation (SD) 10.8) years, and the mean duration of injury was 83.5 (41.6) months. The distribution of the SCI level was 12 (60%) cervical and 8 (40%) thoracic. The participants' occupations included 3 taxi drivers, 4 street vendors, 3 civil servants, 4 factory operators, 2 mouth and foot painting artists, and 4 unemployed individuals. The reasons for unwillingness to increase IC frequency were inconvenient work environment in 8 cases, avoiding poor work performance stigma in 5 cases, and not wanting to increase self and caregiver's loads in 7 cases (Table I). Concomitant

Table I. Basic demographic data for the patients with supra-sacral spinal cord injury (SCI) with neurogenic detrusor overactivity (NDO) and detrusor sphincter dyssynergia (DSD)

Characteristics	
Total number of patients	20
Age, years, mean (SD)	38.6 (10.8)
Injury duration, months,	30–182
Mean (SD)	83.5 (41.6)
Injury level, *n* (%)	
Cervical	12 (60)
Thoracic	8 (40)
AIS scale, *n* (%)	
Grade A	12 (60)
B	5 (25)
C	2 (10)
D	1 (5)
Occupation, *n*	
Taxi driver	3
Street vendor	4
Civil servant	3
Factory operator	4
Mouth and foot painting artist	2
Unemployment	4
Reason for unwilling to increase frequency of IC	
Inconvenient work place	8
Worry to influence working performance	5
Worry to increase self and caregiver workload	7

SCI: spinal cord injury; NDO: neurogenic detrusor overactivity; DSD: detrusor sphincter dyssynergia; SD: standard deviation; AIS: American Spinal Injury Association Impairment Scale; IC: intermittent catheterization.

Table II. Video-urodynamic study parameters at baseline and at 12 weeks after concomitant injections

	Baseline	12 weeks after injection	*p*-value
Volume of first DO, mL, mean (SD)	220 (125)	280 (156)	0.019*
Maximal Pdet, cm H_2O, mean (SD).	100 (28)	68 (22)	< 0.001*
Plp, cm H_2O, mean (SD)	89 (27)	61 (22)	< 0.001*
MUCP, cm H_2O, mean (SD)	98 (21)	79 (18)	0.001*
Cystometric bladder capacity, mL, mean (SD)	293 (136)	384 (116)	0.003*
PVR, mL, mean (SD)	244 (130)	301 (128)	0.108
PVR/cystometric bladder capacity ratio, mean (SD)	82 (17)	78 (20)	0.459
SBP change mmHg, mean (SD)	23 (21)	16 (12)	0.037*
DBP change mmHg, mean (SD)	11 (10)	10 (11)	0.363

*Statistical significance is at $p < 0.05$

DO: detrusor overactivity; Pdet: detrusor pressure; Plp: leak point pressure; MUCP: Maximal urethral closing pressure; PVR: post void residual; SBP: systolic blood pressure; DBP: diastolic blood pressure.

BoNT-A injections significantly improved the VUD parameters at 12 weeks. The filling volume of DO onset increased significantly from 220 (125) to 280 (156) mL ($p = 0.019$). Both the maximal detrusor pressure and maximal urethral pressure profiles decreased from 100 (28) to 68 (22) cmH_20 ($p < 0.001$) and from 98 (21) to 79 (18) cmH_20 ($p < 0.001$), respectively. The maximal cystometric bladder capacity increased from 293 (136) to 384 (116) mL ($p = 0.003$). However, there was no significant increase in PVR after treatment (244 (130) vs 301 (128) mL; $p = 0.108$). During the VUD study, the mean SBP decreased significantly from 23 (21) to 16 (12) mmHg ($p = 0.037$), but the mean diastolic blood pressure (DBP) did not decrease (Table II).

The bladder diaries recorded at baseline, and 4, 12, and 24 weeks revealed a persistent increase in spontaneous voided volume (Fig. 1A). There was a significant increase only at 4 and 12 weeks after Bonferroni correction of the *p*-value because of multiple comparisons (statistical significance at $p < 0.0167$). The PVR increased significantly at 4 and 12 weeks (Fig. 1B), while the bladder capacity increased significantly at 4, 12, and 24 weeks (Fig. 1C). According to these results, the PVR ratio (PVR/bladder capacity) showed no statistically significant differences at 4, 12, and 24 weeks (Fig. 1D). There was no significant change in daily IC frequency (Fig. 2A) or daily diaper pad usage (Fig. 2B) at baseline, 4, 12, and 24 weeks. The UDI-6 scores improved significantly at 4 and 12 weeks (Fig. 3A). The IIQ-7 scores only improved significantly at 12 weeks (Fig. 3B). Table III summarizes the results of all voiding diaries and questionnaires. The frequency (patients' visit response) and intensity of 6 patients with pre-BoNT-A injections AD (SBP elevation > 20 mmHg during the VUD study) decreased (measurement during VUD study) after concomitant BoNT-A injections (Table IV). There were no major injection-related side-effects, and only 2 patients experienced mild haematuria for 1 day.

DISCUSSION

These results demonstrate that a combination of detrusor and EUS BoNT-A injections may decrease detrusor and urethral pressures without increasing IC frequency and diaper pad usage in patients who empty their bladder via reflex voiding in addition to IC and are unwilling to increase IC frequency.

The meta-analysis results indicate that BoNT-A is effective in treating NDO after SCI. The use of BoNT-A injections is associated with a decrease in incontinence episodes, bladder pressure, and AD events (23). The current study data also demonstrated a significant decrease in detrusor leak point pressure and maximal urethra closure pressure, and an increase in bladder volume of the first DO after treatment. These VUD study improvements could prevent the progression of NLUTD and decrease the risk of renal failure in SCI patients. However, approximately 70% of patients require periodic IC after treatment, and a possibly subsequent UTI could result in a new problem (24). Patients with SCI who use voiding as their primary method of bladder emptying are often very reluctant or functionally unable to undergo IC (25). Furthermore, studies have demonstrated that the IC rate decreases gradually, from approximately 45%–50% at rehabilitation discharge to 15%–20% after 30–45 years of NLUTD (26, 27). In a long-term real-life study on BoNT-A injections for NDO treatment, the IC discontinuation rate after 7 years was 11.3%. The 2 most common reasons were IC-related difficulties and personal convenience (28). The difficulty of catheterization is exacerbated by a spasmodic and unrelaxed urethra, which can potentially result in false tract trauma or AD. Patients and physicians may be hesitant to use current BoNT-A injections for the treatment of NLUTD because of these drawbacks. Some male SCI patients with NDO and DSD empty their bladders by reflex spontaneous voiding and/or adjunct IC when the environment is not conducive to IC.

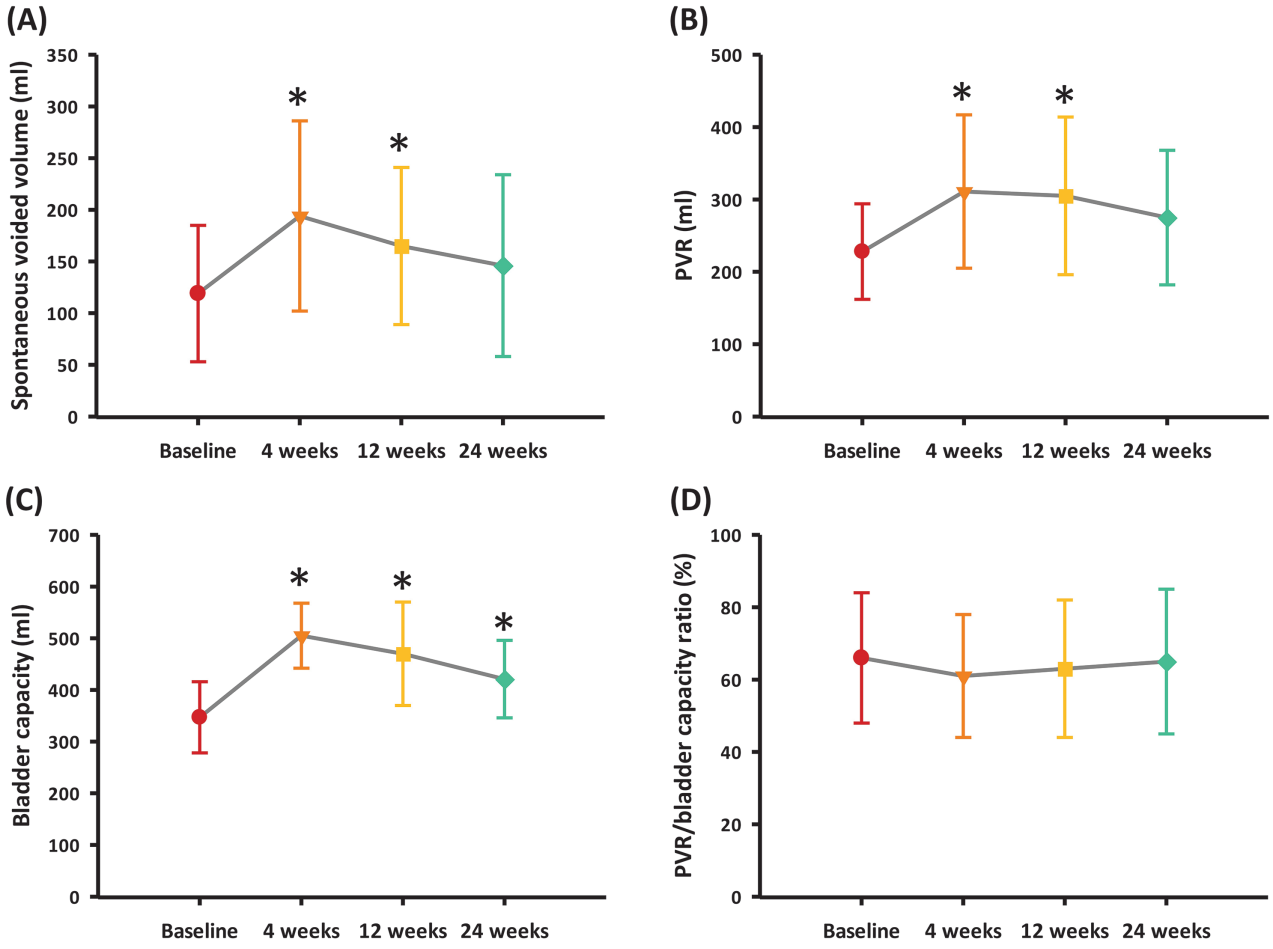

Fig. 1. Comparison of voiding diaries parameters change from baseline to 24 weeks. (A) Spontaneous voided volume, (B) post-void residual, (C) voiding diary bladder capacity, and (D) post-void residual/bladder capacity ratio.*Statistical significance is at $p < 0.0167$ (Bonferroni correction of p).

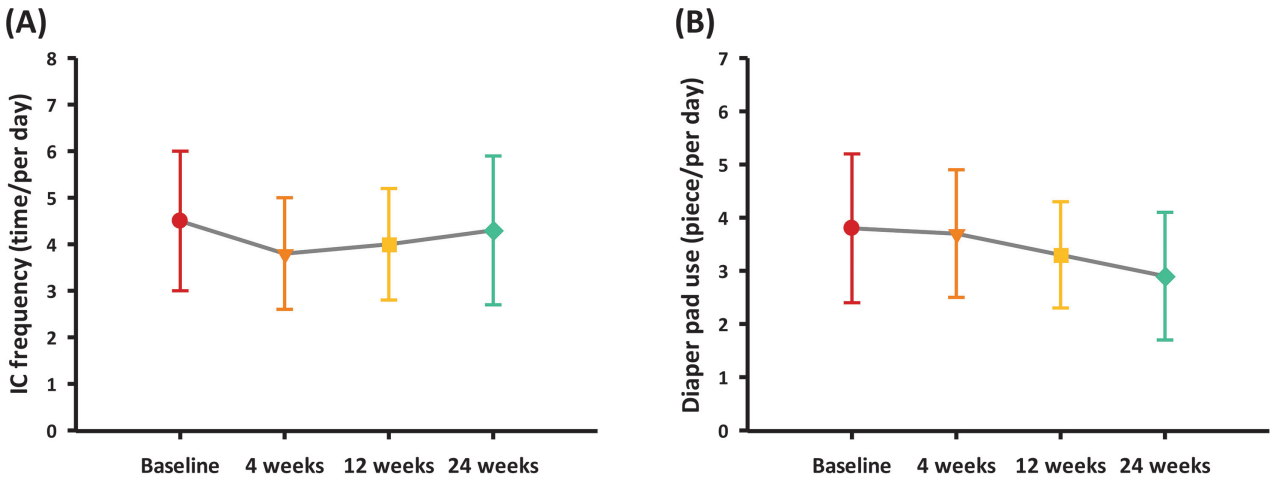

Fig. 2. Comparison of (A) intermittent catheterization (IC) frequency and (B) diaper pad use from baseline to 24 weeks. Statistical significance is at $p < 0.0167$ (Bonferroni correction of p).

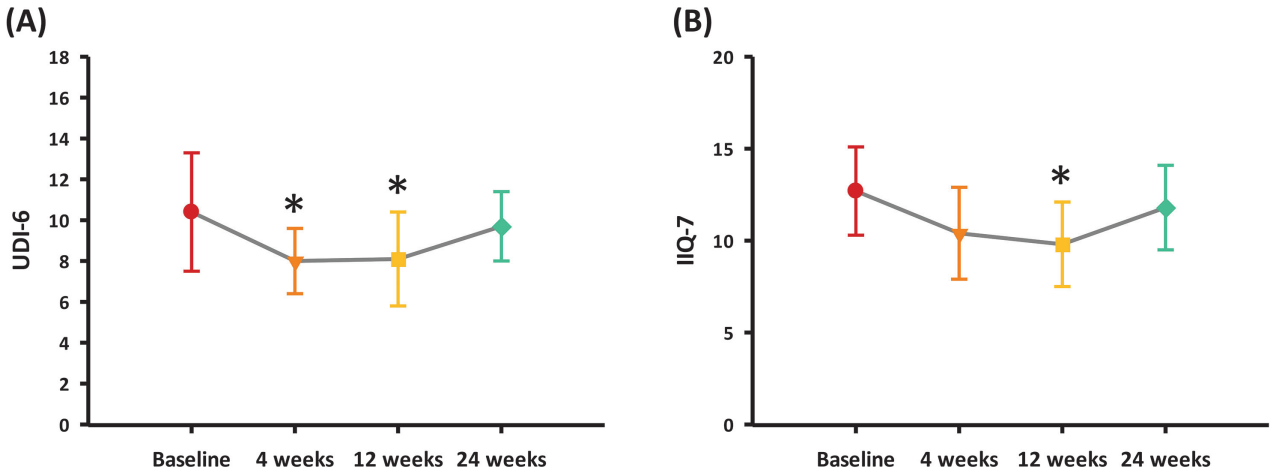

Fig. 3. Comparison of (A) Urinary Distress Inventory, Short Form (UDI-6) and (B) Incontinence Impact Questionnaire, Short Form (IIQ-7) scores from baseline to 24 weeks. *Statistical significance is at $p < 0.0167$ (Bonferroni correction of p).

Dosage reduction (100 U) of detrusor BoNT-A injections for SCI patients with NDO and DSD has been recommended as a technique for minimizing the risk of increasing PVR, urinary retention, and subsequent need for IC. However, the dose trade-off does not appear to meet the primary treatment goal of lowering maximal detrusor pressure and incontinence rate (29). Currently, there is no single approach for treating NDO and DSD simultaneously. The primary aim of NDO treatment is to ensure that the detrusor pressure remains within safe limits. However, a meta-analysis revealed that injecting BoNT-A into the EUS resulted in variable improvements in maximal detrusor pressure (30). In our 2 previous prospective studies, injections only into the EUS for DSD treatment were found to significantly reduce integrated electromyography and static and maximal urethral pressures, but not maximal detrusor pressure. A combination of low-dose EUS and standard-dose detrusor BoNT-A injections might be feasible in cases where patients prefer to preserve spontaneous voiding function or where IC is not acceptable. If additional severe incontinence occurs post-EUS injection, it should be questioned. However, the possibility of transient de novo stress urinary incontinence after BoNT-A injections for DSD treatment is low (approximately 4%) (31). A German study on idiopathic DO patients demonstrated that injecting low doses (50–100 U) of BoNT-A into the EUS in addition to detrusor injection could be an option for reducing the risk of significantly increasing residual urine (32). Only 1 published study reported on combined injections in SCI patients with NDO and DSD. Huang et al. used the same BoNT-A doses as the current study treatment dose (i.e. 200 U for the detrusor and 100 U for the EUS) (33). This study demonstrated that combined injections were an effective treatment for lowering maximal detrusor

Table III. Voiding diary parameters and questionnaire scores at baseline, and 4, 12 and 24 weeks after concomitant injections

	Baseline	4 weeks	12 weeks	24 weeks
Spontaneous voided volume, mL, mean (SD)	119 (66)	194 (92)	165 (76)	146 (88)
p-value		< 0.001*	0.003*	0.046
PVR, mL, mean (SD)	228 (66)	311 (106)	305 (109)	275 (93)
p-value		0.001*	0.01*	0.022
Bladder capacity, mL, mean (SD)	347 (69)	505 (63)	470 (100)	421 (75)
p-value		< 0.001*	< 0.001*	0.001*
PVR/bladder capacity ratio, mean (SD)	66 (18)	61 (17)	63 (19)	65 (20)
p-value		0.12	0.39	0.83
IC frequency, time/per day, mean (SD)	4.5 (1.5)	3.8 (1.2)	4.0 (1.2)	4.3 (1.6)
p-value		0.03	0.288	0.635
Diaper pad use, piece/per day, mean (SD)	3.8 (1.4)	3.7 (1.2)	3.3 (1.0)	2.9 (1.2)
p-value		0.943	0.135	0.031
UDI-6, mean (SD)	10.4 (2.9)	8.0 (1.6)	8.1 (2.3)	9.7 (1.7)
p-value		< 0.001*	< 0.001*	0.130
IIQ-7, mean (SD)	12.7 (2.4)	10.4 (2.5)	9.8 (2.3)	11.8 (2.3)
p-value		0.002	< 0.001*	0.119

*Statistical significance is at $p < 0.0167$ (Bonferroni correction of p).

PVR: post-void residual; IC: intermittent catheterization; UDI-6: Urinary Distress Inventory, Short Form; IIQ-7: Incontinence Impact Questionnaire, Short Form.

Table IV. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes during video-urodynamic (VUD) study (at baseline and 12 weeks after injections) in 6 patients with autonomic dysreflexia (AD) improvement

	Baseline		12 weeks after injections	
Patient number	SBP change, mmHg	DBP change, mmHg	SBP change, mmHg	DBP change, mmHg
1	98	54	47	32
2	44	32	10	15
3	30	15	12	6
4	33	15	15	9
5	48	25	23	16
6	29	10	13	5
Mean (SD)	47.0 (26.2)	25.2 (16.2)	20.0 (14.0)	13.8 (10.0)

SD: standard deviation.

pressure and maximal urethral closure pressure to protect the upper urinary tract and improve quality of life (QoL) for the patients with short-term (12 weeks) follow-up. However, it did not demonstrate any differences in bladder evacuation method, IC frequency, and PVR before and after combined injections. The most common bladder evacuation method in Western countries is IC, followed by triggered reflex voiding and suprapubic cystostomy catheterization (27). In a survey for NLUTD treatment after SCI in Taiwan, approximately 80% of patients reported needing an indwelling catheter to manage their bladder, followed by reflex voiding (34). The main reasons for this discrepancy could be a lack of adequate infrastructure for IC and a robust social welfare system in developing countries. Workplace accommodations, such as easily accessible toilets, are essential for a successful return to work (35). The bladder programme may vary from person to person depending on their specific needs. Seventy percent (14/20) of enrolled participants in the current study use triggered reflex voiding at work and self-catheterization off work to empty their bladders. It is inconvenient for outdoor workers to perform IC while on duty. Factory operators and civil servants also worry that IC may delay their scheduled work and decrease their performance. The remaining patients (6/20) initiate IC through a third party because of difficulties in hand coordination. Hence, these patients do not want to increase the workload of their caregivers by having frequent ICs.

Our concomitant injections preserved the spontaneous voiding of patients. Although PVR increased statistically from baseline to 4 and 12 weeks after injections, the PVR ratio (PVR/bladder capacity) did not change significantly. The mean injury duration (83.5 (41.6) months) of our participants was longer than that of previous combined injections studies (39.08 (16.29) months) (33), which could explain the high PVR at baseline. All of our patients were catheter-free during their work, and they used a diaper pad in case of occasional urine leaks. The mean diaper pad usage did not change significantly during the 24-week follow-up period. Interestingly, the effect of injections on the mean spontaneous voided volume appeared to have lessened at 24 weeks (no statistical difference, with Bonferroni correction). The mean diaper pad usage also had a decreasing trend at 24 weeks. According to a previous report, the duration of BoNT-A-induced detrusor paralysis was 9 months or more compared with the duration after injection into the EUS, which was 3–4 months (10). These results strongly suggest that smooth and striated muscles react differently to the toxin. Holds et al. discovered axonal and unmyelinated sprouts in the human striated muscle after BoNT-A injection, indicating that nerve sprouting contributes to early recovery of muscular activity (36). Conversely, Haferkamp et al. reported no increase in axonal sprouting after injections into the human bladder (37). The treatment difference between the smooth and striated muscles may explain why the EUS progressively regained its tonicity at 12 weeks, but the detrusor muscle remained paralyzed at 24 weeks. Subsequent decrease in spontaneous voided volume and mean diaper pad usage is rational.

The filling volume of DO onset and cystometric bladder capacity significantly increased from 220 (125) to 280 (156) mL and from 293 (136) to 384 (116) mL, respectively. The mean SBP change also decreased significantly from 23 (21) to 16 (12) mmHg. According to the guidelines from the Consortium for Spinal Cord Medicine, pressure levels that are 20–40 mmHg higher than baseline could be a sign of AD (21, 22). Detrusor BoNT-A injections may modulate the afferent C-fibres by decreasing nerve growth factors and inhibiting adenosine triphosphate release in the bladder (38, 39). Furthermore, BoNT-A injections improve bladder compliance by reducing chemical irritation, wall fibrosis, and mechanical stiffness. These urodynamic outcome improvements may partly explain why the severity and frequency of AD in 6 of the patients in the current study decreased after combined injections.

NDO and DSD can cause urodynamically measured increased bladder storage pressures, increased PVR, UTI, catheterization difficulties, and urinary incontinence, which can negatively impact health-related quality of life (HR-QoL) (40). The physical and

psychological benefits of the injections on voiding function result in decreased urinary tract distress and improved QoL for patients with incontinence. The mean UDI-6 scores improved significantly at 4 and 12 weeks, while the mean IIQ-7 scores improved at 12 weeks, but not at 24 weeks. The improvements in UDI-6 and IIQ-7 scores appear to be associated with the toxin effect on the EUS more than on the detrusor muscle.

Although this study confirms the effects of concomitant injection of 200 U BoNT-A and 100 U BoNT-A into the detrusor and EUS, respectively, in selected SCI patients with NDO and DSD, there are still some limitations. First, there are only 20 male patients, which is insufficient evidence. Larger prospective, controlled studies are still required to establish the overall effectiveness of the proposed method. Secondly, in terms of generalizability of the results, all of our enrolled patients are males who are unwilling, or find it inconvenient, to increase IC frequency. However, males account for 80% of the SCI population. Thirdly, the VUD study was conducted only at baseline and 12 weeks, and prolonged toxin effects on NDO and DSD are not available. However, our voiding diary follow-up period was 24 weeks after treatment. We could observe the restoration of storage and voiding dysfunction at these periods.

In conclusion, when administering BoNT-A injections to SCI patients for NLUTD treatment, physicians should consider the patient's expectations and ability to manage their bladder. Achieving complete dryness at the expense of regular IC is an impractical treatment goal for all patients with NLUTD. Concomitant detrusor and EUS BoNT-A injections may decrease detrusor and urethral pressures without increasing the PVR ratio, IC frequency, and diaper pad usage. This treatment may be an alternative for male SCI patients with NDO and DSD who are unwilling, or find it inconvenient, to increase IC frequency and wish to preserve spontaneous voiding.

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The authors have no conflicts of interest to declare.

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