Research Article

A single-blind randomized control trial of trigonal versus nontrigonal Botulinum toxin-A injections for patients with urinary incontinence and poor bladder compliance secondary to spinal cord injury

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Objective: To evaluate the effect of trigonal Botulinum toxin-A (BTX-A) injections on patients with urinary incontinence (UI) and poor bladder compliance (BC) secondary to spinal cord injury (SCI).

Design: A single-blind randomized control trial.

Setting: Department of urology in three hospitals.

Participants: SCI patients with UI and poor BC were randomly assigned to either the experimental group or the control group.

Interventions: The experimental group received an injection of 240 U BTX-A into the detrusor plus 60 U BTX-A into the trigone, while the control group received 300 U BTX-A into the detrusor sparing the trigone.

Outcome Measures: Video urodynamic outcomes, including vesicoureteric reflux (VUR), detrusor leak point pressure (DLPP), and detrusor leak point volume (DLPV), were measured at baseline and week 12. UI episodes, voiding volume, and Incontinence Quality of Life (I-QoL) were assessed at baseline, week 2, 4, 8 and 12.

Results: No patient reported new-onset VUR. Compared with baseline data, a significant improvement was achieved in both groups, whereas compared with DLPP and DLPV, a significant difference was noted between the two groups 12 weeks after injection. In the experimental group, the improvement of mean weekly UI episodes, voiding volume, and I-QoL were significantly better than those in the control group at 4, 8, and 12 weeks, respectively (all $P < 0.05$). Systemic complications of BTX-A injection were not reported.

Conclusion: Trigonal BTX-A injection is more effective and safer than nontrigonal BTX-A injection for SCI patients with UI secondary to neurogenic-poor BC and does not result in VUR.

Keywords: Randomized controlled trial, Bladder trigone, Botulinum toxin-A, Poor bladder compliance, Spinal cord injury

Introduction

Bladder compliance (BC) is the relationship between change in bladder volume and change in detrusor pressure.¹ Poor BC means an incremental rise in bladder pressure during the storage phase and is

commonly found in patients with spinal cord injury (SCI). Detrusor leak point pressure (DLPP) is the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased abdominal pressure.² According to the current knowledge, sustained elevated DLPP in poor BC causes hydronephrosis or vesicoureteric reflux (VUR).³ Hence, maintaining detrusor pressure within safe limits has become a top priority in the treatment of SCI patients.⁴ As the second-line treatment, BTX-A has been demonstrated to improve clinical and

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urodynamic parameters for SCI patients with poor BC who have an inadequate response or intolerable side effects to anticholinergic medication.⁵

At present, the location of BTX-A injection, especially injection with or without bladder trigone is still a challenging area for the urologist on the technical details. According to European consensus report recommendations, urologists typically injected BTX-A into the detrusor muscle and spared the trigone to avoid the theoretical risk of inducing VUR.⁶ However, to our knowledge, the grade C recommendation is relatively low and weak due to lack of directly applicable clinical studies of good quality. Studies have demonstrated that the bladder trigone is rich in adrenergic and muscarinic innervation compared to the other area of the bladder.^{7–11} Its smooth muscles are more sensitive to small pressure changes. Therefore, an advantage of trigonal BTX-A injection is that it may improve clinical efficacy. Until now, many studies showed that the risk of VUR after trigonal BTX-A injection is a non-existent risk.^{12–19} Furthermore, Abdel-Meguid TA reported trigone-including injections are superior to trigone-sparing injections for the treatment of pharmacologically refractory idiopathic detrusor overactivity.²⁰ A recent review revealed most data for studies on detrusor overactivity with very little data on poor BC.

Methods

This work is a feasibility study of a single-blind randomized controlled trial performed at the Urology Department in three hospitals between June 2012 and May 2018. After study enrollment, all participants underwent a general and urological routine standard evaluation, including a complete history of suspected neuro-urological disorder, a consecutive 7-day voiding diary, self-assessment quality of life by questionnaire, physical examination according to the standard of American Spinal Injury Association impairment scale, blood sample analysis including serum creatinine, urea nitrogen, urinalysis, urine culture, color Doppler ultrasound, and video-urodynamic test. Inclusion criteria were (1) more than 18 years old with UI secondary to SCI; (2) BC value lower than 20 ml/cmH₂O on urodynamics;² (3) an inadequate response to oral anticholinergics or discontinued anticholinergics due to adverse events; (4) patients or their family caregivers were skilled in clean intermittent catheterization. Exclusion criteria included (1) a history of transurethral sphincterotomy, bladder neck or prostatic resection, or bladder surgery; (2) women who were pregnant, lactating, or planning to become pregnant during the course of the trial; (3) acute urinary tract infection; and (4) chronic

indwelling catheter user. All patients provided written informed consent and the local institutional review board at each center approved the protocol.

Eligible patients were prospectively randomized (balanced randomization [1:1]) and assigned to either the experimental group or the control group (Fig. 1). Blinding was maintained by a numbering system and the use of an independent person to prepare the study medication. Patients in the randomized cohort received supplies from the treatment pack with the corresponding number according to the center. Whereas urologists were aware of the allocation group, the study personnel and outcome assessors were kept blinded to the allocation (in the case of a medical emergency).

BTX-A injections were administered via cystoscopy (Ackermann, Schaffhausen, Switzerland) under local anesthesia or epidural anesthesia if necessary. The bladder was filled gradually with 100–150 ml saline until it flattened. 300 U Botox[®] vials (Botox; commercial lot 2024; Allergan, 50 U each) were diluted in 30 ml of normal saline (10 U/ml).²¹ Patients received a total dose of 300 U of BTX-A into the detrusor sparing the trigone (the control group) or 240 U into the detrusor plus 60 U into the trigone (the experimental group) (Fig. 2).

The primary efficacy end-point was changed from baseline in the video urodynamic outcomes, including incidence of VUR, DLPP, and DLPV at week 12 after treatment. Video urodynamic tests were done according to International Continence Society guidelines by Siemens UROSKOP access X-ray system (Wittelsbacherplatz, Munich, Germany) and Laborie delphis TM urodynamic system (Suite, Mississauga, Canada).¹ DLPP and DLPV are defined as the lowest value of detrusor pressure and bladder volume at which leakage is observed in the absence of abdominal strain and detrusor contraction, respectively.² Secondary end-point outcomes included urinary incontinence episodes, voiding volume, and quality of life at baseline, week 2, 4, 8, and 12 after injection. Patients completed a consecutive 7-day voiding diary at baseline and each follow-up visit to assess the changes in UI episodes and voiding volume which was defined as a voided volume by clean intermittent catheterization plus spontaneous voids.²² Quality of life was assessed using the I-QoL. Adverse events were recorded throughout the study.

Within-group changes from baseline in DLPP, DLPV, UI episodes, voiding volume, and I-QoL were analyzed using the paired students' *t*-test. Between-group comparisons of experimental group and control were performed using an ANOVA model. The chi-square test

Figure 1 Flow chart shows screening, randomization, treatment, and follow-up of the study. Note: ^a240 U BTX-A intradetrusor plus 60 U BTX-A intratrigonal injections; ^b300 U BTX-A intradetrusor injections.

was used for categorical data. A P value of 0.05 or less was considered statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows (Version 23; Armonk, NY, USA: IBM Corp).

Results

A total of 120 eligible patients were randomly assigned to either the experimental group ($n = 60$) or the control group ($n = 60$). Three patients refused to receive the allocated procedures. Seven patients were

regarded as lost follow-up (Patients were considered as lost follow-up when they were absent from visit for 4 weeks). For 5 patients who did not attend any visits, their clinical status was unknown. A total of 105 patients (the experimental group, $n = 54$; the control group, $n = 51$) completed 3 months of follow-up and data were available and analyzed.

At baseline, patients in the two groups had similar demographic characteristics, including age, sex, weight, mechanisms of injury, duration of disease, SCI

Figure 2 Distribution of BTX-A injection sites. A:240U into the detrusor plus 60U into the trigone; B:300U of BTX-A into the detrusor sparing the trigone.

level, Association Impairment Scale (AIS) grade, initial bladder management, incontinence episodes, voiding volume, and I-QoL (Table 1). None of the patients reported new-onset unilateral or bilateral VUR. Compared with baseline data, a significant improvement (Fig. 3) was achieved in both the experimental group and the control group with a significant difference in DLPP and DLPV noted between the two groups by 12-week post-injection (Table 2).

At each time point, mean weekly UI episodes, mean voiding volume, and I-QoL improved significantly from baseline data in patients of both groups (all $P < 0.05$) (Figs 4–6). At week 4, patients in the experimental group improved more than the control group for mean weekly UI episodes (-22.61 vs. -19.93 , $P = 0.034$), voiding volume (202.61 ml vs. 171.66 ml, $P = 0.042$), and I-QoL (23.87 vs. 20.25 , $P = 0.038$). Furthermore, comparison in improvements in mean weekly UI episodes, voiding volume, and I-QoL at week 8 and week 12 between the two groups also yielded significant differences (all $P < 0.05$).

The adverse events at 12 weeks postoperatively are listed in Table 3. Fifteen patients (14.29%) had urinary tract infection with a similar incidence across all treatment groups. All were successfully treated with oral antibiotics. During the first week post-injection, five patients in each group experienced mild transient hematuria, while 4 in the experimental group and 2 in the control group reported mild bladder discomfort. All these cases resolved within 1–2 days requiring no intervention. Five patients (2 in the experimental group and 3 in the control group) reported autonomic dysreflexia events. The condition was controlled with oral nifedipine and resolved without sequelae. These events were unlikely

Table 1 Demographic characteristics at baseline.

Characteristic	Experimental group $n = 54$	Control group $n = 51$
Age, yr		
Mean $\pm$ SD	32.94 ± 8.31	31.66 ± 11.04
Sex, n (%)		
Male	36(66.66)	35(68.62)
Female	18(33.34)	16(31.38)
Weight, kg		
Mean $\pm$ SD	50.08 ± 12.77	48.61 ± 13.51
Mechanisms of injury, n (%)		
Traumatic injury	43(79.63)	44(86.27)
Spinal surgery	11(20.37)	7(13.73)
Disease duration, month		
Mean $\pm$ SD	11.09 ± 7.44	10.26 ± 7.85
Level of spinal cord injury, n (%)		
Cervical	8(14.81)	7(13.73)
Thoracic	42(77.78)	40(78.43)
Lumbosacral	4(7.41)	4(7.84)
AIS grade, n (%)		
A	28(26.27)	30(28.57)
B	20(19.05)	17(16.19)
C	6(5.71)	4(3.81)
Initial bladder management, n (%)		
Intermittent catheter	54 (100)	51(100)
Prior anticholinergic drug use	54 (100)	51(100)
UI episodes, n /week		
Mean $\pm$ SD	41.62 ± 28.04	43.06 ± 29.88
Voiding volume, ml		
Mean $\pm$ SD	101.19 ± 50.37	109.06 ± 61.42
I-QoL		
Mean $\pm$ SD	38.39 ± 18.03	40.22 ± 16.97

Abbreviations: SD, standard deviation; AIS, American Spinal Injury Association impairment scale; I, Urinary incontinence; Voiding volume, voided volume by CIC plus spontaneous voids.

related to the study treatment since all these patients had a history of previous episodes of dysreflexia before injections.

Discussion

In 1897, Botulinum toxin was discovered as a neurotoxin and the most poisonous natural toxin.²³ In 1988, Dykstra and colleague first reported BTX-A injection into the external urethral sphincter for neurogenic detrusor-sphincter dyssynergia secondary to SCI.²⁴ Furthermore, in 2000, the application of BTX-A for neurogenic detrusor overactivity with poor bladder compliance in SCI patient was first investigated by Schurch *et al.*²⁵ Since then, BTX-A is regarded as a minimally invasive surgery with excellent functional short-term and long-term benefits in people with neuro-urological diseases.²⁶ However, most urologists have spared the bladder trigone in clinical injections to prevent possible VUR that may arise from the inhibition of the active

Figure 3 An example of video urodynamic output before and after BTX-A injection: (A and B) video urodynamic profile of a 34-year-old male SCI patient with sustained elevated storage pressures at baseline. (C and D) Urodynamic profile after BTX-A injection showing improvement in DLPP (57 cm H₂O to 36 cm H₂O) and DLPV (220 to 409 ml) in the same patient.

trigonal antireflux mechanism.^{5,21,25–27} Interestingly, until now, trigonal BTX-A injection is not without consequences.

To our knowledge, this is the first randomized controlled trial to compare the effects between trigonal BTX-A injection and nontrigonal BTX-A injection for patients with neurogenic-poor BC and UI secondary to SCI. Although the follow-up period was relatively short, our study revealed that trigonal BTX-A injection did not induce VUR. In 2006, Lucioni A *et al.*

evaluated two points of injections (total 20U BTX-A) into the trigonal region for 24 patients in the treatment of overactive bladder.²⁸ Although routine urodynamic tests were not performed, no patients experienced flank pain or pyelonephritis related to VUR. Similar results were reported by others.^{12–18} Furthermore, one study reported that one patient with VUR (grade 2 right, grade 1 left) at baseline showed no change in VUR grade after trigone-including injections (100 U BTX-A).¹⁹ Moreover, Mascarenhas Fone and his colleagues even observed one patient with grade II unilateral VUR had complete resolution of the reflux after total 300 U BTX-A injection into detrusor including 50 U BTX-A into the trigone.²⁰ In agreement, our findings support the notion that trigonal injections do not influence the active trigonal antireflux mechanism in neurogenic patients.

Based on EAU neuro-urology guideline, the most important aim for the treatment of neuro-urological poor BC is to protect the function of the upper urinary tract in SCI patients both in the filling phase and voiding phase.³ In our study, significant improvements of BC were evident after the total 300-U dose of BTX-A injection either including or sparing

Table 2 Video urodynamic characteristics at baseline and week 12.

Characteristic	Experimental group <i>n</i> = 54	Control group <i>n</i> = 51	P value
<i>DLPP</i>			
Baseline	62.14 ± 19.01	61.77 ± 18.30	0.919
Week 12	23.69 ± 10.28	28.01 ± 11.06	0.041
P value	<0.001	<0.001	
<i>DLPV</i>			
Baseline	148.08 ± 48.12	151.92 ± 49.16	0.687
Week 12	294.58 ± 60.46	270.86 ± 58.91	0.045
P value	<0.001	<0.001	

DLPP = Detrusor leak point pressure; DLPV = Detrusor leak point volume.

Figure 4 Reduction in weekly urinary incontinence episodes(UI) compared to baseline.

Figure 6 Improvement in I-QoL compared to baseline.

Figure 5 Increment in voiding volume compared to baseline.

bladder trigone. Interestingly, trigonal BTX-A injection was superior to nontrigonal BTX-A injection with respect to the protection of renal function. Specially,

Table 3 Total adverse events between groups.

	Experimental group n = 54	Control group n = 51	P* value
Urinary tract infection	8	7	NS
Hematuria	5	5	NS
Bladder discomfort	4	2	NS
Autonomic dysreflexia	2	3	NS

NS, nonsignificant.

* Chi-square test.

we found (1) patients in the experimental group showed greater improvement (146.5 ml) in DLPV than that in the control group (118.94 ml); and (2) most importantly, were the changes in DLPP. Although patients in both groups showed satisfactory bladder filling at low pressures (40cmH₂O), we noticed that DLPP in the experimental group was much lower than that in the control group.²⁹ To explain this seemingly improvement of BC in both groups of patients, we supposed that the impaired BC in this study was likely to result from hypertrophic detrusor rather than hypertonic detrusor, because only the latter would cause phasic pressure increases.³⁰ In 2009, Alexander Roosen reported that trigone myocytes employ membrane L-type-Ca²⁺ and CL⁻ channels to generate spontaneous activity.¹⁰ In 2016, J Todd Purves demonstrated that

bladder trigonal region was most densely innervated by the completed 3D maps.¹¹ Obviously, trigonal BTX-A injections would be the potentially optimal treatment to reduce the abnormal detrusor pressure and protect the renal function, since BTX-A acts at the sensory nerve endings and the synaptic nerve junctions. Therefore, based on our experience, higher bladder capacity and lower leak point pressure may minimize the risk of renal damage in SCI patients.

Better urodynamic results were associated with better improvement of subjective results, especially to the patient's quality of life, an important treatment outcome.³ Specifically, we observed that the outcome of mean change from baseline in I-QoL initiated difference between both groups at week 4, and kept the same tendency at week 8 and week 12. By analyzing the findings of the present study, we could conclude that (1) the patients in the experimental group showed greater increase in bladder voiding volume than those in the control group; and (2) patients with poor BC tended to have a better response to BTX-A injections, indicated by that patients with injections including bladder trigone showed better effect than the patients with injections excluding the trigone in terms of reduction of urinary incontinence episodes per week.

No systemic or serious adverse event of treatment has occurred in the present trial, similar to the other studies reported by the most published literature.^{12–20}

The lack of a placebo arm is an obvious limitation of this study. However, it was difficult, for ethical reasons, to inflict a placebo injection on patients. Another limitation is the effects of only one injection were assessed, with a maximum follow-up 12 weeks. Further study of long-term follow-up after repeated injections is necessary.

Conclusion

The present study demonstrates that trigonal BTX-A injection is more effective and safer than nontrigonal BTX-A injection for SCI patients with UI secondary to neurogenic-poor BC and does not result in VUR.

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Disclaimer statements

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Conflicts of interest Authors have no conflict of interests.

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