Tzu Chi Medical Journal 24 (2012) 201–204

Contents lists available at SciVerse ScienceDirect

Tzu Chi Medical Journal

journal homepage: www.tzuchimedjnl.com

Original Article

Improvement in autonomic dysreflexia after detrusor onabotulinumtoxinA injections in patients with chronic spinal cord injuries

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ARTICLE INFO

Article history:
Received 15 November 2012
Received in revised form
23 November 2012
Accepted 26 November 2012

Keywords:
Incontinence
Neurogenic bladder
Quality of life

ABSTRACT

Objectives: To investigate the therapeutic effects of repeated detrusor onabotulinumtoxinA (BoNT-A) injections on autonomic dysreflexia (AD) in patients with chronic spinal cord injuries (SCI).
Materials and Methods: A total of 49 patients with SCI were enrolled to receive two sets of 200 U BoNT-A injections into the detrusor at baseline and 6 months later. The primary end points were improvement in the severity of AD and net change in the grade of incontinence. Secondary end points included net changes in the scores of the Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire, and quality of life index as well as urodynamic parameters.
Results: A total of 31 men and 18 women with cervical ($n = 27$) or thoracic ($n = 22$) SCI were enrolled. They had a mean age of 41.6 years and duration of injury of 8 years. Fifteen patients did not have AD at baseline or after treatment. AD was completely resolved in three patients, and improved in 18; treatment made no difference in three patients and AD was exacerbated in 10. There were no significant differences in any urodynamic variables between patients with and without AD. A significantly greater improvement in the UDI-6 was noted in patients without AD and those in whom AD improved than in those with AD. The occurrence of AD was also not significantly associated with persistent urinary incontinence after the BoNT-A injections. There was no significant difference in the quality of life index between patients with and without AD at the end point.
Conclusion: Detrusor BoNT-A injections improved AD in 62% of SCI patients with AD at baseline.

1. Introduction

Autonomic dysreflexia (AD) is a potentially life-threatening condition. AD occurs most often in individuals with spinal cord injuries (SCI) above the T6 level [1]. It is characterized by severe paroxysmal hypertension (episodic high blood pressure) associated with throbbing headaches, profuse sweating, nasal stuffiness, flushing of the skin above the level of the lesion, bradycardia, and apprehension and anxiety, which is sometimes accompanied by cognitive impairment [2]. Patients with chronic SCI may develop AD during bladder overdistention, stool impaction, or urinary tract infection (UTI).

Studies have shown that onabotulinumtoxinA (BoNT-A) injected into the detrusor can restore urinary continence, lower the rate of UTI, decrease intravesical pressure, and increase bladder compliance in up to 80% of SCI patients [3,4]. Although repeated injections of botulinum toxin A are necessary to achieve the desired effects, most patients tolerate the procedure in exchange for a better quality of life (QoL) [5]. Repeated injections restore renal function or halt renal deterioration in patients with SCI [6].

BoNT-A has been proven to be effective for the treatment of neurogenic detrusor overactivity (NDO) [7]. BoNT-A is one of the most powerful neurotoxins; it inhibits the release of neurotransmitters from the nerve fibers and urothelium [8,9]. BoNT-A also has an antinociceptive effect on the bladder wall. The current literature also suggests that noxious (painful) stimuli are the primary initiators of AD [10,11]. In previous studies, some patients with SCI and detrusor sphincter dyssynergia (DSD) reported resolution or improvement of AD after urethral or detrusor BoNT-A injections [10,11]. However, other patients reported exacerbation or occurrence of AD after BoNT-A injections. No previous study appears to

Conflict of interest: none.

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1016-3190/$ – see front matter
http://dx.doi.org/10.1016/j.tcmj.2012.11.003

have investigated the association of AD and detrusor BoNT-A injection.

In this study, we investigated the therapeutic effects of repeated detrusor BoNT-A injections on urinary incontinence and AD in patients with chronic SCI. We also investigated whether any factors could predict the resolution or exacerbation of AD after BoNT-A injections.

2. Materials and methods

Forty-nine patients with SCI and DSD were consecutively enrolled in this prospective study and received two sets of 200 U BoNT-A injections into the detrusor muscle at baseline and 6 months later. Patients were then monitored for therapeutic efficacy of the injections, which was evaluated by urinary incontinence and an increase in bladder capacity. The effects of BoNT-A on AD were also assessed at baseline and after repeat injection 6 months later.

All patients were aged 18 years or older and had a history of chronic suprasacral SCI for 1 year or more. For all patients, the diagnosis of DSD was made based on video urodynamic studies. In addition, all patients voided by reflex or abdominal stimulation with or without clean intermittent catheterization, were free of indwelling catheters and cystostomy, and were free of UTI on enrollment. All patients had been treated with antimuscarinic agents for at least 1 year, which had failed to resolve the urinary incontinence. Exclusion criteria included detrusor underactivity and large bladder compliance, proven intrinsic sphincteric deficiency, Grade 2 or higher vesicoureteral reflux, and hypersensitivity to BoNT-A or any type of botulinum toxin.

During the screening period and at each visit after BoNT-A injection, patients were asked to report AD symptoms such as hypertension, sweating, erythema in the upper extremities, headaches, and blurred vision during the last 3 months prior to the end point. The severity of AD was also classified as mild, moderate, or severe if the AD symptoms occurred occasionally, often, or frequently, respectively.

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

BoNT-A injection was performed in the operating room under light intravenous general anesthesia. A total of 200 U of BoNT-A (Allergan Co., Irvine, CA, USA) dissolved in 20 mL of normal saline was injected into 40 sites in the detrusor muscle including the lateral and posterior walls and the dome, sparing the trigone. The injection sites were widely distributed to cover the whole bladder wall. A 14F Foley catheter was routinely inserted after the BoNT-A injections, and patients were discharged with catheter removal the next morning and monitored in the outpatient clinic thereafter. All patients were instructed to continue clean intermittent catheterization or abdominal stimulation to empty their bladders. BoNT-A injections were repeated 6 months later. Before each subsequent set of BoNT-A injections, video urodynamic studies were performed, during which AD was evaluated at full bladder or when patients had a bladder reflex to void.

After BoNT-A injection, antimuscarinic agents were discontinued. Patients were monitored every 3 months for 12 months to gauge improvements in urinary incontinence and AD. The urogenital distress inventory (UDI-6) and the incontinence impact questionnaire (IIQ-7) [12] were used to assess incontinence distress and the impact of urinary incontinence on daily life, respectively. In addition, we extracted the three incontinence related scores (urgency, stress, and insensible incontinence) from the UDI-6 to score the overall incontinence grade. QoL was also evaluated using the QoL index (QoL-I) self-assessment adapted from the International Prostatic Symptom Score [13]. The patient perception of bladder condition questionnaire, a patient-reported measure of bladder condition, was used to assess patient satisfaction with the global treatment outcome. Patient satisfaction was based on an improvement in the patient perception of bladder condition by two or more points after the second set of BoNT-A injections [14].

There were two primary end points: (1) improvement in the severity of AD from baseline to 12 months, and (2) net change in the grade of incontinence from baseline to 12 months. Secondary end points included net changes in the scores of the UDI-6, IIQ-7, and QoL-I, as well as the changes in urodynamic parameters including cystometric bladder capacity, voiding detrusor pressure at maximum flow rate (Qmax), postvoid residual volume, and bladder compliance from baseline to 12 months.

All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

Table 1
The changes of autonomic dysreflexia in patients with spinal cord injury at baseline and after onabotulinumtoxinA injections.

	Male SCI	Female SCI	Total
No AD	10 (32.3%)	5 (27.8%)	15 (30.6%)
Complete resolution of AD	3 (9.7%)	0 (0.0%)	3 (6.1%)
Improvement of AD >50%	8 (25.8%)	7 (38.9%)	15 (30.6%)
Improvement of AD >25%	2 (6.5%)	1 (5.6%)	3 (6.1%)
No change of AD	2 (6.5%)	1 (5.6%)	3 (6.1%)
Exacerbation of AD	6 (19.4%)	4 (22.2%)	10 (20.4%)

AD = autonomic dysreflexia; SCI = spinal cord injury.

3. Results

A total of 31 men and 18 women with cervical (n = 27) or thoracic (n = 22) SCI were enrolled. They ranged in age from 22 years to 74 years (mean, 41.6 years) and the duration of injury ranged from 1 year to 35 years (mean, 8.0 years). At baseline, AD was reported in 34 patients (21 men and 13 women). After two sets of BoNT-A injections, AD was reported in 31 patients (18 men and 13 women). There was no significant difference in the occurrence of AD between the cervical and thoracic levels or between genders.

Analysis of AD at baseline and after BoNT-A injections revealed that 15 patients did not have AD at baseline or after treatment. Complete resolution of AD was noted in three patients, improvement in AD was noted in 18, and no difference in AD was found in three patients, while exacerbation of AD occurred in 10 patients (Table 1). The main symptoms of AD in these patients at baseline and after BoNT-A injections are listed in Table 2.

Comparison of urodynamic parameters at baseline and after BoNT-A injections showed no significant difference in any urodynamic variable between patients with and without AD, except that patients with AD had a significantly lower Qmax and larger postvoid residual volumes (Table 3) than patients without AD. There were no significant differences in the changes in urodynamic

Table 2
The main symptom of autonomic dysreflexia at baseline and after onabotulinumtoxinA injections.

	Baseline	Post-treatment
Increase extremity reflex	8	9
Hypertension	5	4
Sweating	9	13
Flushing or erythema	4	2
Headache	6	3
Blurred vision	2	0

Table 3
The urodynamics variables of patients with and without autonomic dysreflexia at baseline and after onabotulinumtoxinA injections.

Baseline	Non-AD ($n = 15$)	AD ($n = 34$)	p
CBC	215.1 ± 104.7	276.3 ± 160.2	0.130
Pdet	39.6 ± 19.9	36.4 ± 21.7	0.597
Qmax	7.45 ± 6.13	3.78 ± 4.53	0.020
Volume	97.9 ± 81.9	78.6 ± 115.7	0.513
PVR	117.3 ± 73.9	197.7 ± 122.4	0.010
Compliance	37.1 ± 49.9	35.1 ± 25.7	0.867
Post-treatment	Non-AD ($n = 18$)	AD ($n = 31$)	p
CBC	392.0 ± 185.7	379.1 ± 176.3	0.851
Pdet	24.1 ± 18.8	19.6 ± 16.9	0.510
Qmax	4.40 ± 5.28	0.82 ± 2.17	0.064
Volume	75.0 ± 83.7	18.1 ± 47.4	0.068
PVR	317.0 ± 170.6	360.9 ± 195.0	0.545
Compliance	23.7 ± 15.7	29.8 ± 17.9	0.365

AD = autonomic dysreflexia; CBC = cystometric bladder capacity; Pdet = detrusor pressure ; PVR = postvoid residual volume; Qmax = maximum flow rate.

variables among patient groups without AD, with improved AD, and without improved AD (Table 4).

There were no significant differences in the changes in the IIQ-7 and QoL-I from baseline to the end point among the three groups, but a significantly greater improvement in the UDI-6 was noted in patients without AD and with improved AD than in patients without improved AD (Table 5).

Among the 31 patients with AD at the end point, seven (23%) had UTIs and four (13%) still had detrusor overactivity (DO). Among the 18 patients without AD at the end point, eight (44%) had UTIs and 10 (55%) had DO. There was no significant difference in the association of AD with UTI or DO. The occurrence of AD was also not significantly associated with persistent urinary incontinence after BoNT-A injections.

Patients with persistent urinary incontinence had significantly lower QoL-I than those without urinary incontinence after the BoNT-A injections (3.13 ± 1.55 vs. 1.20 ± 0.92, $p = 0.005$). However, there was no significant difference in the QoL index between patients with and without AD at the end point (1.94 ± 1.52 vs. 2.00 ± 2.83, $p = 0.962$).

4. Discussion

The results of this study revealed that AD may resolve, persist, or exacerbate after detrusor BoNT-A injections in patients with chronic SCI. Overall, 62% of the 34 patients with AD at baseline had improvement in the severity of AD after BoNT-A injections. Although AD was completely abolished in three patients, it was exacerbated in 10 patients after detrusor BoNT-A injections.

AD is a potentially life-threatening condition that is considered a medical emergency requiring immediate attention. It is believed to be triggered by cutaneous or visceral afferent stimuli that originate below the level of the spinal cord lesion [1]. The most common causes of AD are bladder distention and stool impaction. UTI can also trigger AD, regardless of whether there is an indwelling catheter. In spinal cord transection, these afferent impulses are unable to travel past the injury, resulting in an enhanced spinal cord reflex to the autonomic nervous system in response to stimuli. It is believed that these afferent stimuli trigger and maintain an increase in blood pressure via sympathetically mediated vasoconstriction in the muscle, skin, and splanchnic vascular beds [15].

Previous treatments of AD included removal of triggering stimuli and administration of antihypertensive or vasodilator agents. In clinical trials of detrusor BoNT-A for treatment of NDO, decreased severity and abolishment of AD were observed and reported [10,11]. This study confirmed that the severity of AD could be reduced after detrusor BoNT-A injections in 62% of SCI patients with NDO. Although some patients might have AD exacerbation, this novel treatment could be applied for treatment of patients with severe AD that affects QoL.

Recent research suggests that noxious stimuli are the primary initiators of AD, and that AD induced by noxious stimulation increases with time after SCI. However, Burton et al found that activation of pain receptors in muscle and skin below the lesion in individuals with SCI did not trigger AD [9]. They suggested that not all noxious stimuli trigger AD, and some non-noxious stimuli also trigger it. It is important to consider non-noxious sources of stimulation in addition to noxious triggers. Detrusor injection of BoNT-A induces trauma to the bladder wall, causing acute inflammation in the suburothelial nerve plexus. These noxious stimuli from the bladder wall might result in activation of the autonomic nervous system and exacerbate AD in the acute stage of detrusor BoNT-A injections.

Botulinum toxin A modulates afferent activity of the bladder in association with reduced DO and overactive bladder symptoms in NDO patients [16]. In a chronic SCI rat model, intravesical BoNT-A significantly inhibited the afferent response without impairing efferent bladder function [17]. A clinical study has suggested that BoNT-A has an antinociceptive effect on bladder afferent pathways in patients with neurogenic detrusor overactivity, producing both symptomatic and functional improvements [8].

The results of this study provide evidence that AD can be reduced in the majority of patients after detrusor BoNT-A injections, suggesting the antinociceptive response to BoNT-A in the bladder wall might have an effect on the spinal cord by blocking the transmission

Table 4
The changes of urodynamics variables among patients without AD, improved AD, and no improved AD from baseline to end point.

		No AD ($n = 15$)	Improved AD ($n = 21$)	No improved AD ($n = 13$)	p
CBC	BL	177.5 ± 95.0	251.1 ± 117.62	230.7 ± 104.4	0.366
	12 mo	392 ± 185.7*	363.1 ± 186.6*	398.2 ± 171*	
Pdet	BL	40.6 ± 21.5	40.4 ± 24.3	42.5 ± 14.5	0.456
	12 mo	24.1 ± 18.8*	23.3± 17.4*	15.3 ± 16.3*	
Qmax	BL	7.60 ± 6.48	3.83 ± 4.90	5.50 ± 5.42	0.582
	12 mo	4.40 ± 5.28*	1.08 ± 2.61	0.50 ± 1.58*	
Volume	BL	82.5 ± 68.6	82.8 ± 145.4	83.7 ± 74.2	0.457
	12 mo	75.0 ± 83.7	24.8 ± 57.8	10.2 ± 32.3*	
PVR	BL	95.0 ± 54.01	168.3 ± 109.1	147.0 ± 75.9	0.676
	12 mo	317 ± 170.6*	338.3 ± 213.9*	388.0 ± 177*	
Compliance	BL	19.5 ± 22.8	33.8 ± 25.6	29.2 ± 29.3	0.755
	12 mo	23.7 ± 15.7	34.8 ± 15.3	23.7 ± 19.6	

*$p < 0.05$ between baseline (BL) and 12 months.
AD = autonomic dysreflexia; CBC = cystometric bladder capacity; Pdet = detrusor pressure; PVR = post void residual volume; Qmax = maximum flow rate.

Table 5
The changes of UDI-6, IIQ-7 and QoL indexes among three groups.

		No AD ($n = 15$)	Improved AD ($n = 21$)	No improved AD ($n = 13$)	p
UDI-6	BL	13.8 ± 2.66	11.67 ± 3.50	9.10 ± 3.54	0.035
	12 mo	7.10 ± 2.51*	7.75 ± 3.98*	7.20 ± 4.80	
IIQ-7	BL	15.9 ± 5.24	13.58 ± 7.28	10.70 ± 5.60	0.449
	12 mo	6.10 ± 5.32*	7.08 ± 7.29*	5.30 ± 5.66	
QoL-I	BL	4.50 ± 1.27	4.92 ± 1.08	4.10 ± 1.60	0.704
	12mo	1.90 ± 1.29*	2.92 ± 1.83*	2.20 ± 1.55*	

*$p < 0.05$ between baseline (BL) and 12 months.
AD = autonomic dysreflexia; IIQ-7 = incontinence impact questionnaire; QoL-I = quality of life index; UDI-6 = urogenital distress inventory.

of sensory stimuli below the spinal cord lesion. Intravesical BoNT-A treatment in rats also significantly blocked the dysreflexia response (high arterial pressure with bradycardia) induced by cystometry after spinal cord transection. Intravesical BoNT-A also significantly lowered nerve growth factor concentrations in the bladder and the T4 dorsal root ganglion segment [18]. These results suggest that BoNT-A treatment modulated sensory and motor transmission, as well as reduced inflammatory conditions in the bladder and spinal cord. It is also possible that the chronic symptomatology of bladder hypersensitivity is due to central sensitization and persistent abnormality or activation of the afferent sensory system [19]. In this regard, inhibition of neuroplasticity of the sensory fibers in the suburothelial space by BoNT-A injections into the detrusor muscle could be a therapeutic target to reduce the severity of AD in patients with chronic SCI.

We failed to identify any predictive factors for the reduction or exacerbation of AD after BoNT-A injection into the detrusor. There was no significant difference in the baseline or post-treatment urodynamic variables among patients without AD, with improved AD, and with exacerbated AD. The incidence of UTI and persistent DO after BoNT-A injection were also similar among groups. Additionally, the level of SCI and the duration of SCI did not significantly differ among groups. Recent evidence suggests that the urothelium plays a prominent role in modulating bladder sensory nerve ending excitability. It is conceivable that factors and processes affecting the plasticity of bladder neurons after SCI may be partly due to changes occurring in the urothelium. In early SCI, disruption to bladder uroepithelial integrity results in increased permeability of the urothelium to urine and urine-borne substances, resulting in cystitis or inflammation of the bladder [20]. These urothelial changes and significant deficits in tight junction proteins could be detected in chronic SCI, suggesting that early pathological changes to the bladder continue throughout the chronic phase of injury. Whether SCI patients with AD have greater inflammation in their bladder walls and dorsal root ganglia than those without AD has not been elucidated. It is possible that BoNT-A detrusor injections have a reductive effect on chronic inflammation in the bladder wall as well as the spinal cord and result in improvement in the severity of AD. AD might not be eradicated in patients with severe inflammation in the bladder wall after inadequate dosing of BoNT-A.

Interestingly, we found that the presence of AD did not influence the patient's perception of QoL. Nonetheless, patients with persistent urinary incontinence had lower QoL indices compared with those without AD or urinary incontinence. Thus, most SCI patients tolerated AD, but not urinary incontinence, after detrusor BoNT-A injection therapy.

The limitations of this study included the small patient number and lack of a control arm to demonstrate that AD was induced by BoNT-A but not by the injection technique.

5. Conclusion

This study revealed that detrusor BoNT-A injections improved AD in the majority of SCI patients with AD at baseline, while AD was exacerbated in some patients after detrusor BoNT-A injection therapy. A higher dose of BoNT-A or a longer treatment period might result in better outcomes.

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