Botulinum Toxin-A Injections Into Neurogenic Overactive Bladder—To Include or Exclude the Trigone? A Prospective, Randomized, Controlled Trial

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Purpose: The short-term outcomes of initial detrusor injections vs combined detrusor-trigone botulinum toxin-A injections were determined in patients with spinal cord injury-neurogenic detrusor overactivity.

Materials and Methods: Adults with refractory spinal cord injury-neurogenic detrusor overactivity who strictly discontinued anticholinergics were recruited for the study. At a 1:1 ratio patients randomly received 300 U botulinum toxin-A intradetrusor injections excluding the trigone (detrusor arm) or 200 U intradetrusor plus 100 U intratrigonal injections (combined arm). Study end points were determination of the impact on incontinence episodes, complete dryness, quality of life, reusing anticholinergics, maximum detrusor pressure, reflex volume, maximum cystometric capacity, vesicoureteral reflux and adverse events. Patients were evaluated at baseline, and 2, 8, 12 and 18 weeks after injection. Statistical significance was considered at $p < 0.05$.

Results: Analysis included 18 patients per arm with no significant baseline differences. On within group analysis all parameters improved significantly compared to baseline. On between group analysis in the detrusor vs the combined arm at week 8 incontinence decreased by 52.4% vs 80.9% (number needed to treat 1.91 vs 1.23 patients, $p < 0.001$), complete dryness was achieved in 33.3% vs 66.7% of patients (number needed to treat 3 vs 1.5, $p < 0.001$) and quality of life score was decreased by 46.76% vs 48.13% (number needed to treat 2.14 vs 2.08, $p < 0.44$). The absolute difference was 60% vs 82.5% for reflex volume ($p < 0.001$), 66.2% vs 68.4% for maximum cystometric capacity ($p < 0.22$) and −42.3% vs −41.9% for maximum detrusor pressure ($p < 0.21$). At week 18 anticholinergics were needed again in 9 (50%) and 4 patients (22.2%) patients, respectively. No patient showed new or upgraded vesicoureteral reflux or reported significant adverse events.

Conclusions: In the short term all parameters improved significantly in each arm. The superiority of including rather than excluding the trigone was significant.

Key Words: urinary bladder, neurogenic; spinal cord injuries; botulinum toxin type A; urinary incontinence; urodynamics

Abbreviations and Acronyms

AD = absolute difference
AE = adverse effect
BTX = botulinum toxin
BTX-A = BTX type A
CIC = clean intermittent catheterization
MCC = maximum cystometric capacity
NDO = neurogenic detrusor overactivity
NNT = number needed to treat
$Pdet_{max}$ = maximum detrusor pressure
QOL = quality of life
RV = reflex volume
SCI = spinal cord injury
VUR = vesicoureteral reflux

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Botulinum toxin type A in patients with overactive bladder due to NDO has been used as second line treatment due to intolerance or failure of treatment with an appropriate dose of antimuscarinics for an appropriate period.[1–3] There is currently no clear consensus on the optimal dose, number and sites of BTX-A injection, which significantly impact the clinical outcome. The reported dose of BTX-A injected into the bladder is usually 200 to 300 U, which is typically injected directly in the detrusor or less

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commonly in the suburothelium, mostly sparing the trigone.[2,4,5] In current practice whether to include or exclude the trigone in BTX-A bladder injections is based on assumption rather than on a solid level of evidence-based medicine.[5–7] According to European consensus report recommendations on BTX-A use the depth and site of injections should be within the detrusor muscle and outside the trigone.[5] However, the grade of recommendation was low, that is grade C (recommendation made despite the absence of directly applicable clinical studies of good quality).

The BTX mechanism of action was previously thought to be mediated only by prolonged blockade of the presynaptic release of acetylcholine at the neuromuscular junction. However, recent data support the belief that BTX acts on motor and sensory pathways by inhibiting the release of a number of neurotransmitters and neuropeptides, and downregulating the expression of purinergic and capsaicin receptors on afferent neurons.[2,8–10] Although the trigone is rich in sensory fibers and its smooth muscles are sensitive to small pressure changes,[11] the role of the trigone in NDO has not been well explored and needs further investigation.

The objectives of this study were to determine the short-term efficacy outcomes and AEs of initial detrusor vs combined detrusor-trigone BTX-A injections in adults with SCI and refractory neurogenic urinary incontinence due to NDO who strictly discontinued anticholinergics before and after injections. To our knowledge this study provides the first level 1b evidence (evidence obtained from an individual randomized trial) in this regard in patients who did not receive concomitant anticholinergics during the study.

MATERIALS AND METHODS

Setting

This prospective, single-blind, parallel, randomized, controlled clinical study was done at a single institution between November 2006 and October 2009. The study received ethics committee approval and informed consent was obtained from each patient before study enrollment.

Study Population, and Inclusion and Exclusion Criteria

A total of 38 adults with SCI, neurogenic urinary incontinence and NDO refractory to anticholinergic medications were recruited for study. At study entry patients were on CIC or on indwelling urethral catheters and willing to use CIC. Patients with indwelling urethral catheters were converted to CIC at least 2 weeks before baseline evaluation and injections to help control urinary tract infections and allow a homogeneous patient cohort at baseline. Patients discontinued anticholinergic medications a minimum of 2 weeks earlier than baseline evaluation and injections, and were maintained off anticholinergics a minimum of 8 weeks after injections to allow for medication washout and eliminate the bias of such medications on the intervention effect. Patients with urinary incontinence and NDO due to neurological disease other than SCI were excluded from study to ensure homogeneity and avoid contaminating the study sample. Patients who refused CIC or refused to discontinue anticholinergics, those who received previous BTX-A bladder injections and those with uncontrolled urinary tract infection were also excluded to avoid compromising incontinence data.

Study Design

At baseline it was planned that all patients would receive a total dose of 300 U BTX-A. Patients were prospectively randomized 1:1 to receive the whole 300 U of BTX-A into the detrusor, excluding the trigone (detrusor arm), or 200 U into the detrusor plus 100 U into the trigone (combined arm). Randomization was done immediately before injection using sealed envelopes and all patients were blinded to randomization.

End Points

The primary study end point was the impact of each injection protocol on the number of incontinence episodes between CICs per 24 hours, the number of patients who became completely dry, defined as less than 1 incontinence episode per 24 hours, QOL using the International Prostate Symptom Score-QOL subset, $Pdet_{max}$ and the need to reinstitute anticholinergics. Secondary end points were changes in RV, defined as bladder volume at the start of the first involuntary contraction, and MCC, VUR and AEs.

Baseline and Followup Evaluation

Patients were evaluated at baseline, and at weeks 2, 8, 12 and 18 after injection. All outcome parameters and AEs were considered for analysis at weeks 2 and 8 before allowing anticholinergics. The need to reinstitute anticholinergics was evaluated at weeks 12 and 18. At baseline patients were initially assessed by appropriate history and physical examination, urinalysis, and culture sensitivity tests and imaging as appropriate. At baseline and before the followup visits at weeks 2 and 8 QOL was assessed. Also, patients were asked to document a 3-day bladder diary, reporting the number and times of CIC, and incontinence episodes between CICs. Videourodynamics were done at baseline and 8 weeks after injection according to the good urodynamic practices recommended by the International Continence Society.[12] Urodynamic parameters were defined according to International Continence Society standardization reports.[13,14]

Injections

At cystoscopy the bladder was filled gradually with saline until it flattened. Using a 23 gauge needle injections were allocated uniformly and evenly throughout the designated area, including the dome and posterior wall, excluding the trigone in the detrusor arm and including the trigone in the combined arm (fig. 1). In the detrusor arm 3 Botox® vials (100 U each) were reconstituted in 30 ml normal saline (10 U/ml) and 30 injections (1 ml each) were administered into the detrusor. In the combined arm 2 Botox vials were reconstituted in 30 ml normal saline (6.7 U/ml) and 30 injections (1 ml each) were administered into the detrusor. An additional Botox vial (100 U) was reconsti-

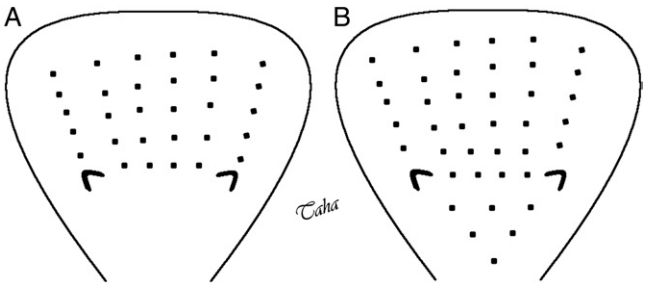

Figure 1. Injection templates. *A*, detrusor. *B*, combined detrusor-trigone.

tuted in 5 ml normal saline (20 U/ml) and 10 injections (0.5 ml, 10 U each) were allocated throughout the trigone, sparing a 5 mm distance to the vicinity of the ureteral orifices and the bladder neck.

Statistical analysis was done with SPSS® 11.0. Intent to treat analysis and sample size calculation were previously described as 18 patients per group, suggesting 2-sided $p < 0.05$ with 80% power as significant. Discrete variables, shown as the count or rate, were evaluated by the chi-square test. Comparison between groups was done using ANOVA. NNT to benefit, which is shown when applicable, was calculated as 1 divided by the absolute risk reduction and expressed as a proportion.

RESULTS

Initially 38 patients who met study inclusion criteria were recruited, of whom 2 violated the study protocol by receiving anticholinergics before the end of the week 8 injections and were excluded from study (fig. 2). Thus, analysis included 34 male and 2 female patients with a mean ± SD age of 25 ± 3.1 years (range 20 to 37). Of the patients 21 were on CIC and 15 were originally on indwelling urethral catheters before conversion to CIC. The mean interval since SCI was 31 ± 13.7 months (range 10 months to 11 years). Each arm included 18 patients with no statistically significant differences between the arms in any demographic or baseline characteristic (tables 1 and 2).

Findings at the 2 and 8-week followups, when no patient had yet reinstituted anticholinergics, were almost identical (table 1). On within group analysis all outcome parameters improved significantly compared to baseline in each arm. However, on between group analysis changes in incontinence, complete dryness and RV were significantly different in the detrusor vs the combined arm while changes in QOL, MCC and $Pdet_{max}$ showed a nonsignificant difference in the 2 arms (tables 1 and 2).

At week 8 the number of incontinence episodes per 24 hours decreased by 52.4% and 80.9% in the detrusor and combined arms ($p < 0.001$) with a NNT of 1.91 and 1.23 patients, respectively. No patient in either group reported being completely dry at baseline but 33.3% and 66.7% in the detrusor and combined arms became completely dry after injections ($p < 0.001$) with a NNT of 3 and 1.5, respectively. QOL scores decreased by 46.76% (NNT 2.14 patients) in the detrusor arm compared to 48.13% (NNT 2.08) in the combined arm ($p < 0.44$). In the detrusor vs the combined arm the AD was 60% vs 82.5% for RV ($p < 0.001$), 66.2% vs 68.4% for MCC ($p < 0.22$) and −42.3% vs −41.9% for $Pdet_{max}$ ($p < 0.21$, table 2).

At week 12 in the detrusor arm 2 patients (11.1%) required reinstitution of a decreased dose of anticholinergics compared to none in the combined arm. At week 18 anticholinergics remained completely discontinued in 9 patients (50%) and decreased to half or less of the pre-injection dose in 9 (50%) in the detrusor arm compared to 14 (77.8%) and 4 (22.2%) in the combined arm, respectively.

At baseline unilateral grade 2 and 3 VUR was evident in 2 patients in the detrusor arm while 2 in the combined arm had unilateral grade 1 and 3 VUR, respectively. At week 8 no patient had new onset VUR or upgrading of preexisting VUR. No systemic AEs were reported in any case. Three patients per each arm reported mild transient hematuria while 1 in the detrusor arm and 3 in the combined arm reported mild bladder discomfort requiring no medication.

DISCUSSION

In the last decade BTX-A has revolutionized treatment for intractable neurogenic urinary incontinence.[15] Several studies show that BTX-A bladder injections are safe and effective for decreasing NDO. In most of these studies detrusor injections were done while excluding the trigone.[2,4,5] In a European consensus report Apostolidis et al summarized results in 1,018 patients in whom NDO was mostly due to SCI or multiple sclerosis.[5] Despite heterogeneous designs almost all single injection studies showed significantly improved outcomes, including

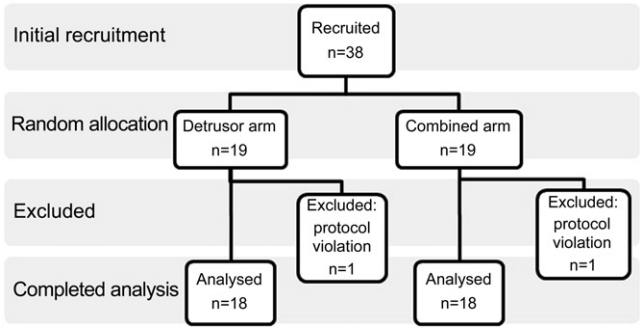

Figure 2. Flow chart shows population recruitment and exclusion

Table 1. *Subjective and QOL findings at baseline, and 2 and 8 weeks after injection in 18 patients per arm off anticholinergics*

Arm* (parameter)	Baseline	Wk 2	Wk 8
	Incontinence		
Detrusor:			
Mean ± SD No. episodes/24 hrs (range)†	5 ± 0.94 (2.3–7.3)	2.33 ± 0.72 (0.7–3)	2.38 ± 0.79 (0.3–3.3)
% AD		−53.4	−52.4
NNT		1.87	1.91
Combined:			
Mean ± SD No. episodes/24 hrs (range)†	5.13 ± 1.08 (2.3–7.7)	1.02 ± 0.47 (0.3–1.7)	0.98 ± 0.45 (0.3–1.7)
% AD		−80.1	−80.9
NNT		1.24	1.23
Between arm p value	0.70	<0.001	<0.001
	Complete Dryness‡		
Detrusor:			
No. pts	0	6	6
% AD		33.3	33.3
NNT		3	3
Combined:			
No. pts	0	12	12
% AD		66.7	66.7
NNT		1.5	1.5
Between arm p value	Not significant	<0.001	<0.001
	QOL Score		
Detrusor:			
Mean ± SD (range)	4.17 ± 0.79 (3–6)	2.33 ± 0.69 (1–4)	2.22 ± 0.65 (1–4)
% AD		−44.12	−46.76
NNT		2.27	2.14
Combined:			
Mean ± SD (range)	4.28 ± 1.13 (3–6)	2.33 ± 0.49 (2–3)	2.22 ± 0.55 (1–3)
% AD		−45.56	−48.13
NNT		2.19	2.08
Between arm p value	0.77	0.43	0.44

* Within arm p <0.001.
† On 3-day bladder diary.
‡ Less than 1 incontinence episode per 24 hours.

incontinence episodes (mean 69% decrease, range 32% to 100%), MCC (mean 85% increase, range 11% to 303%) and $Pdet_{max}$ (mean 44% decrease, range 5% to 83%). A mean of 56.6% (range 30% to 87%) of patients with SCI-NDO became fully continent. QOL improved independent of the questionnaire used (mean 57%, range 35% to 78%). The mean duration of efficacy in single injection studies was 8 months (range 12 to 36 weeks).[5]

Since the trigone is rich in sensory fibers and its muscles are sensitive to minute pressure changes,[11] it likely has a role in initiating involuntary contractions, which then propagate throughout all bladder muscles. Based on this assumption trigonal denervation may help decrease such involuntary contractions. In the current study we prospectively investigated the short-term outcome measures of detrusor vs combined detrusor-trigone BTX-A injections for refractory neurogenic urinary incontinence due to NDO after SCI. An effort was made to ensure study population homogeneity. Thus, only adults with NDO due to SCI were recruited and those on in-

Table 2. *Urodynamic findings at baseline and 8 weeks after injection in 18 patients per arm off anticholinergics*

Parameter	Detrusor Arm		Combined Arm		p Value
	Mean ± SD (range)	% AD	Mean ± SD (range)	% AD	
RV (ml):					
Baseline	212.8 ± 51.2 (132–294)		205.1 ± 48.7 (139–288)		0.09
Wk 8	340.4 ± 46.1 (261–363)	60	374.2 ± 47.9 (259–446)	82.5	0.04
MCC (ml):					
Baseline	244.6 ± 57.4 (156–347)		228.4 ± 47.1 (152–305)		0.37
Wk 8	406.5 ± 55.4 (297–473)	66.2	384.6 ± 49.7 (273–458)	68.4	0.22
$Pdet_{max}$ (cm H_2O):					
Baseline	63.9 ± 11.2 (43–78)		60.2 ± 10 (40–77)		0.30
Wk 8	36.9 ± 5.1 (29–46)	−42.3	35.0 ± 3.6 (28–44)	−41.9	0.21

* Within arm p <0.001.

dwelling urethral catheters were converted to CIC before injection. Since many patients may concomitantly use anticholinergics with BTX-A injections, resulting in bias when evaluating the effect of the intervention, we limited our study to patients who strictly discontinued anticholinergics before and after injection. Thus, findings at 2 and 8-week followups were emphasized, at which times no patient had yet reinstituted anticholinergics.

Improvement was evident in all measured parameters on within group analysis in each arm vs baseline. Nevertheless, the superior efficacy of including rather than excluding the trigone in the injection protocol was obvious. On between group analysis the end points of incontinence, complete dryness and RV improved significantly in the combined arm vs the detrusor arm. The NNT for incontinence revealed the clinical efficacy of each injection protocol but favored the combined arm. Treating 1.87 patients with detrusor injections and treating 1.24 with the combined injection template decreased an extra incontinence episode after 2 weeks. Similarly the NNT for complete dryness at 2 weeks showed better efficacy of the combined arm vs the detrusor arm (1.5 vs 3 patients).

Improvements in incontinence and complete dryness were reflected as significant QOL improvements on within group analysis, although this did not translate into a statistically significant difference on between group analysis. Confounders, eg social or psychological factors, or nonacceptance of chronic disability, may have influenced QOL statistical analysis. While RV showed statistically significant difference favoring the combined arm, MCC and $Pdet_{max}$ showed nonsignificant differences between the 2 arms. The improved incontinence rate in each arm can be explained by the significant changes in RV, MCC and $Pdet_{max}$ on within group analysis. The significant change in RV on between group analysis probably increased this improvement in the combined arm. The need to reinstitute anticholinergic medications further indicated the superiority of including the trigone in the injection protocol since 50% of patients reinstituted anticholinergics in the detrusor arm compared to only 22.2% in the combined arm at week 18.

No patient reported systemic or significant AEs of treatment, or experienced new onset VUR or upgrading of preexisting VUR. In previous studies a single BTX-A injection in the trigone did not induce de novo VUR[6,16] or worsen preexisting VUR in patients with nonneurogenic overactive bladder.

In our patients the total injected dose (300 U) was equal in each arm. However, there is concern about the unequal allocated doses into the detrusor in each arm (300 vs 200 U), which may have had an unidentified impact on the outcome. This concern is probably offset by the previous findings of Schurch et al, who compared 300 and 200 U BTX-A intradetrusor injections for NDO and reported similar efficacy for the 2 doses.[17] An additional limitation of this study is the short-term followup without exploration of long-term outcomes or the potential need for reinjection. Given that BTX-A effects are brief and repeat injections are usually required after 6 to 9 months to sustain the clinical effect,[5,18–20] we are concerned about the consequences of re-injections in the trigone. While it seems that a single detrusor injection of BTX-A causes only minor trauma and does not produce fibrotic or permanent structural changes in the bladder wall,[21] long-term AEs of repeat injections and the potential for fibrosis remain to be elucidated. A large-scale, multicenter, long-term, double-blind, randomized, controlled trial addressing the potential flaw of unequal detrusor doses and concern about trigonal fibrosis is justified and may help eliminate any confounders influencing the power of statistical analysis.

CONCLUSIONS

Improvements in all measured parameters were evident in each arm compared to baseline. The superior efficacy of including rather than excluding the trigone was obvious, as shown by significantly improved incontinence, complete dryness and RV in the combined vs the detrusor arm. The long-term AEs of trigonal injection and the potential for trigononal fibrosis remain to be clarified.

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