



## Neuro-urology

# Botulinum Toxin A Detrusor Injections in Patients with Neurogenic Detrusor Overactivity Significantly Decrease the Incidence of Symptomatic Urinary Tract Infections

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### Article info

#### Article history:

Accepted August 20, 2007

Published online ahead of print on August 28, 2007

#### Keywords:

Botulinum toxin A  
 Neurogenic bladder  
 Neurourology  
 Urinary infection

### Abstract

**Objectives:** To study the effect of botulinum toxin A (BoNTA) injections into the detrusor muscle on the incidence of symptomatic urinary infections in patients with neurogenic detrusor overactivity.

**Methods:** Between February 2004 and June 2005, 30 patients (18 men, 12 women), mean age  $39.4 \pm 12.1$  yr, with neurogenic detrusor overactivity received an injection of 300 U Botox<sup>®</sup> (Allergan Inc., Irvine, CA, USA) into the detrusor. Fifteen patients had multiple sclerosis, 14 had spinal cord injury, and 1 had myelitis. Twenty-two patients had urinary incontinence. Patients were either resistant to anticholinergic medications, had discontinued treatment because of adverse effects, or had contraindications to anticholinergic drugs. Before and 6 wk after injection, each patient kept a bladder diary and underwent urodynamic investigation, retrograde and voiding cystourethrography, and urine culture. All symptomatic urinary infections (pyelonephritis, orchitis, prostatitis) occurring in the 6 mo before and the 6 mo after injection were recorded.

**Results:** Before injection, the mean number of symptomatic urinary infections over 6 mo was  $1.75 \pm 1.87$ . After injection, the mean was  $0.2 \pm 0.41$  ( $p = 0.003$ ), and only 3 patients presented symptomatic urinary infections. These patients were those who showed less improvement in their urodynamic parameters after injection (volume of the first uninhibited contraction, maximum bladder pressure, and maximum cystometric capacity, respectively;  $p = 0.0037$ ,  $p = 0.0002$ ,  $p = 0.0027$ , ANOVA).

**Conclusions:** BoNTA injections into the detrusor muscle significantly decreased the incidence of symptomatic urinary infections. This effect seems to be related to improvement in urodynamic parameters, reflecting improved reservoir capacity at low pressure.

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## 1. Introduction

Botulinum toxin injections into the detrusor muscle are an effective and safe treatment of neurogenic detrusor overactivity [1]. They are carried out after failure of cholinergic drugs, or intolerance or contraindications to these medications [2]. These injections reduce incontinence and improve the patients' quality of life [1,3–6].

Patients with neurogenic bladder and sphincter disorders have a high risk of symptomatic urinary infections [7–9], which can eventually lead to renal failure and bladder cancer [10]. These infections are a major cause of morbidity and are one of the main reasons for hospitalisation in patients with neurological disorders [8,11].

In patients with neurogenic lower urinary tract dysfunction, the risk of symptomatic urinary infections is increased by vesicoureteral reflux and high bladder pressure, and by the presence of an indwelling catheter [7,8]. Because vesicoureteral reflux is more likely when bladder pressure is high [12], when patients urinate by intermittent catheterisation, the main factor that increases the risk of symptomatic urinary infections is still detrusor overactivity.

The aim of this study was to assess the impact of botulinum toxin A (BoNTA) injections into the detrusor muscle on the incidence of symptomatic urinary infections in patients with neurogenic detrusor overactivity.

## 2. Methods

### 2.1. Population

Between February 2004 and June 2005, a prospective non-randomised study was carried out in 30 patients (18 men and 12 women), mean age  $39.4 \pm 12.1$  yr, with neurogenic detrusor overactivity and recurrent symptomatic urinary infections. Their neurological disorders are presented in Table 1. For the patients with multiple sclerosis, the disability was quantified with the use of the Expanded Disability Status Scale [13]. For the patients with spinal cord injury, the neurological and functional status was assessed according to the American Spinal Cord Injury Association classification [14]. The mean duration of the neurological disorder was  $13.3 \pm 19.1$  yr. All patients voided by clean intermittent self-catheterisation. They were either resistant to anticholinergic medications, had discontinued treatment because of adverse effects, or had contraindications to these treatments. Twenty-nine patients were treated with anticholinergics before inclusion. These patients continued the drugs during the study, and before and after BoNTA injections in all cases. No patient had urinary calculi or a bladder tumour, and no patient was receiving preventive treatment for urinary infections.

**Table 1 – Neurological disorders of patients treated with botulinum toxin A injections into the detrusor muscle**

	n
Multiple sclerosis	15
Median EDSS (range)	3.5 (1.5–5)
Spinal cord injury	14
ASIA A	11
ASIA C	2
ASIA D	1
Level $\geq$ T6	5
Level $<$ T6	9
Myelitis	1
ASIA A	1

EDSS, expanded disability status scale; ASIA, American Spinal Injury Association classification.

### 2.2. Preoperative evaluation

One month before inclusion, patients kept a bladder diary for 3 d, and underwent urine culture, urodynamic investigation (Medtronic Duet<sup>®</sup>, Minneapolis, MN, USA) according to the guidelines of the International Continence Society (ICS) [15,16], retrograde and voiding cystourethrography, renal ultrasound, and 24-h creatinine clearance.

For 6 mo, between inclusion and BoNTA injections, the patients kept a diary, recording each episode of symptomatic urinary infection, the results of urine culture, and the antibiotic treatment received and its duration. Urine cultures were interpreted according to Kass criteria (bacterial count in culture  $>10^5$  colony-forming units per millilitre and  $>10$  leucocytes per high-power field (magnification,  $\times 400$ ) [23]. Symptomatic urinary tract infection was defined by the association of bacteriological criteria and symptoms such as fever, intensification of spasticity, intensification of autonomic hyperreflexia, pain and worsening of the neurological status. Uncomplicated cystitis and asymptomatic cystitis were excluded. In case of suspicion of urinary tract infection, the patients were seen in our institution in all cases. A complete physical examination was performed by a physical medicine and rehabilitation physician or by a neurourologist in all cases.

### 2.3. Operative technique

Six months after inclusion, patients received BoNTA injections into the detrusor muscle. In all cases, this was the first injection of the toxin. Injections were always performed under rigid cystoscopy, under general anesthesia in 14 cases and local anesthesia in 16. They consisted of injection into the detrusor of 300 U of botulinum toxin A (Botox<sup>®</sup>, Allergan Inc., Irvine, CA, USA) in 30 different sites, sparing the bladder trigone. Ten units diluted in 1 ml of physiological saline were injected in each site. Cardiac and respiratory functions were systematically monitored. The patients left the hospital on the evening of the same day in 14 cases and the next day in 16 cases.

## 2.4. Postoperative evaluation

Patients had follow-up visits at 6 wk and 6 mo after BoNTA injection. Six weeks after the injection, the patients kept a 3-d urinary diary and underwent urine culture, urodynamic investigation according to ICS guidelines, retrograde and micturitional urethrocytography, and ultrasound examination of the kidneys and bladder.

For 6 mo after BoNTA injections into the detrusor, the patients kept a diary recording every symptomatic urinary infection, the results of urine culture, and the treatment received and its duration.

## 2.5. Statistical analysis

Statistical relationships between pre- and postoperative parameters were sought by the Yates corrected chi-square test for classes and Student *t* test for quantitative variables.

The respective effects of BoNTA injections and of urodynamic or clinical parameters on symptomatic urinary tract infections were tested with the use of two-way analysis of variance (ANOVA). When an interaction was observed between two factors, the effect of BoNTA injections was studied for each urodynamic and clinical parameter with the Student *t* test. A *p* value <0.05 was considered statistically significant.

## 3. Results

During the 6 mo before BoNTA injections into the detrusor, the mean number of symptomatic urinary infections was  $1.77 \pm 0.39$  per patient. All patients had at least one episode of symptomatic urinary infection. Infection was acute pyelonephritis in 28 cases (53%), prostatitis in 15 (28%), and orchitis in 10 cases (19%). The causal organisms are shown in Table 2.

In the 6 mo after the BoNTA injections, the mean number of symptomatic urinary infections decreased significantly ( $0.2 \pm 0.41$  per patient, *p* = 0.003). The incidence of postoperative bacteriuria was 43%. Only three patients had symptomatic urinary infections. Of these patients, two had spinal cord injury and one had multiple sclerosis. Infection was a pyelonephritis in one case, a prostatitis in one case, and an orchitis in one case. The causative organism was *Escherichia coli* in 66% and *Pseudomonas aeruginosa* in 34%. The causative organism was the same with the preoperative in one case. Of these three patients, a second BoNTA injection into the detrusor was performed in two cases and a bladder augmentation was performed in one case.

The results of pre- and postoperative clinical, urodynamic, and radiological evaluation, and the comparison between pre- and postoperative findings are presented in Table 3. The three patients with persistent infections after treatment had

**Table 2 – Causal organisms of symptomatic urinary infections in the 6 mo before detrusor botulinum toxin injections**

Organism	%
<i>Escherichia coli</i>	26
<i>Enterococcus faecalis</i>	15
<i>Staphylococcus aureus</i>	14
<i>Klebsiella pneumoniae</i>	13
<i>Pseudomonas aeruginosa</i>	12
<i>Proteus mirabilis</i>	11
<i>Staphylococcus epidermidis</i>	9

median volume at first desire to void of 118.9 ml (range, 48.4–263.5) before BoNTA injection and 220.0 ml (range, 81.1–520.8) after BoNTA injection; median maximum cystometric capacity of 253.1 ml (range, 266.0–72.1) before BoNTA injection and 225.0 ml (range, 164.5–243.5) after BoNTA injection; median volume of the first uninhibited contraction of 177.9 ml (range, 103.3–213.8) before BoNTA injection and 168.5 ml (range, 124.7–227.9) after BoNTA injection; and median maximum bladder pressure of 40.7 cm H<sub>2</sub>O (range, 30.8–49.4) before BoNTA injection and 31.2 cm H<sub>2</sub>O (range, 22.4–36.4) after BoNTA injection.

A relationship between the effect of BoNTA injections on urodynamic parameters and the occurrence of postoperative urinary infections was revealed by two-way ANOVA. The three patients who had postoperative symptomatic urinary infections were those in whom BoNTA injections had had the least effect on the increase in maximum cystometric capacity (*p* = 0.0027), the decrease in maximum bladder pressure (*p* = 0.0002), and the increase in volume of the first uninhibited contraction (*p* = 0.0037) (Table 4). No relationship was found between changes in the parameters of retrograde and voiding cystourethrography and renal ultrasound and the risk of development of postoperative urinary infections.

## 4. Discussion

Injections of BoNTA into the detrusor muscle are an effective treatment for neurogenic detrusor overactivity after failure of or resistance to anticholinergic drugs [1]. These injections reduce the incidence of incontinence due to neurogenic detrusor overactivity and improve patients' quality of life [3–5]. Reduced incontinence is due to decreased detrusor overactivity [2,17]. In our series, our results with regards to the decrease in episodes of incontinence and detrusor overactivity after BoNTA injection were identical to those previously reported [3,4,18].

**Table 3 – Clinical, urodynamic and radiological data before and after detrusor botulinum toxin injections**

	Preoperative	Postoperative	p
<b>Clinical parameters</b>			
Mean number of catheterizations/24 h	6.4 ± 1.9	5.0 ± 0.7	0.046
Mean functional bladder capacity (ml)	210.7 ± 59.4	408.3 ± 106.8	<0.0001
Incontinence between catheterizations			
Yes	22	2	<0.0001
No	8	28	
<b>Urodynamic parameters</b>			
Mean volume of first void (ml)	186.5 ± 120.9	304.5 ± 176.2	0.021
Mean maximum cystometric capacity (ml)	290.3 ± 150.7	442.1 ± 167.1	0.002
Mean volume at first uninhibited contraction (ml)	187.1 ± 98.6	180.2 ± 44.3	ns
Mean maximum bladder pressure (cm H <sub>2</sub> O)	53.5 ± 22.4	16.5 ± 3.2	<0.0001
Detrusor overactivity			
Yes	30	5	<0.0001
No	0	25	
Mean bladder compliance (ml/cm H <sub>2</sub> O)	45.4 ± 39.6	47.6 ± 43.7	ns
<b>Radiological parameters</b>			
Renal and bladder ultrasound			
Normal	27	28	ns
Urinary calculi	0	0	
Pyelocaliceal dilatation	2	1	
Signs of chronic pyelonephritis	1	1	
Retrograde and voiding cystourethrography			
Vesicoureteral reflux			
Yes	6	2	ns
No	24	28	
Bladder diverticulum			
Yes	4	4	ns
No	26	26	

ns, not significant.

Statistical relationships between pre- and postoperative parameters were sought by the Yates corrected chi-square test for classes and Student t test for quantitative parameters.

**Table 4 – Variation in urodynamic and radiological parameters according to the persistence or otherwise of urinary infections after BoNTA injections**

	Patients without infections after treatment (n = 27)		Patients with persistent infections after treatment (n = 3)		p
	Before injections	After injections	Before injections	After injections	
<b>Urodynamic parameters</b>					
Mean volume at first micturition (ml)	194.3 ± 126.2	315.5 ± 171.6	143.5 ± 109.6	274.0 ± 224.8	ns
Mean maximum cystometric capacity (ml)	298.7 ± 150.9	476.0 ± 120.2	197.0 ± 108.5	211.0 ± 41.3	0.0027
Mean volume of the first uninhibited contraction (ml)	153.1 ± 47.7	472.7 ± 152.8	165.0 ± 56.7	173.7 ± 51.8	0.0037
Mean maximum bladder pressure (cm H <sub>2</sub> O)	57.0 ± 22.2	12.1 ± 12.3	40.3 ± 9.3	30.0 ± 7.1	0.0002
<b>Radiological parameters</b>					
Renal and bladder ultrasound					
Normal	25	26	2	2	ns
Urinary calculi	0	0	0	0	
Pyelocaliceal dilatation	1	0	1	1	
Signs of chronic pyelonephritis	1	1	0	0	
Retrograde and voiding cystourethrography					
Vesicoureteral reflux					
Yes	6	2	0	0	
No	21	25	3	3	
Bladder diverticulum					
Yes	3	3	1	1	
No	24	24	2	2	

BoNTA, botulinum toxin A; ns, not significant.

On the other hand, as far as we are aware, this is the first demonstration that BoNTA injections in patients with neurological disorders decrease the incidence of symptomatic urinary infections. We also demonstrated that this decrease is related to the effect of the toxin on detrusor overactivity.

Urinary infections are the principal cause of morbidity in the neurological patient [8,10]. In addition, 50–80% of neurological patients who urinate by intermittent catheterisation have bacteriuria [7,19]. However, because such colonisation does not threaten the urinary apparatus in the long term and is not a risk factor of symptomatic urinary infections [20], it does not require treatment. On the other hand, symptomatic urinary infections (prostatitis, pyelonephritis, orchiepididymitis) threaten the urinary apparatus and the vital prognosis [10,21]. These infections must therefore be treated but preventive measures are also necessary to avoid their occurrence.

One of the principal difficulties in management of symptomatic urinary infections in the neurological patient is diagnosis. The symptoms are nonspecific and a variety of biological criteria have been proposed [20,22]. If symptomatic urinary infections were suspected in our patients, they were systematically examined by a physical medicine and rehabilitation physician or by a neurourologist to rule out any other cause of the symptoms. From a bacteriological viewpoint, in the absence of specific criteria for patients urinating by self-catheterisation, we used the criteria proposed by Kass [23]. The diagnosis of symptomatic urinary infection was established only if both clinical and bacteriological signs were present.

High bladder pressure is very likely to lead to damage to the upper urinary tract and the development of symptomatic urinary infections [7,24]. It promotes vesicoureteral reflux and ischaemic injury to the bladder walls, creating favourable conditions for infection [7,25]. It has been reported that these complications can be prevented by reducing bladder pressure, which can be achieved by anticholinergic drugs [26]. However, in up to 30% of cases, this treatment fails or is poorly tolerated [27,28]. Now when urine leaks or urgency persists, botulinum toxin injections into the detrusor muscle are usually performed [29]. In this study, we have shown that BoNTA injections in these indications reduce the incidence of symptomatic urinary infections by treating detrusor overactivity. If complications, particularly symptomatic urinary infections, persist despite well-conducted anticholinergic treatment and other predisposing factors such as urinary stones or a bladder tumour are absent, the success

of this treatment emphasises the need to perform urodynamic tests to determine if persistent high bladder pressure is present. If high bladder pressure is determined, BoNTA injections into the detrusor can be performed. Moreover, if the injections are efficacious, they could be repeated in patients experiencing recurrent urinary tract infections.

Apart from the effect of botulinum toxin on detrusor overactivity and its impact on the risk of development of symptomatic urinary infections, we cannot rule out other pathophysiological mechanisms such as an anti-inflammatory effect or prevention of bacterial adherence to the bladder wall. Cui [30] reported that botulinum toxin had an antioedematous effect in a rat model of inflammatory pain [30]. However, it has not been observed in human models of inflammatory pain [31], nor has it ever been studied in the bladder.

## 5. Conclusion

In patients with recurrent symptomatic urinary infections and persistent neurogenic detrusor overactivity despite anticholinergic treatment, injections of BoNTA into the detrusor muscle decrease the incidence of these infections. The effect seems to be related to the therapeutic action of the toxin on detrusor overactivity.

## Conflicts of interest

The authors have nothing to disclose.

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**Editorial Comment on: Botulinum Toxin A Detrusor Injections in Patients with Neurogenic Detrusor Overactivity Significantly Decrease the Incidence of Symptomatic Urinary Tract Infections**

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Intradetrusor injection of botulinum toxins is a standard treatment for patients with neurogenic

detrusor overactivity and lower urinary tract symptoms (LUTS) where anticholinergic drugs are not sufficiently effective or poorly tolerated. Specifically, botulinum toxins are able to reduce the daily urinary incontinence episodes, reduce maximal voiding detrusor pressure, and increase both maximal cystometric capacity and bladder compliance, allowing a reduction in the dose or discontinuance of antimuscarinic treatment and a substantial improvement in the patient's quality of life [1,2].

Gamé et al reported on a small series of patients with neurogenic LUTS undergoing their first

botulinum toxin A (BoNTA) injection. Specifically, the patients were evaluated in a very complete way, including urodynamic studies before and after the injections, ultrasound scanning, retrograde and voiding cystourethrography, and urine culture. Finally, the authors were able to prove that BoNTA injections significantly reduced the occurrence of urinary tract infections (UTIs), with patients developing UTI after the BoNTA treatments being the same where BoNTA was less effective, according to the urodynamic data [3].

The study was well performed and well reported but it includes only 30 patients. The findings on UTI were quite original, but the number of events was very limited and this experience can be considered as a pilot one. Moreover, no data were provided on the symptoms of such patients to allow a clearer comprehension and it was not shown that repeated BoNTA injections were effective in the prevention of further infections in patients failing to respond to the first treatment.

Could the persistence of UTI after BoNTA injection be an indication for retreatment? The

prospect is interesting, but the data shown in the present study are not sufficient to provide a new standard clinical indication for a repeated BoNTA injection.

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DOI: [10.1016/j.eururo.2007.08.040](https://doi.org/10.1016/j.eururo.2007.08.040)

DOI of original article: [10.1016/j.eururo.2007.08.039](https://doi.org/10.1016/j.eururo.2007.08.039)