



## Neuro-urology

# Do Repeat Intradetrusor Botulinum Toxin Type A Injections Yield Valuable Results? Clinical and Urodynamic Results after Five Injections in Patients with Neurogenic Detrusor Overactivity

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### Abstract

**Objectives:** To study repeat intradetrusor botulinum toxin injections for the treatment of neurogenic detrusor overactivity in terms of safety and improvement of continence status and urodynamic parameters.

**Material and methods:** This study was based on 20 consecutive patients (13 males, 7 females; median age, 41.1 yr) who received at least five intradetrusor injections of botulinum toxin and who were followed by clinical and urodynamic evaluation after at least four injections. The results of 100 injections and corresponding follow-ups were analyzed and compared with baseline.

**Results:** No toxin-related side effects were observed after the first or repeat injections. All patients had a baseline urodynamic study and at least four urodynamic studies after botulinum toxin injections. Clinical continence improved significantly after the first injection and then remained constant after repeat injections. The median reflex volume increased significantly from a median of 200 ml at baseline to values between 440 and 500 ml at follow-up studies. The presence of neurogenic detrusor overactivity decreased significantly by 60–75%. Maximum cystometric capacity increased significantly 2.3-fold. Maximum detrusor pressure during cystometry decreased significantly 5.8-fold from a median of 70 cm H<sub>2</sub>O to values of about 20 cm H<sub>2</sub>O. Median compliance at baseline (60 ml/cm H<sub>2</sub>O) did not change significantly. **Conclusion:** Repeat intradetrusor botulinum toxin A injections are a safe and valuable treatment option for neurogenic detrusor overactivity over a period of several years. The beneficial effect of the toxin on clinical and urodynamic parameters remains constant after repeat injections.

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## 1. Introduction

Intradetrusor injections of botulinum toxin type A were introduced in 2000 as a minimally invasive treatment option for neurogenic detrusor overactivity positioned between ineffective or poorly tolerated oral anticholinergic treatment and invasive surgery [1]. A single dose of 300 units of Botox<sup>®</sup> (Allergan Inc., USA) botulinum toxin type A injected into the detrusor smooth muscle results in effective and sustained inhibition of the overactive neurogenic detrusor, as confirmed by a recent randomized placebo-controlled study [2].

More recently, the effects of the treatment on quality of life were proven in both neurogenic and nonneurogenic detrusor overactivity [3], and a cost consequence analysis confirmed cost-effectiveness of the treatment in neurogenic and nonneurogenic patients [4]. The efficacy of a single toxin injection decreases with time, and usually after 6–9 mo, a reinjection is necessary to sustain the clinical effect [1,5,6]. Most reports in the literature on botulinum toxin therapy for neurogenic bladders are based on the results of a single injection [7]. Because most patients might require retreatment, the efficacy and safety of multiple injections need to be addressed. However, those data are not clearly evaluated in the available clinical studies.

This study was based on a series of 20 consecutive patients who received at least five intradetrusor injections, and who were followed by clinical and urodynamic evaluation after at least four injections. The medium-term safety and efficacy of repeat injections, defined as improvement of continence and urodynamic parameters, were evaluated.

## 2. Methods

### 2.1. Botulinum toxin injections

Approval of the study was obtained from the local ethics committee. The experimental nature of the treatment was explained to the patients before the first injection and before each repeated injection; all patients signed a written informed consent. All patients received 300 units of botulinum toxin type A (Botox) at each injection sequence, injected endoscopically into the detrusor muscle at 30 sites (10 units/ml per site, sparing the trigone) according to the original technique described in 2000 [1]. Injections were performed under local anesthesia by three physicians (E.C.K., P.D., A.R.) with the use of a disposable 7F injection needle and a 22F rigid cystoscope. Before each injection, patients were informed about the potential side effects of the toxin and were instructed to pay attention to general weakness, diplopia, blurred vision, dysarthria, or dysphagia. Patients were systematically questioned about the development of these symptoms at the

follow-up urodynamic examination. Repeat injections were scheduled according to a preassigned 7-mo reinjection protocol. This approach was based on the clinical observation that, usually at 7 mo, the efficacy starts to decrease, and soon after detrusor overactivity, symptoms, and incontinence reappear. The aim of this protocol was to ensure a continuous effect of the toxin and to avoid reappearing incontinence episodes.

### 2.2. Baseline and follow-up visits

At baseline and follow-up visits, patients were asked whether they had experienced any urinary incontinence during the previous 4 wk. Results were recorded as continent or not continent. Concomitant anticholinergic medications and their dose were also recorded. All urodynamic studies were performed in the same institution with the use of the same technique and equipment (Medtronic Duet system, Medtronic Inc., USA). Results were evaluated by two physicians (P.D., E.C.K.). Urodynamic studies at baseline and after toxin injections were performed according to “Good Urodynamic Practice” recommended by the International Continence Society [8] by using body warm saline solution and a filling rate of 50 ml/min and a 500-ml filling limit during cystometry. Maximum cystometric bladder capacity, reflex volume (filling volume at the beginning of first bladder contraction), maximum detrusor pressure during cystometry and compliance were defined as urodynamic outcome criteria.

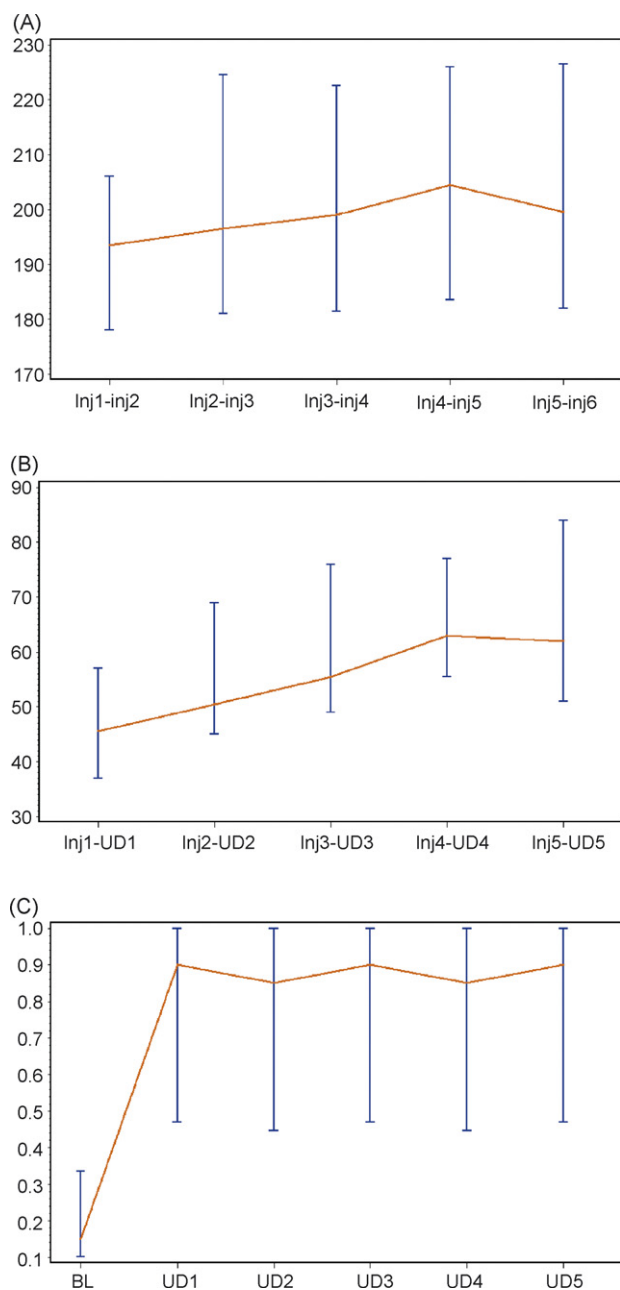
### 2.3. Data analysis

When no contraction was observed, reflex volumes were recorded as the values for bladder capacity. For compliance, infinite values were replaced by the arbitrary value of 100 ml/cm H<sub>2</sub>O for convenience of plotting. Follow-up measurements were compared by nonparametric analysis of variance by using ranks associated with individual measurements for each patient (Conover F approximation of the Friedman test) [9,10], with a limit of significance of 5%. If a test was significant, detailed study of follow-up times was performed by pairwise comparison of corresponding least square mean values, with significance corrected by means of the Bonferroni adjustment. The 95% confidence intervals for the percent of overactive patients were calculated according to Fleiss [11]. All computations were performed with the SAS/STAT module, version 8.2 (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1. Patients

Twenty consecutive patients (13 males, 7 females; sex ratio, 65% vs. 35%; median age at time of the first injection, 41.1 yr [interquartile range, 22.2–67.5]) who had received at least five intradetrusor botulinum toxin injections for the treatment of neurogenic detrusor overactivity in our institution were included in this study. Sixteen patients had



**Fig. 1 – (A) Interinjection intervals (in days; median and interquartile interval). (B) Intervals between injection and urodynamic studies (in days; median and interquartile interval). (C) Continence percent with 95% confidence interval.**

traumatic spinal cord injury (15 paraplegics, 1 tetraplegic), 2 patients had nontraumatic spinal cord injury, and 2 had multiple sclerosis. At the time of inclusion, the mean history of the lesion or first diagnosis of multiple sclerosis was 11 yr (interquartile range, 5–23). All 20 patients had neurogenic detrusor overactivity, and 17 of 20 (85%) suffered from urinary incontinence. All patients performed intermittent self-catheterization for bladder man-

agement. At baseline 19 of 20 patients were on anticholinergics. One patient had a severe incompatibility with anticholinergics and was therefore not treated. Irrespective of small changes in dose, all patients on anticholinergics continued this medication after the injections.

**3.2. Botulinum toxin injections and interinjection intervals**

The results of 100 injections were analyzed. No toxin-related side effects were observed after the first and repeat injections. The interinjection intervals did not vary significantly, but tended to increase (Fig. 1A). The interval between injections and the corresponding urodynamic study tended to increase after the first and second injection; this increase became significant after the third injection ( $p < 0.0397$ ), the fourth injection ( $p < 0.0011$ ), and the fifth injection ( $p < 0.0014$ ). For details see Fig. 1B.

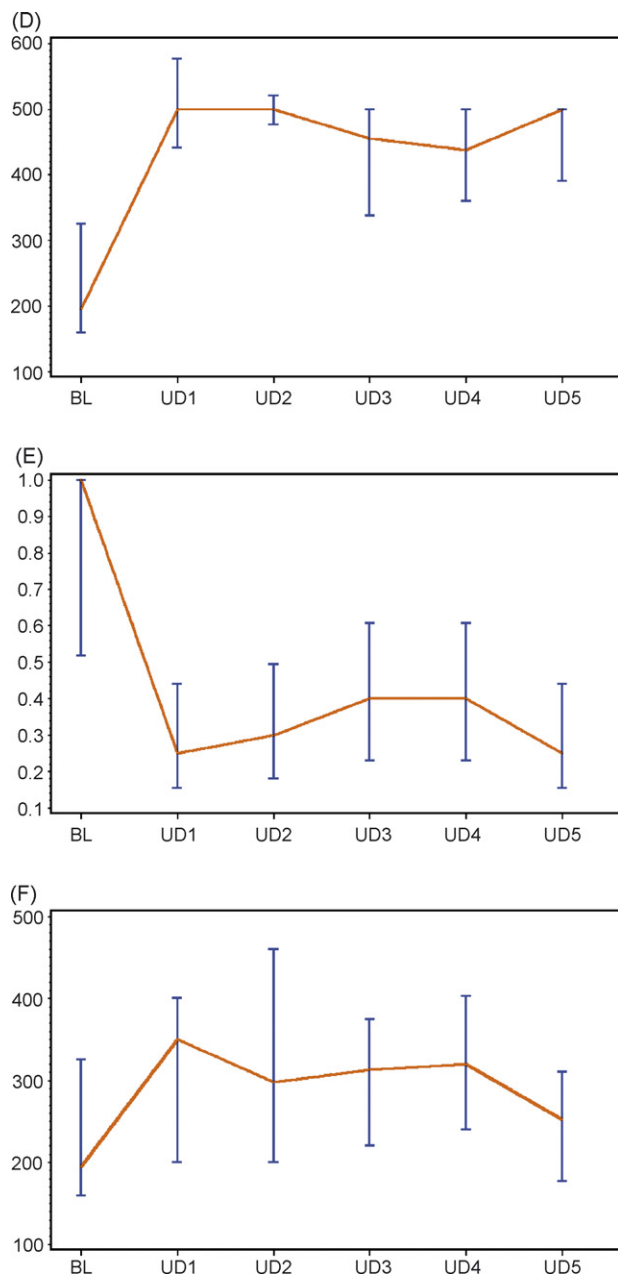
**3.3. Clinical and urodynamic results**

A total of 104 urodynamic studies were performed. All patients had a baseline urodynamic study followed by five consecutive injection plus urodynamic study sequences. In some instances urodynamic studies were missing, but on the whole for each patient at least four of the five post-baseline studies were done. Clinical continence improved significantly after the first injection (Fig. 1C) and then remained constant after repeat injections (Table 1). The median reflex volume increased from a median of 200 ml at baseline to values between 440 and 500 ml at follow-up (Fig. 2D). The presence of neurogenic detrusor overactivity (percentage of patients with uninhibited detrusor contractions) decreased dramatically by 60–75% (Fig. 2E). When patients with persistent detrusor overactivity were

**Table 1 – Time intervals between consecutive injections, and between injections and urodynamic studies**

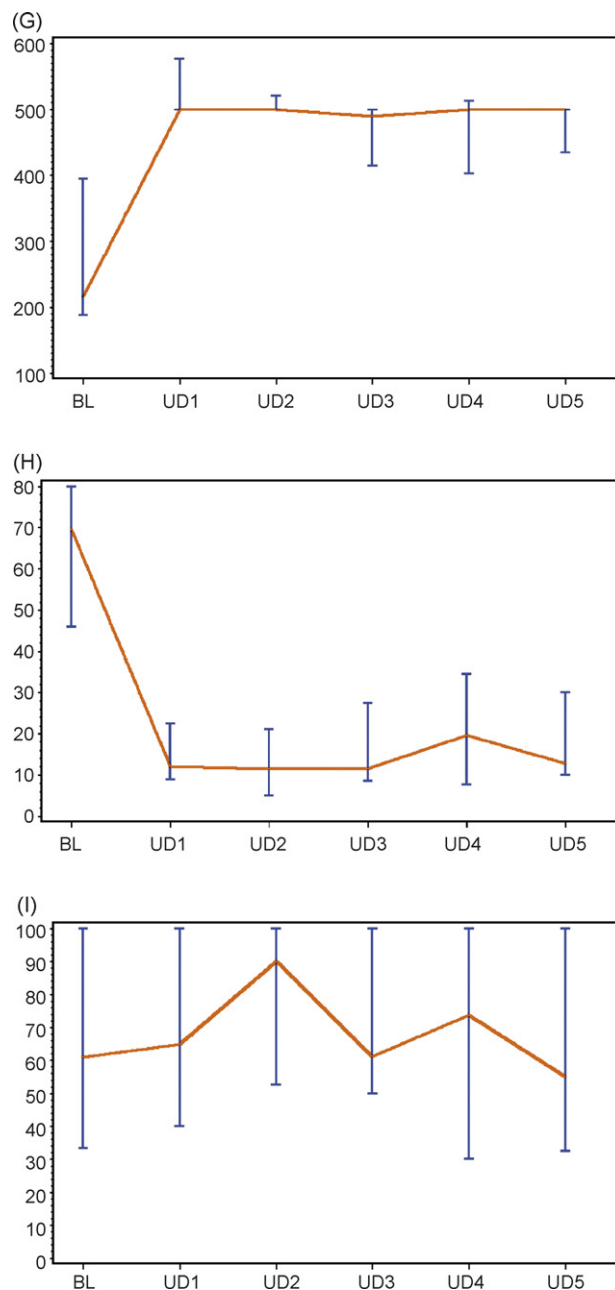
Type of interval	Interval no.	Duration (d) <sup>a</sup>
Between injections	Inj1–inj2	193.5 [178–206]
	Inj2–inj3	196.5 [181–224.5]
	Inj3–inj4	199 [181.5–222.5]
	Inj4–inj5	204.5 [183.5–226]
	Inj5–inj6	199.5 [182–226.5]
Between injections and corresponding UDs	Inj1–UD1	45.5 [37–57]
	Inj2–UD2	50.5 [45–69]
	Inj3–UD3	55.5 [49–76]
	Inj4–UD4	63 [55.5–77]
	Inj5–UD5	62 [51–84]

Inj, injection; UD, urodynamic evaluation.  
<sup>a</sup> Median and interquartile interval.



**Fig. 2 - (D) Reflex volume in all patients (in milliliters; median and interquartile interval). (E) Overactivity percent with 95% confidence interval. (F) Reflex volume in patients with persisting overactivity after injection (in milliliters; median and interquartile interval).**

analyzed separately, the increase in reflex volume was still present but less impressive (Fig. 2F). Maximum cystometric capacity increased significantly 2.3-fold (Fig. 3G), but this increase was limited by the filling limit during cystometry of 500 ml. Maximum detrusor pressure during cystometry decreased 5.8-fold (Fig. 3H) from a median of 70 cm H<sub>2</sub>O at baseline to values of about 20 cm H<sub>2</sub>O at follow-up studies. Median compliance at



**Fig. 3 - (G) Maximum cystometric bladder capacity (in milliliters; median and interquartile interval). (H) Maximum detrusor pressure (in cm H<sub>2</sub>O; median and interquartile interval). (I) Detrusor compliance (in ml/cm H<sub>2</sub>O; median and interquartile interval).**

baseline (60 ml/cm H<sub>2</sub>O) did not change significantly in follow-up studies (Fig. 3I).

#### 4. Discussion

Our results in 20 patients with neurogenic detrusor overactivity contribute to the rising amount of data to show that repeat intradetrusor injections of

**Table 2 – Evaluation results at baseline and at each urodynamic study**

Evaluation no.	Continence percent <sup>a</sup>	Reflex volume in all patients (ml) <sup>b</sup>	Overactivity percent <sup>a</sup>	Reflex volume in patients with persisting overactivity after injection (ml) <sup>b</sup>	Maximum cystometric bladder capacity (ml) <sup>b</sup>	Maximum detrusor pressure (cm H <sub>2</sub> O) <sup>b</sup>	Detrusor compliance (ml/cm H <sub>2</sub> O) <sup>b</sup>
BL	0.15 [0.10–0.34]	195 [159.5–325]	1 [0.52–1]	195 [159.5–325]	216.5 [187.5–395]	69.5 [46–80]	61 [33.5–100]
UD1	0.90 [0.47–1]	500 [441–576.5]	0.25 [0.15–0.44]	350 [200–400]	500 [500–576.5]	12 [9–22.5]	65 [40–100]
UD2	0.85 [0.45–1]	500 [476.5–520]	0.30 [0.18–0.49]	298 [200–460]	500 [500–520]	11.5 [5–21]	90 [52.5–100]
UD3	0.90 [0.47–1]	455 [337.5–500]	0.40 [0.23–0.61]	312.5 [220–375]	490 [415–500]	11.5 [8.5–27.5]	61.25 [50–100]
UD4	0.85 [0.45–1]	437.5 [360–500]	0.40 [0.23–0.61]	320 [240–402.5]	500 [402.5–512.5]	19.75 [7.75–34.5]	73.75 [30–100]
UD5	0.90 [0.47–1]	500 [390–500]	0.25 [0.15–0.44]	252.5 [177–310]	500 [435–500]	12.75 [10–30]	55 [32.5–100]

BL, baseline urodynamic evaluation; UD1 to UD5, evaluation following injection number 1 to urodynamic evaluation following injection number 5.

<sup>a</sup> Value with 95% confidence interval.

<sup>b</sup> Median and interquartile interval.

**Table 3 – Pairwise comparison of evaluations of five urodynamic parameters investigated**

	UD1	UD2	UD3	UD4	UD5
<b>Clinical continence</b>					
BL	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
UD1		0.5586	1	0.5586	1
UD2			0.5586	1	0.5586
UD3				0.5586	1
UD4					0.5586
<b>Presence of detrusor overactivity</b>					
BL	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
UD1		1	1	1	1
UD2			1	1	1
UD3				1	1
UD4					1
<b>Reflex volume</b>					
BL	<0.0001	<0.0001	0.0012	0.0068	0.0026
UD1		1	0.0286	0.0056	0.0141
UD2			0.7548	0.2246	0.4505
UD3				1	1
UD4					1
<b>Maximum cystometric bladder capacity</b>					
BL	<0.0001	<0.0001	0.0113	0.0518	0.0518
UD1		1	0.0227	0.0046	0.0046
UD2			1	0.3519	0.3519
UD3				1	1
UD4					1
<b>Maximum detrusor pressure</b>					
BL	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
UD1		1	1	1	1
UD2			1	0.3796	0.3796
UD3				1	1
UD4					1

UD1 to UD5, evaluation following injection number 1 to urodynamic evaluation following injection number 5; BL, baseline urodynamic evaluation.

For each of the five clinical parameters described, values at a given time (eg, UD3, vertical display) were compared with every preceding value (eg, BL, UD1, and UD2, horizontal display). Significances at the 5% level of the Friedman test after Bonferroni correction are given.

botulinum toxin A might be as safe and efficient as the first injection. In our study, at 4–8 wk after each injection when the maximum effect of the treatment was expected, urodynamic parameters like reflex volume, voiding pressure, and maximum cystometric bladder capacity as well as urinary incontinence improved significantly after the first injection, and this improvement sustained after every reinjection (Tables 2 and 3).

Published studies present a number of limitations because they report results from mixed populations (Botox<sup>®</sup> and Dysport<sup>®</sup> from Ipsen Limited, UK) [6], which are based on small groups without statistical analysis [12], or present a wide range of numbers of injection per patient [6,12,13]. Grosse et al [6] studied the effect of 2–7 repeat botulinum toxin injections to treat neurogenic detrusor overactivity due to acquired spinal cord lesions in adults. A sustained clinical improvement was observed at all follow-up studies. Persistent urodynamic improvement as well as absence of change in detrusor compliance were also documented, but only after 2 repeat injections. No increase in drug tolerance was observed after multiple treatments. More recently, in a pediatric population, Schulte-Baukloh et al [12] reported the outcome of repeat botulinum toxin injections in children with neurogenic detrusor overactivity who had received at least 3 injections. Although this study did not comprise any statistical analysis, there was no evidence for drug tolerance, or decreasing or lack of efficacy as measured by reflex volume, maximal detrusor pressure, maximum cystometric bladder capacity, and bladder compliance. Recently, Karsenty et al [13] studied a total number of 91 injections in 17 patients with neurogenic detrusor overactivity treated by three or more injections [13]. The mean number of injections

per patient was 5.4 (range, 3–9), and the first and last reinjections were compared with baseline. Maximum cystometric bladder capacity and reflex volume increased significantly after the first and last reinjection compared with baseline. Maximum detrusor pressure decreased significantly after the first and last reinjection compared with baseline. No change in compliance was noted.

When used for therapeutic purposes, the beneficial effect of a botulinum toxin injection usually lasts for several weeks or months; a repeat injection is then necessary to maintain the effect. In studies of botulinum toxin treatment for blepharospasm, the toxin effect generally lasted 2–4 mo [14], and a similar duration of efficacy was observed after toxin injection into the striated external urethral sphincter for treatment of detrusor sphincter dyssynergia [15,16]. However, when injected into a smooth muscle, the effect of a single toxin injection lasted considerably longer. For the treatment of achalasia, Martinek et al [17] observed a symptom-free period of 11.5 mo after the first injection, and 10.5 mo after the second injection. When injected into the detrusor smooth muscle, the effect of botulinum toxin usually lasts 6–9 mo [2,5,6]. The reason for the prolonged efficacy in smooth muscle is unknown, but the lack of axonal sprouting observed in detrusor biopsies after toxin injection [18] and the decreased density of P2X3-immunoreactive and TRPV1-immunoreactive fibers after botulinum toxin injection have been recently discussed [19]. Recently, the knowledge about the mechanism of action of intradetrusor botulinum toxin application was considerably extended by Apostolidis and coworkers [20]. They proposed that the primary effect of the toxin rely not only on the inhibition of release of acetylcholine but also on the inhibition of adenosine triphosphate and substance P, and on reduction in the axonal expression of the capsaicin and purinergic receptors. The authors concluded that the summation of afferent and efferent effects might be responsible for the effective and long-lasting detrusor inhibition caused by the toxin.

The results of repeated botulinum toxin injections into striated muscle have been extensively analyzed, revealing constant efficacy even after 10 or more injections. Furthermore, repeat injections do not appear to cause muscle atrophy or any other degenerative changes in striated muscle [21]. However, as botulinum toxin injections into the detrusor are increasingly used more frequently in clinical practice for the treatment of neurogenic detrusor overactivity, the constant efficacy after repeated injections must be confirmed. A urodynamic study was available after 84% of injections in

our population, reflecting very close monitoring of the effect of each injection. Only the Botox brand with a dose strength of 300 units was used, and three experienced surgeons performed the procedure using a well-defined and constant preparation, dilution, and injection protocol. All urodynamic studies were validated by two different urologists. This study therefore confirms the results of previous studies on repeat injections. Eight years after introduction of the technique, there is now a growing body of evidence that intradetrusor injections of botulinum toxin A are effective and safe even after multiple injections. Concerning the duration of action, we clearly want to point out that our data can neither assess the duration of the effect of a single injection nor of repeat ones.

Important limitations of this study like the small number of patients enrolled, the lack of clinical data on patient symptoms, and lack of the use of validated questionnaires need to be considered. Furthermore, it should be noted that we report on a group of patients who responded well to treatment. The clinical experience shows that, although rare, primary and secondary nonresponder to the toxin exist. There is a need for further research using validated instruments to measure especially the clinical benefit of repeat injections, and to consider the duration of the effect and the question of primary and secondary resistance to the toxin.

## 5. Conclusion

This study shows that repeat intradetrusor injections of botulinum toxin A are a safe and valuable treatment option for neurogenic detrusor overactivity over a period of several years. The effect of botulinum toxin therapy on clinical and urodynamic parameters remained constant after repeat injections.

## Conflicts of interest

André Reitz, Christophe Fermanian, and Eva Comperat have no disclosures. Pierre Denys, Brigitte Schurch, and Emmanuel Chartier-Kastler are consultants for Allergan Inc.

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