

Sustained Clinical Efficacy after Repeat Intradetrusor Botulinum Toxin Type A in the Treatment of Neurogenic Detrusor Overactivity

Dear Editor,

Despite the introduction of more potent and uroselective antimuscarinic agents, many patients with neurogenic detrusor overactivity still suffer from refractory incontinence. Intradetrusor botulinum toxin injections had been shown to be safe and effective in treating such patients who had failed medical therapy.¹ In a systemic review of the use of botulinum toxin in these patients, the duration of effect of the first injection was variable, ranging from 24 to 36 weeks.² Recent literature had thus begun to study the efficacy of repeat injections. We report our experience of repeat intradetrusor botulinum injections in the treatment of neurogenic detrusor overactivity and its clinical efficacy.

Patients with neurogenic detrusor overactivity who had received repeat intradetrusor botulinum injections at Tan Tock Seng Hospital in the period from May 2004 to January 2009 were recruited. All of them were doing intermittent self-catheterisation. Repeat injection was offered when there was an increase in incontinent episodes, an increase in catheterisation frequency or at the patient's request. All patients had undergone video urodynamic evaluation and completed a 3-day voiding diary before the first injection. All patients received 300 units of botulinum toxin type A (Botox, Allergan) injected into the detrusor muscle cystoscopically at 30 random sites (10 units/mL/site), sparing the trigone.

Urodynamic outcomes reported included maximum cystometric capacity, reflex volume at first involuntary contraction, maximal rise in detrusor pressure during involuntary contraction and compliance. When no involuntary contraction was observed, the bladder volume and detrusor pressure at cystometric capacity were recorded as reflex volume and maximum detrusor pressure, respectively, for the purpose of data analysis. Clinical outcomes were obtained from 3-day voiding diaries 6 weeks after each injection. Continence rate, use of antimuscarinic medication, number of incontinent episodes per day, frequency of catheterisations per day and maximum catheterised volume were reported.

Measurements after the first injection and repeat injection were compared against baseline values. Continence and use of antimuscarinic medication were compared using McNemar's test for matched data. All other continuous variables were compared against baseline values using the nonparametric test, specifically the Wilcoxon signed rank test. All statistical analysis were performed using STATA

V10.2 (Stata Corp, College Station, Tx, USA), and level of significance was set at 5%.

Ten patients, with a median age of 58 years, received a total of 14 repeat intradetrusor Botox injections during the study period (Table 1a). Median time from injury to first injection was 5 years. The median interinjection interval between the first and second injections was 19 months. This did not differ significantly with that between the second and third injections of 13 months. There was no adverse side-effect after the first or repeat injections of botulinum toxin.

Baseline urodynamic studies showed that all 10 patients had involuntary detrusor contractions; accompanying leakages were documented in 8 of them. Six weeks after the first injection, 7 consented to post-injection urodynamic evaluation. There were significant improvements in the rise in detrusor pressure, reflex volume and cystometric capacity. There was no change in bladder compliance (Table 1b).

All 10 patients were incontinent at baseline with leakage experienced in between catheterisations. All were on antimuscarinic medication at baseline; 7 were taking tolterodine and 3 were taking oxybutinin. Clinical outcomes after the first injection and after repeat injections were compared against baseline. Continence after 1 injection improved significantly to 88%; this was sustained at 91% after repeat injections. Use of medication after 1 injection decreased significantly to 40%, and was sustained at 25% after repeat injections. The number of incontinent episodes

Table 1a. Profile of 10 Patients who Underwent Repeat Intradetrusor Botulinum Injection (Interquartile Range in Parentheses)

Age (y)	58 (41-64)
Sex	
Male	7
Female	3
Number of first injection	10
Number of second injection	10
Number of third injection	4
Aetiology	
Trauma	7
Cervical myelopathy	2
Lupus myelitis	1
Injury to first injection (y)	5 (4-10)
Interinjection interval (mo)	
Injection 1 to injection 2	19 (11-26)
Injection 2 to injection 3	13 (11-25)

Table 1b. Clinical and Urodynamic Outcomes after Intradetrusor Botulinum Injection

	Base- line	First injection	P value (vs base- line)	Repeat injection	P value (vs base- line)
Clinical outcomes	n = 10	n = 10		n = 14	
Continence (%)	0	88	<0.05	91	<0.05
Use of medication (%)	100	40	<0.05	25	<0.05
Incontinent episodes/day	2.5	0	<0.05	0	<0.05
Catheterised volume (mL)	300	400	<0.05	450	<0.05
Number of catheterisation/ day	5.5	5	0.34	5.25	0.34
Urodynamic outcomes	n = 10	n = 7			
Involuntary contraction	100%	43%	<0.05		
Max rise in Pdet (cm water)	61	10	<0.05		
Reflex volume (mL)	143	345	<0.05		
Cystometric capacity (mL)	281	360	<0.05		
Compliance (mL/cm water)	41	51	0.50		

per day at baseline was 2.5; this improved significantly to zero after 1 injection and was sustained after repeat injections. The maximum catheterised volume at baseline was 300 mL; it improved significantly to 400 mL after 1 injection and was sustained at 450 mL after repeat injections. There was no improvement over baseline in the frequency of catheterisation after 1 injection or repeat injections.

We previously reported that intradetrusor botulinum toxin is efficacious for refractory neurogenic detrusor overactivity after 1 injection.³ The current study demonstrated that repeat injection is also efficacious and similar effects can be sustained. The sustained urodynamic efficacy of repeat injections had been demonstrated by previous groups.^{4,5} In our study, we shift the focus to the clinical efficacy of repeat injections. Sustained improvement was noted in the continence rate, usage of medication, maximum catheterised volume and leak episodes after repeat botulinum toxin injections. However, there was no decrease in the frequency of catheterisation despite an increase in bladder

capacity from a median of 300 to 450 mL. One possible explanation is that each patient had worked out a daily schedule incorporating a fixed time for catheterisation and found it difficult to change the schedule to take advantage of the increased bladder capacity. This was confirmed on subsequent interviews with the patients.

Unlike patients in North America, Europe or the United Kingdom, where healthcare is state-funded or insurance-based, our patients had opted for repeat injections voluntarily with no financial reimbursement, having to pay out-of-pocket for the procedure. Their decision to undergo repeat injections was based solely on their favourable clinical experience after their first injection. Our results, therefore, reflected the true clinical value of repeat injections as perceived by the patients.

Previously reported interinjection intervals, based on protocol-driven studies, ranged from 7 to 19 months.^{4,5} The interinjection interval in our study was significantly longer at 13 to 19 months. Our patients had opted for repeat injections when they experienced worsening clinical outcomes such as recurrent leakage or when they had to restart their antimuscarinic medication. This demonstrated that the interinjection interval may be longer than the oft quoted duration of about 9 months, especially when the patients themselves make the decision. This option of reinjection timing is a reasonable policy in the absence of clear literature data on the most appropriate reinjection interval.² We have since changed our practice to allow patients to indicate when they wish to have reinjection.

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