Botulinum Toxin A for Idiopathic Detrusor Overactivity

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Abstract

Introduction: This prospective study aims to evaluate botulinum toxin type A (BTX-A, Botox®) as a treatment for idiopathic detrusor overactivity (IDO) for patients with symptoms of overactive bladder (OAB). Materials and Methods: Nineteen patients with IDO were treated with intradetrusal injection of 200 units of BTX-A under cystoscopic guidance. There were 10 males and 9 females, with a mean age of 60 years (range, 38 to 87). Subjective responses were measured using the International Prostate Symptom Score and quality of life (QOL) score, as well as incontinent episodes, functional capacity and voiding intervals obtained from the voiding diary. They were recorded prior to, and at 6 weeks, 3, 6 and 9 months after BTX-A injections. Urodynamic studies were performed between 6 weeks to 3 months post-treatment. Results: There was statistically significant improvement in subjective parameters at 3 months post-treatment involving QOL (P = 0.002), incontinence episodes (P = 0.004), functional capacity (P = 0.01) and voiding interval (P <0.001). Reflex volume was significantly increased (P = 0.003), and maximal detrusal pressure (P = 0.001) as well as leak volume (P = 0.013) were significantly decreased during follow-up. Results of a gender-based subgroup analysis reveal that BTX-A may be more efficacious in females. Observed side effects included a patient who needed to perform CISC for about 3 months, a patient who had gross haematuria needed bladder washout and 3 patients who required treatments for urinary tract infection. Conclusion: Overall BTX-A, which is well received by most patients, has become a very important part of the armamentarium for the treatment of IDO.

Ann Acad Med Singapore 2010;39:714-718

Key words: Botox®, Idiopathic detrusor overactivity, Overactive bladder, Urodynamics

Introduction

Overactive bladder (OAB) is characterised by feelings of urgency to urinate, with or without incontinence and is usually accompanied by frequency and nocturia.[1] These symptoms are due to involuntary contractions of the detrusor muscle. Idiopathic detrusor overactivity (IDO) exists when there is no defined cause. Patients with IDO are usually treated with anticholinergic agents to reduce the bladder contractions. However, their efficacy is limited by systemic side effects such as dry mouth, dizziness, or constipation which result in poor compliance to therapy.[2]

Botulinum Toxin type A (BTX-A, Botox®) has been used in the field of Urology for the treatment of voiding dysfunction of different aetiologies. It was first used in the treatment of spinal-injured patients with detrusor-sphincter dyssynergia.[3] It has also been used as chemical sphincterotomy for voiding dysfunction.[4,5] To date, the most widespread application of BTX-A has been in the treatment of urinary urgency and incontinence due to detrusor overactivity.[6-8] For the treatment of neurogenic detrusor overactivity resulting in urge incontinence, studies show that intradetrusal injection of 300 U of BTX-A reduces or eliminates the need for anticholinergics and achieves continence in these patients.

Following the remarkable efficacy seen in studies with neurogenic detrusor overactivity, a number of researchers have investigated the use of BTX-A in patients with IDO. Earliest reports by Loch et al[9] revealed efficacy in 20 out of 30 patients using 200 U of BTX-A, lasting for 8 months. Reported complications include acute urinary retention and high residual urine. Another study by Radziszewski and Borkowski[10] reported marked improvement of bladder overactivity in 12 patients. This is a relatively new indication for the use of botulinum toxin, but if proven safe and efficacious, will be of great benefit to this group of patients.

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Materials and Methods

This study was approved by our institutional review board and ethics committee.

All patients who presented to the urology outpatient clinic with signs and symptoms of overactive bladder were reviewed for the study. Those diagnosed with idiopathic detrusor overactivity in whom anticholinergic therapy had failed or were contraindicated were enrolled in the study. Failure of anticholinergic therapy was defined as persistence of symptoms of frequency, urgency and urge incontinence refractory to anticholinergic therapy.

Exclusion criteria included patients with myasthenia gravis, and other irritative causes of the bladder such as bladder infection, stones, cancer and interstitial cystitis. Patients with bladder oversensitivity and those with urodynamic evidence of obstruction as well as detrusor overactivity were also excluded.

A routine history and physical examination as well as a full urological assessment were performed. This included urinalysis, kidneys, ureters and bladder (KUB) X-Ray, urine cytology and International Prostate Symptom Score (IPSS) and quality of life (QOL) score to assess their urinary symptoms. The patients were asked to perform a voiding diary over a period of 3 days with special attention given to the episodes of urgency and urge incontinence. Standard voiding cystometry was done with 6F double lumen catheter and a rectal tube at a filling rate of 30 ml per minute. Video fluoroscopy was not routinely performed. Parameters such as cystometric capacity, reflux volume (volume at which uninhibited contractions occurs), maximal detrusal contraction and maximal flow rate and post void residual volume were recorded.

Every patient was thoroughly informed about the procedure and informed consent was obtained before treatment.

Patients were admitted for treatment in a day surgery setting. All the patients received detrusor injections of 200 U of BTX-A diluted in 20 ml of normal saline under general anaesthesia. A routine cystoscopy was done to exclude any bladder lesions. A twelve-degree cystoscope was inserted, and using a flexible injector from Bards, 10U of BTX-A was injected into each of 20 sites of the bladder sparing the trigone. Care was taken not to create a weal as this would indicate a suburothelial injection. After the treatment, patients were monitored in the recovery room and uroflow and residual urine assessments were done to ensure no acute urinary retention.

Follow-ups were conducted to assess any complications by the nurse practitioner via telephone consultation in the initial few days. The patients were also instructed to keep a voiding diary to record the voiding intervals, capacity and incontinence episodes. Repeat urodynamic assessments were done from 6 weeks to 3 months post-treatment. Clinical follow-ups were also conducted at regular intervals, during which IPSS and QOL scores were assessed.

Data were collected from the patients' voiding diaries, IPSS, QOL questionnaire and urodynamic parameters. Statistical analysis was performed using the computer statistical package SPSS. For paired continuous data, the non-parametric test (Wilcoxon signed rank test) was used. $P < 0.05$ was considered statistically significant.

Results

A total of 19 patients (10 males and 9 females) aged 38 to 87 years (mean 60.2 ± 12.6) were enrolled in our study. Three out of the 10 males had history of a previous transurethral resection of prostate (Table 1).

In this study, we have witnessed the efficacy of the treatment on majority of the subjects. At 3 months, 11 out of 16 patients (69%) showed improvement in IPSS score and 13 out of 16 patients (81%) showed improvement in QOL scores. Patients' self reported questionnaire on their urinary symptoms and quality of life with respect to their urinary problems showed improvement from a mean of 17 (range, 2 to 30) to 13 (range, 2 to 32). QOL scores improved from a mean of 5 (i.e. feels very unhappy) to 3 (i.e. mixed feeling). It is encouraging to note that improvement in QOL scores, functional capacity, voiding intervals and incontinence episodes per day achieved statistical significance (Table 2).

We performed an objective analysis of the patients' response to BTX-A by comparing the pre-treatment and 3 months post-treatment urodynamic studies. The post-treatment urodynamic studies were performed at a mean of 102 days. Uninhibited contractions during filling phase were completely eliminated in 4 patients (21%). Reflex volumes for these patients were recorded as maximal cystometric capacities. There was statistically significant improvement in the reflex volume, the maximal detrusal contraction pressure and the leakage volume. Maximal flow rate was not affected after BTX-A injections (Tables 3 and 4).

Gender based subgroup analysis revealed that QOL score, incontinence episodes per day, functional capacity and voiding intervals were significantly improved for females whereas only voiding intervals was significantly improved for males. Correspondingly, the objective measurements of reflex volumes, maximal detrusal contraction pressure and voided volume also showed a more significant improvement among the females (Table 5).

In terms of treatment complications, the worst side effect prior to the commencement of the study was urinary retention as this may cause great inconvenience to the patients. The incidence of urinary retention was only 5.26% after treatment, with only 1 patient (Case 2) having to perform

Table 1. Patients' Demographic Data, IPSS and QOL Scores and Voiding Diary Records

Case	Sex	Age	Cause	IPSS/QOL			Capacity (ml)			Incontinence episodes/day			Voiding interval (mins)		
				Baseline	3 mths	6 mths	Baseline	3 mths	6 mths	Baseline	3 mths	6 mths	Baseline	3 mths	6 mths
1	Female	71	Primary	18/6	9/1	5/2	100	200	200	5	1	0	60	180	240
2	Female	60	Primary	19/6	8/2	4/2	150	200	200	3	0	0	45	180	240
3	Male	74	Primary	29/5	NR	20/4	50	100	125	2	0	1	15	120	60
4	Male	65	Primary	10/6	15/5	13/6	200	100	100	2	0	0	60	90	90
5	Male	55	Primary	27/6	20/5	NR	80	100	100	0	0	0	60	60	60
6	Male	87	Obstructive	19/5	NR	20/5	NR	50	70	0	0	0	60	120	120
7	Female	64	Primary	18/4	21/3	18/2	100	150	200	1	0	0	60	60	60
8	Male	58	Primary	17/6	11/2	11/3	200	250	300	4	1	0	60	90	120
9	Male	66	Obstructive	14/6	10/3	9/3	400	350	400	2	1	1	60	150	150
10	Female	45	Primary	30/6	NR	6/1	75	180	230	0	0	0	60	150	150
11	Female	49	Primary	9/5	2/2	4/1	200	250	300	3	0	0	90	180	180
12	Male	69	Obstructive	21/3	32/5	NR	100	100	NR	0	0	0	60	60	NR
13	Male	74	Primary	12/5	6/2	13/3	50	200	75	3	0	3	90	60	90
14	Female	40	Primary	7/6	11/6	12/5	280	300	250	3	3	3	240	300	240
15	Female	38	Primary	2/5	8/3	NA	150	300	NA	0	0	NA	60	180	NA
16	Male	64	Primary	25/6	17/6	NA	100	100	NA	0	0	NA	30	60	NA
17	Male	52	Primary	21/6	10/3	NA	200	200	NA	0	0	NA	60	60	NA
18	Male	49	Primary	6/5	4/2	NA	250	360	NA	0	0	NA	120	150	NA
19	Female	63	Primary	19/6	10/0	NA	50	300	NA	3	0	NA	30	90	NA

NR: Not recorded; NA: Not available at time of manuscript.

Table 2. Comparing the IPSS/QOL Sores and Voiding Diary Data Pre-Treatment and 3 Months after Botox Injection

	Pre-treatment	3 months post-treatment	*P* value
IPSS	17.0 ± 7.9	12.1 ± 7.5	0.066
QOL	5.4 ± 0.8	3.1 ± 1.8	0.002*
Incontinence episodes/day	1.6 ± 1.6	0.3 ± 0.8	0.004*
Functional capacity (mls)	151.9 ± 93.9	199.5 ± 93.8	0.010*
Voiding interval (minutes)	69.5 ± 47.2	123.2 ± 63.9	0.00*

Values expressed as mean (±standard deviation).
*P value <0.05 considered statistically significant.

clean intermittent self-catheterisation (CISC) over a period of 3 months for a high post-void residual urine. Despite the complication, she reported an improvement in the quality of life as she is now relieved of the constant urge to pass urine.

Other observed side effects included a patient who developed gross haematuria requiring bladder washout and 3 other patients who had minor urinary tract infections.

Duration of the drug efficacy was about 6 to 9 months as observed from the return of the symptoms as such shortening voiding intervals and the return of the urge incontinence.

Discussion

The results of our study show an effective treatment for a condition which can be difficult to manage. Recent studies from various centres have confirmed the efficacy of botulinum toxin for refractory idiopathic detrusor overactivity. Various authors reported excellent efficacy in reducing urinary urgency and frequency as well as incontinence episodes. Schmid et al[11] used 100 U on 100 patients and reported good efficacy in 88% of patients. Rajkumar et al[12] from Glasgow used 300 U on their patients and Popat et al[13] from Queen's Squares, London used the conventional 200 U for IDO cases and all had reported excellent efficacy. Of note, Popat et al[13] reported 19.3% de novo CISC rate in her IDO patients after BTX-A injections.

In our series of 19 patients, we used 200 U of BTX-A in 20 ml of saline injection using rigid cystoscopy into the detrusor muscle. We achieved excellent results especially in the patients with no previous obstructive causes. We had 3 patients in this series who had persistent detrusor overactivity

Table 3. Urodynamic Results of Patients Pre-treatment and 3 Months after Botox Injection

Case	Reflex volume (ml)		Max Pdet (cm water)		Qmax (ml/sec)		Voided volume (ml)		Leak volume (ml)	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	100	161	25	35	19.9	191	25	231	NR	NR
2	49	500	36	0	5	17.6	38	150	230	NR
3	50	276	57	44	4.4	6.3	31	93	214	176
4	210	260	49	43	9.5	16.3	143	261	356	0
5	105	91	155	52	2.4	6	210	159	NR	0
6	125	187	33	37	13.4	8.1	271	134	NR	NR
7	50	302	34	10	16.4	7.7	179	302	20	0
8	114	150	90	52	27.1	14.5	214	220	200	5
9	180	167	61	36	14	14.4	197	201	475	155
10	85	491	40	0	6.1	8.7	216	227	0	0
11	186	286	60	38	23.2	25.4	243	310	0	0
12	48	50	60	60	5.9	5.4	62	103	286	20
13	46	46	106	42	7.8	15.5	106	178	14	34
14	306	300	120	130	22	15.8	228	231	NR	NR
15	30	397	110	0	23.8	15	132	285	NR	NR
16	128	309	43	0	7.9	10.2	267	173	0	0
17	181	213	160	60	31.1	26.1	291	282	0	0
18	161	110	239	60	21.5	20.4	184	270	239	0
19	100	385	62	27	20.3	13.3	161	179	50	0

NR: not recorded.

Table 4. Comparing the Urodynamic Parameters Pre-treatment and 3 Months after Botox Injection

	Pre-treatment	3 months post-treatment	*P* value
Reflex volume (ml)	118.6 ± 71.5	246.4 ± 134.9	0.003*
Maximum detrusal pressure (cm H2O)	81.1 ± 55.7	38.2 ± 30.8	0.001*
Maximal flow (ml/sec)	14.8 ± 8.7	23.0 ± 41.1	0.952
Voided volume (ml)	168.3 ± 83.4	210.0 ± 65.5	0.033*
Leak volume (ml)	148.9 ± 157.6	27.9 ± 59.3	0.013*

Values expressed as mean (±standard deviation).
*P value <0.05 considered statistically significant.

after transurethral resection of prostate (TURP) for detrusor instability secondary to obstruction (Table 1). These patients did not enjoy as good a response compared to those with primary detrusor instability. These patients should perhaps be classified as non-neurogenic detrusor overactivity rather than idiopathic detrusor overactivity according to Blaivas.[14] We postulate that this group of patients are more likely to have more structural changes in the detrusor muscles secondary to prolonged obstruction resulting in thickened bladder wall, severe trabeculations, sacculations and even diverticuli formation. The improvement in quality of life score was also less significant for them because the previously good flow achieved from their TURP was obtunded by the BTX-A injection. Although they had less urgency and urge incontinence, they suffered from a new problem of urinary frequency resulted from higher residual urine and hesitancy. We learnt from our limited experience with these 3 patients that patients' expectations in this group may need to be better managed. Early relief of the obstruction before permanent structural damage set in will most likely produce better long-term results.

We had a patient who had to perform clean intermittent self-catheterisation (CISC) for a period of 3 months. This represents our de novo CISC rate of 5.26%. Despite the inconvenience of having to perform CISC, she had reported excellent quality of life scores from the relief from urgency, frequency and incontinence. This patient subsequently had a second injection 14 months later using 100 U resulting in excellent outcomes without the need for CISC.

The subgroup analysis of BTX-A treatment between males and females showed a possible difference in terms of subjective and objective outcome improvement. However, the significance of outcome data in our analysis was limited due to the small sample size.

Table 5. Gender-based Subgroup Analysis

	Male (n = 10)			Female (n = 9)		
	Pre-treatment	**3 month post-treatment**	***P* value**	**Pre-treatment**	**3 month post-treatment**	***P* value**
IPSS	18.4 ± 7.7	14.3 ± 9.0	0.293	15.4 ± 8.3	10.0 ± 5.3	0.106
QOL	5.3 ± 0.9	3.9 ± 1.6	0.058	5.6 ± 0.7	2.4 ± 1.8	0.018*
Incontinence episodes/day	0.9 ± 1.2	0.1 ± 0.3	0.066	2.4 ± 1.7	0.6 ± 1.0	0.024*
Functional capacity (mls)	158.9 ± 115.5	166.0 ± 110.1	0.400	145.0 ± 72.7	236.7 ± 56.8	0.007*
Voiding interval (minutes)	61.5 ± 28.7	93.0 ± 38.6	0.048*	78.3 ± 62.7	156.7 ± 71.6	0.011*
Reflex volume (ml)	123.4 ± 60.4	170.9 ± 94.5	0.173	113.3 ± 85.6	330.2 ± 126.0	0.011*
Maximum detrusal pressure (cm H2O)	96.3 ± 67.6	43.4 ± 17.9	0.011*	64.1 ± 34.9	32.4 ± 41.3	0.021*
Maximal flow (ml/sec)	11.8 ± 8.7	12.9 ± 6.9	0.445	18.2 ± 7.8	34.3 ± 59.0	0.722
Voided volume (ml)	176.2 ± 89.6	185.4 ± 67.8	0.721	159.6 ± 80.4	237.2 ± 53.9	0.008*
Leak volume (ml)	198.0 ± 178.7	42.8 ± 70.8	0.046*	83.3 ± 104.1	1.00 ± 2.2	0.109

Values expressed as mean (±standard deviation).
*P value <0.05 considered statistically significant.

The minimally invasive nature of this procedure makes it an attractive treatment option. BTX-A appears to have a more acceptable side-effect profile than alternative therapies and has been shown to be effective in patients with IDO who do not respond to anticholinergic medication. In contrast to the daily oral intake of anticholinergics, BTX-A injections have a longer lasting effect and most studies suggest repeated treatment for 9 months or longer.

Further studies on the application of BTX-A in IDO patients should focus on optimum dosing, more precise determination of the duration of effect, factors determining its efficacy and long-term complications of BTX-A injection into detrusor muscle. Gender based studies are also warranted.

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