Botulinum Toxin A for Idiopathic Detrusor Overactivity
Kwok Ying Lie,1 MBCh, MMed, MRCS(Edin), Michael Y C Wong,2 MMed, FAMS, FRCSEd, Lay Guat Ng,1 MMed, FAMS, FRCSEd

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 intradetrusional 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 al9 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 Borkowski10 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.

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 intradetrusional 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.

Key words: Botox®, Idiopathic detrusor overactivity, Overactive bladder, Urodynamics
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 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
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 al11 used 100 U on 100 patients and reported good efficacy in 88% of patients. Rajkumar et al12 from Glasgow used 300 U on their patients and Popat et al13 from Queen’s Squares, London used the conventional 200 U for IDO cases and all had reported excellent efficacy. Of note, Popat et al13 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...
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

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<tr>
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<th>Male (n = 10)</th>
<th>Female (n = 9)</th>
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<tr>
<td></td>
<td>Pre-treatment</td>
<td>3 month</td>
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<tr>
<td><strong>IPSS</strong></td>
<td>18.4 ± 7.7</td>
<td>14.3 ± 9.0</td>
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<tr>
<td><strong>QOL</strong></td>
<td>5.3 ± 0.9</td>
<td>3.9 ± 1.6</td>
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<td>Incontinence episodes/day</td>
<td>0.9 ± 1.2</td>
<td>0.1 ± 0.3</td>
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<td><strong>Functional capacity (mls)</strong></td>
<td>158.9 ± 115.5</td>
<td>166.0 ± 110.1</td>
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<tr>
<td><strong>Voiding interval (minutes)</strong></td>
<td>61.5 ± 28.7</td>
<td>93.0 ± 38.6</td>
</tr>
<tr>
<td><strong>Reflex volume (ml)</strong></td>
<td>123.4 ± 60.4</td>
<td>170.9 ± 94.5</td>
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<td>Maximum detrusal pressure (cm H2O)</td>
<td>96.3 ± 67.6</td>
<td>43.4 ± 17.9</td>
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<tr>
<td>Maximal flow (ml/sec)</td>
<td>11.8 ± 8.7</td>
<td>12.9 ± 6.9</td>
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<tr>
<td>Voided volume (ml)</td>
<td>176.2 ± 89.6</td>
<td>185.4 ± 67.8</td>
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<tr>
<td>Leak volume (ml)</td>
<td>198.0 ± 178.7</td>
<td>42.8 ± 70.8</td>
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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.

REFERENCES