

Botulinum Toxin A (BTX-A) in refractory non-neurogenic overactive bladder: A prospective review of intermediate-term quality of life outcome assessment

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Abstract: *Objective:* To evaluate the efficacy of BTX-A in non-neurogenic (idiopathic) overactive bladder (OAB) patients. *Materials and methods:* All drug refractory non-neurogenic OAB patients that received intravesical BTX-A between January 2004 and January 2009 were recruited prospectively. Patient demographics, voiding diary and urodynamics studies were recorded. King's Health Questionnaires (KHQ) was completed pre and post therapy at 3, 6 and 9 months. The primary end point assessments were number of urgency and urge incontinence as well as quality of life outcomes. All adverse events were also documented. *Results:* A total of 60 patients (28 men, 32 women) with the mean age of 64.2 (28 to 84) years old and a mean follow up was 26.2 (12 to 58) months, were recruited during the 5 years period. No significant adverse side effects or mortality were documented. Three patients (6%) developed a temporary increase in post void residuals requiring short-term catheterisation (< 5 days). Fifty patients (83%) demonstrated significant improvement with regards to their KHQ scores pre and post BTX administration ($p < 0.001$), with the symptomatic benefits diminishing at subsequent 6 and 9 months follow up ($p > 0.05$). 48 patients (80%) reported recurrence of OAB symptoms at the 6 months follow up visit, necessitating reintroduction of anticholinergic therapy for symptomatic control. When looking at specific KHQ domains, significant reduction was noted in storage symptoms specifically of frequency, nocturia, urge and urge incontinence ($p < 0.001$). The improvement in stress incontinence and bladder pain were not significant ($p > 0.05$). The functional bladder capacity increased from 192.7 (60 to 300) mls to 341 (140 to 550) mls while the number of pad use decreased from 3.7 (3 to 7) pads to 0.75 (0 to 1) pad ($p < 0.001$). *Conclusion:* Our results indicate that BTX-A treatment for non-neurogenic OAB appears to be safe and well-tolerated with most patients electing for repeated treatments.

Key words: Overactive bladder; Intravesical BTX-A; Urge incontinence; Stress incontinence.

INTRODUCTION

Overactive bladder (OAB) affects more than 12% of adult population¹ and is characterised by symptoms of urinary urgency, with or without urge incontinence, usually with frequency and nocturia.² OAB is most commonly caused by detrusor overactivity (DO), which is defined as the presence of involuntary detrusor contractions during the filling phase of cystometry, which may be spontaneous or provoked.² In the absence of local or neurological causes, this DO is termed idiopathic or non-neurogenic detrusor overactivity (NNDO).

Management approaches to this debilitating condition usually comprises of bladder retraining and antimuscarinic agents. However a proportion of patients remained affected³ either because they are refractory to antimuscarinics, have discontinued treatment due to significant side effects or have contraindication to these agents. Other treatment options for these drug-refractory patients consist conventionally of more invasive procedures including sacral neuromodulation, augmentation cystoplasty or urinary diversion.⁴ However the advent of intravesical use of botulinum toxin (BTX) has offered another minimally invasive option in the armamentarium of agents which can be used to treat DO.⁵⁻⁹

Although data is abundant on the use of BTX in neurogenic DO,^{5,7,8,10} few studies have evaluated the efficacy of BTX in managing idiopathic DO.¹¹⁻¹⁴ To our knowledge, this is the first Australasian series that reports on the clinical effects of BTX on the treatment of non-neurogenic DO and its impact on the patient quality of life.

MATERIALS AND METHODS

From January 2004 to January 2009, patients from the Concord hospital urodynamic clinic with non-neurogenic OAB who were refractory to at least 2 anticholinergic agents and/or have ceased anticholinergic therapy due to unwanted side effects were enrolled prospectively into the study. All patient demographics, voiding diary and outcome of multi-channel urodynamics studies were recorded. Patients were required to fill a validated King's Health Questionnaires (KHQ) pre and post therapy at 3, 6 and 9 months. Exclusion criteria included neurogenic bladder, bladder outlet obstruction, active urinary tract infection and

muscular weakness such as myasthenia gravis.

Doses of 200 IU of BTX-A (Botox[®], Allergan Inc, CA, USA) were constituted with 10 mls of sterile normal saline for intra-detrusor injection. The injection was administered with a 23G Williams needle (Cook, Queensland, AUSTRALIA) via a 22 French rigid cystoscope transurethraly, as a day procedure under general anaesthesia. The needle tip was placed into detrusor muscle and 1 ml aliquots each containing 20 units were injected without raising any submucosal blebs. 200 IU of BTX-A was injected in 2 rows of five injections to the base of the bladder sparing the dome and trigone. Ureteric orifices were used as markers of the lateral extent of the injection sites. Each patient received a prophylactic dose of cephalothin 1g intravenously and the bladder was emptied at the end of procedure. No urethral catheter was used. Patients were then kept in the day surgery unit for 6 hours to ensure satisfactory voiding.

Patients were followed up prospectively every 3 months with further history and examination, voiding diary and KHQ. The primary end point assessments were number of urgency and urge incontinence as well as quality of life outcomes. Adverse events such as acute urinary retention, clot retention, transient weakness and bladder or urethral pain were documented. The results were analysed using a 2-sample student *t* test with equal variance to compare the results pre and post BTX-A treatment.

RESULTS

A total of 60 patients (28 men, 32 women) with the mean age of 64.2 (28 to 84) years old and a mean follow up was 26.2 (12 to 58) months, were recruited during the 5 years period. The causes of bladder dysfunction requiring Botox-A treatment include 42 patients with idiopathic DO, 6 patients with non-neurogenic poor detrusor compliance and 12 patients with OAB symptoms but no demonstrable DO on urodynamics.

No significant adverse side effects or mortality were documented. Three patients (6%) developed a temporary increase in post void residuals requiring short-term catheterisation (< 5 days). Two patients who were previously on clean intermittent self catheterisation (CISC) due to under-

lying poor bladder compliance continued with CISC practice post BTX-A administration. No patient was admitted with gross hematuria or clot retention.

Of the patient cohort, 50 patients (83%) demonstrated significant improvement with regards to their KHQ scores pre and post BTX administration ($p < 0.001$). The most significant improvement was reported at 3 months ($p < 0.001$) with the symptomatic benefits diminishing at subsequent 6 and 9 months follow-up ($p > 0.05$) (Table 1). The domains with the greatest improvement were incontinence impact (domain 2), physical limitation (domain 4) and emotion (domain 7) (Figure 1). Most patients (80%) reported recurrence of OAB symptoms at the 6 months follow up visit, necessitating reintroduction of anticholinergic therapy for symptomatic control. A total of 37 (62%) patients have repeated BTX-A injection with a mean interval of 11 (7 to 14) months. For those patients who received further intravesical administration of BTX-A, all patients reported similar efficacy and improvement of their urinary symptoms. Out of the 60 patients, 4 were lost to follow-up while the remaining 11 patients did not request for further BTX-A treatment.

Significant reduction was noted in storage symptoms specifically of frequency, nocturia, urge and urge incontinence ($p < 0.001$). The improvement in stress incontinence and bladder pain were not significant ($p > 0.05$). The functional bladder capacity increased from 192.7 (60 to 300) mls to 341 (140 to 550) mls while the number of pad use decreased from 3.7 (3 to 7) pads to 0.75 (0 to 1) pad ($p < 0.001$). For the 6 patients who had poor detrusor compliance as sole finding on the preoperative urodynamics, there was significant improvement noted ($p < 0.001$) with the detrusor compliance normalised on urodynamics at 6 months post injection.

DISCUSSIONS

Botulinum toxin (BTX) is a complex and potent neurotoxin protein produced by anaerobic bacterium *Clostridium botulinum*. It was first isolated by Ermengem in 1897 and later introduced into the field of urology by Schurch and Stohrer for the treatment of detrusor sphincter dyssynergia in patients with spinal cord injuries^{6,7} prior to use in non-neurogenic DO.¹⁵

The role of BTX at the neuromuscular junction has been well described and consisted of inhibition of acetylcholine neurotransmitter release resulting in temporary chemo-denervation and striated muscle relaxation.⁸ However there is also increasing evidence suggesting a much greater extent of neurologic effects of BTX. BTX has been found to inhibit the release of a number of neurotransmitters (including acetylcholine, adenosine triphosphate, and the neuropeptides such as substance P) and down-regulate the expression of purinergic and vanilloid receptors on afferent neurons within the bladder suburothelium;⁸⁻¹¹ hence potentially treating DO and OAB by both sensory and motor pathways. Of the seven serotypes of BTX, type A and B have been used

TABLE 1. – Mean KHQ scores pre and post BTX-A.

KHQ Domains	Preoperative	3 months postoperative*	6 months postoperative**	9 months postoperative**
1. General Perception	50	25	40	50
2. Incontinence Impact	100	44	63	100
3. Role Limitations	67	29.9	33	63
4. Physical Limitations	83	36.7	41	81
5. Social Limitations	66	25.9	41.2	63.3
6. Personal Relationships	33	21	26.1	31.4
7. Emotions	100	33	56	88.7
8. Sleep/Energy	50	29	40	46.7
9. Severity Measures	80	25	41	76.5

* denotes $p < 0.001$ between preoperative and 3 months postoperative;
 ** denotes $p > 0.05$ (NS) between 3 months and subsequent 6 and 9 months postoperative.

with clinically beneficial outcomes in various neurologic disorders.³ Recently BTX-A has been shown to inhibit the release of norepinephrine, suggesting a potential role in inhibiting afferent/sensory innervations of lower urinary tract and central desensitisation through a decrease in central uptake of substance P⁹ contributing to overall decrease in frequency and urgency.¹⁰ Although there have been numerous published literature on the efficacy of BTX-A in the treatment of DO and OAB, this drug is not yet approved by many government regulatory bodies.^{3,15}

At present there is no consensus on the dose, percentage of dilution, injection site (intradetrusor or suburothelium), the number of injections and rate of BTX use in neurogenic or non-neurogenic OAB. Recent studies have shown that doses of 100 or 200IU of BTX-A is effective in treating idiopathic DO¹⁶ while doses over 200IU are commonly used in patients with neurogenic DO.^{10,17} In a double-blind, placebo-controlled randomized dose ranging trial, Dmochowski¹⁸ have shown either 100 or 150 units of BTX to have the best efficacy and safety profile in the treatment of idiopathic OAB. There have been published literature revealing similar efficacy of BTX-A in both suburothelial or detrusor injections.^{9,19} This may be attributed to the diffusion of BTX-A between detrusor and suburothelial space as evident in magnetic resonance study.²⁰ Kuo¹⁹ reported superior clinical efficacy of BTX-A when administered in suburothelial and into detrusor compared to bladder base injections, with no documented incidence of vesico-ureteric reflux when injecting BTX-A into the trigone.

Several large volume studies published on BTX-A in idiopathic OAB refractory to anticholinergics such as by Schmid²¹ has shown significant improvement in bladder function with regards to subjective symptoms, quality of life and urodynamics parameters. Rajkumar²² published the use of 300 IU BTX-A in his group of idiopathic non-anticholinergic responders showing significant improvement in the bladder symptoms after the initial 6 weeks follow up; with therapeutic effects of BTX-A lasting over 20-24 months. Although all the patients were able to void following the administration of 300 units of BTX-A, 4 patients demonstrated post void residuals of more than 200 mls. Jeffrey²³ also reported similar efficacy with Dysport 500IU with significant subjective and objective improvements in patients with refractory IDO. Our series has shown significant improvement in patients' quality of life events as well as symptoms of frequency, urgency and urge incontinence. The effects of BTX lasted for an average of 6 months in our experience and majority of patients were happy to undergo the treatment again. As with most published literature, the beneficial effects of BTX were maintained throughout the 24 weeks period with most patients electing for repeat treatment when the clinical effects wear off. Therefore the safety of repeated BTX injection on the structural changes in the bladder caused by either the toxin or repeated micro-scarring of

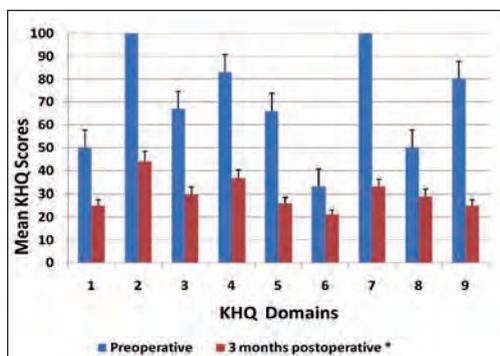


Figure 1. – Mean KHQ scores pre and post BTX-A (at 3 months) ($p < 0.01$).

bladder is a potential source of concern. Apostolidis²⁴ concluded that repetitive injection of BTX did not appear to produce any significant inflammatory changes, fibrosis, or dysplastic changes apart from presence of eosinophils which might be treatment-related effect. Nonetheless the patient numbers are too small from which to draw definitive conclusion. Grosse²⁵ found no evidence of increased drug tolerance after multiple treatments. BTX produced from 1997 onwards has much lower antigenic potential and the development of resistance to BTX treatment is uncommon.

Several factors have been shown to limit the therapeutic efficacy of BTX. Patients with pre-existing bladder wall fibrosis and low bladder compliance or OAB symptoms with painful bladder or interstitial cystitis appeared to respond less favourably.²⁶ In our experience, the administration of intravesical BTX does not appear to improve symptoms of painful bladder; perhaps there were other sensory pathways not accounted for by BTX. However we have demonstrated improvement in bladder symptoms in patients with poor bladder compliance as well as significant increase in the mean functional bladder capacity following administration of BTX; validating the effects of BTX in temporary chemodenervation and smooth muscle relaxation. In contrast to the reported literature¹⁴ that up to 45% of patients who received high doses of BTX would require clean intermittent self catheterisation (CISC), we did not identify any new patient with prolonged voiding dysfunction apart from those who previously perform CISC for poorly compliant and hypocontractile bladder. While we acknowledge the modest numbers of patients, our series has excellent intermediate term follow up and a consistent protocol was instituted for each patient. Unfortunately the literature pertaining to longer-term use and outcome of BTX is sparse. To our knowledge this is the first published study on BTX-A in non-neurogenic OAB in an adult Australasian patient cohort. Despite the numerous longitudinal studies on BTX in refractory non-neurogenic OAB, only a well-designed randomised double blinded control trial can address the issues surrounding BTX and its cost-effectiveness over other therapeutic options.

CONCLUSIONS

BTX-A significantly reduce the symptoms and improve quality of life in patients with drug refractory non-neurogenic OAB. Our results indicate that BTX-A treatment appears to be safe and well tolerated with most patients electing for repeated treatments. However the lack of general consensus with regards to BTX would require more well-designed, randomised controlled trials before BTX could be accepted and approved by various government bodies for use in treating this debilitating condition.

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