

## INTRADETRUSOR BOTULINUM TOXIN A INJECTION FOR LONG-TERM INDWELLING CATHETER COMPLICATIONS: A SINGLE CENTRE EXPERIENCE

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### Abstract

#### Background

Botulinum toxin was first described in 1895. It is a potent neurotoxin released by clostridium, a gram-negative, anaerobic, rod-shaped bacterium. Initially, it was considered to be the cause of life-threatening disease. However, research demonstrated it to be a novel and effective therapy in managing a range of diseases, including some that affect the urinary bladder. It was approved by the Food and Drug Administration (FDA) in 1898.

#### Objectives

This study aimed to evaluate the long-term effects of intravesical botulinum toxin A (BTA) injections in patients with an indwelling long-term catheter for detrusor overactivity. The patients selected for this study were experiencing significant catheter-associated symptoms such as bypassing, bladder spasms, intractable pain, blockages, and recurrent infections.

#### Method

A retrospective cohort study was conducted in patients that received intravesical BTA after the failure of symptom management using oral anticholinergic and beta 3-adrenoceptor agonist. A group of 12 patients was identified, and they were followed up in the clinic after receiving treatment.

#### Results

All of the patients included in this study had relief of their symptoms following administration of intravesical BTA. Almost 58% (n = 7) of patients required 3 or fewer treatments with BTA to gain symptom control, with the remaining patients gaining control after 4 treatments. There were no significant adverse events reports with only mild and temporary side effects, such as haematuria, experienced.

#### Conclusion

This study demonstrated that intravesical BTA can significantly improve symptoms associated with long-term indwelling catheters and may help avoid more complex and invasive interventions.

**Key words:** *Botulinum toxin A, Overactive bladder, Indwelling catheter, Neurogenic bladder*

## INTRODUCTION

Detrusor overactivity is a condition in which the bladder cannot effectively function as a reservoir, and involuntary detrusor contractions occur. This overactivity may be neurogenic and associated with spinal cord injury, multiple sclerosis, and Parkinson's disease. Others could be secondary to bladder pathology, outlet obstruction, or even idiopathic in which no apparent cause is found. It can lead to a heterogeneous group of symptoms, namely storage dysfunction in frequency, urgency, and incontinence. These are termed neurogenic detrusor overactivity (NDO), Non-Neurogenic, and idiopathic detrusor overactivity (IDO).<sup>1-3</sup>

In some patients with NDO and IDO, a long-term indwelling catheter will be inserted to manage their symptoms and improve their quality of life. Unfortunately, insertion of an indwelling catheter and the chronic decompression of the bladder can shrink the bladder and other related symptoms. In addition, detrusor overactivity can become apparent in a different group of patients who are fitted with a catheter for other reasons such as poor mobility, chronic retention and in those who are poor candidates for surgery. Occasionally, these catheters may lead to and are associated with symptoms such as pain, bypassing, catheter blockages, and recurrent urinary tract infections; all of which negatively impact a patient's day-to-day life and performance.<sup>4</sup> Oral antimuscarinic and beta 3-adrenoceptor agonist medications are the first-line treatment in managing these overactivity adverse symptoms. However, using these medications could be challenging in the elderly, and the side effect profile can be not very well tolerated because of constipation, visual disturbance and dry mouth. In addition, the therapeutic efficiency of these medications can diminish over time.<sup>5</sup> Bladder wash in the community has been widely trialled and is often found as a non-sustainable solution and is considered very labour intensive.

Botulinum toxin A (BTA) is used to manage a variety of conditions such as strabismus, cervical dystonia and hyperhidrosis, and has widespread use in the cosmetic industry.<sup>6</sup> More recently, there is a gradually growing body of evidence to support the

use of intravesical BTA in the management of adverse side effects from long-term indwelling catheters.<sup>5</sup>

## PATIENTS AND METHODS

The data for this cohort of patients was collected retrospectively from clinic letters and discharge summaries on the Trust's electronic patient record. The patients included had long-term indwelling catheters associated with bothersome symptoms. All the patients included have been offered a flexible cystoscopy to exclude other causes of the blockage or bladder spasm such as bladder stones or malignancy, but none of our 12 patients had a urodynamics assessment after the decision of having a long term catheter. They were initially treated as per our local departmental policy with two different antimuscarinic and beta 3-adrenoceptor agents, if not contra-indicated, at the maximum dose with no response and the patient could not tolerate the side effects of these tablets. Ultimately, intravesical BTA was offered, as a last resort to help manage their symptoms. Follow-up was carried out on a 6 monthly basis by a specialist nurse-led telephone clinic which assessed the patients' symptoms and quality of life following the administration of BTA.

## RESULTS

A total of 12 patients were included in the study, of which 6 were known to have underlying NDO, and 6 patients had IDO. Of the 12 patients, 11 had a suprapubic catheter, with one patient with a urethral catheter. Eight of the patients were identified as females (66.6%), and 4 were males (33.3%) with a mean age of 70 years (46–87). The indication for long-term indwelling catheter varied and included failure of clean intermittent self-catheterisation (41.5%, n = 5), multiple sclerosis (24.9%, n = 3), spinal cord compression (8.3%, n = 1), cerebral palsy (8.3%, n = 1), motor neurone disease (8.3%, n = 1) and cerebrovascular accident (8.3%, n = 1). All of our 12 patients faced a combination of side effects to their indwelling catheters with urine bypass as the most commonly experienced side effect with a frequency of 91.7% (n = 11). This was followed by pain in 50% (n = 6), catheter blockage in 33.3% (n = 4) and recurrent urinary tract

infection in 33.3% (n = 4). Eight patients were initially treated with a single antimuscarinic medication at a time with a maximum dose. Should that fail or become non-tolerated, another antimuscarinic agent was trialled or a beta 3 agonist if not contraindicated. Four of the patients who experienced recurrent urinary tract infections were trialled on low-dose prophylactic antibiotics in addition to the standard antimuscarinic or beta 3 agonists.

All of our 12 patients had the BTA (Botox® onabotulinum toxin) delivered via a flexible cystoscopy route under local anaesthesia. Due to a lack of clear evidence on using BTA in patients with long-term catheters, the dose given was based on the operator's discretion. It varied between 100 U (41.5%, n = 5), 200 U (50%, n = 6) and 300 U (8.3%, n = 1). The BTA was diluted in 10 mL of normal saline, and 0.5 ml (5 units) was injected into the detrusor muscle at 20 different sites (excluding the trigone). All patients had a urinalysis before the procedure and received a single dose of 160 mg of gentamicin as per our hospital antimicrobial guidance. The majority of patients tolerated the procedure well, with only one patient (8.3%) reporting mild pain, one patient (8.3%) reporting a single episode of vomiting and 3 patients (24.9%) reporting mild haematuria that settled without intervention.

Telephone follow-up at 3 monthly intervals for up to 3 years from the first BTA administration demonstrated an overall satisfaction with good response to treatment, and almost all patients reported good improvement in their symptoms. Two patients (16.6%) did not require further BTA injections and were successfully discharged after the first dose. A second injection was required in 10 patients with a mean duration of symptom control for 9.6 months (range: 6-23). Five patients required a third injection, and 2 patients required the fourth injection.

## DISCUSSION

The placement of long-term catheters can significantly impact the quality of life if they are associated with complications, as discussed above. Oral antimuscarinic medications or beta 3 agonists have played an essential role in managing these side effects

through relaxation of the bladder wall. However, these medications have their own side effect profile: constipation, gastric upset, visual disturbance, xerostomia, and arrhythmias. As a result, intravesical treatment was developed for patients who could not tolerate the side effects or had no therapeutic benefits from traditional oral treatments. A study by Satio et al. demonstrated intravesical instillations of oxybutynin chloride were an effective treatment for detrusor overactivity with minimal side effects reported. However, the study was conducted in a small sample size of 6 patients; therefore, efficacy in patients with long-term catheters cannot be sure. Additionally, the treatment required daily administration and, therefore, may not be an easy option to administer in a neurogenic patient and will be cost-effective.<sup>7</sup> Intravesical capsaicin is another effective therapy for the management of detrusor overactivity. It works by selectively activating afferent receptors that contain unmyelinated C-fibres. The effects can last up to 6 months; however, the installation is reported to cause severe burning pain, and repeat administration is required.<sup>8</sup>

Over the past two decades, BTA has been widely used to manage detrusor overactivity that has not responded to conventional oral treatments. It has a paralysing effect on the detrusor muscle by preventing the release of acetylcholine (Ach) at the neuromuscular junction of motor neurons. However, very few studies have been conducted within this domain. Young et al. conducted a prospective study on 54 patients with long-term catheters experiencing adverse effects such as chronic pain and bypassing. They were treated with intra-detrusor BTA injections with improvements in quality of life and symptoms demonstrated.<sup>9</sup> Another study conducted in 2005 by Lekka et al. demonstrated a mean continence period of 38 weeks in 3 patients with multiple sclerosis, who were experiencing urethral bypassing despite indwelling suprapubic catheters, following administration intravesical BTA.<sup>10</sup> Additionally, Vaidyanathan et al. reported significant symptomatic improvement and quality of life for a tetraplegic patient experiencing bothersome symptoms associated with an indwelling suprapubic catheter.<sup>11</sup>

In our retrospective study of 12 patients, almost 58% (n = 7) required no more than 3 doses of BTA to achieve a long-lasting, satisfactory result, with the remaining patients requiring a fourth dose to control their symptoms. In addition, our patients reported very mild side effects with no significant adverse events experienced. These results further demonstrate the benefits of intravesical BTA injections in managing patients with complications of long-term indwelling catheters.

### LIMITATION

Although the outcomes of our study have a satisfactory result, the small number of samples and lack of proper and direct questionnaire to objectively assess the symptoms and quality of life improvement, given the nature of being a retrospective study, are considered the major limitations in the study.

### CONCLUSION

Despite the small and heterogeneous cohort of patients, our initial results of intradetrusor injection of BTA have proved a good and safe minimal invasive intervention for those with complications of the long-term indwelling catheter and failed other treatment options. Our analysis has demonstrated quite good results with the number of injections required to reach the desired outcome, with only mild pain and light temporary haematuria without significant after-effect. The treatment is more widely used at our Trust, and elsewhere in the country; hence multi-institutional cooperation could help identify a larger group of patients and shape a standard practice in managing this group of patients.

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