

The Use of Botulinum Toxin Injections to Treat the Overactive Bladder

Botulinum toxin, the most lethal poison known to mankind, has through research, been transformed from a dangerous and feared entity to a novel drug able to help and sometimes cure conditions previously difficult to treat. Such a challenge was posed by the treatment of patients with detrusor overactivity (DO), resulting in an overactive bladder syndrome with its distressing symptoms of urinary frequency, urgency, incontinence and nocturia.¹ Until recently, there have been limited options available to patients with DO, who have failed to respond to established first line oral therapies and clean intermittent self-catheterisation (CISC), and a therapeutic chasm existed between these non-invasive treatments and surgery namely augmentation cystoplasty. The advent of intradetrusor injection of botulinum neurotoxin A (BoNT/A) is fast filling this void, and has revolutionised the management of DO. As further research into this exciting treatment modality proceeds, other indications of its use in urological practice including in children, patients with painful bladders, and indwelling catheters is being evaluated.

There are seven serotypes of BoNT, designated A to G, each with a different antigenic profile and biochemical action, however with the same pharmacological effect. BoNT's are metalloproteases specific for the three proteins that form the core of the neuroexocytosis machinery. They work by binding to and entering inside peripheral cholinergic terminals, causing a sustained block of acetylcholine (ACh) release at the neuromuscular junction and in cholinergic autonomic nerves, with ensuing flaccid paralysis.²

Background

It has long been known that an area in the dorsal tegmentum of the pons, the pontine micturition centre (PMC), is central to bladder storage and appropriate voiding. Intact projections from the PMC to the sacral spinal cord (S2–S4) determine parasympathetic outflow to the detrusor and reciprocal activity of the motor neurones innervating the striated urethral sphincter. Synergistic activity between the detrusor and the sphincter depends on the integrity of the connections with the pontine region. A condition known as 'detrusor sphincter dyssynergia' (DSD) results from interruption or damage to these pathways, however the most marked abnormality occurring as a consequence from disconnection from the PMC is a segmental reflex that causes a detrusor contraction in response to bladder distension. Following any form of spinal cord lesion, previously quiescent unmyelinated C fibres become mechanosensitive and respond to bladder stretch.³ Detrusor contractions are caused by this afferent activity, through synaptic activity in the sacral spinal cord.⁴ It is this that is responsible for the emergence of DO. DO is defined as a urodynamic observation characterised by involuntary detrusor contractions during the filling phase that may be spontaneous or provoked.¹

An attempt to block the efferent limb of the detrusor segmental reflex arc, in the hope of relieving the symptoms caused by DO was originally carried out in 1998 at a rehabilitation centre in Switzerland. Schurch et al injected patients with complete spinal cord injury suffering from intractable neurogenic detrusor overactivity and incontinence, and demonstrated striking improvements in urodynamic and clinical parameters lasting up to nine months.⁵

Minimally Invasive Intradetrusor Injection of BoNT/A

The original technique used a rigid cystoscope and a wide diameter injection needle. Patients with spinal lesions above

T5 had 40mls of 2% lignocaine instilled to anaesthetise the bladder. The bladder was then injected with 200–400 units of BoNT/A (Botox®), in 20–30 points avoiding the trigone. It was concluded that 300 units of Botox® might be the most effective dose.

Standard practice in the UK for performing a rigid cystoscopy would require either regional or general anaesthesia. This would mean even though a procedure such as intradetrusor BoNT/A injections could be done as a day case, recovery facilities would still be required. The minimally invasive outpatient technique developed in the Department of Uro-Neurology, at the National Hospital for Neurology and Neurosurgery,⁶ allows for the treatment to be carried out under local anaesthetic, as an outpatient, obviating the need for any recovery ward or inpatient stay.

Pre-operative work-up

The main indication for intradetrusor BoNT/A is intractable urodynamically proven DO. Patients are made aware that this is as yet an unlicensed indication for the use of BoNT/A, and full informed consent is taken. As there is a tendency for the post void residual volume to increase following treatment, patients should be willing and able to perform CISC should the need arise.

Prior to injection urinalysis is performed to rule out any urinary tract infection (UTI). UTI at the time of planned injection is an absolute contraindication to the procedure. Other exclusion criteria include: bladder malignancy, bleeding disorders, anticoagulation therapy, neurotransmission disorders or drugs affecting neuromuscular transmission (e.g. aminoglycosides), pregnancy or planning a family.

The minimally invasive injection technique

There are no specific pre-operative preparation instructions and the patient comes to the clinic immediately before the procedure is planned. Following oral antibiotic prophylaxis, the unsedated patient is positioned supine, adequately prepared and draped. Local anaesthetic gel is applied to the urethra and the bladder is accessed using a standard flexible cystoscope. The cystoscope should have a 2.2mm working channel that can accommodate a 27 G, 4mm needle which locks into a reusable sheath to protect the scope and facilitate the injections (Figure 1).

If at cystoscopy the bladder mucosa is free of any inflammation and lesions (Figure 2), the BoNT/A is then reconstituted and the bladder injected. Of the formulations of BoNT/A available, Botox® (Allergan Ltd., UK) is used in our department. This is available as single use vials of 100 units of the neurotoxin complex which is diluted using 10mls of 0.9% normal saline without preservative (10U/ml). Care should be taken when reconstituting the drug, as vigorous agitation will denature the compound. The bladder is filled to 100mls and injected over 20–30 equidistant sites over the bladder wall and the dome of the bladder. Patients with neurogenic DO (NDO) receive 300U of Botox®, and those with idiopathic DO (IDO) receive 200U. The injections are mapped out using 6 rows of 5 injections for patients with NDO and 4 rows of 5 for IDO patients (Figure 3). The trigone is not injected for the reasons of tolerability, access using a flexible cystoscope and the potential of vesico-ureteric reflux by paralyzing the ureteric ostia.

Post-operative patient follow-up

A 3-day antibiotic course is completed, and the patient is reviewed at 4 weeks post injection to check if they are emp-



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Figure 1: View inside the bladder showing bladder ready for injection. The needle and sheath are visible.



Figure 2: Flexible sheath containing needle.

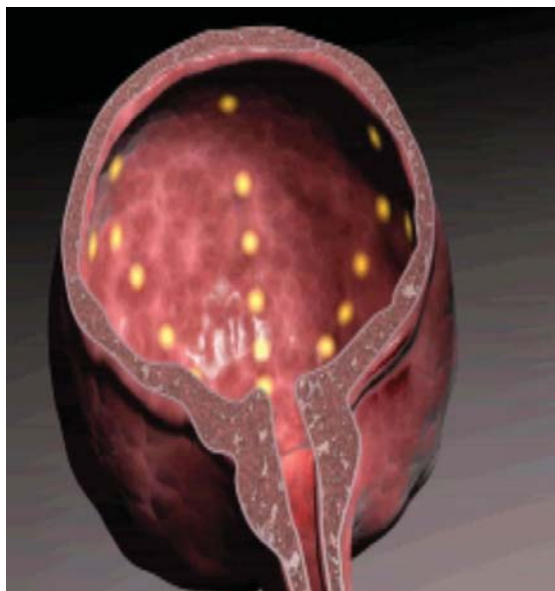


Figure 3: Illustration of the bladder with the injection points mapped out.

tying to completion. This is done by a simple handheld ultrasound bladder scanner, however as a part of our research protocol, urodynamics is performed at 4 and 16 weeks post treatment. If the post void residual volume is greater than 100mls and the patient is symptomatic, with no reduction in frequency, urgency and incontinence, and/or suffering from repeated UTI's, they are instructed how to perform CISC.

The effects of the injections are generally noticed within a week, and the patients are advised to cut back, and eventually stop concurrent anticholinergic treatment. When the effects of BoNT/A start to wear off, they may then need to reintroduce their anticholinergics.

Results

Efficacy data from cohort studies report a success rate of 89-100% in patients with spinal NDO.⁵⁷ A retrospective multicentre study demonstrated a success rate of 96%, with clin-

ical and urodynamic improvement at 12 and 36 weeks post treatment; 73% of patients who were previously incontinent were 'dry' at 12 weeks follow up.⁸ These findings have been confirmed in a randomised placebo controlled trial.⁹

In our own series of 44 patients with spinal NDO and 31 with IDO treated with minimally invasive outpatient intradetrusor Botox®, we found significant improvements in urinary urgency, frequency, incontinence, bladder capacity and end-filling detrusor pressures,⁷ in all patients. A success was defined as a greater than 25% improvement in 2 parameters, clinical and/or urodynamic. Ameliorations of symptoms were reflected in the observed improvement in the quality of life data, complementing previous publications.¹⁰

Of the patients who were not already performing CISC, 69.2% of patients with NDO required CISC post-treatment compared with 19.3% of those with IDO. The procedure is quick (approximately 15 minutes) and well-tolerated, the average discomfort score on a 0-10 verbal pain scale being 3.2. This duration of effect was maintained after repeat treatment (mean 10.7 months, range 7- 12). These findings are similar to results from other studies.¹¹ The side-effects have been minor following treatment and include macroscopic haematuria in 2 patients, urinary tract infection in 3, and 1 patient experienced transient flu-like symptoms. Generalised adverse events such as muscle weakness that have been rarely reported¹² have been not encountered in our experience.

Conclusions

Minimally invasive outpatient intradetrusor BoNT/A is shown to be a safe, effective, and well-tolerated treatment for patients with intractable detrusor overactivity. This simple yet innovative technique is easily reproducible and may be performed by any practitioner who is trained to carry out diagnostic flexible cystoscopy.

As yet unlicensed, intradetrusor BoNT/A is being adopted by increasing numbers of centres throughout the UK and worldwide. This treatment option is known to have a significant positive impact on patients' quality of life, and is now emerging as an important modality in the management of refractory lower urinary tract symptoms, independent of aetiology, challenging the future place of invasive surgical measures such as augmentation cystoplasty.

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Our project is funded by a grant from the Multiple Sclerosis Society, and one of the aims is to make this treatment widely available for patients with MS. We therefore encourage visits from other centres of urologists, uro-gynaecologists, neurologists and rehabilitation doctors who wish to learn the technique and assist them by providing supporting paperwork for them to obtain local ethical approval. To date we have had 35 visitors and to our knowledge we are the only centre in the UK that provides this service. For more information contact Vinay Kalsi.