BANGLADESH JOURNAL OF
UROLOGY
Bangladesh J. Urol. 2025; 28(1): 16-21
www.banglajol.info/index.php/BJU
DOI: https://doi.org/10.3329/bju.v28i1.81873

Original Article

ISSN : 2304 - 8514 (Print)
ISSN : 2304 - 8522 (Online)

Use of botulinum toxin in urological diseases diagnosed by Urodynamic study in neuro-urology, BMU experiences

ATM Aman Ullah[1], M Sahabuddin Molla[2], Sabika Mistry[3]

Received: 01-01-2024
Accepted: 28-01-2024
Conflicts of interest: None

Abstract:
The use of botulinum toxin A (BTX-A) has revolutionized the treatment of non-neurogenic and neurogenic lower urinary tract dysfunction (NLUTD) as Multiple sclerosis (MS), spinal cord injury (SCI), cerebrovascular accident (CVA) and parkinsonism disease (PD) over the past three decades. Initially, botulinum toxin was utilized as a sphincteric injection to manage detrusor sphincter dyssynergia. However, it is now primarily administered as an intradetrusor injection to treat overactive bladder (OAB) and neurogenic detrusor overactivity (NDO). Its use in urology is increasingly expanding for various conditions, e.g., idiopathic OAB, Refractory OAB, Benign prostatic hyperplasia, bladder neck obstruction, Interstitial cystitis, spina bifida, neurogenic bladder, and external sphincter dyssynergia. Urodynamic studies (UDS) were conducted, and doses were adjusted based on the condition being treated. Botox injections are available in Bangladesh and have become cost-effective. At our institute, the results and patient experiences have been promising. A retrospective study conducted between 2023 and 2024 involved patients treated with Botox following diagnosis via urodynamic study.

Conclusions: *Outcome of BTX-A in urology depends on proper counselling and to discuss possible expected results. There is rising focus on the long-term outcomes of BTX-A for NDO management, bladder neck obstruction, refractory OAB, and reflux diseases.*

Keywords: Botulinum toxin, Neurogenic, Non urogemic problem

Introduction:

Botulinum toxin (BTX) is a neurotoxin synthesized by *Clostridium botulinum*, an anaerobic, rod-shaped, gram-positive bacterium. BTX-A has been used in NLUTD for over three decades and began with the work of Denis Dykstra, who reported the first sphincter injections for detrusor sphincter dyssynergia in 1988. In 2000, Brigitte Schurch reported the first use of intradetrusor injections to treat NDO in patients with spinal cord injury (SCI) and multiple sclerosis (MS). Over the past three decades, the use of BTX-A has transformed the field of neuro-urology, starting with sphincter injections for detrusor-sphincter dyssynergia and evolving into intradetrusor injections, which are now the preferred treatment for NDO patients unresponsive to anticholinergic therapies. This article provides an overview of the use of BTX-A for NLUTD, including strong supporting evidence and recent relevant insights. At present, BTX is used in urology all over the world in many indications such as non-neurogenic OAB, neurogenic OAB due to spinal cord injury (SCI) and multiple sclerosis (MS), Parkinson's disease, spina bifida, and CVA, Bladder neck hypertrophy (BNH), bilateral vesicoureteral reflux,

1. Professor of neuro-urology, Department of Urology, BMU, Dhaka, Bangladesh
2. Senior Staff Nurse Urodynamic Study Urology Department, BMU, Dhaka, Bangladesh
3. Senior Staff Nurse Urodynamic Study Urology Department, BMU, Dhaka, Bangladesh
Correspondences: Prof. ATM Aman Ullah, Professor of neuro-urology, Department of Urology, BMU, Dhaka, Bangladesh, Email: amanpg@gmail.com

non-obstructive retention, premature ejaculations, and interstitial cystitis.

Methods:

This study was conducted between April 2023 to October 2024 retrospectively on the use of BTX in neuro-urology. The research strategy included the use of Botox with patients in refractory OAB, neurogenic overactive bladder, BNH, and bilateral vesicoureteral reflux (Total number of patients = 9). Basic principles of BTX Mechanism of Action BTX-A action, when injected in the lower urinary tract (either bladder, bladder neck, or sphincter), has for long been thought to rely mostly on its known effect of blocking the presynaptic vesicular release of acetylcholine (ACh) at the neuromuscular junction.

Results:

UDS was conducted on 221 patients from April 23 to March 2024 at the urodynamic center at BSMMU with different diseases and post-operative states among them, 83 were OAB, 70 were Underactive bladders and rest were normal. Among them nine patients consented to Botox injection. These include detrusor overactivity following conditions of OAB (4 patients), Neurogenic OAB (2 patients), BNH (2 patients), and reflux with CRF (one patient). In all cases, 2 doses (2 session) of Botox were given except for VUR where 3 doses (3 sessions) were given in three-month intervals. Follow-up care was provided after 6-7 months. All the patients were incontinence-free, as confirmed by their history and ultrasonogram. They also showed an increased voiding interval, with a change in maximum cystometric capacity (MCC) from baseline ranging from 113 to 140 ml. In one case of BNH patient developed urosepsis and needed treatment with sensitive antibiotics after hospitalization. In terms of quality of life all patients reported being very good.

Table I: Urodynamic finding in different diseases at urology department

Name of disease	Underactive (no's)	OAB	Normal	Total
PLID	4	1	0	5
Laminectomy	5	5	8	18
BNI	1	0	0	1
Meningocele	1	5	0	6
S tumor	1	0	0	1
Transverse myelitis	1	0	0	1
LUTS	57	59	51	167
SCI	0	4	0	4
Nocturnal enuresis	0	1	0	1
Stroke	0	2	0	2
VP Shunt	0	1	0	1
Parkinsonism	0	2	0	2
TURP	0	1	0	1
Down syndrome	0	1	0	1
APR	0	0	2	2
Stress incontinece	0	0	3	3
Fulgaration	0	0	3	3
BNI	0	0	1	1
Total	70	83	68	221

Table II : Outcomes of Intradetrusor botulinum Toxin A in Patients with different diseases

Overactivity with number	Treatment Arms & BTX-A Doses	Mean Change in Number of UI Episodes/ Week at 6 months	Mean Change in MCC (mL) at 6 months
OAB (4)	100 unit	0	113
NOAB (2)	200 unit	0	140
BNH (2)	100 unit	0	114
Reflux disease (1)	100 unit	0	134

Discussion:

The mechanism of BTX-A in the lower urinary tract (bladder, bladder neck, or sphincter) has long been believed to primarily involve inhibiting the release of acetylcholine (ACh) from presynaptic vesicles at the neuromuscular junction. However, recent research suggests that for intradetrusor injections, BTX-A works through two mechanisms: it affects both the afferent pathways and the efferent pathways. BTX A - is known to block presynaptic neurotransmitter release. Unlike the dual afferent and efferent mechanisms of action observed with intradetrusor injections, sphincter injections are believed to function primarily through an efferent mechanism by inhibiting acetylcholine (ACh) release from presynaptic vesicles at the neuromuscular junction, thereby preventing the release of neurotransmitters such as ACh, substance P, and adenosine triphosphate (ATP) into the synaptic cleft. In addition to its effect on the efferent cholinergic and purinergic pathways (ACh, ATP), BTX-A produces an afferent desensitization through the purinergic pathway (ATP and P2X3 receptors) and decrease of TRPV1 receptors as well as its possible action on neurotrophic factor). It has also been demonstrated to inhibit the exocytosis of sensory peptides, including substance P and calcitonin gene-related peptide (CGRP), from sensory neurons.[1-2]

Brigitte Schurch: Pioneering Works: In the 2000s, Brigitte Schurch and Manfred Stohrer were the first to report the use of intradetrusor onabotulinumtoxinA injections for treating NDO. In their series that included 21 SCI patients with NDO refractory to anticholinergics from two institutions (Zurich, Switzerland and Murnau, Germany), they observed resolution of incontinence in 90.5% of patients and notable progress in all urodynamic parameters was observed six weeks following the injection of either 200 U or 300 U of onabotulinumtoxinA (BOTOX® , Allergan, Inc., Irvine, CA) and this effect was maintained at 36 weeks during the last follow up visit.[3,4] Subsequently, Schurch led a prospective, multicenter, European study that included 200 neurogenic patients, mostly with SCI, who received intradetrusor injections of 300 U of onabotulinumtoxinA.**5** The results of this largest series reported in 2004 confirmed the preliminary findings with 73.3% of patients experiencing complete resolution of their urinary incontinence and improvement in all relevant urodynamic parameters at 12 and 36 weeks. In 2005, Brigitte Schurch published the first phase 3 randomized controlled trial (RCT), providing strong evidence of the effectiveness of intradetrusor onabotulinumtoxinA in treating neurogenic detrusor overactivity (NDO) in patients with spinal cord injury (SCI) and multiple sclerosis (MS).[6] It should be noted that all initial work was done in patients with NLUTD, who were self-catheterization dependent.

Injection Techniques: Injection techniques have been used with rigid cystoscope and spinal anesthesia, and injection sites the bladder wall including trigone or not. Recent findings have challenged this belief and propose that protocols should include the trigone, as it may offer additional sensory benefits due to the trigone's high density of nociceptive bladder afferents.[7] The recommended dilution protocol for NDO is 200 U onabotulinumtoxinA/20 mL of sterile 0.9% saline solution injected in 20 sites. Recent randomized trials have proposed that using fewer injection sites in protocols might yield similar efficacy.[8] In a recent prospective study, Avallone and colleagues presented encouraging results using BTX-A administered at just one to three injection sites. However, additional research is required to validate these findings, as their study involved a mixed cohort of OAB and NDO patients and lacked a control group.[9] Finally, onabotulinumtoxinA has usually been administered into the detrusor to treat NDO using needles typically 22 gauge and equal to 5 mm in length but, as evidenced in OAB and interstitial cystitis, one RCT found no significant difference between suburothelial and intradetrusor injections in NDO patients.

Under spinal anesthesia, inoculation of 100 U of onabotulinumtoxinA, BOTOX®, diluted in 4 cc of normal saline solution (divided into 4 injections of 1 cc each) into the bladder neck at 3, 6, 9, and 12 o'clock position.

In our study all patients were incontinence free, had increased voiding interval, and displayed MCC change from baseline of 113-140 ml. Most patients had an overall satisfaction with Inj Botox, reported no complications and experienced an improved quality of life. However, one BNH patient developed urosepsis and was treated with sensitive antibiotics.

Published studies indicate that the use of BoNT is safe, with common side effects such as urinary tract infections, voiding difficulties and mild hematuria, requiring clean intermittent catheterization generally being short-lived, ranging from 2 weeks to 2 months.[10,11,12] Treatment failure has been reported in 8-40%

of idiopathic DO and in 5-10% of neurogenic DO[11,12,] and these failures are more commonly seen among older patients, and in patients with history of frequent urinary tract infections, increased pressure at reflex detrusor contraction and low bladder compliance as well as the development of antibody against BoNT-A[13,14.]

Nonetheless, the relatively long duration of intravesical BoNT effect, which remains sustained with repeated injections, appears to provide a more cost-effective treatment option with higher quality adjusted life-year for many patients compared to the use of oral therapy, incontinence aids and reconstructive surgery.[15,16.] Cost-effectiveness analysis using Markov analytical and decision analysis models showed that BoNT is cheaper and more cost-effective than sacral neuromodulation and/or augmentation cystoplasty over 3 years.[17,18]

Transurethral injection into the bladder neck, particularly the anterior urethral wall, offers a promising and safe new treatment option for urinary retention in patients with BNH who are not suitable for surgery or have not responded to medical treatments. As our case has shown, after bladder neck injection, the patient presenting with a history of recurrent episodes of urinary retention had major improvements in post void residue and IPSS scores. Besides, the use of transurethral approach provides a direct view of the bladder neck, median lobe, and transition zone and presents a secure method as compared to transrectal and transperineal injections.[19]

Multiple minimally invasive procedures that deal with medically resistant, surgically contraindicated BPH have emerged. One of the latter techniques "Urolift" is used to relieve urinary symptoms caused by BPH. It is a minimally invasive approach that lifts the enlarged prostate, relieving obstruction, and can be done under local anesthesia.[20] However, such technique, like others, deals mainly with BPH rather than high bladder neck presented in our case and may not be recommended for patients with high bladder neck or modest median lobe

Wrapping up this case report, botulinum toxin injection into the bladder neck appears to offer a new promising treatment option for BNH. However, further trials are needed to establish the validity of this new indication as well as the adequate dosage of the toxin required. It is important to establish follow-up protocols, define appropriate intervals between injections, and address comorbidities associated with this treatment. The simplicity of the procedure, the absence of anesthesia requirements, the potential for outpatient treatment, and the effectiveness of this minimally invasive approach for persistent LUTS caused by BNH appear to hold significant promise.

In patients with neurogenic bladder, low-grade VUR is commonly treated with a combination of Botulinum Toxin A injections, anticholinergic drugs, and clean intermittent catheterization (CIC). However, for refractory VUR**,** the effect of CIC combined with anticholinergic drugs is controversial. Endoscopic injection of DXHA is typically effective for treating VUR, but its efficacy is limited in patients with neurogenic bladder. The treatment of these patients is primarily aimed at detrusor overactivity and poor compliance. For refractory VUR in patients with neurogenic bladder, surgical treatment (i.e., ureteral reimplantation, bladder enlargement, or both[21] is recommended. In recent years, detrusor injection of botulinum toxin A (BTX-A) has proven safe and effective in the treatment of neurogenic bladder with low compliance and high pressure[22] and can alleviate or cure secondary VUR in some patients[23]. A retrospective study included 72 patients who were treated with BTX-A injections into the bladder wall and/or urethral sphincter between January 1997 and December 2007. Seven patients had both neurogenic bladder and VUR (mean age 10.8.1 years). All patients were followed for 6–12 months. The VUR resolved, and no recurrences were observed for 12–33 months.[24]

Conclusions:

Outcome of BTX A in urology depends on proper counselling and to discuss possible expected results. There is also a growing interest in long-term result of BTX-A for NDO, refractory OAB, BNH, and low grade VUR and their management. There is a possible new indication for urethral sphincter injections with a with a promising result.

References:

1. Apostolidis A, Rahnama'i MS, Fry C, et al. Do we understand how botulinum toxin works and have we optimized the way it is administered to the bladder? ICI-RS 2014. Neurourol Urodyn. 2016;35:293-298.

2. Jhang JF, Kuo HC. Botulinum toxin A and lower urinary tract dysfunction: pathophysiology and mechanisms of action. Toxins (Basel). 2016;8:120.

3. Schurch B, Schmid DM, Stöhrer M. Treatment of neurogenic incontinence with botulinum toxin A. N Engl J Med. 2000;342:665

4. Schurch B, Stöhrer M, Kramer G, et al. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000;164(3 Pt 1): 692-697.

5. Reitz A, Stöhrer M, Kramer G, et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol. 2004;45:510-515.

6. Schurch B, de Sèze M, Denys P, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: results of a single treatment, randomized, placebo controlled 6-month study. J Urol. 2005;174:196-200.

7. Hui C, Keji X, Chonghe J, et al. Combined detrusor trigone BTX-A injections for urinary incontinence secondary to neurogenic detrusor overactivity. Spinal Cord. 2016;54:46-50.

8. Denys P, Del Popolo G, Amarenco G, et al. Efficacy and safety of two administration modes of an intra-detrusor injection of 750 units Dysport® (abobotulinumtoxinA) in patients suffering from refractory neurogenic detrusor overactivity (NDO): a randomised placebo-controlled phase IIa study. Neurourol Urodyn. 2017;36:457-462.

9. Avallone MA, Sack BS, El-Arabi A, et al. Less is moreA pilot study evaluating one to three intradetrusor Nitti VW, Dmochowski R, Herschon S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol 2013;189:2186-9

10. Apostolidis A, Dasgupta P, Denys P, et al. Recommendations on the use of botulinum toxin in the treatment of lower urinary tract disorders and pelvic floor dysfunctions: a European consensus panel report. Eur Urol 2009;55:100-20.

11. Chancellor MB, Elovic E, Esquenazi A, et al. Evidence-based review and assessment of botulinum neurotoxin for the treatment of urologic conditions. Toxicon 2013;67:129-40.

12. Dowson C, Khan MS, Dasgupta P, Sahai A. Repeat botulinum toxin-A injections for treatment of adult detrusor overactivity. Nat Rev Urol 2010;7:661-7

13. Sahai A, Khan MS, Le Gall N, Dasgupta P. Urodynamic assessment of poor responders after botulinum toxin-A treatment for overactive bladder. Urology 2008;71:455-9

14. Schulte-Baukloh H, Bigalke H, Miller K, et al. Botulinum neurotoxin type A in urology: antibodies as a cause of therapy failure. Int J Urol 2008;15:407-15

15. Kalsi V, Popat RB, Apostolidis A, et al. Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. Eur Urol 2006;49:519-27

16. Wefer B, Ehlken B, Bremer J, et al. Treatment outcomes and resource use of patients with neurogenic detrusor overactivity receiving botulinum toxin A (Botox) therapy in Germany. World J Urol 2010;28:385-90

17. Leong RK, Wachter SG, Joore MA, van Kerrebroeck PE. Cost-effectiveness analysis of sacral neuromodulation and botulinum toxin A treatment for patients with idiopathic overactive bladder. BJU Int 2011;108(4):558-64

18. Watanabe JH, Campbell JD, Ravelo A, et al. Cost analysis of interventions for antimuscurinic refractory patients with overactive bladder/ Urology. 2010;76(4):835-40

19. Chuang Y. C., Minimally invasive therapy for BPH, *Incontinence and Pelvic Floor Dysfunction*. (2007) 1, no. supplement 2, 21–24.

20. McNicholas T. A., Woo H. H., Chin P. T., Bolton D., Fernández Arjona M., Sievert K.-D., Schoenthaler M., Wetterauer U., Vrijhof E. J. E. J., Gange S., and Montorsi F., Minimally invasive prostatic urethral lift: surgical technique and multinational experience, *European Urology*. (2013) 64, no. 2, 292–299, https://doi.org/10.1016/j.eururo.2013.01.008, 2-s2.0-84879979870.

21. Y. Hayashi, Y. Kato, T. Okazaky, et al., The effectiveness of ureteric reimplantation during bladder augmentation for high-grade vesicouretericreflflux in patients with neurogenic bladder: Longterm outcome. J. Pediatr. Surg. 42, 1998–2001 (2007)

22. C.Q. Wu, I. Franco, Management of vesicoureteral reflux in neurogenic bladder. Investig. Clin. Urol. 58(Suppl 1), S54–S58 (2017). https://doi.org/10.4111/icu.2017.58.S1.S54. Epub 2017 Jun 2

23. M. Riccabona, M. Koen, M. Schindler, et al., Botulinum-A toxin injection into the detrusor: A safe alternative in the treatment of children with myelomeningocele with detrusor hyperreflflexia. J. Urol. 171, 845–848 (2004)

24. G. Mosiello, M.L. Salsano, M.P. Pascali, D. Camanni, M. De Gennaro, A minimally invasive approach in the treatment of vesicoureteral reflux in neurogenic bladder in children. Eur. Urol. 55(1), 254–256 (2009). https://doi.org/10.1016/j.eururo.2008.07. 030. Epub 2008 Jul 18.