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Title Page

Botox rechallenge – An additional tool in the management of an incompletely emptying bladder and inadequate overactive symptom control following sacral neuromodulation.

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Running Title: Botox rechallenge an additional tool
Key Words: OAB, overactive bladder, acute urinary retention, Botox, BoNT-A, DO-DU, UUI

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/luts.12332

Abstract word count – 216
Total word count - 1084

Abbreviations

AUR: acute urinary retention

BoNT-A: botulinum toxin type A

DO-DU: detrusor overactivity and detrusor underactivity

IDC: indwelling catheter

ISC: intermittent self-catheterisation

OAB: overactive bladder

PVR: post void residual

SNM: sacral neuromodulation

UDS: urodynamics

UUI: urge urinary incontinence

Abstract

Case

Two female patients aged 70 and 72 with video-urodynamics confirmed detrusor overactivity with detrusor underactivity (DO-DU). Patients were refractory to medical therapies and had previously failed intravesical botulinum-toxin-A (BoNT-A) at other centres secondary to urinary retention and difficulty with self-catheterisation. Placement of an Interstim™ II device (Medtronic, Minneapolis, MN) for sacral neuromodulation (SNM) as alternative third line treatment partially improved overactive bladder (OAB) symptoms while significantly improving voiding symptoms. Post void residual (PVR) of patients improved from a median of 118ml (110-125ml) to 20ml (18-26ml), and 213ml (195-230ml) to 70ml (60-73ml) respectively. Addition of medical therapies post-SNM failed to modify OAB symptoms further and re-challenge with dose reduced BoNT-A was undertaken.

Outcome

OAB symptoms were significantly improved by addition of BoNT-A, while urinary retention was avoided (median PVR post-BoNT-A 38ml (34-40ml) and 185ml (150-205ml) respectively). Reduction in incontinence pad use, as well as resolution of night-time incontinence in both patients and daytime incontinence in one patient was achieved.

Conclusion

DO-DU patients treated by SNM who have improved bladder emptying (PVR <100ml), but incomplete resolution of OAB symptoms should be trialled on adjunct medical therapies to improve OAB symptoms. If OAB symptoms are still inadequately controlled, consideration of re-challenge with BoNT-A, particularly with dose reduction, appears to be efficacious and avoids symptomatic retention in this challenging cohort.

Introduction

Overactive bladder (OAB) is a prevalent syndrome of urgency and frequency which can affect continence and lead to medical, social and economic detriment to the patient. Its prevalence is reported as 6% to 17%, increasing with age, although this may underestimate symptoms in men due to misclassification [1-3]. Pharmacotherapy for OAB predominantly targets the cholinergic or B3 adrenergic pathways and may be used as monotherapy or in synergistic combination [4-6]. Inhibitory treatments of OAB, including botulinum-toxin-A (BoNT-A) carry precautions associated with their use for patients with incomplete bladder emptying (post void residuals (PVR) >100ml at baseline) as it may lead to acute urinary retention (AUR) [7, 8]. Previously called detrusor hyperactivity with impaired contractility (DHIC), patients with detrusor overactivity and detrusor underactivity (DO-DU) are best served by sacral neuromodulation (SNM) as it adds to OAB symptom control, while improving bladder underactivity [9, 10]. Although adjunct pharmacotherapy may supplement the efficacy of SNM, there are currently no published descriptions of addition of BoNT-A therapy following implantation of a SNM device – although it is being used anecdotally [11, 12].

We present two DO-DU patients where previous BoNT-A therapy led to AUR who were successfully re-challenged with BoNT-A following implantation of an Interstim™ II device (Medtronic, Minneapolis, MN) failed to give adequate control to OAB symptoms.

Case Report

Two female patients aged 70 and 72 with video-urodynamics (UDS) confirmed detrusor overactivity and detrusor underactivity were treated following a 15-20 year history of urge urinary incontinence (UUI). Both patients were refractory to a prolonged trial of first and second line therapies involving physiotherapy directed

pelvic floor muscle therapy and bladder retraining, and pharmacotherapy with various anticholinergics including in combination with a B3-adrenergic agonist.

Patients were evaluated with cystoscopy, showing revealed grade 2 bladder trabeculation without other anatomical abnormality. UDS revealed detrusor overactivity, impaired contractility during voiding and was negative for stress incontinence (Table 1). Patients rated voiding symptoms on a local questionnaire. (Figure 1).

Patient one reported terminal urge incontinence occurring on a 1-2 hourly basis both day and night (4-5 large pads/24hr) on a voided volume chart and had a 100ml functional bladder capacity at UDS limited by onset of detrusor overactivity and terminal urge leakage. Prior trial of 55 units of BoNT-A resulted in no subjective improvement, and symptomatic retention requiring indwelling catheter (IDC) for four weeks, due to hand arthropathy preventing intermittent self-catheterisation (ISC).

Patient two complained of urinary frequency and flooding urge incontinence (3 large pads/24hr). She had 550ml bladder capacity at UDS with onset DO at 250ml. She had BoNT-A treatment on two prior occasions, initially with 100units and subsequently with dose reduction to 55units. In both cases she suffered symptomatic AUR managed by nurse assisted intermittent catheterisation due to difficult urethral access through a narrow introitus. She was adamant she would not ISC again without trialling another treatment.

Both patients underwent stage one SNM lead placement at the right S3 nerve root with bellows achieved at 0.3mA. Initial improvement of OAB symptoms in both led to implantation of an Interstim™ II device. Satisfaction with OAB symptom control waned over time (SNM function and placement was investigated and found unchanged) despite re-addition of medical therapies at approximately 10 months and 14 months respectively. PTNS was not offered at our institution.

In both patients, there was a significant improvement in bladder emptying and also a perceived improvement in usual urine flow, although not as apparent on flow study. Median PVR and median maximum flow (Qmax) change from 118ml to 20ml; 13ml/s to 18ml/s in patient one and 213ml to 70ml; 26ml/s to 24ml/s in patient two. Following further discussion with both patients regarding risk for ISC and long-term IDC, re-challenge with dose reduced BoNT-A (55units) was carried out at minimum 12months post-SNM implantation.
Patient one had resolution of night-time incontinence and significant improvement in sensation of urgency. She was able to go from four incontinence pads per day to one at night. Patient two had complete resolution of night and daytime UI, with an improvement in frequency from 2 hourly to 4-5 hourly. She was able to go from three incontinence pads per day to none. (Table 2) (Table 3)

Discussion

Functional urologists often encounter the complex patient with refractory OAB and underlying DO-DU in whom the risk of urinary retention and acceptability of ISC may influence the choice of third line therapy. BoNT-A carries a particularly high risk of AUR in patients with impaired bladder contractility and a PVR >100ml, therefore patients must often forgo this choice of treatment[8]. Hoag et al reported on 36 patients were previously treated with BoNT-A (9 who discontinued use due to retention) who underwent SNM. In that series, 73.9% of patients were satisfied with OAB control following SNM, which leaves 26.1% of patients who were not [13].

The cause of DO-DU is unknown, although theories varying from variation in ovarian hormones in post-menopausal women to muscle ischaemia due to chronicity of OAB symptoms are believed to play a part [9]. The mechanism of improved voiding due to SNM is unknown, although it's postulated that improved voiding is due to inhibition of afferent pudendal signalling inhibiting urethral and somatic sphincter complexes of the guarding reflex avoiding outflow obstruction [9, 14]. Given that SNM may improve lower urinary tract symptoms (LUTS) in both aspects of DO-DU by improving detrusor function, this may explain the stability in PVR and lack of AUR despite rechallenging patients with BoNT-A.

Despite improvement in impaired contractility, failure to control OAB symptoms despite use of SNM synergistically with B3 agonists or anti-cholinergic medications lacks recommendation on next treatment strategy. Six-monthly BoNT-A therapy following SNM is a less invasive management option than addition of PTNS, bilateral SNM implantation, or augmentation cystoplasty which have been suggested as alternatives [12]. Patients having suffered AUR secondary to BoNT-A or those with a baseline PVR >100ml and DO-DU who have an improvement in voiding with SNM, might be considered for re-challenge with dose reduced BoNT-A to control OAB symptoms.

In this limited case series, dose reduced BoNT-A with concurrent SNM in patients with DO-DU and incomplete OAB symptom control did not result in AUR, while significantly improving OAB symptoms. DO-DU patients treated by SNM who have incomplete response of OAB symptoms should be trialled on B3 agonists or anti-cholinergic medications prior to more invasive treatment strategies. These two cases represent a complex challenge, and in selected situations, knowing that one can safely rechallenge with BoNT-A after partial SNM response for salvage while avoiding AUR adds another useful tool to our treatment algorithm.

Consent

Written consent was obtained from patients in regard to the publication of article content for educational purposes.

Conflicts of interest

We declare no outside funding and no conflicts of interest in the publication of these works.

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	Patient 1	**Patient 2**
Storage Phase		
Onset DO		
Volume (ml)	51	259
Pdet (cm H2O)	15	5
SUI	no leak	no leak

UUI	Terminal leak	no leak
Voiding phase		
Fluoroscopy	Open outlet, nil descent	Open outlet, nil descent
Voided volume (ml)	37	433
Pdet at Qmax (cm H2O)	15.4	55.1
Qmax (ml/s)	13	26
PVR (ml)	118	213

Table 1 – Video Urodynamics on patients prior to sacral neuromodulation

LUTS	**Baseline**	**Post SNM**	**Post BoNT-A (55Units)**	**Repeated BoNT-A (55Units)**
Frequency (1-5)	4	4	2	2
Urgency (1-5)	5	4	2	2
Daytime Incontinence	Yes	Yes	Yes	Yes
Pads/Day	3-4	3-5	1-2	1-2
Night-time incontinence	Yes	Yes	No	No
Pads/Night	1-2	1-2	0	0
Median Qmax (ml/s, range)	13	18	/	/
Median PVR (ml, range)	118 (110-125)	20 (18-26)	133 (120-135)	38 (34-40)
Acute urinary retention	Yes with 55 Units BoNT-A	No	No	No

Table 2 - Patient 1 interventions and symptom control outcomes

LUTS	**Baseline**	**Post SNM**	**Post BoNT-A (55Units)**	**Repeated BoNT-A (65Units)**
Frequency (1-5)	4	3	2	2
Urgency (1-5)	5	4	1	1
Daytime Incontinence	Yes	Yes	No	No
Pads/Day	4-5	3-4	0	0
Night-time incontinence	Yes	Yes	No	No
Pads/Night	1-2	1	0	0
Median Qmax (ml/s, range)	26	24	/	/
Median PVR (ml) (range)	213 (195-230)	70 (60-73)	93 (75-104)	185 (150-205)
Acute urinary retention	Yes with 55 Units BoNT-A	No	No	No

Table 3 - Patient 2 interventions and symptom control outcomes

How severe are the following symptoms?	Rarely/ Never	Occasionally	Sometimes	Often	Always
Strong urge to urinate which is hard to ignore (Urgency)	1	2	3	4	5
Repeated regular trips to the toilet where little to no urine is passed (frequency)	1	2	3	4	5
Notably slow urine stream	1	2	3	4	5
Feeling of incompletely emptying bladder	1	2	3	4	5

Figure 1 - Lower Urinary Tract Symptom Survey

How severe are the following symptoms?	**Rarely/ Never**	**Occasionally**	**Sometimes**	**Often**	**Always**
Strong urge to urinate which is hard to ignore (Urgency)	1	2	3	4	5
Repeated regular trips to the toilet where little to no urine is passed (frequency)	1	2	3	4	5
Notably slow urine stream	1	2	3	4	5
Feeling of incompletely emptying bladder	1	2	3	4	5

LUTS_12332_Figure 1 - Lower Urinary Tract Symptom Survey.png

	Patient 1	Patient 2
Storage Phase		
Onset DO		
Volume (ml)	51	259
Pdet (cm H2O)	15	5
SUI	no leak	no leak
UUI	terminal	no leak
Voiding phase		
Fluoroscopy	Open outlet, nil descent	Open outlet, nil descent
Voided volume (ml)	37	433
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LUTS_12332_Table 1 – Video Urodynamics on patients prior to sacral neuromodulation.png

LUTS	Baseline	Post SNM	Post BoNT-A (55Units)	Repeated BoNT-A (55Units)
Frequency (1-5)	4	4	2	2
Urgency (1-5)	5	4	2	2
Daytime Incontinence	Yes	Yes	Yes	Yes
Pads/Day	3-4	3-5	1-2	1-2
Night-time incontinence	Yes	Yes	No	No
Pads/Night	1-2	1-2	0	0
Median Qmax (ml/s, range)	13	18	/	/
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Acute urinary retention	Yes with 55 Units BoNT-A	No	No	No

LUTS_12332_Table 2 - Patient 1 interventions and symptom control outcomes.png

LUTS	Baseline	Post SNM	Post BoNT-A (55Units)	Repeated BoNT-A (65Units)
Frequency (1-5)	4	3	2	2
Urgency (1-5)	5	4	1	1
Daytime Incontinence	Yes	Yes	No	No
Pads/Day	4-5	3-4	0	0
Night-time incontinence	Yes	Yes	No	No
Pads/Night	1-2	1	0	0
Median Qmax (ml/s, range)	26	24	/	/
Median PVR (ml) (range)	213 (195-230)	70 (60-73)	93 (75-104)	185 (150-205)
Acute urinary retention	Yes with 55 Units BoNT-A	No	No	No

LUTS_12332_Table 3 - Patient 2 interventions and symptom control outcomes.png