

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Difficulty passing urine or being unable to completely empty the bladder (urinary retention) can happen if the muscle controlling release of urine from the bladder (urethral sphincter) does not relax. In some people, it can happen without any known cause (idiopathic) and with no physical obstruction to the urine flow (non-obstructive). In this procedure, botulinum toxin type A is injected into the urethral sphincter. The aim is to relax it and allow urine to be passed more easily, without needing to use a catheter to empty the bladder. The effects are temporary, and the procedure may need to be repeated every few months.

Contents

[Introduction](#)

[Description of the procedure](#)

[Efficacy summary](#)

[Safety summary](#)

[The evidence assessed](#)

[Validity and generalisability of the studies](#)

[Existing assessments of this procedure](#)

[Related NICE guidance](#)

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

[Additional information considered by IPAC](#)

[References](#)

[Literature search strategy](#)

[Appendix](#)

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Abbreviations

Word or phrase	Abbreviation
Clean intermittent catheterisation	CIC
Cystometric bladder capacity	CBC
Detrusor overactivity with inadequate contractility	DHIC
Detrusor sphincter dyssynergia	DSD
Detrusor underactivity	DU
Dysfunctional voiding	DV
Detrusor voiding pressure	Pdet
Electromyography	EMG
Endoscopic ultrasound	EUS
Functional profile length	FPL
International Prostate Symptom Score	IPSS
IPSS storage sub-score	IPSS-S
IPSS voiding sub-score	IPSS-V
Lower urinary tract symptoms	LUTS
Maximal urethral closure pressure	MUCP
Maximal urinary flow rate	Qmax
Patient Perception of Bladder Condition score	PPBC
Poor relaxation of the urethral sphincter	PRES
Post-void residual urine volume	PVR
Quality of life	QOL
Randomised controlled trial	RCT
Standard deviation	SD
Total IPSS score	IPSS-T
Urethral pressure profile	UPP
Urethral sphincter dysfunction	USD
Urinary tract infection	UTI

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Video-urodynamic study	VUDS
Voided volume	VV
Voiding efficiency	VE

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and professional opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2022

Procedure name

- Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Professional societies

- British Society of Urogynaecology
- British Association of Urological Surgeons.

Description of the procedure

Indications and current treatment

Idiopathic non-obstructive urinary retention is the inability to completely empty the bladder with no physical obstruction (in the urethra or bladder neck) to normal urine flow. It can be caused by USD. This can be because of DV, urethral sphincter hyperactivity or inadequate relaxation of the urethral sphincter (for example, Fowler's syndrome in younger women), or bladder functional problems

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

(detrusor muscle underactivity, or detrusor hyperreflexia and inadequate contractility). But the specific underlying cause of the condition is unknown. Idiopathic non-obstructive urinary retention is often asymptomatic, but some people have lower abdominal discomfort and pain. Also, it can cause complications such as recurrent UTIs and chronic kidney disease.

Current treatments for non-obstructive urinary retention include urotherapy (that is, education and rehabilitation for bladder and bowel management), an alpha adrenoreceptor-blocker medicine, urethral dilatation or CIC. When the condition is refractory to these treatments, it may be treated with [sacral nerve stimulation](#) or urinary diversion procedures.

What the procedure involves

Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention is usually done under EMG, or electrical stimulation and cystoscopy guidance. It is usually done with the person awake and lying in the lithotomy position. A local anaesthetic may be used. Botulinum toxin type A diluted with normal saline is injected directly into the external urethral sphincter using a syringe needle. A transperineal route is used in women and a transurethral route is used in men.

The dose and number of injections, and the depth and position of injections on the EUS, vary and depend on the discretion of the clinician. After the treatment, an overnight catheter is inserted for drainage. People are discharged from hospital the next day and have oral antibiotics for a week. The aim of the procedure is to relax the sphincter muscle and restore voiding function. It may be repeated every few months.

Outcome measures

IPSS

The IPSS is a tool for classifying the severity of LUTS and assessing the impact of LUTS on QOL.

The IPSS questionnaire is intended to be completed by the patient. It contains 7 questions relating to symptom severity (each question is scored from 0 [best] to 5 [worst]) and 1 question relating to QOL due to urinary symptoms (scored from 0 [best] to 6 [worst]).

The IPSS severity score is interpreted as:

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

- Score 20 to 35: severely symptomatic.
- Score 8 to 19: moderately symptomatic.
- Score 0 to 7: mildly symptomatic.

Limitations of the IPSS questionnaire include lack of assessing incontinence, post-micturition symptoms and bother caused by each separate symptom.

Printable versions of the IPSS questionnaire are widely available online, for example, from the [Royal United Hospital Bath NHS trust website](#).

PPBC

PPBC is a single item tool used to measure to assess the patient's subjective perception of urinary (bladder) problems. It is scored on a 6 point rating scale ranging from 1 (no problems) to 6 (many severe problems).

Efficacy summary

Success rate

In an RCT of 73 patients with medically refractory DV or DU comparing the effects of botulinum toxin type A (from now, botulinum) with normal saline urethral sphincter injections, there was an analysis of 62 patients who completed 1 month of follow up. This found that the overall success rate for both groups combined (defined as reduction of PPBC by more than or equal to 2) was 44%. Also, there was no statistically significant difference in success rate between patients who had botulinum injections and those who had saline placebo injections (37% [14/38] compared with 54%, [13/24], $p=0.114$). Subgroup analysis showed that there was no statistically significant difference in success rate for the patients with DV (botulinum 44% [7/16] compared with placebo 68% [10/15], $p=0.200$) and the patients with DU (botulinum 32% [7/22] compared with placebo 33% [3/9], $p=0.935$). The success rates after a second botulinum injection increased from 29% to 57% among patients with DV and from 25% to 50% among patients with DU (Jiang 2016).

In a case series of 27 patients with idiopathic low detrusor contractility treated with botulinum injection into the urethral sphincter, there was an overall success rate was 89% (24/27; Kuo 2007a).

In a case series of 66 patients who had 50 units ($n=33$) and 100 units ($n=33$) of botulinum into the urethral sphincter, there was no statistically significant

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

difference in the overall success rate between the 2 doses (85% [28/33] compared with 91% [30/33], $p=0.452$; Kuo 2007b).

In a retrospective case series of 81 patients with non-neurogenic DV (55 with midurethral DV, 19 with distal urethral DV, and 7 with bladder neck dysfunction and midurethral DV), treated with botulinum injection into the urethral sphincter, the treatment was successful in 68% (55/81) of patients and failed in 32% (26/81) of patients. Treatment success was defined as an improvement of VE by 10% and patient-reported global response assessment by more than or equal to 1% (Jiang 2021).

Clinical outcomes

IPSS

In the RCT analysis of 62 patients, statistically significant improvements from baseline in IPSS-V, IPSS-S, IPSS-T were seen in the botulinum injection and placebo groups after first EUS injections at 1-month follow up ($p<0.05$). Patients who had botulinum injections had statistically significantly less improvement in IPSS-V, IPSS-S and IPSS-T than patients in the placebo group. Subgroup analysis showed that the outcomes were similar between the DV and DU groups after first injection. There was a statistically significantly greater reduction in IPSS-T in the placebo group than in the botulinum group in patients with DV ($p=0.026$). In patients with DU, the placebo group had statistically significantly greater reductions in IPSS-V and IPSS-T than the botulinum group ($p=0.036$ and 0.002). Repeated botulinum injection into the urethral sphincter in the botulinum group ($n=19$) resulted in improvement in IPSS-V, IPSS-S, IPSS-T in patients with DV and DU (Jiang 2016).

In a case series of 10 patients with a primary disorder of urethral sphincter relaxation (Fowler's syndrome) treated with 100 units of botulinum injection into the external urethral sphincter, the mean symptom scores on the IPSS questionnaire improved from 25.6 to 14.1. Also, the mean 'bother' score on IPSS reduced from 6.1 to 3.5 at 10-week follow up (Panicker 2016).

PPBC

In the RCT analysis of 62 patients, statistically significant improvements from baseline were seen in both botulinum and placebo groups at 1-month follow up after first injection ($p<0.05$). Repeated botulinum injections into the urethral sphincter in the botulinum group ($n=19$) resulted in improvement in PPBC in patients with DV and DU (Jiang 2016).

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

In a retrospective analysis of 56 patients with refractory idiopathic external urethral sphincter dysfunction who had botulinum injections into the external urethral sphincter, patients with DV (n=23) had no statistically significant differences in treatment improvement rates compared with patients with PRES (n=33). The rates of good subjective outcomes (65% [15/23] compared with 64% [21/33], p=0.903) and objective outcomes (74% [17/23] compared with 67% [22/33], p=0.562) were not statistically significantly different between the 2 groups at 1-month follow up (Ou 2021).

Recovery of detrusor function

In the case series of 27 patients, there was recovery of detrusor contractility in 48% (13/27) of patients (7 with DV and low detrusor contractility with concomitant PRES, 3 with DHIC and 3 with DU) and no recovery in 52% (14/27) of patients. Detrusor contractility recovery was defined as an increase in Pdet and Qmax and reduced PVR volume). Patients with recovery could void without abdominal straining, but patients without recovery continued to void with increased abdominal pressure (Kuo 2007).

Duration of treatment effect

In the case series of 27 patients, patients with recovery of detrusor contractility (n=13) had a statistically significantly longer duration of treatment effect than those without recovery (n=14; 14±7.6 months compared with 4.6±2.5 months, p<0.001; Kuo 2007).

In the case series of 66 patients, the mean duration of treatment effect was statistically significantly shorter in the 50 units botulinum injection group than the 100 units group (6.4±3.6 months compared with 8.4±3.4 months, p= 0.022; Kuo 2007b)

QOL

In the RCT analysis of 62 patients, QOL statistically significantly improved from baseline in both botulinum injection and placebo groups at 1-month follow up after first injection (botulinum group from 4.5±1.9 to 3.0±1.9 and placebo group from 5.4±0.9 to 2.4±1.9, p<0.05 compared with baseline or before injection). Compared with placebo, botulinum injection into the urethral sphincter resulted in statistically significantly less improvement in QOL (p<0.01 between the groups after treatment). Repeated botulinum injection into the urethral sphincter (n=19) resulted improvement in QOL index in patients with DV and DU (p<0.05; Jiang 2016).

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

In the case series of 27 patients, 10 out of 13 patients with recovery of detrusor contractility had an excellent outcome. QOL index assessed using a questionnaire (with a scale ranging from 0 to 6) improved by more than 2 points and reduction in PVR by more than 50%. Three patients had an improved outcome (QOL index improved by 1 point with improvement of urodynamic parameters). Of these who reported no recovery (n=14), 1 had an excellent outcome, 10 had an improved result and 3 had a failed result (no improvement in QOL; Kuo 2007).

In the case series of 66 patients with voiding dysfunction (of any aetiology) treated with botulinum injection into the external urethral sphincter (100 units and 50 units), the overall treatment results were excellent in 61% (20/33) and 70% (23/33) of patients respectively. 'Excellent' was defined as a more than 2-point improvement in the QOL index, 50% or more reduction in PVR and 25% or more reduction in MUCP. The overall treatment results were improved in 30% (10/33) and 15% (5/33) of patients respectively. 'Improved' was defined as an improvement in the QOL index of 1 point, 50% or more reduction in PVR or 25% or more reduction in MUCP. Treatment failed in 9% (3/33) and 15% (5/33) patients respectively. 'Failed' was defined as no improvement in QoL regardless of the urodynamic improvement (Kuo 2007b).

Urodynamic parameters

In the RCT analysis of 62 patients, after first injections in both groups, there was a statistically significant increase ($p < 0.05$) in Qmax (botulinum group from 5.3 ± 5.7 to 9.8 ± 9.5 and placebo group from 6.3 ± 5.1 to 9.5 ± 6.6) and in VE (botulinum group from 29.6 ± 28.3 to 44.1 ± 35.3 and placebo group from 34.4 ± 34.2 to 56.1 ± 36.4). But there was only a statistically significant improvement in VV in the botulinum group (from 119.9 ± 82.2 ml to 191.0 ± 140.1 ml) and only a statistically significant improvement in PVR in the placebo group (from 279.3 ± 246.9 to 146.6 ± 160.5 , $p < 0.05$). There were no statistically significant differences in changes in the other VUDS parameters (Pdet cm/H₂O, CBC) between the botulinum and placebo groups after the first injection. Subgroup analysis showed that, in patients with voiding dysfunction (n=31), there were only statistically significant improvements in VUD parameters in the botulinum group, including Pdet (from 40.3 ± 23.0 cmH₂O to 31.6 ± 22.3 cmH₂O), Qmax (from 6.4 ± 5.4 ml/sec to 11.1 ± 10.1 ml/sec) and VV (from 119.9 ± 82.2 ml to 191.0 ± 140.1 ml). In patients with DU (n=31), there were statistically significant improvements in Qmax in both groups (botulinum group from 4.5 ± 6.0 ml/sec to 8.8 ± 9.1 ml/sec, and placebo group from 3.4 ± 3.7 ml/sec to 10.6 ± 9.2 ml/sec) and VE (botulinum group from 20.8 ± 28.5 to 39.4 ± 36.0 and placebo group from 17.0 ± 31.5 to 61.6 ± 40.7). In the DU group, reduction in PVR, was statistically significantly greater in the placebo group (from 415.0 ± 304.0 ml to 131 ± 169.1 ml) than in the

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

botulinum group (from 350.0 ± 174.6 ml to 293 ± 233.1 ml, $p=0.046$ between the groups after treatment). There were no statistically significant changes in VUD parameters after repeated botulinum injections (Jiang 2016).

In the case series of 27 patients, there was a statistically significant reduction in the PVR (from 328 ± 134 ml to 31 ± 35 ml, $p < 0.05$ compared with baseline or before injection) and a statistically significant increase in the Qmax (from 4.7 ± 5.6 ml/sec to 13 ± 6.6 ml/sec, $p < 0.05$ compared with baseline or before injection) in patients with and without recovery of detrusor contractility after urethral injections of botulinum. Pdet statistically significantly reduced (from 47 ± 39 cmH₂O to 32 ± 27 cmH₂O, $p < 0.05$ compared with baseline or before injection) in patients without recovery but statistically significantly increased it in patients with recovery (from 7.4 ± 9.2 cmH₂O to 24 ± 13.1 cmH₂O, $p < 0.05$ compared with baseline) (Kuo 2007).

In the case series of 66 patients, there were statistically significant reductions in urodynamic parameters (Pdet, PVR, MUCP), and a statistically significant increase in Qmax with both doses of botulinum (50 units and 100 units) after treatment compared with baseline. But no statistically significant differences were noted between groups after treatment (Kuo 2007b).

In the case series of 10 patients, with 100 units of botulinum injection into the urethral sphincter, there was an improvement in Qmax (from 8.12 ml/sec to 15.8 ml/sec), a decrease in PVR (from 260 ml to 89 ml) and an improvement in the mean static UPP (from 113 cmH₂O to 90 cmH₂O), at 10-week follow up (p value not assessed; Panicker 2016).

In the retrospective case series of 81 patients with DV, patients with a successful treatment outcome after botulinum injection into the urethral sphincter had a statistically significant change in urodynamic parameters (decrease of Pdet, PVR volume and bladder outlet obstruction index, and an increase in VE) at follow up compared with the treatment failure group (Jiang 2021).

In the retrospective analysis of 56 patients, for both patients with DV (n=23) and patients with PRES (n=33), botulinum injections into the EUS resulted in statistically significantly improved Qmax (DV: 7.3 to 10.2 ml/sec, $p < 0.01$; PRES: 7.4 to 10.2 ml/sec, $p < 0.05$) and VE (DV: 0.47 to 0.59 ml/sec, $p < 0.01$; PRES: 0.43 to 0.60 ml/sec, $p < 0.01$) after the injections. Also, there was a statistically significant decrease in FS ($p=0.023$), US ($p=0.004$) and CBC ($p=0.044$ in the DV group than the PRES group after the injections (Ou 2021).

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Safety summary

De novo UTI

New UTIs, which resolved with medical treatment, were reported in 5% (3/62) of patients at 1-month follow up in the RCT. It is not clear whether they were in the treatment or placebo group (Jiang 2016).

A UTI developed in 3 patients (with a history of recurrent UTI) in the case series of 10 patients (Panicker 2016).

Urge urinary incontinence

Urge urinary incontinence, which resolved with medical treatment, was reported in 5% (3/62) of patients at 1-month follow up in the RCT. It is not clear whether they were in the treatment or placebo group (Jiang 2016).

Micturition pain

Pain during micturition, which resolved with medical treatment, was reported in 3% (2/62) of patients at 1-month follow up in the RCT. It is not clear whether they were in the treatment or placebo group (Jiang 2016).

Difficulty in urination (mild and resolved within 3 days after treatment) was reported in 9% (7/81) of patients in the case series of 81 patients (Jiang 2021).

Haematuria

Haematuria, which resolved with medical treatment, was reported in 3% (2/62) of patients at 1-month follow up in the RCT (Jiang 2016).

Haematuria (mild and resolved in 3 days) was reported in 6% (5/81) of patients in the case series of 81 patients (Jiang 2021).

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, professional experts are asked about anecdotal adverse events (events that they have heard about) and about theoretical adverse events (events that they think might possibly occur, even if they have never happened).

For this procedure, professional experts listed the following anecdotal adverse events: discomfort during the procedure and a degree of oozing of blood. They did not describe any theoretical adverse events.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention. The following databases were searched, covering the period from their start to 13-10-2021: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the internet were also searched. No language restriction was applied to the searches (see the [literature search strategy](#)). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The [inclusion criteria](#) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	<p>Clinical studies were included. Emphasis was placed on identifying good quality studies.</p> <p>Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study.</p> <p>Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.</p>
Patient	Patients with idiopathic chronic non-obstructive urinary retention.
Intervention/test	Botulinum toxin type A injection into the urethral sphincter.
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

List of studies included in the IP overview

This IP overview is based on 313 patients from 1 RCT and 5 case series.

Other studies that were considered to be relevant to the procedure but were not included in the main [summary of the key evidence](#) are listed in the [appendix](#).

Summary of key evidence on botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Study 1 Jiang Y-H (2016)

Study details

Study type	RCT (NCT01733290)
Country	Taiwan, Helsinki
Recruitment period	2012-2014
Study population and number	N=73 patients with DV or DU refractory to medical or behavioural treatment. (48 in botulinum injection group versus 25 in placebo group)
Age and sex	Mean age 65.2± 15.2 years (range, 28 to 87 years); botulinum injection group 64.7 years versus placebo injection group 66.9 years; p= 0.562. Sex: overall 66% (48/73) women; At 1 month, botulinum injection group had 76% (29/38) women, placebo injection group had 76% (19/25) women
Patient selection criteria	Inclusion criteria: patients more than 20 years of age with a 3-month history of medically refractory non-neurogenic voiding dysfunction (DV and DU diagnosed by video-urodynamic studies). DV was diagnosed in patients with an open bladder neck and narrow membranous urethra, a poorly relaxed urethral sphincter, and a normal to-high voiding pressure with a low and/or intermittent urinary flow during voiding. DU was diagnosed in patients with low voiding pressure and low flow rate, a post-void residual volume >300 mL, and a low VE (<33%) and the presence of a relaxed urethral sphincter during voiding. Exclusion criteria: anatomic bladder outlet obstruction conditions, including benign prostatic obstruction in men, bladder neck obstruction or contracture, and urethral stricture, active UTI, interstitial cystitis, and occult or overt neuropathy (including

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

	cerebrovascular accidents, diabetes mellitus, multiple sclerosis, Parkinson's disease, and spinal cord injury).
Technique	<p>All injections were done under general anaesthesia through a transurethral route in men and perineal route in women.</p> <p>Treatment group (n=48) received injections of botulinum (100U diluted was with 5ml saline) into the external urethral sphincter. Men received 10 injections using a 23 gauge needle. Each injection site received 10U of botulinum or 0.5ml of normal saline. Women received 5 urethral sphincter injections of botulinum solution or 1.0ml of normal saline circumferentially into the urethral sphincter using a 27 gauge 1ml syringe needle.</p> <p>Placebo group (n=25) received normal saline (5ml) injections (10 in men and 5 in women)</p> <p>After injections, a Foley catheter was inserted overnight in men but not in women. Patients are discharged next day and oral antibiotics are given for a week.</p> <p>48 in the botulinum group and 25 in placebo group received first injection, and 19 and 13 patients in each group received a second botulinum injection after 1 month.</p>
Follow up	1 month.
Conflict of interest/source of funding	Study was approved by Tzu-Chi General Hospital. No external funding for this study.

Analysis

Follow-up issues: short follow-up period with high loss to follow-up. 11 patients (10 in botulinum group and 1 in placebo group) were lost to follow-up during the study period. Data were available in 38 patients in botulinum injection group and 24 patients in placebo injection group at 1 month follow-up.

Study design issues: small number of patients were randomly allocated in a 2:1 ratio by block randomisation. Patients, doctors and nurses were blinded. Video-urodynamic studies were done according to International Continence Society recommendations. Different routes of injection were used for men and women. The primary outcome was change in PPBC score at 1 month from baseline. Other endpoints assessed were changes from baseline in IPSS, QOL (assessed according to IPSS system questionnaire and was scored from 0 to 6, representing excellent to bad), VV, PVR, Pdet and adverse events. If patients were not satisfied with the treatment result, repeated urethral sphincter botulinum injection was done regardless of patient allocation. Patients receiving a second injection were assessed in the same manner used for the first treatment.

Study population issues: baseline patient characteristics and urodynamic parameters were not statistically significantly different between the 2 study groups. Patients with 2 different indications were included in the study.

Key efficacy findings

Number of patients analysed: 62 (38 botulinum injection versus 24 placebo injection)

Overall success rate (reduction of PPBC ≥ 2) at 1 month: 43.5%

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

	Botulinum injection % (n=38)	Placebo injection % (n=24)	P value
Success rate (PPBC>2)	36.8 (14/38)	54.2 (13/24)	0.114

Subjective clinical outcomes: changes of symptom scores and VUDS parameters after first EUS injection

		Botulinum injection (n=38)	Placebo injection (n=24)	P value (between baseline data of groups)	P value (between the groups after treatment)
IPSS-V	Baseline	15.2±5.6	14.5±6.7	0.468	0.002
	1 month	12.7±7.0*	6.0±6.6*		
IPSS-S	Baseline	10.7±4.0	11.0±4.3	0.518	0.074
	1 month	8.5±3.8*	7.1±4.2*		
IPSS-T	Baseline	25.8±8.2	25.5±8.8	0.776	0.001
	1 month	21.2±8.6*	13.1±9.5*		
QOL-index	Baseline	4.5±1.9	5.4±0.9	0.024	0.014
	1 month	3.0±1.9*	2.4±1.9*		
PPBC	Baseline	4.8±1.7	5.0±1.7	0.761	0.066
	1 month	3.4±2.0*	2.7±2.1*		
CBC (mL)	Baseline	378.9±154.2	397.8±223.5	0.585	0.201
	1 month	404.6±182.4	360.0±140.7		
Pdet (cmH ₂ O)	Baseline	22.7±24.7	25.3±24.6	0.444	0.161
	1 month	19.2±19.6	30.5±25.1		
Qmax (mL/s)	Baseline	5.3±5.7	6.3±5.1	0.344	0.558
	1 month	9.8±9.5*	9.5±6.6*		
Vol (mL)	Baseline	104.8±112.2	102.4±101.4	0.942	0.627
	1 month	170.7±140.5*	148.5±144.7		
PVR (mL)	Baseline	295.7±194.1	279.3±246.9	0.965	0.141
	1 month	251.7±214.0	146.6±160.5*		
VE (%)	Baseline	29.6±28.3	34.4±34.2	0.530	0.336
	1 month	44.1±35.3*	56.1±36.4*		

Data are presented as mean±SD; *p value <0.05 versus baseline

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Subgroup analysis

Changes of symptom scores and VUDS parameters after first EUS injection

		DV (n=31)			DU (n=31)		
		Botulinum (n=16)	Placebo (n=15)	P value [^]	Botulinum (n=22)	Placebo (n=9)	P value [^]
IPSS-V	Baseline	12.7±6.6	14.1±5.8		17.0±3.8	15.1±8.4	
	1 month	8.3±7.6*	5.7±5.8*	0.089	16.0±4.3	6.6±8.2*	0.036
IPSS-S	Baseline	11.4±4.3	12.1±4.0		10.1±3.8	9.8±4.5	
	1 month	8.5±3.7*	6.3±3.9*	0.089	8.5±3.9	8.4±4.5	0.831
IPSS-T	Baseline	24.1±10.3	26.2±7.8		27.1±6.2	24.3±10.7	
	1 month	16.8±10.4*	12.0±8.0*	0.026	24.4±5.2*	15.0±11.8*	0.002
QoL-I	Baseline	4.4±1.7	5.4±1.0		4.6±2.0	5.4±0.9	
	1 month	2.8±2.1*	2.4±2.1*	0.089	3.0±1.9*	2.4±1.8*	0.107
PPBC	Baseline	4.8±1.4	5.4±1.4		4.7±1.9	4.4±1.9	
	1 month	3.3±1.9*	2.5±2.2*	0.085	3.5±2.1*	3.0±1.8*	0.814
CBC (ml)	Baseline	359.0±172.6	334±176		393.9±141	497±262.5	
	1 month	365.0±154.4	354±125.7	0.860	434.7±199.4	369±169.2	0.042
Pdet (cmH ₂ O)	Baseline	40.3±23.0	35.6±25.1		9.2±16.4	9.1±12.8	
	1 month	31.6±22.3*	32.1±22.6	0.473	9.8±10.0	27.9±30.0	0.070
Qmax (mL/s)	Baseline	6.4±5.4	7.9±5.2		4.5±6.0	3.4±3.7	
	1 month	11.1±10.1*	8.9±4.7	0.099	8.8±9.1*	10.6±9.2*	0.445
Vol. (mL)	Baseline	119.9±82.2	136.3±109		93.9±130.9	45.9±54.9	
	1 month	191.0±140.1*	117.5±63.7	0.020	155.0±142.0	200±219.7	0.182
PVR (mL)	Baseline	225.0±200.7	198±168.2		350.0±174.6	415±304.0	
	1 month	198.0±179.1	156±160.5	0.770	293.0±233.1	131±169.1*	0.046
VE (%)	Baseline	42.1±27.8	44.9±32.2		20.8±28.5	17.0±31.5	
	1 month	50.5±34.6	52.8±34.6	0.969	39.4±36.0*	61.6±40.7*	0.094

*p<0.05 versus baseline. [^] p value between groups after treatment. Data are presented as mean±SD.

Changes of symptom scores and VUDS parameters after first and second EUS botulinum injections in botulinum group (n=19)

	DV (n=7)	DU (n=12)
--	----------	-----------

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

	Changes after 1 st injection	Changes after 2 nd injection	P value	Changes after 1 st injection	Changes after 2 nd injection	P value
IPSS-V	-4.0±5.5	-3.4±5.4	0.848	-1.0±4.0	-6.3±7.0*	0.035
IPSS-S	-2.3±3.9	-3.4±3.3*	0.563	-2.1±3.8	-4.5±5.7*	0.250
IPSS-T	-6.3±6.7*	-6.9±3.5*	0.846	-3.0±5.0	-10.7±10.8*	0.051
QOL-index	-1.0±2.2	-2.0±1.5*	0.337	-1.8±1.8*	-3.1±2.2*	0.144
PPBC	-0.9±2.7	-1.7±1.8*	0.502	-0.9±1.6	-1.8±1.7*	0.202
CBC (ml)	60.6±105.5	143.3±143.0*	0.242	32.1±72.8	77.2±148.5	0.381
Pdet (cmH ₂ O)	-8.1±14.7	-13.4±21.1	0.597.5	2±10.7	3.8±10.0	0.719
Qmax (mL/s)	1.3±5.2	2.6±6.0	0.676	-0.6±3.8	5.4±5.5*	0.008
Vol (mL)	17.9±64.7	29.7±55.8	0.720	-10.3±94.5	57.5±150.5	0.206
PVR (mL)	29.1±104.2	21.3±124.7	0.900	-1.3±174.4	-70.9±179.3	0.367
VE (%)	-7.7±25.8	-1.9±31.8	0.715	-0.2±17.2	19.5±37.1	0.113

*p<0.05 versus baseline.

Changes of symptom scores and VUDS parameters after first placebo injection and second EUS botulinum injections in placebo group (n=13)

	DV (n=9)			DU (n=4)		
	Changes after 1 st placebo injection	Changes after 2 nd Botulinum injection	P value	Changes after 1 st injection	Changes after 2 nd injection	P value
IPSS-V	-6.1±4.7*	-4.5±7.1	0.585	-7.0±8.9	-7.8±8.7	0.908
IPSS-S	-5.3±4.4*	-2.9±6.1	0.354	-0.0±3.6	-2.3±5.1	0.498
IPSS-T	-11.4±7.9*	-7.4±12.1	0.419	-7.0±6.3	-10.0±4.5*	0.468
QOL-index	-2.3±2.1*	-1.1±2.5	0.289	-1.75±1.5	-2.5±2.1	0.580
PPBC	-2.4±2.1*	-1.6±3.7	0.578	-1.25±1.0	-2.5±2.1	0.317
CBC (ml)	-10.0±245.7	-29.6±225.9	0.876	-133.5±336.7	-88.5±274.7	0.843
Pdet (cmH ₂ O)	-3.3±14.1	-8.7±7.9*	0.719	33.8±47.0	10.8±28.8	0.436
Qmax (mL/s)	1.0±5.4	1.6±4.5	0.800	3.8±4.3	2.5±4.1	0.691
Vol (mL)	2.2±123.6	-5.0±88.6	0.893	180.0±260.6	69.5±102.2	0.462
PVR (mL)	-54.0±201.7	-107.6±236.3	0.621	-400.2±309.2	-251.3±296.5	0.513
VE (%)	16.6±27.3	15.5±27.6	0.936	64.5±38.9*	22.3±29.1	0.133

*p<0.05 versus baseline.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Key safety findings

Complications at 1 month	% (n)
De novo urgency urinary incontinence*	4.8 (3/62)
De novo stress urinary incontinence*	n=1
UTI*	4.8 (3/62)
Micturition pain*	3.2 (2/62)
Haematuria*	3.2 (2/62)

No serious adverse events were reported. All complications resolved after medical treatment.

Study 2 Kuo H-C (2007a)

Study details

Study type	Case series
Country	Taiwan
Recruitment period	2002-2005
Study population and number	N=27 patients with idiopathic low detrusor contractility (3 had DV, 5 had low detrusor contractility with PRES 10 had DHIC, and 9 had DU)
Age	Mean age not reported; 81% (22/27) women.
Patient selection criteria	<u>Inclusion criteria:</u> presence of bladder and urethral dysfunction (idiopathic low detrusor contractility confirmed on VUD studies and defined no evident neuropathy, no functional or anatomic bladder outlet obstruction, a low or no Pdet combined with a Qmax of less than 10 mL/s, and a large PVR of more than 150 mL or urinary retention difficult urination, with a hyperactive or poorly relaxed urethral sphincter), patients in whom treatment with conventional medications had failed. <u>Exclusion criteria:</u> with bladder outlet obstruction.
Technique	urethral injection of botulinum (50 units or 100 units) performed under general anaesthesia and cystoscopy guidance, directly into the urethral sphincter in men and periurethrally in women. 100 units is diluted with 8ml saline.
Follow up	More than 1 year
Conflict of interest/source of funding	Allergan company provided botulinum injections.

Analysis

Follow-up issues: 2 weeks after injection and thereafter regular monthly follow-up.

Study design issues: small retrospective study. Video-urodynamic studies were performed at baseline and after treatment. Patients were randomly assigned to receive of either 50 units or 100 units of botulinum injection. Video-urodynamic studies were done according to International Continence Society recommendations. The outcomes (changes in urodynamic parameters) were compared between patients with and without recovery of detrusor contractility. The QoL index was assessed according to the IPSS (scored from 0 to 6, representing excellent to bad).

Study population issues: patients with different indications were included. Results for each indication were not presented separately. Authors state that age was not statistically significantly different between the 2 groups.

Other issues: patients were advised not to use alpha-adrenergic blockers or skeletal muscle relaxants during study period.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Key efficacy findings

- Number of patients analysed: 27

Changes in urodynamic parameters in patients with and without recovery of detrusor contractility after botulinum injections

Recovery of detrusor contractility [^]	First bladder sensation (ml)	Pdet or Pves (cm H ₂ O)	Qmax (mL/s)	PVR (mL)	Duration of effect ^{^^} (months)
Yes 48% (13/27)					
Baseline	233 ± 106	7.4 ± 9.2	4.7 ± 5.6	328 ± 134	
After treatment	191 ± 87	24 ± 13.1*	13 ± 6.6*	31 ± 35*	14 ± 7.6
No 52% (14/27)					
Baseline	368 ± 132	47 ± 39†	4.8 ± 4.3	228 ± 122	
After treatment	297 ± 121	32 ± 27*	7.0 ± 3.6	132 ± 71*	4.6 ± 2.5 (p<0.001)

*p<0.05 between baseline and after treatment. Data are presented as mean±SD.

[^] defined as an increase in Pdet and Qmax and reduced PVR volume (in 7 patients with DV or low detrusor contractility combined with PRES, 3 with DHIC, and 3 with DU)

^{^^} length of time from treatment and return of voiding symptoms to pre-treatment level.

Treatment outcomes

	Recovery of detrusor contractility [^]	Without detrusor contractility recovery ^{^^}
Excellent (QOL index improved by >2 and reduction in PVR by >50%)	N=10	N=1
Statistically significantly improved (QOL index improved by >2 and reduction in PVR by <50%)	-	-
Improved (QOL index improved by 1 and improvement of UD parameters)	N=3	N=10
Failed (no improvement in QOL)	-	N=3

[^]all could void without the aid of abdominal straining.

^{^^} continued to void with increased abdominal pressure

Overall success rate of treatment was 89% (24/27)

Key safety findings

None reported

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Study 3 Kuo H-C (2007b)

Study details

Study type	Case series
Country	Taiwan
Recruitment period	Not reported
Study population and number	N=66 patients with voiding dysfunction treated with botulinum injections into the EUS. (50 unit injection group [n=33] versus 100 unit injection group [n=33]) (DSD n=6, DV [n=21], PRES [n=11], or DU with non-relaxation of the urethral sphincter [n=28])
Age and sex	Mean age: 64.8 years and 60.0 years in the 50 and 100 units injection groups, (p>0.05). Sex: 54% (18/33) and 58% (19/33) women in the 50 and 100 units injection groups, (p>0.05)
Patient selection criteria	<u>Inclusion criteria:</u> presence of bladder and urethral dysfunction (idiopathic low detrusor contractility) confirmed on VUD studies (no anatomic bladder outlet obstruction, difficult urination, and urinary retention or a large PVR volume, and low detrusor pressure with a hyperactive or poorly relaxed urethral sphincter), patients with voiding dysfunction in whom treatment with conventional medications (such as α -blockers and skeletal muscle relaxants) had failed. <u>Exclusion criteria:</u> with bladder outlet obstruction.
Technique	botulinum injections into the urethral sphincter (50 units in 33 patients or 100 units in 33 patients) performed under light intravenous general anaesthesia and cystoscopy guidance transurethrally in men at the 3, 6, 9 and 12 o'clock positions at a depth of about 5 mm and transcutaneously and periurethrally in women at a depth of 15mm. 100 units is diluted with 8ml saline. Both groups received same volume of injection but different doses.
Follow up	More than 12 months
Conflict of interest/source of funding	Allergan company provided botulinum injections. Study was supported by grants from the National Science Council of Taiwan.

Analysis

Follow-up issues: 2 weeks after injection and regular monthly follow-up thereafter.

Study design issues: small retrospective study. Video-urodynamic studies and urethral pressure profilometry were performed according to International Continence Society recommendations at baseline and after treatment. Patients were randomly assigned to receive of either 50 units or 100 units of botulinum injection. The outcomes (changes in urodynamic parameters and treatment effect) were compared from baseline to after

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

treatment in each group and also between the 2 groups of patients. The QoL index was assessed according to the IPSS questionnaire (and scored from 0 to 6, representing excellent to bad).

Study population issues: patients with voiding dysfunction of different aetiologies were included but the allocation of patients with different aetiologies in the 50 unit and 100 unit treatment groups was not equal.

Other issues: other medications such as alpha-adrenergic blockers or skeletal muscle relaxants were not used during study period. No repeat injections were given to patients.

Key efficacy findings

- Number of patients analysed: 66

Changes in urodynamic parameters and QOL in patients with 50 units and 100 units of botulinum injections

	MCUP (cm H ₂ O)	FPL (cm)	Pdet (cm H ₂ O)	Qmax (mL/s)	PVR (mL)	QOL index	Mean duration of effect (months) ^{^^}
50 units injection (n=33)							
Baseline	66.6 ± 34.4	3.3 ± 0.5	51.6 ± 40.7	5.6 ± 5.3	285 ± 154	4.1 ± 0.9	
After treatment	48.9 ± 27.3 (p<0.001)	3.1 ± 0.3 (p=0.186)	37.5 ± 35.4 (p<0.001)	8.3 ± 5.4 (p=0.016)	120 ± 145 (p<0.001)	1.9 ± 1.2 (p<0.001)	6.4 ± 3.6
100 units injection (n=33)							
Baseline	61.9 ± 26.0	3.8 ± 1.0	53.8 ± 38.9	5.8 ± 4.8	261 ± 157	4.0 ± 1.0	
After treatment	49.5 ± 21.5 (p=0.049)	4.1 ± 1.0 (p=0.493)	33.0 ± 31.7 (p=0.006)	10.5 ± 5.9 (p<0.001)	114 ± 107 (p<0.001)	2.2 ± 1.2 (p<0.001)	8.4 ± 3.4 (p=0.022)*

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

*between the 2 groups; Data are presented as mean±SD.

^^ length of time from treatment and return of voiding symptoms to pre-treatment level.

Treatment outcomes

	50 units of injection % (n=33)	100 units of injection % (n=33)
Excellent (QOL index improved by >2 and 50% reduction in PVR and ≥ 25% reduction in MUCP)	69.7 (23/33)	60.6 (20/33)
Improved (QOL index improved by 1 and improvement of VUD parameters by either a ≥ 50% reduction in PVR or a ≥ 25% reduction in MUCP)	15.2 (5/33)	30.3 (10/33)
Failed (no improvement in QOL regardless of urodynamic improvement)	15.2 (5/33)	9 (3/33)
Overall rate of success	84.9 (28/33)	90.9 (30/33) p=0.452

Treatment outcomes in patients with different aetiologies

	Excellent %(n)	Improved % (n)	Failed % (n)	p value
Poor relaxation of urethral sphincter (n=11)				0.182
50 units (n=5)	60 (3/5)	40 (2/5)	0	
100 units (n=6)	100 (6/6)	0	0	
DU (n=28)				0.066
50 units (n=19)	68.4 (13/19)	10.5 (2/19)	21.1 (4/19)	
100 units (n=9)	33.3 (3/9)	55.6 (5/9)	11.1 (1/9)	
DV (n=21)				0.399
50 units (n=6)	83.3 (5/6)	16.7 (1/6)	0	
100 units (n=15)	53.3 (8/15)	33.3 (5/15)	13.3 (2/15)	

Data on 6 DSD patients are not presented here as this indication is out of the scope of this assessment.

Key safety findings

None reported

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Study 4 Jiang (2021)

Study details

Study type	Retrospective case series
Country	Taiwan
Recruitment period	2016
Study population and number	N= 81 women with non-neurogenic DV
Age	Age not reported; 100% women
Patient selection criteria	<u>Inclusion criteria:</u> all women with DV (confirmed on VUD studies) refractory to medical treatment who received urethral botulinum 100 units, evidence of radiographic obstruction at the middle urethra with an open bladder neck and urodynamic findings, with baseline and postoperative urodynamic data were included. <u>Exclusion criteria:</u> no urethral stricture or anatomic bladder outlet obstruction.
Technique	Urethral botulinum injections were done under light intravenous general anaesthesia 100 units reconstituted to 4 ml with normal saline to create a solution equivalent to 25 U/ml. botulinum was injected into the urethral sphincter along the urethral lumen at the 2, 5, 7, 9, and 12 o'clock positions.
Follow up	3 months
Conflict of interest/source of funding	None

Analysis

Follow-up issues: short follow-up period.

Study design issues: retrospective analysis; DV was classified into 3 groups according to the site of obstruction. Successful treatment outcome was defined as an improvement of VE by 10% and reported global response assessment by ≥ 1 . global response assessment was reported as excellent (+3), markedly improved (+2), mildly improved (+1), no change (0) or worsened (-1), according to their perception of voiding after the botulinum injection. Changes in urodynamic parameters between the treatment success and failure groups and among three DV subgroups were assessed.

Key efficacy findings

- Number of patients analysed: 81

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Changes in urodynamic parameters between the treatment success and failure groups

	Treatment successful [^] % (n)		Treatment failure % (n)		
	67.9 (55/81)		32.1 (26/81)		
	Baseline	Follow-up	Baseline	Follow-up	P value
First sensation filling (ml)	152.3 ± 79.5	150.4 ± 94.3	119.2 ± 52.4	131.7 ± 105.6	0.652
Full sensation (ml)	225.2 ± 97.0	206.9 ± 102.8	195.4 ± 67.7	173.1 ± 125.9	0.910
Urge sensation (ml)	257.8 ± 107.6	232.1 ± 119.9	226.0 ± 82.6	192.8 ± 136.3	0.839
Pdet (cmH ₂ O)	59.9 ± 38.8	44.4 ± 33.6*	51.2 ± 36.0	36.2 ± 35.7	0.959
Compliance	60.9 ± 52.8	64.2 ± 63.8	69.6 ± 84.7	57.3 ± 61.2	0.526
Qmax (mL/s)	8.51 ± 6.21	8.83 ± 8.19	7.53 ± 4.72	4.85 ± 4.33	0.254
Volume (ml)	146.2 ± 108.2	160.1 ± 140.7	126.5 ± 87.1	82.9 ± 73.4	0.185
PVR (mL)	206.0 ± 137.5	132.6 ± 156.1*	195.3 ± 101.6	243.3 ± 239.2	0.032
CBC (ml)	352.2 ± 145.2	292.6 ± 136.9 *	321.9 ± 116.6	326.2 ± 215.4	0.185
VE	42.7 ± 28.3	58.2 ± 36.8 *	40.3 ± 27.4	34.3 ± 32.4	0.057
Bladder outlet obstruction index	42.9 ± 41.8	26.7 ± 39.5 *	36.1 ± 37.4	26.5 ± 32.8	0.630

Data are presented as mean±SD; * statistically significant difference between baseline and follow up.

[^]defined as an improvement of VE by 10% and reported global response assessment by ≥1.

Lower urinary tract symptoms before and after treatment among the 3 DV subgroups

Lower urinary tract symptoms	Total % (n=81) ^{^^}		Bladder neck dysfunction and DV 8.6% (7/81)		Midurethral DV 67.9% (55/81)		Distal urethral DV 23.5% (19/81)	
	Baseline	Follow-up ^{^^}	Baseline	Follow-up	Baseline	Follow-up	Baseline	Follow-up
Storage symptoms	70.4 (57/81)	50.6 (41/81)	71.4 (5/7)	42.9 (3/7)	72.7 (40/55)	54.5 (30/55)	63.2 (12/19)	42.1 (8/19)
Frequency/urgency/nocturia	19	17	1	1	10	10	8	6
Urge incontinence	38	24	4	2	30	20	4	2
Voiding symptoms	87.7 (71/81)	42 (34/81)	85.7 (6/7)	28.6 (2/7)	87.3 (48/55)	38.2 (21/55)	89.5 (17/19)	57.9 (11/19)
Difficulty urination	67	34	5	2	45	21	17	11
Urinary retention	4	0	1	0	3	0	0	0
Painful symptoms	13.6 (11/81)	4.9 (4/81)	14.3 (1/7)	0	9.1 (5/55)	3.6 (2/55)	0	0

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Bladder pain	6	2	1	0	5	2	0	0
Micturition pain	5	2	2	1	3	1	0	0

^^ between 1 to 3 months after injection.

Key safety findings

	% (n)
Haematuria (mild, resolved in 3 days)	6.2 (5/81)
Difficulty in urination (mild resolved in 3 days after treatment)	8.6 (7/81)

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Study 5 Panicker JN (2016)

Study details

Study type	Case series
Country	UK
Recruitment period	2009-2012
Study population and number	N= 10 women with a primary disorder of urethral sphincter relaxation (Fowler's syndrome) with impaired voiding (n=5) or complete urinary retention (n=5)
Age	mean age 40 (25–65) years, all women
Patient selection criteria	<u>Inclusion criteria:</u> patients with a diagnosis of Fowler's syndrome (elevated UPP, sphincter volume, and abnormal EMG) <u>Exclusion criteria:</u> urological and neurological causes for voiding dysfunction; a history of previous urethral surgery, neurological disease, pregnancy, current UTI, and those taking anticoagulants.
Technique	After 2% lidocaine injection, 100 units of botulinum (dissolved in 2ml saline) was injected into the external urethral sphincter on either side under EMG guidance. This was done as an outpatient procedure.
Follow up	10 weeks
Conflict of interest/source of funding	No conflicts of interest. Study partly funded from National Institute for Health Research (NIHR), Urology foundation, and In Comb project. Allergan provided botulinum injections.

Analysis

Follow-up issues: short follow-up period; patients were reviewed at 1, 4 and 10 weeks.

Study design issues: small pilot study in one centre. Baseline symptoms were assessed using the IPSS questionnaire, and Qmax and PVR were measured. The primary outcome was restoration of voiding for women with urinary retention and $\geq 50\%$ improvement in Qmax in women with impaired voiding, at 10 weeks. The secondary outcomes measured were improvements in PVR and IPSS at 10 weeks.

Key efficacy findings

- Number of patients analysed: 10

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Patient reported symptom scores and VUD parameters

	Baseline	10 weeks
Mean IPSS score	25.6	14.1
Mean 'bother' score on IPSS	6.1	3.5
Mean Qmax (mL/s) in people who could void	8.12	15.8
Mean Qmax in people with complete retention who could void spontaneously		14.3
Mean PVR (mL)	260	89
Mean static UPP (cmH ₂ O)	113	90 (p=0.037)

7 women chose to return for repeat injections.

Key safety findings

Unable to void (at week 10, continued with CSIC)	1
UTI (in those with history of recurrent UTI)	3

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Study 6 Ou Y-C (2021)

Study details

Study type	Case series
Country	Taiwan
Recruitment period	2002-2019
Study population and number	N= 106 women receiving sphincteric botulinum-A injections for refractory EUS dysfunction. Indications: N=56 idiopathic EUS dysfunction (23 DV and 33 PRES) N=50 neurogenic EUS dysfunction (20 DSD, and 30 PRES)
Age	mean age 61.8 ± 19.7 years; all women
Patient selection criteria	<u>Inclusion criteria:</u> women who had received urethral sphincteric botulinum injections due to refractory voiding dysfunction caused by EUS dysfunction (diagnosed using image characteristics of VUDS during voiding phase) were retrospectively reviewed.. <u>Exclusion criteria:</u> patients with complicated clinical conditions such as a history of lower urinary tract reconstruction or urethra stenosis were excluded.
Technique	botulinum-A injection (100 units) diluted in 5 mL of normal saline was injected into the urethral sphincter (5 injections were done circumferentially via a perineal route under general anaesthesia).
Follow up	1 month
Conflict of interest/source of funding	No conflicts of interest. Study was supported by grants from the National Cheng Kung University Hospital.

Analysis

Follow-up issues: short follow-up period; patients were reviewed at 1, 4 and 10 weeks.

Study design issues: retrospective analysis with small number of patients; urinary function assessments such as uroflowmetry, and VUDs were done according to the International Continence Society recommendations. Baseline and post treatment urinary parameters were assessed and subjective and objective outcomes were assessed 1 month after the injections. Subjective outcomes reported in the medical records were graded as “good” or “poor” according to the patient’s perceptions of improvement (no validated questionnaires were used). Objective outcomes were graded as “good” if there was a 50% improvement in the Qmax or PVR after the injection. Other issues: data on patients with neurogenic EUS dysfunction (n=50) and mixed data on outcome predictors for both neurogenic and idiopathic sphincter dysfunction has not been presented here as it is out of the remit of this overview.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Key efficacy findings

- Number of patients analysed: 106

Therapeutic outcomes and VUD parameters -idiopathic voiding dysfunction

		DV % (n=23)	PRES % (n=33)	P value
Good subjective outcome		65 (15/23)	64 (21/33)	0.903
Good objective outcome		74 (17/23)	67 (22/33)	0.562
Urinary flow parameters				
Qmax	Baseline	7.3±3.2	7.4±5.4	0.980
	Follow-up	10.2 ** ±5.7	10.2 * ±7.7	
VV	Baseline	139.7 ±94.3	130.5 ±125.6	0.559
	Follow-up	174.7 ±104.7	190.9 ±124.6	
PVR	Baseline	160.8 ±98.5	188.1 ±147.5	0.657
	Follow-up	134.1 ±99.4	171.0 ±221.8	
CBC	Baseline	300.4 ±135.4	318.7 ±127.8	0.328
	Follow-up	308.8 ±118.9	360.4 ±203.5	
VE	Baseline	0.47 ±0.23	0.43 ±0.32	0.616
	Follow-up	0.59 ** ±0.30	0.60 ** ±0.32	
VUDs parameters				
First sensation of filling	Baseline	117.7 ±89.6	164.4 ±74.3	0.086
	Follow-up	110.4 ±69.8	151.8 ± 72.4	
Full sensation	Baseline	191.7 ±90.9	250.3 ± 108.3	0.023
	Follow-up	163.3 ±77.4	251.7 ± 109.8	
Urge sensation	Baseline	228.9 ±111.9	286.3 ± 127.0	0.004
	Follow-up	180.3 ±83.4	293.8 ±114.1	
Compliance	Baseline	92.4 ±125.4	74.4 ±87.5	0.194
	Follow-up	44.5 ±35.6	65.5 ±66.4	
Pdet	Baseline	53.6 ±29.0	13.0 ±11.9	0.136
	Follow-up	51.1 ±31.2	11.9 ±15.4	
Qmax	Baseline	5.8 ±2.5	4.2 ±5.4	0.334
	Follow-up	6.3 ±4.3 6.7 ±6.6	6.7 ±6.6	
BOOI	Baseline	41.9 ±30.8	4.6 ±11.3	0.116
	Follow-up	38.5 ±33.0	-1.5 ±15.9	
PVR	Baseline	217.2 ±128.2	314.3 ±248.6	0.118
	Follow-up	174.4 ±135.9	305.2 ±263.1	

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

CBC	Baseline	340.5 ±126.7	402.8 ±237.1	0.044
	Follow-up	303.9 ±141.6	430.0 ±198.3	
VE	Baseline	0.40 ±0.22	0.22 ±0.27	0.769
	Follow-up	0.47 ±0.33	0.39 ±0.38	

*p <0.05 within group differences in changes after treatment.

**<0.01 within group differences in changes after treatment.

Validity and generalisability of the studies

- Studies were limited with small number of patients and short period of follow-up. There was only 1 RCT comparing botulinum with placebo treatment.
- Patients refractory to conventional treatments and with heterogeneous non-neurogenic sphincter functions/causes (DV, DU, and PRES, Fowler's syndrome) were included in the studies.
- There is no standardised treatment protocol. botulinum injections were diluted with saline but the dose, number of injections, sites and depth of injection given varied across studies and in some studies repeat urethral injections were given.
- Most of the included studies were conducted by a research group in Taiwan and only 1 small study was from the UK.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Sacral nerve stimulation for idiopathic chronic non-obstructive urinary retention. NICE interventional procedures guidance 536 (2015).

Available from <http://www.nice.org.uk/guidance/IPG536>

NICE guidelines

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

- Lower urinary tract symptoms in men: management. NICE clinical guideline CG97 (2010). Available from <http://www.nice.org.uk/guidance/CG97>
- Urinary incontinence in neurological disease: assessment and management. NICE guideline CG148 (2012). Available from <http://www.nice.org.uk/guidance/CG148>
- Urinary incontinence and pelvic organ prolapse in women: management
- NICE guideline NG 123 (2019) Available from <http://www.nice.org.uk/guidance/NG123>

Additional information considered by IPAC

Professional experts' opinions

Expert advice was sought from consultants who have been nominated or ratified by their professional Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by professional experts, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three professional expert questionnaires for botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention were submitted and can be found on the [NICE website](#).

Patient commentators' opinions

NICE's Public Involvement Programme will send questionnaires to NHS trusts for distribution to patients who had the procedure (or their carers). When NICE has received the completed questionnaires, these will be discussed by the committee.

Company engagement

There is no specific device used for this procedure. Therefore, no structured information requests were sent to companies.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Issues for consideration by IPAC

- Botulinum injections into the EUS for idiopathic chronic non-obstructive urinary retention is currently done on an off-label basis.

References

1. Jiang Y.-H, Wang C-C, Kuo H-C. (2016) OnabotulinumtoxinA urethral sphincter injection as treatment for non-neurogenic voiding dysfunction – A randomized, double-blind, placebo-controlled study. *Sci. Rep.* 6, 38905; doi: 10.1038/srep38905.
2. Kuo H-K (2007) Recovery of detrusor function after urethral botulinum A toxin injection in patients with idiopathic low detrusor contractility and voiding dysfunction. *Urology*, 69: 57-62.
3. Kuo H-K (2007) Comparison of the therapeutic effects of urethral injections of 50 and 100 units of botulinum A toxin for voiding dysfunction. *Tzu Chi Medical Journal*. 19, 3, 134-138.
4. Jiang Y-H, Lee C-L, Chen S-F et al. (2021) Therapeutic effects of urethral sphincter botulinum toxin A injection on dysfunctional voiding with different videourodynamic characteristics in non-neurogenic women. *Toxins*, 13, 362, 1-10.
5. Panicker JN, Seth JH, Khan S et al. (2016) Open-label study evaluating outpatient urethral sphincter injections of onabotulinumtoxinA to treat women with urinary retention due to a primary disorder of sphincter relaxation (Fowler’s syndrome). *BJU Int.* 117, 809–813.
6. Ou Y-C, Huang K-H, Jan H-C et al. (2021) Therapeutic efficacy of urethral sphincteric botulinum toxin injections for female sphincter dysfunctions and a search for predictive factors. *Toxins*, 13, 398, 1-10.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	13/10/2021	Issue 10 of 12, October 2021
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	13/10/2021	Issue 10 of 12, October 2021
International HTA database (INAHTA)	13/10/2021	-
MEDLINE (Ovid)	13/10/2021	1946 to October 12, 2021
MEDLINE In-Process (Ovid)	13/10/2021	1946 to October 12, 2021
MEDLINE Epubs ahead of print (Ovid)	13/10/2021	October 12, 2021
EMBASE (Ovid)	13/10/2021	1974 to 2021 October 12
EMBASE Conference (Ovid)	13/10/2021	1974 to 2021 October 12

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

Literature search strategy

- 1 exp botulinum toxins/ 17187
- 2 (botox or botulinum toxin* or botulinum neurotoxin* or clostridium botulinum or e211kpy694 or meditoxin or neuronox or neurotoxin or oculinum or onabotulinumtoxin a or onabotulinumtoxina or vistabel or vistabex or Bocouture or Xeomin or Dysport or azzalure or BTX-A or BoNT-A).tw. 28271
- 3 1 or 2 31222
- 4 Urinary retention/ 4819
- 5 ((non-obstruct* or nonobstruct* or "non obstruct*") adj4 (urin* or bladder*)).tw. 248
- 6 ischuria*.tw. 36
- 7 (Fowler* adj4 syndrome*).tw. 66
- 8 (Neuropathic* adj4 bladder* adj4 dysfunction*).tw. 121
- 9 (Neurogenic* adj4 bladder*).tw. 4466
- 10 (voiding adj4 (dysfunction* or difficult* or problem* or disorder*)).tw. 3939
- 11 (urethral sphincter adj4 (relax* or fail* or dysfunct* or difficult* or disorder*)).tw. 141
- 12 Urethra/ and (relax* or fail* or dysfunct* or difficult* or disorder*).tw. 4009
- 13 or/4-12 16335
- 14 3 and 13 381
- 15 animals/ not humans/ 4863620
- 16 14 not 15 372
- 17 limit 16 to ed=20210119-20211013 15

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the [summary of the key evidence](#). It is by no means an exhaustive list of potentially relevant studies.

Additional papers identified

Article	Number of patients/follow up	Direction of conclusions	Reasons for non-inclusion in summary of key evidence section
DasGupta R. Fowler CJ. (2003) The management of female voiding dysfunction: Fowler's syndrome - a contemporary update. Current opinion in urology. 13 (4):293–299.	Review	Botox, sacral nerve stimulation has shown some efficacy in the treatment of young women with urinary retention. Although how it works is still not fully understood but is being addressed by ongoing research.	Review
Fenner A (2015) Botox injections are effective for Fowler's syndrome. Nature Reviews Urology 12, 653;	Research highlights of a pilot study	On botulinum improves patient-reported lower urinary tract symptoms and objective measures of bladder function in women with Fowler's syndrome, according to data published.	Review
Jiang YH, Chen SF, Jhang JF et al. (2018) Therapeutic effect of urethral sphincter on a botulinum toxin A injection for urethral sphincter hyperactivity. Neuro-urology and	Retrospective case series N=95 patients with voiding dysfunction (idiopathic voiding dysfunction n=38) due to urethral sphincter hyperactivity and treated with	Satisfactory outcomes were reported in 58 (61.1%) patients, of these 20 were with idiopathic voiding dysfunction. Patients with non-neurogenic voiding dysfunction had a	Outcomes not reported separately for idiopathic voiding dysfunction.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

<p>Urodynamics. 37:2651–2657.</p>	<p>injections of 100 U on a botulinum toxin A into the urethral sphincter. 1 month follow-up.</p>	<p>statistically significantly longer therapeutic duration than those with neurogenic voiding dysfunction (9.55 ± 4.18 versus 7.44 ± 2.91 months, $P = 0.033$). Increased urinary incontinence was reported in 18 patients, including 6 with stress urinary incontinence and 12 with urgency urinary incontinence.</p>	
<p>Jiang YH, Jhang JF, Chen SF et al. (2019) Videourodynamic factors predictive of successful on a botulinum toxin A urethral sphincter injection for neurogenic or non-neurogenic detrusor underactivity. Lower Urinary Tract Symptoms.11:66–71.</p>	<p>N=60 patients (27 with non-neurogenic and 33 with neurogenic DU) refractory to medical treatment had on botulinum injections into the urethral sphincter. Follow-up 1 month</p>	<p>Treatment outcome was statistically significantly better in patients with non-neurogenic than neurogenic DU ($p=0.039$). The duration of the therapeutic effect was similar between patients with non-neurogenic and neurogenic DU (mean 7.37 versus 7.69 months, respectively; $P = 0.788$). In all, 12 patients reported de novo urinary incontinence after urethral botulinum injection, 4 of whom developed stress urinary incontinence and 8 who had exacerbated urgency urinary incontinence. Urethral sphincter injection of on botulinum is</p>	<p>Outcomes no reported separately for idiopathic aetiology (n=10)</p>

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

		effective in 60% of patients with DU. Careful video urodynamic interpretation of bladder neck opening enables urologists to select appropriate candidates for on botulinum treatment.	
Kuo H-K. (2003) Botulinum A toxin urethral injection for the treatment of lower urinary tract dysfunction. The Journal of Urology. Vol. 170, 1908–1912.	Prospective case series N=103 patients had botulinum for various types of lower urinary tract dysfunction (DSD in 29, DV in 20, nonrelaxing urethral sphincter in 19, cauda equina lesion in 8, peripheral neuropathy in 14 and idiopathic DU in 13) Botulinum 50 units in 48 patients and 100 units in 55 patients. Follow-up 1 month.	40 (39%) patients had an excellent result and 47 (46%) had statistically significant improvement. The total success rate was 84.5%. Among these patients mean maximum voiding pressure, MUCP and post-void residual decreased statistically significantly at 2 to 4 weeks after treatment. Among 45 patients with urinary retention the indwelling catheters were removed or clean intermittent catheterization was discontinued in 39 (87%).	Different aetiologies were included and overall therapeutic results were presented. These patients might have been included in the studies (Kuo 2007) added to the summary of evidence.
Kuo HC. Effectiveness of urethral injection of botulinum A toxin in the treatment of voiding dysfunction after radical hysterectomy. Urol	N=30 patients with difficult urination after radical hysterectomy due to cervical cancer received urethral injection of 100 units of botulinum (n	Urethral injection of botulinum can be effectively used to treat patients with DU and non-relaxing urethral sphincter after radical	Not sure if this is idiopathic as occurred after hysterectomy.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

Int 2005; 75: 247–51	= 20) or medical treatment (n = 10)	hysterectomy with few adverse effects.	
Kao Y-L, Huang K-H, Kuo H-C et al. (2019) The therapeutic effects and pathophysiology of botulinum toxin A on voiding dysfunction due to urethral sphincter dysfunction. <i>Toxins</i> , 11, 728, 1-17.	Review	Botulinum has been applied to various causes of USD, including DV, Fowler’s syndrome, and poor relaxation of the external urethral sphincter. A large proportion of patients with different causes of USD report statistically significant improvement in voiding after sphincteric botulinum injections. Botulinum is still a reasonable option for refractory voiding function. To date, studies focusing on urethral sphincter botulinum injections have been limited to the heterogeneous aetiologies of USD.	Review
Osman NI. & Chapple CR (2014) Fowler’s syndrome—a cause of unexplained urinary retention in young women? <i>Nature Reviews. Urology</i> . 11, 87–98.	Review	Most studies of Fowler’s syndrome are limited due to small cohorts with no control group and a lack of video urodynamic data. Whether Fowler’s syndrome represents a distinct cause of urinary retention or results from a maladaptive behaviour and is similar to DV is	Review

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention

		unclear. Application of sacral neuromodulation in patients diagnosed with Fowler's syndrome can restore normal voiding, in the absence of any effective pharmacotherapy or surgical treatment.	
Smith CP, Nishiguchi J, O'Leary M, Yoshimura N, Chancellor MB. Single-institution experience in 110 patients with botulinum toxin A injection into bladder or urethra. Urology 2005; 65: 37–41	N=110 received injections of BTX-A into the bladder (n = 42) or urethra (n = 68) for a variety of lower urinary tract disorders (included neurogenic detrusor overactivity and/or DSD, overactive bladder, bladder neck obstruction, and interstitial cystitis) treated with either 100 to 200 U of BTX-A IN external sphincter or by injection into the bladder base using 100 to 300 U of BTX-A diluted in about 10 to 30 mL of sterile saline.	TX-A is equally effective in women as it is in men. When injected into the sphincter, the risk of stress incontinence is low. Bladder injections with BTX-A are effective for not only neurogenic detrusor overactivity, but also overactive bladder. BTX-A can even be considered for interstitial cystitis	Various aetiologies (neurogenic and non-neurogenic) included.

IP overview: Botulinum toxin type A injection into the urethral sphincter for idiopathic chronic non-obstructive urinary retention