REVIEW ARTICLE

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Technical aspects of botulinum toxin type A injection in the bladder to treat urinary incontinence: reviewing the procedure

G. Karsenty,[1] R. Baverstock,[2] K. Carlson,[2] D. C. Diaz,[3] F. Cruz,[4] R. Dmochowski,[5] S. Fulford,[6] A. Giannantoni,[7] J. Heesakkers,[8] A. Kaufmann,[9] L. Peyrat,[10] J. Thavaseelan,[11] P. Dasgupta[12]

SUMMARY

Aims: Standardise the injection technique with botulinum toxin type A (BoNT A) in the bladder of patients with overactive bladder (OAB) [idiopathic overactive bladder (iOAB) or neurogenic overactive bladder (nOAB) with urinary incontinence], using a literature review and a survey of an International expert panel. **Methods:** PubMed literature searches of BoNT A in adults with iOAB/nOAB together with a survey of 13 experts from 10 countries. **Results:** Data from 21 articles and completed questionnaires were collated. The procedure can be carried out in an out-/inpatient setting. Dose used in clinical studies vs. clinical practice was 300 and 200 U for nOAB and 200 and 100 U for iOAB. Recent studies have also demonstrated that there are no clinically relevant benefits between 100 and 150 U in iOAB or between 300 and 200 U in nOAB, though adverse effects are increased with higher doses. Usually, 30 sites for nOAB (range: 6.7–10 U/ml) and 20–30 sites for iOAB (range: 5–10 U/ml) are injected in clinical studies vs. 20–30 sites of 1 ml/injection for 200 U in nOAB and 10–20 sites of 0.5–1 ml/injection for 100 U in iOAB in clinical practice. BoNT A is usually injected directly into the detrusor, sparing the trigone. Flexible or rigid cystoscopes are used. The needle should be typically 22–27 gauge and 4 mm in length and should have a stopper to avoid any leakage or perforation of the bladder wall while ensuring a targeted injection. **Conclusion:** Based on the literature and survey analysis, recommendations are proposed for the standardisation of the injection procedure.

Review criteria

Research articles related to botulinum toxin type A (BoNT A) injection in the bladder were sought via PubMed and were identified from key references within articles. Search terms used included various combinations of the following terms: botulinum toxin/onabotulinum AND injection AND procedure or design AND urinary AND/OR incontinence AND/OR overactive bladder AND/OR neurogenic AND/OR idiopathic. No formal evaluation of level of evidence was conducted in developing this review though most of the studies selected were randomised double blind controlled trials.

Message for the clinic

Symptoms of idiopathic overactive bladder/neurogenic overactive bladder significantly decrease health-related quality of life, and BoNT A offers a new licensed modality for treatment. Technical differences in the injection technique have important implications on the outcomes. The long-term aim should be to develop a standardised technique for injection.

[1]Urology and Kidney Transplantation, Aix Marseille University, Marseille, France
[2]Division of Urology, Department of Surgery, vesia [Alberta Bladder Centre], University of Calgary, Calgary, AB, Canada
[3]Department of Urology, University Hospital of the Canary Islands, Canary Islands, Spain
[4]Department of Urology, Hospital S. João and Faculty of Medicine of Porto, Porto, Portugal
[5]Department of Urology, Vanderbilt University Medical Center, Nashville, TN, USA
[6]Department of Urology, The Golden Jubilee Spinal Injury Centre, James Cook University Hospital, Middlesbrough, UK
[7]Department of Urology and Andrology, University of Perugia, Perugia, Italy
[8]Department of Urology, Radboud University Nijmegen MC, Nijmegen, The Netherlands
[9]Center of Neuro-Urology, Kliniken Maria Hilf GmbH, Mönchengladbach, Germany
[10]Department of Urology, University Paris VI, Paris, France
[11]Department of Neurourology and Urodynamics, St John of God Murdoch Hospital and Medical Centre, Perth, Australia
[12]MRC Centre for Transplantation, NIHR Biomedical Research Centre, Guy's Hospital, King's College London, London, UK

Correspondence to:
Gilles Karsenty, Urology, Surgery and Kidney Transplantation Department, University Hospital La Conception, 147 Boulevard Baille, Marseille 13005, France
Tel.: + 33 4 91 43 55 02
Fax: + 33 4 91 43 55 02
Email: gilles.karsenty@ap-hm.fr

Introduction

Overactive bladder (OAB) syndrome and detrusor overactivity (DO) because of idiopathic overactive bladder (iOAB) or neurogenic overactive bladder (nOAB) reasons are associated with symptoms of urgency, urgency or reflex incontinence, frequency and nocturia (1). Prevalence rates for OAB worldwide are estimated to be 10.8% (2). Approximately 60% of patients with OAB seen in clinical practice are women. The symptoms of OAB significantly decrease health-related quality of life (QoL) and lead to depression and anxiety (3). DO in neurologic patients with detrusor sphincter dyssynergia (DSD) generates high pressure in the bladder leading to serious upper urinary tract complications.

Overactive bladder can be managed initially with anticholinergic agents in addition to pelvic floor muscle training and various dietary or behavioural modifications (1). Mirabegron, a novel β3-adrenoceptor agonist, was recently approved by the US Food and Drug's Administration (FDA) for OAB therapy. Phase III multinational randomised, controlled trials have supported the efficacy and tolerability of mirabegron in the clinical trial setting of patients with OAB for up to 12 weeks of therapy and in the long term (12 months) (4). The reported incidence and severity of treatment-emergent and serious adverse effects are similar to antimuscarinics, but with a more than threefold lower incidence of dry mouth compared with tolterodine. Neurogenic detrusor overactivity associated with DSD is initially managed with intermittent self-catheterisation and oral anticholinergics. However, limited efficacy despite their use in high doses and adverse effects, such as dry mouth and constipation, often limit the

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use of oral anticholinergic drugs (5–7). The effects of mirabegron on neurogenic urinary incontinence are not yet studied.

The introduction of botulinum toxin type A (BoNT A) offers a new modality for the treatment iOAB and nOAB with urinary incontinence. The recent approval of the use of BOTOX® (Allergan, Irvine, CA, USA) (onabotulinumtoxin type A or onabotA) for the treatment of urinary incontinence because of nOAB and iOAB by both the European Medicines Agency (EMEA) and The US FDA highlights the need to focus on technical aspects of BoNT A injection in the bladder.

Based on the results of a literature review of published studies evaluating various injection techniques with BoNT A in adults with iOAB/nOAB and a subsequent survey of international clinical experience among an expert panel, this study aims to propose a standardised technique for BoNT A injection in the bladder.

Methods

Literature analysis

Discussions in this study are limited to BoNT A because it has a more durable effect than botulinum toxin type B which seems to be limited to less than 10 weeks (8,9). Furthermore, only onabotA (Allergan's BoNT A) was taken into account; firstly because it is the only commercially available botulinum toxin currently licensed for use in urinary incontinence because of iOAB/nOAB. Indeed, the licence for Allergan's onabotA was provided as it is the only toxin with large phase III randomised controlled trials (RCTs) in iOAB and nOAB. In addition, although onabotA and Dysport (Ipsen™, Boulogne-Billancourt, Paris, France) are both BoNT A-derived drugs, they differ in terms of pharmacodynamic features (because of variability in neurotoxin-derived bacterial strain, excipients and manufacturing process) and dose contained in each vial (10,11).

A review of available literature was carried out to determine key aspects of the injection procedure with onabotA, including:

- Setting of the procedure
- Anaesthesia
- Infection management (including urinalysis for prophylaxis with antibiotics)
- Type of cystoscope
- Injection dose
- Injection volume
- Injection sites number and position
- Needle selection
- Bladder injection technique.

The National Library of Medicine was searched via PubMed using various combinations of the following terms: botulinum toxin/onabotulinum AND injection AND procedure or design AND urinary AND/OR incontinence AND/OR overactive bladder AND/OR neurogenic AND/OR idiopathic. Each of the studies/articles was reviewed for extracting (i) study and patient numbers/diagnosis (iOAB or nOAB), (ii) injection protocol characteristics, (iii) efficacy data (iv) tolerability data and (v) differences in outcomes with varying doses/injection volume/injection sites/number of injections.

Physicians' survey

The survey was based on a questionnaire covering the above mentioned topics, which was completed by 13 international experts from 10 countries. Results from the literature search were compared with the expert panel survey findings.

Results

PubMed search

The literature search identified 29 articles and 22 of these were selected for the final analysis. The selection criteria for the studies included: articles in English, studies which utilised onabotA; studies with a total number of patients ≥ 30; studies with adult patients diagnosed with iOAB/nOAB with urinary incontinence. Both randomised and non-randomised studies were used (Table 1).

Study and patient characteristics

Of the 3273 patients included in the 22 selected studies (Table 1), 1487 had nOAB and 1856 had iOAB. All selected studies enrolled ≥ 30 patients. Most of the studies were randomised uncontrolled studies. Follow up ranged from 16 weeks up to 12 months.

Injection protocol

In the majority of clinical studies, the amount of onabotA injected was 200–300 U for nOAB and 100–200 U for iOAB (Table 1). Usually 30 injection sites for nOAB (range: 6.7–10 U/ml) and 20 or 30 sites for iOAB of 10 U/ml (range: 5–10 U/ml) in the bladder (usually sparing the trigone) under cystoscopic guidance (flexible or rigid) and with different types of anaesthesia (local or general) were carried out (Table 2).

Efficacy

Dose comparison

A total injection dose of 100–400 U of onabotA has been reported in published studies to date (12–33). The most common doses utilised are 100–200 U for iOAB and 200–300 U for nOAB. However, the

Table 1 Study and patient characteristics of articles selected for literature review

References	NDO/IDO	No. of patients	Study design	Amount of onabotA (U)	Active treatment mean follow up
Brubaker et al. (12)	iOAB	43	Randomised, placebo-controlled	200	12 months
Chapple et al. (13)	iOAB	548	Randomised, placebo-controlled	100	24 weeks
Cruz et al. (14)	nOAB	275	Randomised, placebo-controlled	200 and 300	≥ 1 year
Denys et al. (15)	iOAB	99	Randomised, placebo-controlled	50, 100, or 150	6 months
Dmochowski et al. (16)	iOAB	313	Randomised, placebo-controlled	50, 100, 150, 200 or 300	36 weeks (~8 months)
Giannantoni et al. (17)	nOAB	75	Randomised, active comparator-controlled	300	2 years
Ginsberg et al. (18)	nOAB	416	Randomised, placebo-controlled	200 and 300	≥ 1 year
Granese et al. (19)	iOAB	68	Open label	100	12 months
Herschorn et al. (20)	nOAB	57	Randomised, placebo-controlled	300	≥ 1 year
Kalsi et al. (21)	iOAB	16	Open label	200 (iOAB) and 300 (nOAB)	16 weeks
	nOAB	32			
King and Neville (22)	iOAB	31	Randomised, placebo-controlled	200	9 months
Kuo (23)	iOAB	35	Open label	100, 150 and 200	3 months
	nOAB	40			
Kuo (24)	iOAB	45	Open label	100	3 months
Lucioni et al. (25)	iOAB and nOAB	40	Open label	300	6 months
Nitti et al. (26)	iOAB	557	Randomised, placebo-controlled	100	24 weeks (~6 months)
Popat et al. (27)	iOAB	31	Open label	200 (iOAB) and 300 (nOAB)	16 weeks
	nOAB	44			
Rapp et al. (28)	iOAB	35	Open label	300	6 months
Reitz et al. (29)	nOAB	231	Open label	300	Up to 36 weeks
Schurch et al. (30)	nOAB	31	Open label	200 and 300	Up to 36 weeks
Schurch et al. (31)	nOAB	59	Randomised, placebo-controlled	200 and 300	24 weeks
Smith et al. (32)	iOAB and nOAB	110	Open label	100–200 vs. 100–300	24 weeks
Thavaseelan et al. (33)	nOAB	56	Randomised, active comparator	200 and 300	1 year

onabotA 200 U is now approved by the FDA and EMEA for nOAB for patients insufficiently managed by anticholinergics. The dose of 100 U was approved by FDA and EMEA for iOAB with urinary incontinence refractory to standard pharmacologic treatment.

The mean number of daily incontinence episodes at baseline was between two and seven episodes per day in the selected trials. The studies demonstrate that the efficacy of onabotA is significantly superior to that of both placebo and resiniferatoxin, though it is comparable between 200 and 300 U in nOAB and between 100 and 150 U in iOAB. The mean daily urinary incontinence episodes decreased in all the studies analysed by one to six episodes (Table 3).

The rate of initiation of clean intermittent catheterisation (CIC; *de novo* CIC) after treatment among non-users at baseline varied between 30% and 35% with 200 U; and 42–88% with 300 U for nOAB patients. Among iOAB patients, the rate of initiation of CIC varied from 1% to 13.3% with 100 U; ~4–20% for 150 U; 12–19% for 300 U.

Other adverse effects reported are detailed in Table 4. Muscle weakness was only reported in three studies with nOAB patients, where the degree of weakness seems to be larger with 300 vs. 200 U. Urinary tract infections (UTIs) occurred with a frequency of 28–32% with 200 U and 21–57% with 300 U in nOAB patients and 0–36% with 100 U, 9–44% with 150 U and ~44–48% with 200 U in iOAB.

Volume and injection sites

Published investigations to date have generally used an injection volume ranging from 0.5 to 1 ml/injection site with dosage per site in most studies of 10 U/ml (range: 6.7–33 U/ml). Usually, 30 sites for nOAB (range: 6.7–10 U/ml) and 20–30 sites for iOAB (range: 5–10 U/ml) were injected in clinical studies.

Physicians' survey

Thirteen experts from 10 countries completed the questionnaire covering all aspects of the procedure. Table 5 summarises the various elements of the injection procedure utilised in clinical practice by the 13 physicians surveyed.

Needle selection

Though most studies selected did not compare needles directly, reviews by Dasgupta and O'Leary and Dierich recommend that injection needles should be selected on the basis of avoiding any risk of leakage

Table 2 OnabotA injection protocol characteristics

Study	Dilution (U/ml)	Injection site	Number of injections	Anaesthesia	Outcome
Brubaker et al. (12)	33 U (200 U/6 ml)	Posterior bladder wall in three rows sparing trigone and ureteric orifice	15–20	Local	Study stopped because of high rates of urinary retention and UTI
Chapple et al. (13)	5 U	Intradetrusor injections sparing the trigone	20	Local +/− sedation	Significant improvements vs. placebo in efficacy parameters and I-QOL and KHQ
Cruz et al. (14)	~6.7 U	Intradetrusor injections sparing the trigone	30	Local/general	No difference between the two doses in efficacy/safety parameters, although the 200 U had a more favourable safety profile
Denys et al. (15)	1 ml (3.3, 6.7 and 10 U)	Intradetrusor injections sparing the trigone	15	Local/general	No difference between 100 and 150 U in efficacy/QoL parameters, although the 100 U had a more favourable safety profile
Dmochowski et al. (16)	0.5 ml (2.5–15 U)	Intradetrusor injections sparing the trigone and dome	20	Local	Dose-dependent increase in PVR and CIC use No significant differences in efficacy Optimal dose for IDO: 100 U
Giannantoni et al. (17)	10 U	Detrusor muscle sparing the trigone	30	Sedation or spinal	Significant decrease in rates of incontinence with botulinum toxin compared with resiniferatoxin at 6, 12 and 18 months
Ginsberg et al. (18)	~6.7 U	Intradetrusor injections sparing the trigone	30	Local/general	No difference between the two doses in efficacy/safety parameters, although the 200 U had a more favourable safety profile
Granese et al. (19)	5 U	Detrusor muscle	20	General	Significant improvement in urodynamic parameters, clinical features and quality of life with 100 U – no comparator
Herschorn et al. (20)	10 U	Intradetrusor injections sparing the trigone	30	Local/general	300 U dose efficacious and well tolerated for up to 9 months – no comparator dose
Kalsi et al. (21)	10 U	Dome + base	30 (nOAB) 20 (iOAB)	Local	Intradetrusor BoNT/A produces comparable, significant improvements in QoL in iOAB or nOAB Not a dose-comparison study
King and Neville (22)	20 U	Subepithelially over the trigone + bladder base	10 in each area (total 20)	General	Urgency was improved in all groups but in the bladder base group there was no increase in MCC or PVR
Kuo (23)	7.5–10 U	Posterior and lateral walls of the urinary bladder	40	General	Dose-dependent effect seen with efficacy. Decreased adverse effects with 100 vs. 200 U
Kuo (24)	~5 U	Suburothelial, intradetrusor and bladder base	40 (detrusor) 10 (bladder base)	General	Urgency was improved in all groups but in the bladder base group there was no increase in MCC or PVR
Lucioni et al. (25)	10 U	Trigone included vs. trigone-sparing	30 + 2 in trigone (for trigone-inclusion group)		Improvement in symptom scores between the trigone and trigone-sparing groups was not significant
Nitti et al. (26)	5 U	Bladder sparing the trigone	20	Local +/− sedation	Significant improvements vs. placebo in efficacy parameters and I-QOL and KHQ Open label phase: increased PVR and CIC use dose escalated from 100 to 150 U No differences in efficacy
Popat et al. (27)	10 U	Dome + base	30	Local	Significant improvements in urodynamic and lower urinary tract symptoms in iOAB and nOAB de novo CIC in 69% of nOAB patients (300 U) as compared with 19% of those with iOAB (200 U)

Table 2 Continued

Study	Dilution (U/ml)	Injection site	Number of injections	Anaesthesia	Outcome
Rapp et al. (28)	10 U	Transurethrally in the bladder	30	N/A	Symptoms improved though patients had mild haematuria, pelvic pain and dysuria – no comparator
Reitz et al. (29)	10 U	Detrusor muscle sparing the trigone	30	None, local, spinal or general	Significant improvement of bladder function + subjective satisfaction
Schurch et al. (30)	10 U	Dome	20–30	None or local	Better outcomes observed with 300 vs. 200 U
Schurch et al. (31)	6.7–10 U	Detrusor muscle sparing the base + trigone	30	None, local, spinal, or general	No difference in overall efficacy or adverse events between 200 vs. 300 U
Smith et al. (32)	10 U	100–200 U – four quadrants of the external sphincter 100–300 U-injection into the bladder base	30–40	Light sedation	Effective + safe Greater number of injections nOAB vs. iOAB
Thavaseelan et al. (33)	6.7–10 U	N/A	N/A	Sedation	Authors did not comment re differences between doses

or perforation of the bladder wall, and ensuring targeted injection (34,35). Stoppers on needles tend to prevent the risk of perforation. Needles are typically 22 to 27-gauge and equal to 4 mm in length (35).

The currently available needles for onabotA injection used by the physicians surveyed are summarised in Table 6, in the order of preference and rationale provided by the physicians.

Discussion

Protocol

Generally, this is a simple procedure which can be carried out in an outpatient or inpatient setting (depending on local regulations or patient factors). The whole procedure usually takes no more than 30 min. All the physicians surveyed agree that urodynamic examinations must be carried out before the first procedure for all patients being considered for BoNT A treatment. However, at re-injection urodynamic examinations are not necessarily carried out in most centres as re-injection is commonly determined on symptom reappearance. Injection is not recommended if an active UTI is present.

The type of cystoscope used can be flexible or rigid. The most common method of sedation used in clinical practice and publications is a local anaesthetic, lidocaine for 10–30 min. No study has compared these variables though the FDA recommended that both rigid or flexible cystoscopes, as well as local or general anaesthesia, can be used when standardising the approval of the licence for BOTOX® in nOAB and iOAB (10). The procedure is generally carried out in patients who have tried anticholinergics first.

Prophylactic antibiotics should be administered prior to the treatment day (for approximately 1–3 days), on the treatment day, and approximately 1–3 days post-treatment (10). Avoiding amino glycosides is recommended before or after the procedure as the effect of BoNT A may be potentiated by these (10). Longer term antibiotic use may be necessary for long-term catheter users. According to the survey and clinical studies, UTIs are common with the procedure despite provision of prophylactic antibiotics.

Injection dose

The objectives of treatment with BoNT A are different in nOAB and iOAB. In nOAB, the purpose of BoNT A injections is to provide low pressure bladder filling and avoid incontinence episodes between self-catheterisation or spontaneous voidings when anticholinergics have failed. The license of onabotA use in nOAB (the only botulinum toxin licensed for this procedure) is limited to this case. In iOAB, the expectation from onanotA is to suppress urgency

Table 3 Impact of onabotA on the number of incontinence episodes

Study (primary time point)	Mean baseline incontinence episodes (over time)	Mean reduction in incontinence episodes at primary time point	p (change from baseline vs. comparator)	No of patients initiating CIC after treatment *
Brubaker et al. (12) (60 days)				
200 U onabotA	21.44	Specific values	< 0.0001	12 (43%)
Placebo	19.00 (over 3 days)	not provided		0
Chapple et al. (13)				
100 U onabotA	5.5	−2.95	< 0.001	19 (6.9%)
Placebo	5.7 (daily)	−1.03		2 (0.7%)
Cruz et al. (14) (6 weeks)				
200 U onabotA	32.5	−21.8	< 0.01	13 (30%)
300 U onabotA	31.2	−19.4	< 0.01	19 (42%)
Placebo	36.7 (weekly)	−13.2		5 (12%)
Denys et al. (15) (3 months)				
50 U onabotA	3.9	Represented as 50%	Overall = 0.08	3
100 U onabotA	5.9	decrease in urgency		1
150 U onabotA	3.9	and urge incontinence		4
Placebo	5.9 (daily)	episodes: 23% PBO; 16% 50 U; 19% 100 U; 19% 150 U		1
Dmochowski et al. (16) (12 weeks)				
50 U onabotA	Values not specified (weekly)	−17.4	Not provided	3 (5.4%)
100 U onabotA		−20.7		6 (10.9%)
150 U onabotA		−18.4		10 (20%)
200 U onabotA		−23.0		11 (21.2%)
300 U onabotA		−19.6		9 (16.4%)
Placebo		−19.4		0
Giannantoni et al. (17) (6 months)				
300 U onabotA	4.8	−3.4		0
Resiniferatoxin	5.4 (daily)	−3.2	< 0.05	0
Ginsberg et al. (18) (6 weeks)				
200 U onabotA	32.3	−21	< 0.05	21 (35%)
300 U onabotA	31.1	−22.7	< 0.05	23 (42%)
Placebo	28.3 (weekly)	−8.8	NS	6 (10%)
Granese et al. (19) (3 months)				
100 U onabotA	5.7 (daily)	−3.9	< 0.0001	1 (5%)
Herschorn et al. (20) (6 weeks)				
300 U onabotA	3.06	−1.75	< 0.0001	At 36 weeks:
Placebo	4.03 (daily)	−0.73		5 (17.2%)
				2 (7%)
Kalsi et al. (21) (16 weeks)				
200 onabotA (iOAB)	3.4	−2.9	0.0003	2 (12.5%) (iOAB)
300 U onabotA (nOAB)				15 (88.2%) (nOAB)
King and Neville (22) (6 weeks)				
200 U onabotA	Specific value not provided = weekly incontinence episodes		0.0005	Not reported
Placebo	Improved in the in the BoNT A group vs. placebo group (65.8% vs. 26.8%)			
Kuo (22) (3 months)				
100 U onabotA				
Suburothelial	6.8	−1.9	0.868 (Suburothelial	Not provided but acute urinary retention was:
Detrusor	11.3	−3.8	vs. bladder base)	Suburothelial n = 2 (13.3%)
Bladder base	11.1 (3 days)	−5.5	0.315 (detrusor vs. bladder base)	Detrusor n = 2 (13.3%)
				Bladder base n = 0

Table 3 Continued

Study (primary time point)	Mean baseline incontinence episodes (over time)	Mean reduction in incontinence episodes at primary time point	p (change from baseline vs. comparator)	No of patients initiating CIC after treatment *
Nitti (26) (12 weeks)				
100 U onabotA	5.5	−2.64	< 0.001	15 (5.4%)
Placebo	5.1 (daily)	−0.87		1 (0.4%)
Popat et al. (27) (16 weeks)				
200 U onabotA (iOAB)	13.6	−5.3	0.0002	6 (19.3%)
300 U onabotA (nOAB)	12.3 (per 24 h)	−5.7	< 0.0001 (vs. baseline)	30 (69%)
Rapp et al. (28) (3 weeks)				
300 U onabotA				0
Schurch et al. (31) (24 weeks)				
200 U onabotA	1.9	−1.1	< 0.05	Constant CIC frequency throughout study
300 U onabotA	2.8	−0.9	< 0.05	
Placebo	3 (daily)	−0.1		

Kuo (23) and Lucioni et al. (25) did not evaluate incontinence episodes. Reitz et al. (29), Thavaseelan et al. (33), Rapp et al. (28), Smith et al. (32) and Schurch et al. (30) did not report the results of change in incontinence episodes and/or CIC rates (Schurch et al. (30) had all the patients at baseline on CIC). Popat et al. (27) was an open-label study therefore p-values are vs. baseline not vs. a comparator. CIC, clean intermittent catheterisation. *Developed urinary retention requiring CIC after the procedure.

Table 4 Adverse effects with onabotA vs. comparator in randomised trials

	Urinary tract infections	Dysuria	Haematuria	Muscular weakness	Injection site pain
nOAB					
OnabotA 200 U (n %)	Cruz et al. (14) 25 (27.5) Ginsberg et al. (18) 38 (28) Schurch et al. (31) 6 (31.6)	Cruz et al. (14) 2 (2.2)	Cruz et al. (14) 5 (5.5) Ginsberg et al. (18) 6 (4) Schurch et al. (31) 1 (5.3)	Cruz et al. (14) 6 (6.6) Ginsberg et al. (18) 4 (3)	Schurch et al. (31) 0
OnabotA 300 U (n %)	Cruz et al. (14) 34 (38.2) Ginsberg et al. (18) 36 (28) Herschorn et al. (20) 16 (57) Schurch et al. (31) 4 (21.1)	Cruz et al. (14) 5 (5.6)	Cruz et al. (14) 7 (7.9) Ginsberg et al. (18) 6 (5) Herschorn et al. (20) 2 (7) Schurch et al. (31) 1 (5.3)	Cruz et al. (14) 4 (4.5) Ginsberg et al. (18) 9 (7) Herschorn et al. (20) 3 (11)	Schurch et al. (31) 2 (10.5)
Placebo (n %)	Cruz et al. (14) 20 (22.2) Ginsberg et al. (18) 26 (18) Herschorn et al. (20) 16 (55) Schurch et al. (31) 3 (14.3)	Cruz et al. (14) 2 (2.2)	Cruz et al. (14) 3 (3.3) Ginsberg et al. (18) 4 (3) Herschorn et al. (20) 2 (7) Schurch et al. (31) 0	Cruz et al. (14) 1 (1.1) Ginsberg et al. (18) 4 (3) Herschorn et al. (20) 0	Schurch et al.(31) 1 (4.8)
iOAB					
OnabotA 100 U (n %)	Chapple et al. (13) 56 (20.4) Denys et al. (15) 0 (0) Dmochowski et al. (16) 20 (36.4) Nitti et al. (26) 43 (15.5)	Chapple et al. (13) 16 (5.8) Nitti et al. (26) 34 (12.2)	Chapple et al. (13) 10 (3.6)		Denys et al. (15) 19
OnabotA 150 U (n %)	Denys et al. (15) 2 (9.1) Dmochowski et al. (16) 22 (44.0)				Denys et al. (15) 23
OnabotA 200 U (n %)	Brubaker et al. (12) 12 (44) Dmochowski et al. (16) 25 (48.1)				
OnabotA 300 U (n %)	Dmochowski et al. (16) 19 (34.5)				
Placebo (n %)	Brubaker et al. (12) 3 (22) Denys et al. (15) 2 (8.7) Nitti et al. (26) 16 (5.9) Dmochowski et al. (16) 7 (16.3)	Nitti et al. (26) 26 (9.6)			Denys et al. (15) 28

Table 5 Clinical experience of the injection procedure – Results of physicians survey (n = 13)

Country	Dose: injected units for nOAB (U)	Dose: injected units for iOAB (U)	Injection mapping/number	Injection volume per site	nOAB: needle	iOAB: needle	Anaesthesia (time prior to procedure)
Australia, n = 1	300	100	NDO:30 iOAB: 20	nOAB 1 ml iOAB 0.5 ml	BoNee (Coloplast)	BoNee (Coloplast)	Sedation
France, n = 2	200	100	NDO: 30 iOAB: 10	iOAB and nOAB 1 ml	BoNee (Coloplast)	BoNee (Coloplast)	Local (lidocaine) (30 min)
Canada, n = 2	200	100	20	iOAB and nOAB 1 ml	Williams (Cook Medical)	Williams (Cook Medical)	Local (10–20 min)
Germany, n = 1	100–300	100–200	10/100 U 20/200 U 30/300 U	iOAB and nOAB 1 ml	BoNee (Coloplast)	BoNee (Coloplast)	Local (lidocaine) (30 min)
Italy, n = 1	100–200	100	10–20	iOAB and nOAB 0.5–1 ml	BoNee (Coloplast)	BoNee (Coloplast)	Fentanyl injection – mild sedation
The Netherlands, n = 1	100	100	10	iOAB and nOAB 1 ml	Cook Deflux	Cook Deflux	Local (lidocaine) (10 min)
Portugal, n = 1	200	100	30	iOAB and nOAB 1 ml	BoNee (Coloplast)	BoNee (Coloplast)	General
Spain, n = 1	200	100	20–30	iOAB and nOAB 0.5–1 ml	BoNee (Coloplast)	BoNee (Coloplast)	Local (lidocaine) (10–15 min)
UK, n = 1	200	100	NDO: 20 (200 U/20 ml) iOAB: 10 U (100 U/10 ml)	iOAB and nOAB 1 ml	BoNee (Coloplast)	BoNee (Coloplast)	Local (lidocaine) (5 min) with flexi GA or spinal anaesthesia with rigid cystoscope
USA, n = 2	100–200	100	20	iOAB 0.5–1 ml nOAB 1 ml	Rigid: Williams (Cook Medical) Flexible: Olympus or BoNee (Coloplast)	Rigid: Cook Williams: Flexible: Olympus or BoNee occasionally	Local (lidocaine) (30 min)

and urge incontinence episodes in patients not adequately managed by anticholinergic drugs.

The most commonly used dose of onabotA is 300 U in clinical studies and 200 U in clinical practice for nOAB. For iOAB, the most common dose in clinical studies and clinical practice is 100 U. The clinical studies with onabotA in nOAB and iOAB have demonstrated that there are no clinically relevant benefits between 100 and 150 U in iOAB (13,26) or between 300 U compared with 200 U dose in nOAB (14,18,31), suggesting lower doses can be used. Furthermore, the larger doses have been associated with increase in adverse events and initiation of CIC post-treatment as reported by large trials and this survey (14,18,26,31).

Higher dose is used for nOAB vs. iOAB in clinical practice, reflecting clinical studies. Most physicians surveyed use the 200 U dose for nOAB because of:

- The efficacy data reported in literature with this dose, especially recent large-scale RCTs with onabot A.
- It is also the licensed dose in most countries for use in nOAB.
- The physicians' personal experience.

The 100 U dose for iOAB is used by most physicians surveyed:

- To avoid retention (most iOAB patients do not self-catheterise preprocedure as is the case for nOAB patients).
- Because of recent clinical publications, especially recent large-scale RCTs with onabotA.
- Based on the physicians' personal experience.

In one of the first investigations of onabotA injection, Schurch et al. reported that 300 U might be the optimal dose for nOAB (30). Subsequently, they reported the first comparison of 200 and 300 U vs. placebo where the results demonstrated significant improvements in continence, bladder capacity and maximum detrusor pressure in both treatment arms, with no significant difference between the two doses (31). Herschorn et al. reported fewer incontinence episodes with onabotA 300 U vs. placebo at 6 and 24 weeks ($p < 0.01$) and UTIs were the most common adverse effect (20). In the large randomised placebo-controlled study of 275 patients with nOAB, the investigators reported dose-related adverse effects such as UTIs with 300 U vs. placebo compared with 200 U vs. placebo (14). In addition, 12%, 30% and 42% of patients in the placebo, 200 U, and 300 U groups, respectively, initiated CIC post-treatment (14). In the other large-scale randomised, placebo-controlled study with 416 patients with nOAB, a similar dose-related adverse effect profile in the 300 U group compared with the 200 U group was shown (18). In this

Table 6 Needles used by surveyed physicians in order of preference

Needle (n = 13)	Reason for recommending its use (based on physicians' experience)
BoNee (Coloplast), n = 7	4 mm length
	Sharp and stable
	Appropriate rigidity to allow sustaining the injection force
	Less bleeding and less pain compared with other needles
	Reasonable cost
	Easy to use and handle
	Avoids bladder wall perforation (stopper)
	Helps with making the procedure faster
	Flexible, allowing deflexion of flexible cystoscope
Williams needle (Cook Medical), n = 4	Reasonable cost
	Easily available
	Small and flexible
Olympus needle, n = 2	Compares favourably with other flexible injection needles
	May contribute towards lowering pain perception

study, initiation of catheterisation after injection because of urinary retention correlated with increasing dose of onabotA (18). In both of these studies, no clinically relevant benefits of 300 U compared with 200 U onabotA were identified. Indeed, the licence for nOAB was granted for onabotA (BOTOX®) 200 U on the basis of this data (10).

Dmochowski et al. demonstrated durable efficacy with onabotA dose 100 U or greater for primary and secondary efficacy measures (16). However, doses greater than 150 U contributed minimal additional improvement in daily episodes of urinary incontinence. Changes in postvoid residual (PVR) urine volume and the use of CIC were both dose dependent.

Chapple et al. and Nitti et al. conducted two large phase III clinical trials with 557 and 548 patients, respectively, with refractory idiopathic OAB who received onabotA 100 U or placebo into 20 sites in the bladder sparing the trigone (13,26). Patients received onabotA or placebo into 20 sites in the bladder sparing the trigone. The results showed statistically significant improvements for all primary and secondary end-points measured including reduction in incontinence episodes, improvements in treatment benefit scale, micturition episodes, urge episodes, volume voided and two QoL measures (I-QOL and Kings Health Questionnaire).

Brubaker et al. conducted a trial injecting onabotA 200 U in refractory iOAB patients (12). Although the injection of onabotA was shown to be an effective and durable treatment, the trial was stopped early because of increased PVR and UTIs, suggesting that 200 U of onabotA may not be an appropriate dose for iOAB. Kuo et al. reported a randomised comparison of 100, 150 and 200 U in the treatment of refractory iOAB and nOAB (23). Clinical and urodynamic outcomes were similar between the 150 and 200 U groups, with those patients receiving 100 U experiencing less favourable therapeutic results (23). Kuo found that a dose-dependent increase in difficulty voiding and acute urinary retention (100, 150, 200 U) was seen over all doses (23).

Volume and dose per site

Large clinical trials, utilising onabotA have demonstrated optimal efficacy and minimal side effects with 30 injections of 1 ml each (~6.7 U) for nOAB and 20 injections of 0.5 ml (5 U) in the detrusor for iOAB, both sparing the trigone (13,14,18,26). The survey reflected this practice among physicians with variance for iOAB (10–20 injections of 0.5–1 ml per injection, equivalent to 5–10 U per site). For nOAB, 1 ml (6.7–10 U) per site is usually used in clinical practice.

The published data from large clinical trials conducted by Cruz et al. and Ginsberg et al. utilising onabotA demonstrate efficacy with 30 injections of 1 ml each (~6.7 U) for nOAB (14,18). For iOAB, Nitti et al. and Chapple et al. have demonstrated that 0.5 ml (5 U) injections across 20 sites in the detrusor (13,26) are effective in the large-scale trial of 1105 patients. These are the lowest doses which do not compromise efficacy and have the lowest risk of adverse events.

Injection sites and number

OnabotA has been injected directly into the detrusor, sparing the trigone in almost all studies, including the large-scale clinical trials. Clinical experience also reflects clinical studies where the detrusor is injected while sparing the trigone. The majority of participants reported that they prefer the method of injection pattern shown in Figure 1 – horizontal lines across the bladder, sparing the trigone.

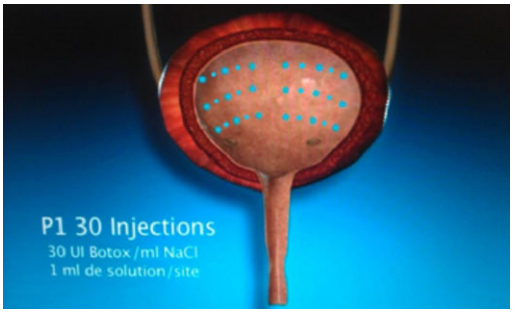

Figure 1 Method of injection used by most physicians from the survey

The first report of intravesical onabotA injection describes a trigone-sparing injection distribution (30), in order to avoid inducing reflux to the upper tracts. However, two small studies with 12 and 20 patients respectively, have demonstrated that trigone injections do not induce reflux in OAB (36,37). Other small studies have demonstrated similar results. A study in 22 patients with iOAB has shown that trigone-including injections are superior to trigone-sparing injections for the treatment of refractory iOAB and do not cause reflux (38). Another study of 18 nOAB patients demonstrated significant superiority for improving all efficacy parameters including vs. excluding the trigone (39). Trigonal injection of onabotA has also been shown to be safe and effective treatment for refractory bladder pain syndrome/interstitial cystitis in a study of 24 women (40). Another pilot study conducted to assess the subjective benefit of trigonal inclusion during onabotA 300 U-injection in 40 patients with iOAB and nOAB, demonstrated a statistically significant improvement in QoL scores in both groups with no difference between the treatment arms (25). However, these data are based on small studies.

In a larger study, Smith et al. reported successful outcomes utilising onabotA injection with trigonal inclusion in iOAB and nOAB (32). However, this study did not make any direct comparison with patients receiving trigone-sparing injections. Subsequently though, the larger multicentre trials with onabotA involved intradetrusor injections, sparing the trigone, which led to the approval of the toxin in iOAB and nOAB (13,14,18,26).

In general, toxin injection is performed using 20–40 evenly distributed injection sites in the detrusor muscle. Karsenty et al. presented data comparing regimens of 30 vs. 10 injections of 300 U onabotA in a population with nOAB and concluded that the lower number of injections did not affect efficacy or safety (41). Most studies though report 30 injections for nOAB and 20–30 injections for iOAB, all sparing the trigone. Figure 1 illustrates the typical injection pattern used for onabotA injections.

Needle selection

BoNT A is injected into the detrusor using a rigid or flexible cystoscope and there is a range of potential needles that may be considered. The principle of using an ultrafine needle – typically 4 mm at its tip – is that it can go down a cystoscope easily without damaging it (34). Burying the needle tip to its hilt ensures that the toxin remains mainly within the bladder wall without leaking significantly into the bladder lumen or extravesical tissues (34).

The physicians surveyed agreed that the key properties of needles used in this procedure should be:

- Avoid risk of leakage or perforation of the bladder wall (stoppers on needles preferred)

Table 7 Recommendations for bladder injection technique

	Recommendations	
Technique	**nOAB**	**iOAB**
Dose	OnabotA 200 U (n = 8) 100–300 U (n = 1)	OnabotA 100 U (n = 6) 100–150 U (n = 2)
Injection site and volume	6.7–10 U/ml (1 ml/site) (n = 9) 20–30 injections (n = 8) 10 injections (n = 1)	5–10 U/ml (0.5–1 ml/site) (n = 9) 30 injections (n = 3) 10–20 injections (n = 6)
Cystoscope	Rigid (n = 7) Flexible (n = 2)	Rigid (n = 6) Flexible (n = 2)
Anaesthesia	Local (n = 6) General (n = 3)	Local (n = 7) General (n = 2)
Needle	Coloplast BoNee (n = 7) Cook Williams (n = 4) Olympus NM-101C-0427 needle (n = 2)	Coloplast BoNee (n = 7) Cook Williams (n = 4) Olympus NM-101C-0427 needle (n = 2)
Re-injection interval	6–12 months	6–9 months

- Ensure targeted injection
- Easy to inject
- Low cost
- Sharpness – able to penetrate easily
- Avoid bleeding
- Carry a low risk of injection pain
- Do not damage the cystoscope
- Flexibility of shaft to allow better tactile feel
- Good quality of connection with syringe (luer lock).

According to the physicians' survey, the BoNee needle was the most frequently used needle in iOAB and nOAB patients as it fulfils the above criteria. Another needle, also frequently used by our survey participants, for the procedure is the Williams needle (Cook Medical). However, the participants also reported that the Williams needle may cause perforation and its ability to penetrate the bladder wall may differ from one needle to another.

Follow up

In the large clinical trials with onabotA, urodynamics were used in follow up with all nOAB patients (14,18). However, in clinical practice a postvoid residue at 2 weeks is usually assessed and after that, further follow up is usually patient/symptom directed.

In onabotA clinical studies, the outcomes evaluated were based on symptoms and QoL for primary and repeat injections. In clinical practice, the outcomes are usually judged by patient communication regarding changes in their symptoms or improvements in their QoL.

Recommendations for bladder injection technique

Table 7 highlights recommendations made by the current authors, based on literature analysis and the physician's survey.

Conclusions

Recent studies together with physicians' survey of onabotA in iOAB and nOAB have shown that injection of the toxin into the detrusor of adults with iOAB who have failed anticholinergic therapy has beneficial effects both on clinical and urodynamic parameters. The duration of effect of onabotA may range from 6 to 12 months, with symptom improvement seen as early as 2 weeks postinjection (13,14,16,18,26).

According to the physicians surveyed in this study, the procedure with BoNT A is conducted in preference to other invasive/surgical procedures for urinary incontinence, e.g. sacral neuromodulation in patients who are refractory to anticholinergic therapy. On average, the BoNT A injection procedure is carried out at least 5–50 times more frequently than any other invasive procedure for urinary incontinence in clinical practice.

The clinical studies with onabotA in iOAB and nOAB have demonstrated that there are no clinically relevant benefits between 100 and 150 U in iOAB or between 300 U compared with 200 U dose in nOAB, suggesting lower doses can be used. A variety of injection numbers and volumes have been used, demonstrating similar efficacy and tolerability. The recommended injection numbers and volumes are 30 injections of 1 ml each (~6.7 U) for nOAB and 0.5 ml (5 U) injections across 20 sites in the detrusor for iOAB. The available evidence suggests that the trigone may be injected without compromising safety or efficacy. However, the majority of large studies performed used an injection protocol which spared the trigone and this is reflected in clinical practice.

Author contributions

All authors took part in the survey for physicians, reviewed and edited the publication which was produced by Gilles Karsenty with editorial assistance from Sabah Al-Lawati at Right Angle

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