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CLINICAL ARTICLE

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Evaluation of the effect of 100U of Onabotulinum toxin A on detrusor contractility in women with idiopathic OAB: A multicentre prospective study

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Abstract

Aims: Intradetrusor injection of Onabotulinum Toxin A (BTX-A) is a third-line treatment for overactive bladder (OAB). Voiding dysfunction and the need for intermittent catheterization are potential complications, consequent to bladder contractility (BC) decrement.

Primary aim: to evaluate BC variation after BTX-A detrusor injection in women with idiopathic OAB.

Methods: A prospective multi-institutional observational study was conducted. Medical history, bladder diary, 24-h pad test, and invasive urodynamic parameters were recorded before and 4–6 weeks after BTX-A 100U administration. BC was measured as Modified Projected Isovolumetric Pressure (PIP1), that is, maximum flow rate (Qmax) + detrusor pressure at Qmax (PdetQmax).

Continuous variables were expressed as median and interquartile range. We compared continuous variables using Wilcoxon test and proportions between two times with Fisher exact test.

Results: No changes in PIP1 were observed ($p > 0.05$) in 45 women enrolled between January 2018 and September 2019. Median age was 54.6 years. At baseline, 91.1% had urge urinary incontinence, with 4.9 ± 2.6 daily pads used and a 24-h pad test of 205.4 ± 70.8 g. Baseline detrusor contractility was normal in all the patients. Postoperatively, an improvement in the 24-h pad test ($p < 0.01$), daily voids ($p < 0.01$), and nocturia ($p < 0.01$) occurred. Urodynamics pointed out a significant reduction of detrusor overactivity rate ($p < 0.01$) and an increase of median maximum cystometric capacity ($p < 0.01$). No difference was observed in median Qmax ($p > 0.05$), PdetQmax ($p > 0.05$), and PVR ($p > 0.05$). No patient needed postoperative catheterization.

Conclusions: The current series provides evidence that detrusor injection of botulinum toxin is an effective option for treating OAB, without causing voiding dysfunction and BC impairment.

KEYWORDS
bladder, bladder contractility, botulinum toxin, overactive bladder, urodynamics

1 | INTRODUCTION

Overactive bladder (OAB) is a common condition afflicting males and females, whose incidence increases with age.[1] The main symptom of this syndrome is urgency (dry OAB), eventually associated to urge incontinence (wet OAB), in absence of neurological causes.[2] In most cases, involuntary detrusor contractions at cystomanometry is the basis of urgency and urge incontinence, even if the case of altered sensitivity in absence of involuntary contraction, eventually associated to low compliance, is well documented in the literature.[3–5]

When first line treatment fails, second line therapy can consist in sacral neuromodulation or endovesical injection of botulinum toxin.[6,7] There is still disagreement about the sequence of administration of these two treatments, and by the current evidence, the preference depends mostly on the complexity of the case and the preference of the patient. Urodynamics, recommended before second line treatments, is useful in patient evaluation and can guide the therapeutic choice.

The principal concern about the treatment with botulinum toxin is the risk of urinary retention, that can need clean intermittent self-catheterization (CISC).[8,9] This complication depends on the mechanism of action of botulinum, that interferes with bladder contractility (BC). It is commonly accepted that elevated postvoid residual contraindicates the intravesical injection of botulinum toxin; nevertheless, even patients with well-balanced micturition have to be informed about the risk of CISC before treatment.[9]

Few studies exploring variations in contractility after Onabotulinum Toxin A (BTX-A) injection exist, showing a dose dependent reduction of contractility and a consequent increase in postvoid residual urine.[10] Even if the approval of 100U of BTX-A for treatment of idiopathic OAB is based on a clinical study showing an adequate symptom relief and an incidence of CISC of 6.9% versus placebo (0.5%),[9] no data exist about the effects of 100U on BC.

The aim of this study is to assess the BC variation after BTX-A detrusor injection in women suffering from idiopathic OAB.

2 | MATERIALS AND METHODS

The present study is a prospective, multicentric, observational analysis including five high volume centres for the treatment of idiopathic OAB. In each centre, women older than 18 years suffering from idiopathic OAB symptoms, with or without urge incontinence, were asked to participate to the study.

Subjects included were females older than 18 years, with OAB (dry and wet), who failed first line treatments (behavioural therapy, pelvic floor rehabilitation, antimuscarinics, β3-agonists). Exclusion criteria were: the administration of botulinum toxin for every indication within 12 weeks before the procedure; previous adoption of second-level treatment for OAB LUTS; chronic urinary retention (postvoid residual volume higher than 100 ml); known or clinically suspected neurological diseases; recurrent urinary tract infections; interstitial cystitis/chronic pelvic pain; pregnancy; known hypersensitivity to BTX-A; history of bladder tumour.

According to data in the literature, chronic postvoid residual was also an exclusion criterion.

Local ethics committee approval for the use of BTX-A with the specific purpose of this study was obtained.

Women undergoing BTX-A detrusor injection for idiopathic OAB were recruited and followed at least 2 months after the treatment. At baseline, patients underwent medical history, physical examination, postvoid residual volume (PVR), 3-day bladder diary (recording voiding frequency and daily episodes of urgency and urge incontinence), 24-h pad test. Complete invasive urodynamic evaluation was also recorded before treatment, to evaluate the presence of detrusoroveractivity, the volume at first involuntary detrusor contraction, the maximum cystometric capacity, and the maximum detrusor pressure during cistomanometry, as well as, during voiding, the maximum flow rate (Qmax) and the detrusor pressure at Qmax (PdetQmax). The presence of bladder outlet obstruction was assessed according to the Blaivas-Groutz nomogram.[11] BC was measured with Modified Projected Isovolumetric Pressure (PIP1), calculated as Qmax + PdetQmax.[12] Urodynamics were performed and the exam report drawn up according to good urodynamic practice.[13]

After written informed consent, 100U of onabotulinumtoxin A were administered. Patients performed urinalyses and urine cultures before treatment; antiplatelets and anticoagulants were discontinued according to the current cardiologic indications.

The procedure was performed by diluting the botulinum toxin (Botox®, Allergan Ltd.) in accordance with the instructions provided by the manufacturer, that is, one 100U vial in 10 ml of saline. The drug was deployed in 20 submucosal wheals, following a radial arrangement that spared the bladder trigone.

Postoperative follow-up included the recording of medical history and any complication, focusing on the occurrence of acute urinary retention or PVR greater than 200 ml, the last being the cut off for CISC. Furthermore, 3-day bladder diary and 24-h pad test were collected at least 4 weeks after the treatment. Urodynamics were repeated 4–6 weeks after the therapy.

The software Stata MP15 (StataCorp LLC) was used for statistical analysis.

For the sample size calculation, we referred to a previous internal pilot study conducted on 10 idiopathic patients who had undergone urodynamics before and after BTX A injections. In this preliminary experience, a postoperative 13% reduction in PIP1 was observed. So, by calculating 20% of patients lost at follow-up, setting the power of the study at 90% and a level of significance of 99% ($p \leq 0.01$), we needed a sample of at least 38 women accepting the protocol and undergoing the treatment, with at least 32 completing the follow-up.

Perioperative data were analyzed using descriptive statistics: frequencies were expressed as percentages, while continuous variable were presented as medians and interquartile ranges.

We used the Wilcoxon test to compare continuous non-normalizable variables and the Fisher's exact test to compare nominal postoperative variables, considering a two-sided p value of <0.05 as statistically significant.

3 | RESULTS

Between January 2018 and September 2019, 45 patients affected by idiopathic OAB have been treated with onabotulinumtoxin A 100U intravesical injections. All of them completed the study and none was lost to follow-up.

Complete baseline features of the population are listed in Table 1. Five patients showed a mild or moderate voiding obstruction according to the Blaivas-Groutz nomogram.

After treatment, PIP1 did not show any statistically significant difference (preoperative PIP1 42 cmH2O—interquartile range [IQR]: 38.3–48; postoperative PIP1 42 cmH2O—IQR: 35–47.1; $p < 0.01$). Similarly, the increase of post-void residual was not statistically significant ($p < 0.01$)

Postoperative bladder diary showed a significant reduction in the daily number of voids ($p < 0.01$) and in nocturia ($p < 0.01$), as well as a significant reduction of weight of urine loss ($p < 0.01$) (Table 2).

Urodynamic data are displayed in Table 3. No difference was found in postoperative Qmax ($p > 0.05$), PdetQmax ($p > 0.05$), while significant increase in maximum cystometric capacity and decrease in median MDP was observed. After the procedure the filling volume at first involuntary contraction was higher than before treatment ($p < 0.01$).

4 | DISCUSSION

The aim of our study was exploring detrusor variations consequent to injection of the lowest dose of BTX-A approved in clinical practice. We did not find any significant reduction of contractility. On the other hand, variations of cystomanometry and consequent improvements of bladder diary were statistically as well as clinically significant.

TABLE 1 Anagraphic and baseline data

	***n* = 45**
Age (year), mean ± *SD* (range)	54.6 ± 11.6 (37–73)
Urge urinary incontinence, *n* (%)	41 (91.1%)
Dailypads used, mean ± *SD* (range)	4.9 ± 2.6 (0–9)
24-h pad test, mean ± *SD* (range)	205.4 ± 70.8 (0–300)
Bladder outlet obstruction, *n* (%)	5 (11.1)
Bladder diary	
Number of voids 24 h, mean ± *SD* (range)	12.1 ± 3.5 (7–20)
Nighttime voids, mean ± *SD* (range)	2.7 ± 1.5 (0–5)
Bladder max capacity (ml), mean ± *SD* (range)	222.3 ± 157.5 (60–550)
Urgency episodes 24 h, mean ± *SD* (range)	9.3 ± 3.9 (3–18)
Incontinence episodes 24 h, mean ± *SD* (range)	4.8 ± 2.9 (0–10)

TABLE 2 Voiding diary and 24-h pad test before and after botulinum toxin administration

	Baseline	6 weeks	*p* value
Nr voids 24 h (median, IQR)	12 (9–14)	7 (6–9)	<0.01
Nr nighttime voids (median, IQR)	3 (1–4)	1 (1–2)	<0.01
Pad test (gr) (median, IQR)	200 (200–250)	65 (40–75)	<0.01

Abbreviation: IQR, interquartile range.

TABLE 3 Urodynamic parameters before and after botulinum toxin administration

	Baseline	6 weeks	*p* value
Volume of first IDC (ml) (median, IQR)	100 (73–128)	190 (131–286)	<0.01
MDP (cmH2O) (median, IQR)	19 (17–26)	18 (16–20)	<0.01
MCC (ml) (median, IQR)	330 (250–360)	445 (370–460)	<0.01
Qmax (ml/s) (median, IQR)	24 (22–26.8)	24 (19–29)	>0.05
PdetQmax(cmH2O) (median, IQR)	17 (15–22)	15 (13–21)	>0.05
PIP1 (median, IQR)	42 (38.3–48)	42 (35–47.1)	>0.05
PVR (ml) (median, IQR)	20 (0–35)	25 (0–40)	>0.05

Abbreviations: IDC, involuntary detrusor contraction; MCC, maximum cystometric capacity; MDP, maximum detrusor pressure; PdetQmax, detrusor pressure at peak flow; PIP1, projected isovolumetric pressure; PVR, postvoid residual; Qmax: peak flow rate.

Contractility was the only parameter that resulted unchanged after BTX-A injection among those usually considered in the literature when exploring urodynamic variations after treatment. In fact, increase of volume at first contraction and reduction of maximum detrusor pressure at first contraction were observed at cystomanometry. Even maximum cystometric capacity was increased, in line with the reduction of micturitions observed at bladder diary. In other words, urodynamic positive effects of filling were preserved, while potentially negative drawbacks during voiding were avoided. These data shed new light on the mechanisms of action linked to the clinical effects of botulinum toxin.

It is generally accepted that BTX-A influences both the afferent and the efferent pathways of detrusor control during filling and voiding.[14–17] The first hypothesis of the mechanism of action was a reduction in acetylcholine (ACh) release at the neuromuscular junctions of detrusor.[14] ACh is transported in vescicles: BTX-A prevents the neurotransmitter release by inhibiting vesicular docking, acting on docking protein SNAP-25. Therefore, the original rationale was that botulinum toxin blocked an abnormal release of ACh.[14] However, in the following years in vitro and in vivo observations have risen alternative hypothesis for OAB, looking at a myogenic origin of spontaneous activity, eventually due to bladder peripheral denervation, able to provoke involuntary contractions.[18] Moreover, the ability of urothelium to release neurotransmitters with paracrine activity on detrusor, modulating the afferent neural pathways, was also documented.[19–21] As a consequence, at least two mechanisms of action for BTX-A shall be supposed: the efferent modulation (reduction of ACh release) and the ability to reduce the afferent transmission and the voiding reflex.

The effects of BTX-A on cystomanometry can be considered clinical confirmations of the modulatory activity of the therapy on contractility and afferent signalling pathways. One possible explanation is that the improvement of MCC and volume to first contraction are linked to the urothelial release of ATP and nitroxide (NO), which are, respectively, reduced and increased by BTX-A in in vitro and in vivo.

Reduction in contractility is instead linked to the interference with ACh release at the neuromuscular junction, which is dose dependent. Trying to explain our results, we can hypothesize that this effect becomes relevant at higher dosages than 100U of BTX-A.

In a randomized controlled study, Rovner showed a dose dependent increase in MCC. A total of 100U of BTX-A produced a mean increase of MCC of 71 ml.[22] Our data are in line with this result. In the literature the estimated reduction of maximum detrusor pressure during filling is 31%.[23]

The urodynamic effects on voiding and contractility are less studied. Randomized controlled trials are still missing. In a retrospective evaluation of 67 patients undergone 200U BTX-A a significant reduction in

contractility was observed. A concrete risk of CISC existed if women had PIP1 ≤ 50 cmH2O (sensitivity 83%, specificity 70%). The Authors registered a reduction of mean PIP1 from 58 to 43 cmH2O.[10] No data exist about the effects of 100U BTX-A on BC, so that our prospective observational experience is the first report about the effect of this dose on detrusor contractility. In the examined cohort the median reduction of PIP1 was null.

If we look at the preserved therapeutic effects of 100U BTX-A on filling cystomanometry and the null effects on voiding (P/F study), we can argue that BTX-A acts on afferent control and urothelial release of neurotransmitters at lower concentrations, while the interference with ACh release at neuromuscular junction starts at higher dosage, increasing the therapeutic effects but also bothering the patients with potential side effects.

The mean value of PIP1 of enrolled women was 48.3 ± 5.96 cmH2O, with a range of values of 29–128 cmH2O and a median of 42 cmH2O. A total of 35/45 patients enrolled had PIP1 ≤ 50 cmH2O. Nevertheless, we did not register any statistically significant increase in postvoid residual (pretreatment PVR 25.4 ± 9.47 ml, posttreatment 36.3 ± 15.19 ml). Our data are in apparent contrast with Sahai et coll, who studied women undergoing injections of 200U BTX-A, but the lower amount of toxin used could explain the difference of results, and could cancel the caveat of the Authors about the risk for CISC in patients with PIP1 ≤ 50 cmH2O. Furthermore, in our population no women required posttreatment CISC, although a posttreatment CISC recourse rate of 6.9% should have been expected, according to Chapple.[9] The reasons for this result are to be found in a more accurate evaluation of the voiding function, as all our patients have performed a preoperative urodynamic evaluation in our experience. The cohort is, therefore, made up of more selected patients, with a baseline PIP1 of 42 cmH2O. Moreover, women with PVR > 100 were excluded for study protocol.

Some considerations are needed about the choice of PIP1 as the measure of contractility in our sample. Tan et all.[24] reported that mean PIP1 in elderly women is 50 cmH2O, with a range of 30–75 cmH2O. However, a clear cut off value for PIP1 in women is still lacking, and most important data about elder woman cannot necessarily be translated to younger women. The PIP1 represents a reliable estimate of BC in women. It is the simplest to apply in routine clinical activity, and therefore, the most repeatable.[12]

In the present analysis, PIP1 was in the supposed range of normal contractility as reported in the literature. This data limits the conclusions of our study to women with well-preserved contractility. On the other hand, it suggests that UDS can be useful in clinical practice in predicting the risk of UR and need of CISC, which is the most feared complication of BTX-A.

Jiang calculated a bladder efficiency (voided volume/total bladder capacity) ≤89% as an independent risk factor for clinically significant post treatment PVR needing CISC.[25] Our study was designed for the evaluation of the variations in contractility, while we cannot do any conclusion about this parameter, which deserves to be studied as a risk factor for CISC.

5 | CONCLUSIONS

This is the first study demonstrating the BTX-A at the dosage of 100U has no detrimental effect on BC, in women with idiopathic OAB without urodynamic evidence of obstruction. The urodynamic results confirm the effect of BTXA on both afferent and efferent control pathways of bladder function.

This study is also an indirect proof of multiple mechanisms of action of botulinum toxin, activated at different dosages of the drug.

The differences emerged comparing our results with studies exploring other dosages of BTX-A, suggest that the effects on sensitivity and bladder function start at lower dosages, so that 100U preserve therapeutic effects while avoiding urinary retention and CISC. The absence of interference with contractility confirms 100U as the ideal dose to administer to idiopathic patients.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Gaetano De Rienzo: project concept, development, data collection, data analysis, manuscript writing and review. **Paolo Minafra**: development, data collection, manuscript writing and review, data analysis. **Ester Illiano**: data collection, manuscript writing, and review. **Enrico Finazzi Agrò**: development, data collection, manuscript writing, and review. **Maurizio Serati**: development, data collection, manuscript writing, and review. **Alessandro Giammò**: development, data collection, manuscript writing, and review. **Francesco Paolo Bianchi**: data analysis, manuscript review. **Pasquale Ditonno**: project concept, development, manuscript writing, and review.

ETHICS STATEMENT

The study was conducted following the Declaration of Helsinki, and the local Ethics Committee approved the study protocol. No clinical trial registration was needed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author [GDR]. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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