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Botulinum toxin in incontinent women with neurogenic bladder after failure with anticholinergic therapy, long-term results: a pilot study

Angela **D'Alfonso** [1], Chiara **Taccaliti** [2,*], Alessandro **Serva** [1], Vikiela **Galica** [3], Matteo **Bruno** [4], Sara **Tabacco** [4], Maurizio **Guido** [1]

[1] Unit of Obstetrics and Gynaecology, Department of Life, Health and Environmental Sciences, University of L'Aquila, L'Aquila, Italy.
[2] Department of Obstetrics and Gynecology, Civitanova Marche Civil Hospital, Civitanova Marche, Italy.
[3] Urological Unit, Santi Antonio e Biagio e Cesare Arrigo Hospital, Alessandria, Italy.
[4] Unit of Obstetrics and Gynaecology, San Salvatore Hospital, L'Aquila, Italy.

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***Corresponding Author:** Chiara **Taccaliti**, M.D. Department of Obstetrics and Gynecology, Civitanova Marche Civil Hospital, viale Pietro Ginevri 1, 62012 Civitanova Marche, Italy.
Email: chiarataccaliti@gmail.com.
ORCID: 0000-0002-6516-5290.

ABSTRACT

Objective. To demonstrate the long-term efficacy and safety of intravesical botulinum toxin in the treatment of patients having neurological problems with a spontaneous voiding phase.
Patients and Methods. It is a prospective pilot study. We analysed 20 women came to the Hospital from March 2019 to March 2020 and underwent trigone-sparing Botulinum toxin bladder infiltration. The primary outcome was the improvement of the voiding diary score at two, four, twelve and twenty-four weeks and 12 months after treatment. Complications and quality of life improvement after treatment were considered as secondary outcomes.
Results. No signs of autonomic dysreflexia were observed during the procedure. Procedure associated pain has an average of 5 on Visual Analogic Scale. First benefits were evident within 2 days; full improvements were evident after 7-10 days. The duration of treatment (voiding diary score improvement) was of 5.5 months on avarage. Among the early complications: mild hematuria (no need of catheter placement) was described in 50% of patients and urinary infection in 20% of patients. None of the patients experienced fever, muscle weakness or worsened constipation. No late complications such as inability to empty bladder was described.
Conclusions. Botulinum toxin detrusor's infiltration remains an effective and safe long term therapy in patients with neurogenic bladder with preserved voiding phase, characterized by improvement in quality of life and reduction of side effects.

INTRODUCTION

The neurogenic bladder represents a complex entity with multiple clinical patterns. It is not a disease in itself, but rather a manifestation of different neurological processes that can interfere with micturition. For this reason, it can include a wide range of manifestations that can go from one extreme to another: from detrusor hyperactivity to complete impaired contractility [1].
Young women are usually affected by stress urinary incontinence, especially during pregnancy and this condition increases with increasing age [2]; instead urge incontinence is more often associated with older age and comorbidities including neurological diseases [3].

Overactive bladder syndrome is defined as urinary urgency with or without urge incontinence; detrusor over-activity is a urodynamic symptom characterized by involuntary detrusor contractions during the filling phase and it may be spontaneous or provoked [4]. In patients without neurological diseases nearly 50% with overactive bladder had detrusor over-activity on urodynamics testing [5].
It is difficult to estimate the incidence and prevalence of the neurogenic bladder, being a condition associated with neurological alterations often located far from the vesicourethral site. For this reason, we are talking about the most frequent clinical conditions that accompany certain neurological entities, so it is possible to configure bladder and vesico-sphincter "patterns" characterizing neurological models as a synthesis of the wide variety of possible functional alterations [1].
The neurological alterations due to the underlying condition are often accompanied by uro-gynecological problems related to pelvic organ prolapse and vulvovaginal atrophy that typically occur with menopause. In patients affected by pelvic organ prolapse and overactive bladder, serum nerve growth factor (NGF) levels were higher and this condition could play an active role in these patients [6].
In patients 6 months from a stroke the most common urodynamic findings show detrusor hyperactivity in about 69% of cases, [7] and the incidence of urge-frequency syndrome associated with incontinence is more common in lesions located on the right side [8-10].
In Parkinson's model, 93% of women register detrusor hyperactivity and generally the sphincter relaxes in a synergistic way [11, 12].
Detrusor hyperactivity without cervico-urethral obstruction is the most common pattern in Multiple Sclerosis and it is identified in about 62% of patients [13].
The urogynecological evaluation of the neurological patient must therefore include a unitary functional vision of the lower urinary tract. In fact, in most cases, the underlying neurological alteration is the predominant etiological cause compared to the anatomical and para-physiological factors. It therefore requires priority consideration during the therapeutic process.
The extensive experience acquired in the treatment of the idiopathic overactive bladder with botulinum toxin has allowed us to treat a large number of neurogenic bladders. In this paper we present the data collected over one year of use of botulinum toxin in patients having neurological problems with a spontaneous voiding phase. The aim of our study remains the long-term efficacy and safety of intravesical botulinum toxin in the treatment of this specific group of patients.
Botulinum toxin is a neurotoxin produced by *Clostridium Botulinum*, its mechanism of action consists in blocking acetylcholine in the neuromuscular junction thus inhibiting the transmission of the nerve impulse. Flaccid paralysis of the muscle fiber follows. The first medical use of neurotoxin dates back to 1981 when Scott used it to correct strabismus, while the first use in bladder urethral pathologies dates back to 1988 when Dykstra and colleagues used the neurotoxin in an attempt to correct a form of bladder-sphincter dyssynergia [14].
Officially, the toxin was approved for use in the bladder pathology since August 2011 when it received FDA approval. It represents one of the most potent neurotoxins known, to the extent that 1 gram of the purified form can kill up to a million people [15].
When the toxin is injected into the neuromuscular junction of the skeletal muscles, the duration of these effects appears to extend from 3 to 6 months, and to more than a year if the injection is made into the smooth muscles [16].

MATERIALS AND METHODS

From March 2019 to March 2020, in our outpatient clinic we evaluated 36 women with confirmed neurological pathology came for urogynecological evaluation for suspected neurogenic bladder.
All the patients underwent an accurate anamnestic collection and a clinical evaluation with physical urogynecological and neuro-urological examinations. With the anamnesis the underlying neurological condition and its possible staging/localization was investigated. The neurological data were then integrated with the physical examination which included 4 basic steps:

1. the evaluation of abdominal-pelvic reflexes (middle abdominal, lower abdominal, clitoral-anal, peri-anal) to verify the integrity of the neuronal circuits involved in the innervation of the lower urinary tract, and more specifically of the bladder-sphincter unit.
2. The execution of the pubococcygeus test with the assessment of the basal tone and voluntary contraction of the levator, simultaneously assessing the presence of dyssynergies.

3. The evaluation of the pelvic organ prolapse with the Pelvic Organ Prolapse - Quantification (POP-Q) system to exclude the presence of prolapses above stage II that could affect vesico-urethral dynamics.
4. The accurate analysis of the drug therapy in progress, administration of the 3-day voiding diary, evaluation of recurrent urinary infections (presence or absence of urease-producing germs, number of episodes/year), regularity of the intestinal tract with complete bowel evacuation, possible presence of vulvo-vaginitis and / or proctitis in place.

All the patients underwent an invasive urodynamic examination; a free uroflowmetry was performed with the evaluation of three main parameters: the voiding volume, the postvoid residual (PVR) that was then compared with the PVR after the invasive examination (in case of significant differences the free uroflowmetry was repeated) and the maximum flow (Qmax) to estimate the residual contractile capacity of the detrusor and sphincter relaxation. The uroflowmetric curve was evaluated to find direct indices for obstructive or restrictive alterations.
The identification/standardization of diagnostic methods for functional cervico-urethral obstruction (or Bladder Outlet Obstruction/BOO) in the female population is, to date, debated and controversial.
All the urodynamic procedures and definitions used respected the Good Urodynamic Practice and International Continence Society (ICS) definitions.
In women with a history of surgery of the urethra and/or bladder neck, a cystoscopy was also performed at the end of the examination to exclude extrinsic/iatrogenic causes of BOO.
An extemporaneous ultrasound examination to evaluate the upper urinary tract, the uterus and/or ovaries was performed in all the women. The toxin used in all the women studied was Onabotulinum toxin A (Botox 100 Units, Allergan).
The infiltration was performed in an outpatient setting after local anesthesia, with a solution of 2% Mepivacaine and Sodium Bicarbonate conveyed into the bladder via a Foley catheter. Before starting the procedure, a venous access was inserted in order to face any possible vagal or allergic reaction and all patients signed an informed consent. The preparation of the solution containing the toxin followed the standard procedure, and the infiltration of the detrusor was performed under cystoscopic vision with the trigone-sparing technique [17] (**Figure 1**). The procedure took an average of 10/15 minutes using a 21 Ch rigid urethrocystoscopy. The trigone-sparing technique involved infiltrating 20 bladder points with 0.5 ml of Botox solution for each site, except in the patient with spinal injury and paraparesis where only 10 injections with 1ml for each site were performed due to the patient's poor compliance with the lithotomy position.
The women were then evaluated in the following 3 days by a telephone interview, then a PVR check was performed at 2, 4, 12, 24 weeks (PVR, voiding diary, Incontinence Quality Of Life Questionnaire-I QOL) and the last check at 12 months, except in case of complications or worsening changes in the basic situation (PVR, voiding diary, I-QOL). After a year, if the effect of the toxin was still present the patients were interviewed by telephone, otherwise they could be proposed for a second infiltration.
As per ICS recommendations, the urodynamic examination was repeated every 2 years, or in the event that the neurological picture showed changes. In any case, it was not recommended to repeat the administering of the toxin before 6 months and, if necessary, a selective anticholinergic therapy as a support was started to contain the symptoms up to the second infiltration. After therapeutic indication, the patients who could not or were unwilling to undergo intermittent catheterization (IC) were excluded from botulinum toxin therapy.
From the sample evaluated, 20 women showing a neurogenic bladder pattern with preserved voiding phase, and with no signs of BOO on uroflowmetry/ urodynamic evaluation, were selected. Eight patients with Multiple Sclerosis, four patients with forms of Parkinsonism, two patients with polio, four patients with cerebro-vascular events, two patients with spinal lesions already having a sacral neuromodulator implantation. 16 women were excluded: three patients with Multiple Sclerosis with a BOO index suggestive of cervico-urethral obstruction not compliant with IC, five patients with Parkinsonism, but with elevated PVR in all measurements plus worsening of motor skills suggestive of a Multiple System Atrophy (MSA) pattern, and finally two patients with Guillian-Barre outcomes with gluteal Herpes Zoster in resolution. Six other patients, instead, refused surgery.
The primary outcome was the improvement of the voiding diary score at two, four, twelve and twenty-four weeks and 12 months after treatment. Complications and quality of life improvement after treatment were considered as secondary outcomes.

Informed written consent was obtained from all participants before the enrolment in the study.
Permission for the publication was taken in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Our Institutional Review Board approved the study (number 05/2019) on February 11th, 2019 and there were no conflicts of interest with regards to this study. Data are reported as mean ± standard deviation or total count and relative percentages (%) for categorical variables. The success of the therapy was measured as voiding diary score improvement of 50% in the first six months and 25% in 12 months after Botulinum toxin injection.

RESULTS

All the treated women were compliant with the treatment performed on an outpatient basis with local anesthesia. None of them showed signs of autonomic dysreflexia during the procedure. Pain during the procedure followed the Visual Analogic Scale (VAS). On average there was a VAS of 5, only in the three patients with paraparesis and lumbar pain there was a VAS of 7-8. The women were discharged after two successive micturitions where the presence/absence of hematuria and PVR were evaluated. The characteristics of the studied population are presented in **Table 1**.
Overall, the first benefits were evident within the first 2 days with the achievement of full improvements after 7-10 days.
In the event of initial worsening, a new urine culture was to be considered given the high incidence

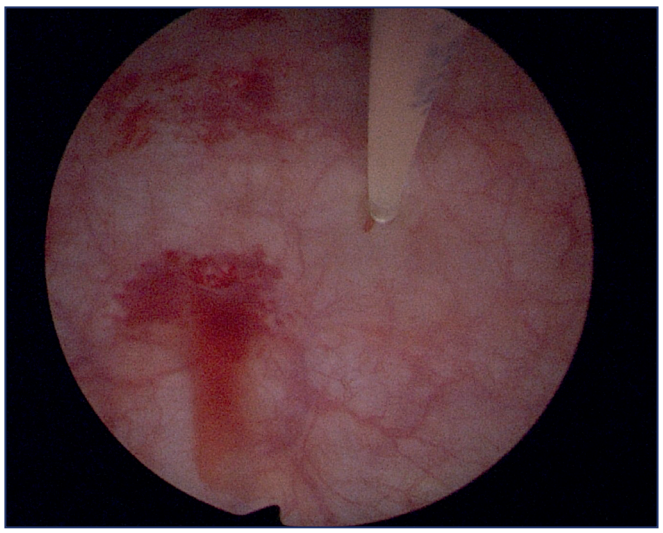

Figure 1. *Botulinum toxin infiltration under cystoscopic vision.*

Table 1. *Patients baseline demographic characteristics.*

	Patients
	n = 20
Age (years)	62 ± 5.3
Vaginal Delivery	2.6 ± 1.4
BMI (Kg/m^2)	30.5 ± 4.5
Menopausal status	100%
Previous Surgery for SUI	10%
Previous anti-muscarinic Therapy	100%
Patients in treatment with AT/NOA	40%

Mean ± Standard Deviation; BMI: Body Mass Index; SUI: Stress Urinary Incontinence; AT: Antiplatelet Therapy; NOA: New Oral Anticoagulants.

of lower urinary tract infections in these patients. In patients with Multiple Sclerosis, 6 out of 8 patients defined themselves as dry, only wearing the safety pantyliner. In two patients, on the other hand, there was a reduction of about half of the urgency episodes (both patients walked assisted by support, thus requiring longer times to reach the toilet). The PVR in these women always remained below 150 ml without the need for completion IC.
In the four patients with Parkinsonism, we had satisfactory results only with two of them who reached full continence. The other two women, who had very reduced spontaneous walking and recurrent urinary infections, after a benefit in the first 6 weeks, returned to the I-QOL scores and to the use of pretreatment anti-incontinence devices. The PVRs in these women were contrasting, varying from 70 to 200 ml, a pattern comparable with that of the pseudo-dissynergy of the striated sphincter and compatible with the neurological pattern of these patients.
We had excellent results with the patient presenting outcomes of Poliomyelitis achieving continence and a duration of treatment of nearly one year, as in the patterns of idiopathic Overactive Bladder. In patients with outcomes from cerebro-vascular events, bladder hyperactivity was under control. The micturition nocturnal frequency of about 2-3 episodes/night remained, but the PVR was always below 100 ml. In the two patient with spinal injury and paraparesis of the lower limbs treated with Sacral Neuromodulation, the results were compromised by urinary infections alternating with bacterial vaginitis, although the PVR was always below 90 ml.
The results from the analysis of the voiding diary and questionnaire are shown in **Table 2**. On average, the duration of treatment was of 5.5 months, with a maximum of one year in the patient with polio outcomes.
The complications of the treatment can be divided into immediate complications (within 24 hours) and

late complications (within 15 days). Among the early complications, hematuria and urinary infections were the most common. As for hematuria, it was mild and no woman required the placement of a catheter. Urinary infections were the most common complications. Eight patients already had a history of recurrent urinary tract infections. A preventive therapy with D-mannose, based on cycles, was recommended in these patients. None of them had urease-producing germs. None of the patients experienced fever, muscle weakness or worsened constipation. The results regarding complications are presented in **Table 3**. No late complications described as inability to empty your bladder on your own, were observed.

Table 3. *Patients' post-operative complications.*

	Patients number (percentage)
Hematuria	10 (50%)
First 36 hours UTIs *	4 (20%)
IC**	2 (10%)
Other***	0

IC: intermittent catheterization; UTI: Urinary Tract Infection. *Mild hematuria, with no need of bladder washing, clot removal or medical therapy. **Prophylactic antibiotic therapy was performed in all cases. ***No patient reported fever, muscle weakness or worsening of constipation.

DISCUSSION

Neurologic patients with voiding phase represent a group of women who may still benefit from low dose botulinum toxin treatment. Peyronett and colleagues have shown that Onabotulinum toxin A leads to a resolution of the detrusor hyperactivity with continent patients in 65% of cases [18].
Studies in the literature agree on the initial treatment with 100 units of onabotulinumtoxin A. In these patients, the preservation of the voiding phase without the need for IC significantly reduces the number of urinary infections. The definition of cervico-urethral obstruction based only on urodynamic definitions remains debated, considering that the issue is still not free from controversies, even for the female population with neurological integrity.
Surely, the electromyography of the perineal plane as an indicator of the external urethral sphincter and the video-urodynamics add important elements for patients suffering from supra-sacral sub-pontine lesions. Another usefulness of video urodynamics remains in the forms of Parkinsonism with/without Dementia with Lewy Bodies, so as to exclude forms of dyssynergy and to better select patients. The lack of these two diagnostic elements represents a future challenge for our group to further increase the accuracy of patient selection. Regarding the type of toxin used, we support the use of onabotulinumtoxina A over apobotulinumtoxina, especially in neurological women. The apobotulinumtoxina formulations provide about 500 Units and this can be disadvantageous, especially for neurological patients. The disadvantages are mainly of two types.
The first concerns the average time elapsing from the second treatment which is shorter in neurological patients (in our experience 5.5 months compared to the idiopathic form of 7.7 months). This could expose neurological patients to a greater quantity of toxin in a shorter time, increasing the risk of autoantibody production and thus reducing the effects in the following infiltrations [19], but at present, repeated treatments do not seem to increase the risk of fibrosis and induration of the bladder wall [20, 21].
The second disadvantage is due to the fact that by increasing the doses to maintain the effect in subsequent infiltrations, we could risk losing the spontaneous voiding phase in patients with progressive neurological diseases. Studies regarding the "switch" from one type of toxin to another are promising, but further confirmatory studies are needed.
This treatment is also proposed to patients affected by interstitial cystitis or bladder pain syndrome and sev-

Table 2. *Pre, 6 months post treatment and 12 months post treatment results of patients voiding diary and questionnaire.*

	Pre-treatment	6 Months Post-treatment		12 Months Post-treatment	
			Variation		Variation
Daytime Urinary Frequency	13.2 ± 4.5	6.1 ± 1.9	- 53.8%	9.2 ± 2.7	- 30.3%
Nocturnal Urinary Frequency	3.9 ± 2.3	1.5 ± 1.1	- 61.6%	2.8 ± 1.3	- 28.2%
Urgency Episodes (in 24 hours)	8.1 ± 1.7	3.5 ± 1.1	- 56.8%	5.9 ± 1,7	- 27.2%
Incontinence Episodes (in 24 hours)	4.2 ± 0.9	1.3 ± 0.7	- 69.1%	3.2 ± 1.0	- 23.8%
Postvoid Residual (ml)	65 ± 13	95 ± 15	+ 40%	73 ± 9	+ 11.0%
I-QOL score*	52 (41-61)	69 (61-80)	+ 17%	61 (48-69)	+ 17.3%

Mean ± Standard Deviation; I-QOL: Incontinence Quality of Life score; *Results presented as Median (Range).

eral trials demonstrated a significant improvement of symptoms, pain, frequency of urination, and maximum bladder capacity but nocturia, dysuria, and maximal urinary flow rate remained unchanged [22]. Kuo HC and collegues demonstrated, in a randomized controlled trial, that intravesical injections of 100 U OnabotulinumtoxinA effectively reduced pain symptoms in patients affected, with an acceptable rate of adverse events (dysuria, hematuria, urinary tract infections) [23].
These preliminary data open to further studies experiences; as the pathology is characterized by an overlapping of symptoms and multiple etiologies, this treatment could be proposed to selected patients and could undoubtedly vary for either case [24].

CONCLUSIONS

Botulinum toxin remains an effective and safe therapeutic long term alternative in patients with neurogenic bladder, and even more so in the subgroup with the preserved voiding phase. Our data agree with the literature data on the significant improvement in the quality of life in these patients, as it reduces the side effects (dry mouth and constipation in particular) deriving from the use of next-generation anticholinergic drugs. In patients with Parkinsonism the results seem promising, but certainly the choice of the patient must be even more elaborate and assisted by electromyography and videourodynamics.
We assert that the collaboration with neurologists is a fundamental element for the management of these patients when the urodynamic results are discordant. Patients suffering from neurogenic bladder always remain a challenge for the urogynecologist in an attempt to find new strategies to improve their quality of life, promoting innovative, minimally invasive interventions, always respecting efficacy and safety.
Further data are needed to confirm the findings in other neurological conditions that involve the lower urinary tract as well.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

A.D'A.: Study design, clinical participation, supervision of study. C.T.: collection of data, writing the manuscript. A.S.: Clinical participation, collection of data, writing the manuscript. V.G.: Clinical participation, collection of data. M.B.: Clinical participation, collection of data. S.T.: Clinical participation, collection of data. M.G.: Study design, clinical participation, supervision of study.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

The Institutional Review Board approved the study (number 05/2019) on February 11th, 2019.

Informed consent

An informed written consent was obtained from all women before the enrolment in the study.

Data sharing

Data are available under reasonable request to the corresponding author.

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