Botulinum Toxin Type A Injection After Failure of Augmentation Enterocystoplasty Performed for Neurogenic Detrusor Overactivity: Preliminary Results of a Salvage Strategy. The ENTEROTOX Study

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OBJECTIVE To evaluate the clinical efficacy, urodynamic effect and safety of Botulinum Toxin A (BTXA) injections after failure of augmentation enterocystoplasty (AE) performed for neurogenic detrusor overactivity.

PATIENTS AND METHODS We performed a multicenter retrospective study that included patients who had AE and at least one injection of BTXA after AE in 15 GENULF (French Speaking Neuro-Urology Study Group) centers. Clinical and urodynamic data were collected from medical files according to a standardized questionnaire and colligated in an anonymous database.

RESULTS Thirty-three patients with an injection of BTXA after AC in 9 out of 15 centers were included. Mean age at the time of AE was 24 ± 15 years. Overall efficacy (defined by clinical efficacy associated with a request by the patient for reinjection) was observed in 58% of the patients. Mean maximum cystomanometric capacity increased by 28% (333 ± 145 vs 426 ± 131 mL; $P = .007$) and maximum detrusor pressure ($P_{det\ max}$) decreased by 43% (44 ± 37 vs 25 ± 18 cm H_2O; $P = .02$) after BTXA. Only one side effect was recorded out of the 152 procedures (transient generalized muscle weakness without respiratory distress).

CONCLUSION In patients with failure after AE performed for neurogenic detrusor overactivity, injection of BTXA in the enlarged bladder was effective in over half of the cases with low morbidity. If this therapeutic approach were confirmed, it could be proposed as an alternative to AE surgical revision. UROLOGY 129: 43–47, 2019. © 2019 Elsevier Inc.

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Since their initial description by Schurch et al in 2000,[1] injections of botulinum toxin A (BTXA) in the bladder wall in order to treat urinary incontinence (UI) owing to neurogenic detrusor overactivity (NDO) in patients resistant to oral anticholinergics and undergoing intermittent catheterizations have proven their efficacy and safety.[2-6]

This treatment is now approved by several regulatory health agencies (FDA, NHS, ANSM) and is recommended in second line in patients with UI owing to NDO linked to multiple sclerosis or spinal cord injuries (SCI).[7]

Intestinal bladder enlargement or augmentation enterocystoplasty (AE) is a surgical procedure that consists in increasing bladder capacity by adding a section of intestinal tissue, usually the ileum, to the bladder. Described in 1889 by Von Mikulicz,[8] AE became popular in the 1950s through the work of Couvelaire to treat bladder retractions secondary to urogenital tuberculosis.[9] In the 1970s, the description by Lapides[10] of clean, intermittent self-catheterization revived interest in AE, particularly in patients with neurogenic bladder due to SCI.

For this indication, AE preserved renal function and restored continence in 70% and 74% of the cases.[11,12] It is recommended as a last-line treatment after clinical and/or urodynamic failure of BTXA injections.[7]

Partial results or failures at a clinical and/or urodynamic level are reported in 26%-30% of the cases after AE.[11,12] They appear early or late and are characterized by the persistence or reappearance of UI owing to capacity reduction, persistent NDO and/or compliance issues. Different hypotheses can explain this dysfunction. Stenosis of the anastomosis between native bladder and the augment may result in quasi-exclusion of the augmented part of the bladder, and therefore, a failure of the treatment. When it is a primary dysfunction, it can also be due to too short an ileal segment used, too large a residual native detrusor left in place or both. These situations can lead to residual detrusor overactivity and/or persistent low compliance. In such cases, we can hypothesize that injection of botulinum toxin could have a positive effect.[13,14]

In late dysfunctions, the main etiologies are ischemia or exclusion of the ileal segment leading to a loss of compliance. Again, in such a situation, botulinum toxin injections could have a positive effect[15,16] and represent an alternative to complex revision surgery.[17,18]

The aim of this study was to collect and evaluate the results and tolerance of BTXA injections following failure of AE in 15 centers in the French Speaking Neuro-Urology Study Group and/or the Neuro-Urology Committee of the French Urology Association.

PATIENTS AND METHODS

Type of Study

This was a multicentric retrospective study in 15 French neuro-urology centers (Marseille, Toulouse, Bordeaux, Lyon, Paris (2), Garches, Strasbourg, Berk, Rennes, Rouen, Nantes, Liège, Lausanne, Montréal) with at least one practitioner who is a member of French Speaking Neuro-Urology Study Group or French Urology Association neuro-urology committee (http://genulf.com – http://urofrance.org).

Participants and Selection Criteria

Each center consulted its database in order to identify adult patients who underwent AE followed by BTXA injection before December 30, 2014.

Evaluation Criteria

The parameters collected from a common data bank were centralized in an anonymous database (Supplementary Table 1). BTXA injection sites were in the native residual detrusor and/or in the enteroplasty muscularis.

The efficacy of the BTXA injection was evaluated by 2 complementary criteria: **Objective efficacy** defined by any measurable improvement in the principal criterion indicating BTXA injection.

- Incontinence cessation (most often from a urinary diary).
- Resolution of other urinary discomfort including reduction in capacity with frequent voiding, recurrent infections, painful bladder, and symptomatic urinary infections.
- Maximum cystomanometric capacity (MCC), $P_{det\ max}$ or compliance.

Overall efficacy defined by a successful **objective** efficacy plus a request for reinjection by the patient.

The urodynamic data before and after BTXA injection in each patient were also compared.

Patients who obtained objective or overall efficacy were compared with those who did not. Collection and description of number and nature of side effects and/or complications evaluated the safety of the procedure.

Statistical Analysis

All of the statistical tests were nonparametric and bilateral. Statistical analyses were performed using SAS software (SAS Institute Inc.). The urodynamic data before and after BTXA injection were compared with the Wilcoxon signed-rank test for continuous quantitative variables and by Fisher's exact test for qualitative variables. In order to study the predictive factors for BTXA efficacy, the nominal qualitative variables were tested by Fisher's exact test and the quantitative variables by a Mann-Whitney test. A value of $P < .05$ was considered as significant.

Ethics committee approval was not required for this study which involved collection of anonymous files (no nominative information was provided by the centers).

RESULTS

Descriptive Results

Thirty-three patients with a mean age of 24 ± 15 years underwent AE and subsequent BTXA injection in 9 out of the 15 centers. The neurologic disease responsible for the bladder-sphincter dysfunction was mainly spinal dysraphism and spinal cord injury in 14 cases (Supplementary Table 2 summarizes all patient demographic characteristics). The characteristics of surgical procedures are described in Table 1. The number of enterocystoplasties ranged from 6 to 20 per year and per center during the study. Eight patients had had AE secondary to BTXA failure.

Table 1. AE technical characteristics and corresponding numbers

Digestive segment used (3 undisclosed cases)	
Small intestine	21 (63.6%)
Colon	9 (27.3%)
Supratrigonal cystectomy (4 undisclosed cases)	
Yes	18 (54.5%)
No	11 (33.3%)
Associated surgical procedure	16 (48.5%)
Continent cystostomy	8 (24.2%)
Stress incontinence surgery	6 (18.2%)
Suburethral band	3
Bladder neck lengthening plasty	2
Artificial urinary sphincter	1
Ureteral reimplantation	5 (15.2%)

Clinical failure of AE was immediate in 16 cases (48.5%) and delayed in 14 cases (42.4%) (unclear for 3 patients). For the delayed failures, the mean time following surgery was 9.0 ± 7.9 years (median: 8 years; mini-maxi: 7 months-26 years). Failure was most often defined by recurrence of UI except in 4 patients who had complications in the upper urinary tract (impaired renal function with or without vesicoureteral reflux). In all of the centers, injections were conducted under vision with a rigid cystoscope using a disposable single-use needle.

Doses, toxin brands, and injection sites are summarized in Table 2. Injection was performed immediately after failure in 12 cases (36.4%) and was delayed in 18 cases (54.5%; mean time between failure and the injection: 5.2 ± 5.8 years). In 3 cases, we were unable to find an actual date for enteroplasty failure.

The mean total number of injections per patient was 4.6 ± 2.8 (median: 4; mini-maxi: 1-10). The mean time between the first and the second injection was 16 months (median: 8 months; mini-maxi: 3-26 months).

Table 2. Clinical efficacy and characteristics of the first BTXA injection

Objective efficacy	**20/33** (60.6%)
Overall efficacy	**19/33** (57.6%)
Toxin brand (n = 33)	
Botox	**25** (**75.8%**)
100 U	1
200 U	9
300 U	15
Dysport	**8** (**24.2%**)
500 U	1
750 U	3
1000 U	4
Number of injection sites (2 undisclosed cases)	
10-20	16 (51.6%)
30	15 (48.3%)
Injection sites (8 undisclosed cases*)	
Residual detrusor	18 (72%)
Residual detrusor + intestinal segment	7 (28%)

The urodynamic technique was not standardized since the study was retrospective and multicentric. All of the UDS studies we have seen were cystomanometric with saline filling. Slow bladder filling between 10 and 30 mL/min was in majority. Abdominal pressure assessment was always performed. Catheter sizes were not available.

* Center investigators were recontacted, they suggested that was very likely that injections had been done only in residual native detrusor but without written data in the medical records.

Eight patients had botulinum toxin before AE. In 5 cases, the reason for AE was not botulinum failure. AE was performed with a continent cystotomy plus bladder neck suspension in 2 patients and ureter reimplantation plus bladder stone removal in 3 patients. Two out of these 5 patients were responders to Botulinum toxin after AE. The 3 remaining patients had AE owing to Botulinum toxin failure. One of these 3 patients was a responder to botulinum toxin after AE but it should be noted that he received injections in both native detrusor and the intestinal augment.

Objective and overall efficacy was obtained respectively in 20 and 19 cases out of 33 (60.6% and 57.6%) after the first injection and remained steady. One patient, who presented objective improvement without requesting reinjection, refused to come back every 6 months for reinjections and opted for a Bricker derivation.

The only serious side effect was generalized muscle weakness without respiratory distress after injection of 300 U of onabotulinum toxin A (Botox) in the residual part of the native bladder.

Comparative Results

At a urodynamic level, injection of BTXA significantly increased mean MCC by 28% (333 ± 145 vs 426 ± 131 mL; $P = .007$) (Table 1) and significantly reduced the P_{detmax} by a mean of 43% (44 ± 37 vs 25 ± 18 cm H_2O: $P = .02$). The number of patients who presented at least one involuntary AE contraction was significantly lower after injection than before. No effect on compliance was observed (Table 3).

The only clinical variable associated with efficacy was injection in 30 sites rather than in 10-20 sites ($P = .029$). Neither the urodynamic variables before AE nor after BTXA injection were associated with the success or failure of the injection (Table 4).

DISCUSSION

In this study, BTXA injections in bladders enlarged by failed AE provided sufficient benefits that prompted 19 out of 33 patients (58%) to request reinjections. For these patients, the key urodynamic parameters, MCC and P_{detmax}, were significantly improved with a mean P_{detmax} value after treatment inferior to the 40 cmH_2O threshold that is considered as protective for the upper urinary tract.[1]

In this context, the interest of this treatment can be found in its simple and relatively noninvasive character compared with revision surgery (reaugmentation), which is heavier and more complex.

We noted an absence of correlation between low MCC and botulinum toxin failure. This could be due to the limited number of patients with low MCC.[19] Another study on patients with spinal dysraphism[20] reported that a relatively high rate of patients with a poorly compliant bladder had good functional results with no improvement in their urodynamic outcomes. The effect of BTX-A on bladder afferent signaling[18] could explain these results. BTX-A may have improved urothelial sensory function in these patients while the fibrotic detrusor muscle could not be cured. This could explain why there was no effect on compliance whereas there was an effect on P_{detmax}.

Table 3. Effect of botulinum toxin injections on urodynamic parameters. Results of a Wilcoxon signed-rank test for quantitative variables (MCC, Pdet $max_{MCC,}$ Compliance) and Fisher's exact test for qualitative variables — presence or absence of Involuntary AE Contraction (IAEC)

	Before Injection	6 Weeks to 2 Months After Injection	Variation (%)	*P*
MCC (mL)	333 ± 145.8	425.8 ± 131.0	+27.9 %	.007*
Pdet max_{MCC} (cm H_2O)	44.2 ± 37.1	25.0 ± 17.9	−43.4 %	.020*
Compliance				
<30 mL/cm H_2O	8	8		NS
≥30 mL/cm H_2O	17	17		
IAEC				
Present	20	12		.009*
Absent	1	9		

Six of the 13 patients with failed BTXA injections had mixed UI. The presence of stress UI associated with NDO could explain some of the so-called failures. In spite of the absence of immediate clinical benefit, the indication for BTXA was justified by the need to control NDO before correcting the stress component.

It is possible that the association between injection in 30 sites and BTXA injection success reflects a greater detrusor surface available and therefore an insufficient initial partial cystectomy. In fact, we observed in this cohort that 67% of the injections in 30 sites were in the cases without supratrigonal cystectomy associated with AE vs only 35% in cases with the presence of supratrigonal cystectomy (the missing 8% corresponded to the patients who had had an injection in the native detrusor and intestinal patch). About the 8 patients who had had botulinum toxin before AE, owing to the low number of patients in this subset of our cohort, it would appear to be impossible to draw any conclusion about the predictive value of the botulinum toxin response before AE.

The practice of BTXA injection in the AE intestinal patch was noted during this retrospective collection. Its justification for the team who proposed it, lies in a publication, reporting its innocuousness and the efficacy of BTXA injections in the rectal submucosa to treat fecal incontinence owing to rectal overactivity.[21]

Only one episode of systemic diffusion was observed (mild general muscle weakness with no respiratory changes) for an elevated dose of toxin (300 U of onabotulinum toxin A) injected in the native residual detrusor. Although we did not observe severe complications following BTXA injections in the intestinal patch and no such complication was reported after injections in the rectal submucosa for fecal incontinence[21,22] or in the 2 only case reports of BTXA injection within an intestinal segment included in the urinary tract,[18,23] we think it is essential to perform a prospective study in patients with AE or vesical replacement in order to evaluate the long-term innocuousness and clinical efficacy of BTXA injections directly in the digestive tissue interposed within the lower urinary tract.

There are limitations to our study. This was a retrospective study with a heterogeneous population. This is due to the very small population concerned by secondary dysfunction of enterocystoplasty. Only specialized tertiary centers are concerned by this technique. The limited number of patients reflected an indication of niche and

Table 4. Exploration for BTXA success factors. Results of Fisher exact tests or Mann-Whitney tests. Comparison between success in supratrigonal cystectomy vs clam was considered not applicable since some patients received injections in the remnant native detrusor only and other in the native detrusor and patch

Sex (M vs F)	*P* = .733
Neurologic pathology (Congenital malformation vs others; medullar injury vs others; multiple sclerosis vs others; unknown etiology vs others)	*P* = .067
Digestive segment used for AE (small intestine vs. colon)	*P* = .691
Supratrigonal cystectomy vs. Clam AE (no reductive cystectomy)	*NA*
Early vs. late failure of AE (from surgery to failure)	*P* = .104
BTXA dosage (maximum dose of Botox or Dysport vs all other doses)	*P* = 0.497
Number of injection sites (30 vs 10, 12, or 20)	***P* = .029***
Injection sites (detrusor + intestinal submucosa vs detrusor alone)	*P* = 1
BTXA indication (incontinence vs complications)	*P* = .130
Pre-AE urodynamic variables	
MCC	*P* = .355
Pdet max_{MCC}	*P* = .186
Pre-BTXA urodynamic variables	
MCC	*P* = .470
Pdet max_{CMC}	*P* = .174
Compliance	*P* = 1.000

recourse after failure of a third line (and usually last line) of treatment. The retrospective character of the study did not enable an evaluation of the clinical efficacy of BTXA by standardized measures. It is for this reason that the criterion to evaluate responders was the association of efficacy evaluated by the therapist with a request for reinjection by the patient. Six patients with BTXA injection failure had mixed UI that blurred the analysis. Indeed, the presence of stress UI associated with residual NDO could in part explain the failures. Although an improvement in MCC would have been obtained in some of these patients, the persistence of stress incontinence episodes did not satisfy them. In such a situation, a combined approach with an associated improvement of urethral resistance would have been more efficient.

CONCLUSION

In the present study, BTXA injections in native detrusor and/or intestinal patch were beneficial to 61% of the patients after failed AE. This benefit was considered as sufficient for reinjection as requested by 58% of the patients. BTXA injection significantly increased the MCC and reduced the P_{detmax}, suggesting protection of the upper urinary tract. BTXA injections after failed or partially successful AE could therefore be proposed as a salvage option before complex revision surgery. Such a new strategy will require prospective multicenter evaluation before it can be recommended.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2019.03.010.

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