The efficacy of botulinum toxin in refractory overactive bladder

Ahmed Farahat, Ahmed El-Azab, Hassan A. Abolella

Department of Urology, Assiut University, Assiut, Egypt

Correspondence to Ahmed Farahat, Department of Urology, Assiut University, Assiut, Egypt.
Tel: 01069569946;
e-mail: ahmedfarahat358@gmail.com

Received 03 February 2021
Revised 17 March 2021
Accepted 02 June 2021
Published 30 December 2021

Journal of Current Medical Research and Practice
2021, 6:331–335

Aim and objectives
The objective of this study was to evaluate the efficacy and safety of botulinum toxin A (BTX-A) injection in patients with refractory overactive bladder (OAB).

Patients and methods
The study was done in Assiut Urology Hospital, Assiut University, from June 2017 to January 2020. The study included 22 patients (15 patients with idiopathic OAB and seven patients with neurogenic OAB). Botox was injected intradetrusor (200 U of Botox for neurogenic OAB and 100 U of Botox for idiopathic OAB). Patients were followed up for 1 year.

Results
The success rate after 3 months reached 81.8% (63.6% became completely dry and 18.2% had improved symptoms) with treatment failed in 18.2%. The improvement continues for 6 months postoperatively and reached 60% (40.9% became completely dry and 18.2% had improved symptoms), and treatment failed in 40.9%. At 6-month interval, the voiding diary parameters showed significant improvement in the number of voids (P = 0.000) and the number of incontinent episodes (P = 0.000). Regarding the adverse effects, urinary tract infection occurred in two (9%) patients after intervention, and urinary retention occurred in two (9%) patients.

Conclusion
BTX-A is an excellent and successful option for patients with refractory OAB. BTX-A is a minimally invasive option for refractory OAB. Complications are uncommon with sustained effect up to 6–12 months.

Keywords:
botulinum toxin A, incontinence, overactive bladder

J Curr Med Res Pract 6:331–335

2357-0121

Introduction

According to the International Continence Society, overactive bladder (OAB) is defined as urgency commonly associated with frequency and sometimes nocturia, in the presence or absence of urgency incontinence, after exclusion of urinary tract infection (UTI) and other obvious pathologies [1].

A large percentage of the population experience OAB. The incidence of OAB is between 7 and 27% in men and 9–43% in women [2]. About 60% of patients are females [3]. OAB negatively impacts the quality of life [2].

OAB is considered a symptomatic diagnosis and is different from detrusor overactivity, which is diagnosed by a urodynamic study [1]. OAB may be classified as idiopathic or neurogenic. Neurogenic detrusor overactivity (NDO) is considered when there is underlying neurologic cause [3].

Lines of treatment of OAB include behavioral changes, pharmacologic drugs, and other invasive methods of treatment. Anticholinergic drugs have been classified as the second line of treatment for OAB [4]. Percutaneous tibial nerve stimulation is a less-invasive method of management for OAB [5]. Sacral neuromodulation is used to treat symptoms of OAB that are refractory to other treatment options [1].

Refractory OAB is defined when there is failure of at least two antimuscarinic drugs and B3 agonists for a period of 3–6 months, or owing to lack of patient compliance because of adverse effects [6].

Botulinum toxin A (BTX-A) injection has approved its effect in reduction of intravesical pressure and in reducing frequency and urgency incontinence attacks. The quality of life is improved in patients with OAB who received Botox injection [3].

The aim of our study was to prove the safety and efficacy of Botox injection in patients experiencing refractory OAB.

Patients and methods

It is a prospective study that include 22 patients with refractory OAB who attended Assiut Urology

Hospital, Assiut University. The patients with active UTI and pregnant females were excluded in our study. The study has Institutional Review Board (IRB) approval no. 17100770.

Preoperative workup and patient evaluation

Good history and questionnaires were taken. Physical examination included abdominal and pelvic examination, general examination, and basic neurologic examination. Urine analysis was performed before further investigations were initiated. Abdominal ultrasound was done to assess upper urinary tract and to assess post-void residual urine volume. OAB is a clinical diagnosis, and so absence of DO finding in urodynamic study is accepted.

Three-day voiding diary was used before intervention, and we analyzed the following parameters: frequency, urge incontinence, nocturia, and nocturnal enuresis. Comparison was done by Mann–Whitney test. At 6-month interval, we measured the voiding diary parameters. The effect of symptoms and incontinence on patient quality of life was assessed by two questionnaires: urogenital distress inventory questionnaire (UDI-6) and incontinence impact questionnaire-7 (IIQ-7).

Technique

The procedure (BTX-A injection) is done under spinal anesthesia in prepared operative room, with a written consent in operative sheet. Before reconstitution, BTX-A vial must be stored at temperature of 2–8°C. After reconstitution, the vials should be used within 24 hr and should be kept in the freezer at 2–8°C. The vial is for single-use only, and any unused solution should not be used again. The vial is diluted with normal saline 0.9%. The vial is diluted gently and not to be shaken. The recommended dilution fluid is normal saline 0.9%.

Initially, diagnostic cystoscopy was done to exclude any pathological abnormality in the bladder. In idiopathic OAB, Boto × 100 IU was reconstituted with normal saline to make 20 ml, divided into two syringes to be injected in 20 points. One milliliter (containing 5 IU of Botox) is injected using a cystoscopic injection/needle (Amecath Company, Egypt, 10th of ramadan city, sharqia) through a 22-Fr rigid cystoscope. In neurogenic OAB, Botox 200 IU was reconstituted with normal saline to make 30 ml divided into three syringes to be injected in 30 points.

The bladder must be semifull to avoid perforation and also not empty to facilitate needle introduction. During the procedure, the lateral and posterior walls were injected at 20 sites avoiding the trigone. The injection sites should be distributed uniformly. The injections were done either intramuscularly or submucosally.

Postoperative follow-up of the patient

Immediate follow-up was started after catheter removal, with calculation of post voiding residual urine (PVR) (should be <200 ml), and then after 2 weeks, 3 months, and 6 months to assess PVR, IIQ-7, and UDI-6 in each visit.

The success rate is measured by the change in voiding parameters (frequency, urgency incontinence) and change in the median UDI-6 score at 3 and 6 months.

Patients are categorized according to their response into the following:

(1) Cured patients: if the score become 0 on the postoperative UDI and complete improvement of all voiding parameters (no frequency, no urgency nor urge incontinence).
(2) Improved patients: if the improvements in the UDI-6 or the voiding parameters are more than 50% from the baseline.
(3) Failed treatment: if the improvement in UDI-6 and voiding parameters are less than 50% from the baseline.

Results

From June 2017 to January 2020, 22 patients with refractory OAB underwent Botox injection as shown in Table 1.

According to our definition of success, after 3 months, 63.6% became completely dry and 18.2% had improved symptoms, with treatment failure in 18.2%. The success rate decreased 6 months after procedure (40.9% became completely dry and 18.2% had improved symptoms), and the treatment failed in 40.9%, as shown in Fig. 1.

Voiding diary parameters

We found significant improvements in almost all the parameters, as shown in Table 2.

Urogenital distress inventory-6 and incontinence impact questionnaire-7 baseline and after intervention

Regarding UDI-6 and IIQ-7 parameters, there was a significant improvement in individual domains and the total score of the two questionnaires after 3 and 6 months, as shown in Tables 3 and 4.

Adverse effects

In our study, UTI occurred in two (9%) patients after intervention, and they were managed conservatively with appropriate antibiotic. Urinary retention occurred in two (9%) patients postoperatively, and they were managed conservatively by CIC, with spontaneous

Table 1 Baseline characteristics of the study participants

Total number	22 patients	100%
Age (years)		
<20	9	40.9
20-<40	9	40.9
≥40	4	18.2
Mean±SEM (range)	26.64±3.04 (9.0-65.0)	
Sex		
Male	8	36.4
Female	14	63.6
Residence		
Rural	15	68.2
Urban	7	31.8
Etiology		
Idiopathic	15	68.2
Neurogenic	7	31.8

Table 2 Voiding diary baseline and after 6 months

	Baseline (*n*=22) [*n* (%)]	6 months (*n*=22) [*n* (%)]	*P*
Nocturnal enuresis			
Yes	16 (72.7)	9 (40.9)	0.033
No	6 (27.3)	13 (59.1)	
Nocturia			
Yes	8 (36.4)	4 (18.2)	0.176
No	14 (63.6)	18 (81.8)	
Number of voids			
Mean±SEM	15.55±1.42	7.59±0.87	0.000
Number of incontinent episodes			
Mean±SEM	6.27±1.03	2.05±0.60	0.000

resolution after 1–2 weeks. Mild hematuria occurred in only one patient after injection, which responded to conservative treatment for 1 day.

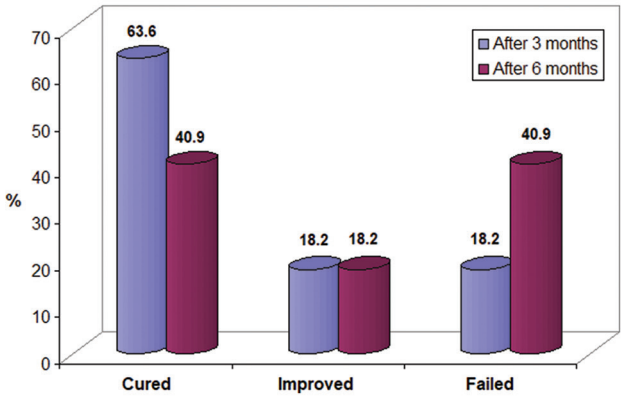
Discussion

Botox injection is considered as a minimally invasive, highly effective, and well-tolerated day procedure with rare complications for patients experiencing refractory OAB [6]. Botox is a recommendable treatment option in case of refusal, contraindication, or failure of pharmacological and nonpharmacological therapies [7]. Botox reduces or even stops the use of oral pharmacological drugs [8]. BTX injections have been noted to decrease episodes of UTIs [9].

Botox is considered to be more cost effective than other invasive lines of treatment like sacral nerve stimulation. Multiple studies have approved the efficacy and safety of BTX-A injection for the management of OAB, with the absence of adverse effects associated with oral medications, such as constipation and dry mouth [7].

In our study, we evaluated the efficacy and safety of Botox injection in the treatment of refractory OAB.

Figure 1



Improvement after 3 and 6 months.

The improvement in parameters of IIQ-7 and UDI-6 was significant at both 3 and 6 months postoperatively, with efficacy continuing up to 9 months.

A total of 22 patients were evaluated using OAB symptom score questionnaire and voiding diary. The success rate after 3 months reached 81.8% (63.6% became completely dry and 18.2% had improved symptoms), with treatment failure in 18.2%. The improvement continued for 6 months postoperatively and reached 60% (40.9% became completely dry and 18.2% had improved symptoms), and the treatment failed in 40.9%.

There is improvement in voiding diary parameters after injection. Mean ± SD baseline urinary frequency decreased from 15.55 ± 1.42 to 7.59 ± 0.87 ($P = 0.000$). Mean ± SD baseline UUI episodes decreased from 6.27 ± 1.03 to 2.05 ± 0.60 ($P = 0.000$).

The first study that evaluated the efficacy of Botox in individuals with NDO was published by Schurch *et al.* [9] on 21 patients who had NDO in 2000. After injection, 89% of patients were improved, and there was a significant improvement in the mean maximum bladder capacity and decrease of detrusor pressure.

In a study done by Kuo [10] on 30 patients with both idiopathic and neurogenic refractory OAB, after BTX-A injection, eight (26.7%) patients became dry, 14 (46.7%) patients were improved, and treatment failed in eight (26.7%) patients.

Moreover, White *et al.* [11] evaluated Botox injection in geriatric patients with OAB. Overall, 76% of the patients were improved, who noted a 50% improvement in frequency per day (11.4 ± 1.67 vs. 5.19 ± 0.83) and number of pads per day (4.0 ± 0.89 vs. 1.3 ± 0.60). Improvement was maintained for 7 months without treatment-related adverse effects. So, intravesical

Table 3 Urogenital distress inventory-6 at baseline and after 3 and 6 months

UDI-6	Baseline (*n*=22) Mean±SEM	3 months (*n*=22) Mean±SEM	6 months (*n*=22) Mean±SEM	*P*[1]	*P*[2]
Q1. Frequency	78.78±5.16	24.24±4.99	37.88±6.32	0.000*	0.000
Q2. Urgency incontinence	71.21±8.29	19.70±6.45	39.39±8.39	0.000*	0.001
Q3. Stress urinary incontinence	18.18±7.18	6.06±3.56	18.18±7.51	0.123	1.000
Q4. Few drops	36.36±9.28	10.60±5.09	21.21±7.77	0.011*	0.039
Q5. Difficulty	24.24±7.33	15.15±4.77	16.66±4.78	0.131	0.129
Q6. Suprapubic pain	7.57±4.87	6.06±2.81	7.57±4.87	0.705	1.000

UDI, urogenital distress inventory. 1. Comparison between baseline and 3 months 2. Comparison between baseline and 6 months.
*: Clinically significant improvment

Table 4 Incontinence impact questionnaire-7 at baseline and after 3 and 6 months

IIQ-7	Baseline (*n*=22) Mean±SEM	3 months (*n*=22) Mean±SEM	6 months (*n*=22) Mean±SEM	*P*[1]	*P*[2]
Prayer	50.00±7.52	15.15±5.69	22.73±6.72	0.000*	0.000
Entertainment	59.08±7.25	18.18±5.25	30.30±6.17	0.000*	0.002
Work	68.17±6.38	16.67±4.78	37.88±7.04	0.000*	0.003
Car	53.03±8.10	16.66±5.70	25.76±7.25	0.000*	0.001
Social	84.84±5.69	42.42±8.26	54.54±8.07	0.000*	0.002
Anxiety	96.96±2.09	53.02±7.49	69.69±7.24	0.000*	0.004
Depression	99.99±0.00	53.03±8.10	68.18±7.43	0.000*	0.002

IIQ, incontinence impact questionnaire. 1. Comparison between baseline and 3 months. 2. Comparison between baseline and 6 months.

BTX-A for OAB in the geriatric patients appears to be efficacious.

In 2012, Kanagarajah *et al*. [6] evaluated the success of Botox in 32 patients with refractory OAB. Regarding urinary frequency, 84% of the patients were improved according to the 3-day voiding diary data. Mean ± SD baseline urinary frequency decreased from 24 ± 11 to 10 ± 4 ($P = 0.02$). There was more than 50% reduction in urgency incontinence attacks in 85% of patients. Mean ± SD baseline incontinence attacks decreased from 7.9 ± 5 to 0 ± 2.6 ($P = 0.02$).

In a study done by Al Edwan *et al*. [12] to evaluate the success of Botox injection in 46 pediatric patients with idiopathic OAB with a mean age of 8.9 years, there was a significant improvement in OAB symptoms and urodynamic parameters with minimal complications.

Regarding the dose of BTX-A used for injection, we used 100 U for idiopathic OAB and 200 U for NDO. In the same line, Cruz *et al*. [13] evaluated the success of Botox in patients with NDO using 200 and 300 U of Botox. No differences were noted in the duration and success between the two doses, but more adverse events were noted with the 300 U dose.

Regarding the adverse effects of BTX injection, in our study, UTI occurred in two (9%) patients after intervention. The PVR in all patients after injection was insignificant, except in two (9%) patients. In one of them, PVR was 150 ml and was asymptomatic, and only conservation is done. The other patient had symptomatic urinary retention with PVR of 250 ml, and catheterization was done for only 1 week. Schurch *et al*. [9] stated that UTI and urinary retention are the most common complications. Moreover, in the study done by Cruz *et al*. [13], UTI was the most common complication during the first 12 weeks. Kalsi *et al*. [14], reported that symptomatic UTI after Botox injection occurred in 9% of patients. Mild hematuria was noted and was found to occur in 2–21% of patients and was self-limiting [15]. In our study, tinge to mild hematuria occurred in only one patient after injection, which responded to medical treatment for 1 day.

The limitations of this study were the limited numbers of patients and short-term follow-up.

Conclusion

BTX-A is an excellent and successful treatment option for patients with refractory OAB. BTX-A represents a minimally invasive option for patients with refractory OAB. Complications are rare, and the effect is usually sustained for 6–12 months.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 White N, Iglesia CB. Overactive bladder. Obstet Gynecol Clin North Am 2016; 43:59–68.

2 Gormley EA, Lightner DJ, Burgio KL, Chai TC, Clemens JQ, Culkin DJ, *et al*. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol 2012; 188 (6 Suppl):2455–2463.

3 Giannantoni A, Proietti S, Costantini E, Gubbiotti M, Rossi De Vermandois J, Porena M. OnabotulinumtoxinA intravesical treatment in patients affected by overactive bladder syndrome: best practice in real-life management. Urologia 2015; 82:179–183.

4 Shamliyan T, Wyman J, Kane RL. Nonsurgical treatments for urinary incontinence in adult women: diagnosis and comparative effectiveness. AHRQ Comparative Effectiveness Reviews 2012; 11:EHC074-EF.

5 Gaziev G, Topazio L, Iacovelli V, Asimakopoulos A, Di Santo A, De Nunzio C, *et al.* Percutaneous tibial nerve stimulation (PTNS) efficacy in the treatment of lower urinary tract dysfunctions: a systematic review. BMC Urol 2013; 13:61.

6 Kanagarajah P, Ayyathurai R, Caruso DJ, Gomez C, Gousse AE. Role of botulinum toxin-A in refractory idiopathic overactive bladder patients without detrusor overactivity. Int Urol Nephrol 2012; 44:91–97.

7 Fabuel Alcaniz JJ, Martinez Arcos L, Jimenez Cidre M, Burgos Revilla FJ. Intravesical botulinum toxin under local anestesia as ambulatory procedure. Arch Esp Urol 2017; 70:635–644.

8 Przydacz M, Golabek T, Chlosta P. How to assess and predict success or failure of intra-detrusor injections with onabotulinumtoxinA. Adv Clin Exp Med 2019; 28:555–567.

9 Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol 2000; 164 (3 Pt 1):692–697.

10 Kuo HC. Urodynamic evidence of effectiveness of botulinum A toxin injection in treatment of detrusor overactivity refractory to anticholinergic agents. Urology 2004; 63:868–872.

11 White WM, Pickens RB, Doggweiler R, Klein FA. Short-term efficacy of botulinum toxin a for refractory overactive bladder in the elderly population. J Urol 2008; 180:2522–2526.

12 Al Edwan GM, Mansi HH, Atta ONM, Shaath MM, Al Adwan R, Mahafza W, *et al.* Objective and subjective improvement in children with idiopathic detrusor overactivity after intravesical botulinum toxin injection: a preliminary report. J Pediatr Surg 2019; 54:595–599.

13 Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, *et al.* Efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: a randomised, double-blind, placebo-controlled trial. Eur Urol 2011; 60:742–750.

14 Kalsi V, Popat RB, Apostolidis A, Kavia R, Odeyemi IA, Dakin HA, *et al.* Cost-consequence analysis evaluating the use of botulinum neurotoxin-A in patients with detrusor overactivity based on clinical outcomes observed at a single UK centre. Eur Urol 2006; 49:519–527.

15 Kuo HC. Therapeutic effects of suburothelial injection of botulinum a toxin for neurogenic detrusor overactivity due to chronic cerebrovascular accident and spinal cord lesions. Urology 2006; 67:232–236.