

Subject Area:

Short-term outcome of onabotulinumtoxin A injection for the treatment of refractory idiopathic detrusor overactivity

Amr M. Elsofy

National Institute of Urology and Nephrology

Ayman M. Gabr

National Institute of Urology and Nephrology

Gamal E. A. Abourjila

National Institute of Urology and Nephrology, abourjilag@gmail.com

Khalid F. Elewa

National Institute of Urology and Nephrology

Follow this and additional works at: <https://jmisr.researchcommons.org/home>



Part of the [Medical Sciences Commons](#), and the [Medical Specialties Commons](#)

Recommended Citation

Elsofy, Amr M.; Gabr, Ayman M.; A. Abourjila, Gamal E.; and Elewa, Khalid F. (2020) "Short-term outcome of onabotulinumtoxin A injection for the treatment of refractory idiopathic detrusor overactivity," *Journal of Medicine in Scientific Research*: Vol. 3: Iss. 1, Article 9.

DOI: https://doi.org/10.4103/JMISR.JMISR_78_19

This Original Study is brought to you for free and open access by Journal of Medicine in Scientific Research. It has been accepted for inclusion in Journal of Medicine in Scientific Research by an authorized editor of Journal of Medicine in Scientific Research. For more information, please contact m_a_b200481@hotmail.com.

Short-term outcome of onabotulinumtoxin A injection for the treatment of refractory idiopathic detrusor overactivity

Gamal E.A. Abourjila, Ayman M. Gabr, Amr M. Elsofy, Khalid F. Elewa

Department of Urology, National Institute of Urology and Nephrology, Cairo, Egypt

Abstract

Introduction

There are many theories behind the etiology of refractory idiopathic detrusor overactivity (IDO), but it is generally accepted that it is caused by a combination of myogenic and neurogenic alterations. It is also believed that mucosal sensory systems make a significant contribution to the disorder as well. Intravesical botulinum toxin A (BoNT/A) prevents acetylcholine release at the neuromuscular junction, resulting in temporary chemodenervation and muscle relaxation. The aim of this work was to assessment of outcome of BoNT/A injection for the treatment of refractory IDO.

Patients and methods

The author included 37 patients who received intravesical BoNT/A for the treatment of refractory IDO. Of these patients, 25 had 3 years of follow-up. All patients were resistant to oral antimuscarinic therapy and/or adrenergic β_3 agonists. BoNT/A was injected intra-detrusor muscle supratrigonally in aliquots of 1 ml delivering 10 units at each injection site, usually at 20 sites.

Results

A total of 37 patients with urgency and urge incontinent were included; of them, 22 patients had urgency incontinence and 15 patients had severe urgency without incontinence. Significant decreases in urgency incontinence episodes with BoNT/A were seen as early as week 2 ($P < 0.001$) and continued through week 12 ($P < 0.001$). Reduction in incontinence episodes was 4–8, which changed to 2–5 after injection. Moreover, 100% reduction in incontinence episodes was minimal and occurred only in 10%.

Conclusion

BoNT/A promotes significant improvement of urinary urgency, urinary frequency, nocturia, and incontinence symptoms. Although there is incidence of complications especially urinary retention and urinary tract infection among patients, BONT/A still is safe and tolerable.

Keywords: Detrusor overactivity, onabotulinumtoxin A, overactive bladder, urgency incontinence, urgency

INTRODUCTION

Overactive bladder (OAB) is defined as a syndrome of urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology [1]. It is very common in the general population. The European Prospective Investigation into Cancer and Nutrition study, which is one of the largest population-based surveys that studied the prevalence of lower urinary tract symptoms and OAB, was conducted in five countries, including Canada, Germany, Italy, Sweden, and the UK. The European Prospective Investigation into Cancer and Nutrition study was a cross-sectional telephone

survey of adults aged greater than 18 years. The study had greater than 19 000 participants and showed an overall OAB prevalence of 11.8%, with similar rates in men and women [2]. There are many theories behind the etiology of OAB, but it is generally accepted that it caused by a combination of myogenic and neurogenic alterations [3]. It is also believed that mucosal

Correspondence to: Gamal E.A. Abourjila, MD, PhD,
Department of Urology, National Institute of Urology and Nephrology,
11321 Cairo, Egypt, Tel: +20 111 5681 0883, Fax: +20222549157.
E-mail: abourjilag@gmail.com

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

Submitted: 4-Dec-2019 Revised: 02-Feb-2020 Accepted: 31-Jan-2020 Published: 11-Jun-2020

How to cite this article: Abourjila GE, Gabr AM, Elsofy AM, Elewa KF. Short-term outcome of onabotulinumtoxin A injection for the treatment of refractory idiopathic detrusor overactivity. J Med Sci Res 2020;3:49-52.

Access this article online

Quick Response Code:



Website:
www.jmsr.eg.net

DOI:
10.4103/JMISR.JMISR_78_19

sensory systems make a significant contribution to the disorder as well [3]. There are three Food & Drug Administration (FDA) approved second-line therapies available for patients with IOAB. Sacral neuromodulation was FDA approved for urgency incontinence and urgency/frequency syndrome in 2007. It is very effective, with low explantation rates; however, the nature of the implantable device necessitates its replacement, and revision surgery is very common [4]. Moreover, not all patients are able or willing to have a metal implantable device inserted. Percutaneous tibial nerve stimulation was FDA approved in 2010 for OAB and is a minimally invasive technique utilizing electrical stimulation of the tibial nerve via a 34 G needle. The technique has a very low risk of adverse events but requires weekly office visits for 12 weeks followed by maintenance therapy, which is not always convenient for patients [5]. Botulinum toxin A (BoNT/A) injection is a safe and effective treatment for adults with refractory OAB. There is sufficient level 1 evidence to support offering BoNT/A injections as a second-line treatment to patients who have failed behavioral therapy and oral medications such as antimuscarinics and $\beta 3$ agonists [6]. Intravesical botulinum toxin A BoNT/A prevents acetylcholine release at the neuromuscular junction, resulting in temporary chemodenervation and muscle relaxation for up to 6 months. In the 20-injection technique, the patients undergo intradetrusor injection in the cystoscopic guidance [7].

PATIENTS AND METHODS

The study was conducted according to the Declaration of Helsinki (1996) and was approved by Institute Ethical Committee. Eligibility criteria included patients 5 years and older with refractory OAB symptoms of urgency, frequency, nocturia, urgency urinary incontinence for at least 6 months. Exclusion criteria included OAB caused by a neurological condition like myasthenia gravis, Eaton-Lambert syndrome, spinal anomalies or surgery, or myotrophic lateral sclerosis. Moreover, we excluded patients with current use of indwelling catheter or clean intermittent catheterization to empty the bladder, patients with evidence of bladder outlet obstruction, patients with impaired bladder compliance, or patients with stress urinary incontinence. Between 2014 and 2017, 41 patients received intravesical BONT/A for the treatment of refractory idiopathic detrusor overactivity, after its introduction into the Department of Urology of our National Institute of Urology and Nephrology. Of these patients, 37 had greater than 3 years of follow-up and four had inadequate records. Thus, 37 patients with 36 months of follow-up were available for evaluation. All patients were resistant to or intolerant of oral antimuscarinic therapy and/or adrenergic $\beta 3$ agonists for at least 6 months. Detrusor overactivity had been confirmed by urodynamic studies in all patients. Preoperative assessment was completed by patient history, bladder diary, ultrasonographic assessment of bladder, and measurement of the post voiding residual (PVR) urine. Generally, patients with OAB are initially treated with conservative measures (lifestyle changes, caffeine intake reduction, pelvic floor exercises, and bladder drill). Various

anticholinergic therapies had been used, at doses up to the maximum recommended level. All patients were subjected to urine analysis and urine culture before the procedure, and the presence of UTI necessitated treatment. Patients were fully informed about the use of BoNT/A including the adverse effects associated with the treatment. The possibility of having to perform lean intermittent self-catheterization (CISC) after the procedure was explained to the patient before the treatment. In injection techniques, our team uses BoNT/A, which is a 900 kD albumin protein, by Allergan pharmaceuticals, Clonshaugh coolock, D17 E 400, Duplin, Ireland. Antibiotic prophylaxis was not routinely given. A rigid 21 Fr injection cystourethroscope (Karl Storz, Tuttlingen, Germany.) was utilized with injection with 25 G needle (5.0 Fr/35 cm, tip length 4 mm). In children, 7 Fr cystourethroscope (Karl Storz) was utilized with flexible injection needle. We considered BoNT/A 200 ml for patients above 18 years and 100 ml below 18 years. Overall, 200 ml of BoNT/A (two vials) was reconstituted with 0.9% normal saline to a dosage of 10 units/ml (children had 100 ml BONT/A 10 unit/ml). Spinal anesthesia was used to administer the treatment, except in children. Cystoscopy evaluation of the bladder is the initial step. The BoNT/A was injected in the intra-detrusor muscle supratrigonally in aliquots of 1 ml, delivering 10 units at each injection site usually at 20 sites across the dome of the bladder. Each injection is made 2 mm deep and roughly 1 cm apart. A volume of 1 ml (10 units/ml) of BoNT/A is then injected in a grid-type pattern for a total of 20 injections. After syringes are utilized, 3 ml syringe with 0.9% saline is used to inject an additional 1 ml saline. This ensures that all active drug is utilized. Postoperative care was done for all patients, and the patients were discharged on the same day. We generally have the patients return 3 weeks following injection. Follow-up of patients included outpatient department visit at least two occasions after the initial injection. There was an initial clinic review 3–4 weeks after treatment and a second review after 8–12 weeks. Assessment was completed by patient history, bladder diary, and ultrasonographic measurement of the PVR urine. Structured health-related quality of life questionnaires were not routinely used. However, all patients went on to have urodynamic studies after treatment at 8 weeks. If the patient had urinary retention, symptomatic difficulties secondary to poor bladder emptying, or large PVR urine (>150 ml), then CISC was instituted. Only 37 patients were observed at the end of the study.

RESULTS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, Illinois, USA) version 16.0. Our study included 37 patients: five patients were between the age 5 and 12 years, three patients between age 12 and 18 years, and 29 patients above age 18 years. The last age group above age 18 years. There were 12 patients (all are female) above 45 years. Median age was 41 years (Tables 1 and 2). In all, 25 patients had 3 years and 12 patients having 2 years of follow-up (Figs. 1 and 2).

urgency



- sever urgency with urgency incontineince
- sever urgency without incontineince.

Figure 1: Distribution of urgency and incontinence.

Of total 37 patients with OAB, 22 patients presented with urgency and urgency incontinence and 15 patients had severe urgency without incontinence. Associated other symptoms included daytime frequency in most patients (32/37), nocturia (12/37), and dysuria 27/37). Most young patients (below 18 years) with urgency incontinence had diurnal and nocturnal wetting (6/8), but most adult patients (above 18 years) with urgency incontinence had only diurnal wetting (16/29). At week 8 after treatment, urgency incontinence (UI) episodes per day were significantly reduced from baseline with BoNT/A. Significant decreases in UI episodes with BoNT/A were seen as early as week 2 ($P < 0.001$) and continued through week 12 ($P < 0.001$). Significantly higher proportions of patients treated with BoNT/A achieved greater than or equal to 48% reduction ($P < 0.001$) and 53% reduction ($P < 0.001$) in UI episodes per day at week 6 and 12 (4–8 changed to 2–5 after injection). Urinary urgency and micturition episodes per day were significantly reduced at week 6 after BoNT/A reduction in urgency episodes and severity changed from 7–11 to 5–7 ($P < 0.001$, Table 3). This reduction occurred in 73% of patients (11/15).

In addition, BoNT/A treatment yielded significantly greater increases in volume per void ($P < 0.001$). Significant improvements were observed in urodynamic outcomes with BoNT/A. At week 6, a significantly greater increase from baseline in MCC was demonstrated with BoNT/A, and significantly greater decreases were seen in maximum detrusor pressure during the storage phase and during the first DC ($P < 0.05$, all end points, Table 3). Maximum bladder capacity (MCC) significantly increased and maximum detrusor pressure decreased. Daytime and nighttime frequency, urgency, and pad use significantly decreased. Postvoid residual volume significantly increased initially but decreased until 12 weeks. Median time to re-injection owing to recurrent OAB symptoms was 8 months (Table 3).

Reduction in incontinence episodes was 4–8, which changed to 2–5 after injection. Moreover, 100% reduction in incontinence episodes was minimal and occurred only in 10%. Foremost, significant adverse effects associated with BONT/A injection

post injection side effects and complication

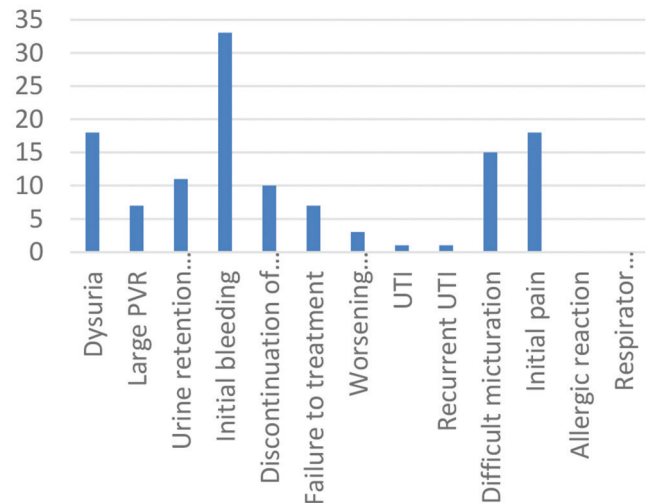


Figure 2: Adverse effects and complications.

Table 1: Demographic data of the patients

Sex	n
Male	18
Female	19
Total	37

Table 2: Age distribution

Age distribution	Years
<12	5
12-18	3
>18	29
Median age	41

Table 3: Efficacy of botulinum toxin A

	Preoperative	Postoperative	P
UI episodes per day	4.8±3.1	2.1±2.5	<0.001
urgency episodes per day	7.4±3.8	4.9±2.3	<0.001
micturition episodes per day	9.5.0±3.1	5.0±2.7	<0.001
MCC (ml)	273.4±141.5	310.2±121.3	<0.005
MDP at first IDC (cm H ₂ O)	46.1±30.5	35.2±21.3	<0.005
Volume per void (ml)	163.7±62.6	268.5±52.6	<0.005
I-QOL total summary score	31.2±13.3	34.2±12.3	<0.005

IDC, idiopathic detrusor contraction; MCC, maximum cystometric capacity; MDP, maximum detrusor pressure; UI, urinary incontinence; I-QOL, Incontinence Quality of Life.

were common. Hematuria and postoperative pain are the most common symptoms observed following toxin injection; however, as 33/37 patient had initial hematuria, 18/37 had initial pain, 15 patients had difficult to initiate micturition (three not required catheterization and 11 required CISC), and 18 patients had dysuria. Overall, 10/11 of CISC patients were relived within

Table 4: Adverse effects and complications

	Patients	Incidence (%)
Dysuria	18	48
Large PVR urine	7	18.9
Retention required CISC	11	29.7
Initial bleeding	33	89.1
Discontinuation of therapy	10	27
Failure to treatment	7	18.9
Worsening symptoms	3	8.1
UTI	1	2.7
Recurrent UTI	1	2.7
Difficult micturition	15	40.5
Initial pain	18	48.6
Allergic reaction	0	0
Respirator side effect	0	0
Extremity weakness	0	0

UTI, urinary tract infection.

3 weeks. Most these adverse effects were minor and not a reason to discontinue the following injection. Given the paralytic nature of BONT/A injection, to date, no severe systemic complication (e.g. respiratory muscle weakness/paralysis) has been reported. Less severe systemic adverse effects, such as extremity weakness, were not reported in our patients. A total of six patients discontinued the BONT/A injection; four patients made the decision owing to failure of treatment and two of them discontinued the treatment owing to worsening symptoms (Table 4). Of all 37 patients, 10 (27%) patients had stopped BONT/A therapy, with the remaining 27 (73%) still on the treatment. Most patients received repeat BONT/A injections, with an average treatment interval of 8 months.

DISCUSSION

BoNT/A blocks the presynaptic release of acetylcholine and causes full or partial paralysis and weakening of overactive muscle. There are several publications relating to the efficacy and safety of intravesical BONT/A in the treatment of resistant IOAB. Most of the published series deal with short-term efficacy and tolerability issues. Cruz *et al.* [8]; Grise *et al.* [9]; and Sahai *et al.* [10], reported an incidence of UTIs of 1.3–64%, the need for CISC of 1.3–42.2%, and high PVR urine of 28.6–53.7%. The present data are comparable with our results, with the incidence of UTI being 5.4%, the need for CISC being 29.7% and significant PVR urine being present in 18.9%.

Although Del Popolo *et al.* [11], and Chancellor *et al.* [12], showed no loss of efficacy, or even improved efficacy with repeated injection, Rovner *et al.* [13] reported that 42.9–70.2% of patients had persistent urinary incontinence 12 weeks after BONT/A injection therapy. We found that the efficacy of therapy in our study is largely consistent with published data by Grise and Sahai. Our initial efficacy rate of improvement was 73%, with a proportion of patients having a subsequent failure to respond, at 27%. Grise *et al.* [9], and Sahai *et al.* [10], reported a 27.8–41.1% primary failure rate.

CONCLUSION

Short-term data are very robust for BoNT/A as a safe and effective treatment for IOAB. BoNT/A promotes significant improvement of urinary urgency, urinary frequency, nocturia, and incontinence symptoms. Although there is some incidence of urinary retention and UTI among patients, BONT/A still is safe and tolerable.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

- Haylen BT, Freeman RM, Swift SE, Cosson M, Davila GW, Deprest J, *et al.* An international urogynecological association (IUGA)/international continence society (ICS) joint terminology and classification of the complications related directly to the insertion of prostheses (meshes, implants, tapes) and grafts in female pelvic floor surgery. *NeurourolUrodyn* 2011; 30:2–12.
- Irwin DE, Milsom I, Hunskaar S, Reilly K, Kopp Z, Herschorn S, *et al.* Population-based survey of urinary incontinence, overactive bladder and other lower urinary tract symptoms in five countries: results of the EPIC study. *Eur Urol* 2006; 50:1306–1315.
- Andersson KE, Fullhase C, Soler R. Urothelial effects of oral agents for overactive bladder. *Curr Urol Rep* 2008; 9:459–464.
- Al-zahrani AA, Elzayat EA, Gajewski JB. Long-term outcome and surgical interventions after sacral neuromodulation implant for lower urinary tract symptoms: 14-year experience at 1 center. *J Urol* 2011; 185:981–986.
- 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.
- Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. *J Urol* 2013; 189:1388–1395
- Karsenty G, Denys P, Amarenco G, De Seze M, Game X, Haab F, *et al.* Botulinum toxin A (Botox) intradetrusor injections in adults with neurogenic detrusor overactivity/neurogenic overactive bladder: a systematic literature review. *Eur Urol* 2008; 53:275–87.
- Cruz F, Herschorn S, Aliotta P, *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.
- Grise P, Ruffion A, Denys P, Egon G, Chartier Kastler E. Efficacy and tolerability of botulinum toxin type A in patients with neurogenic detrusor overactivity and without concomitant anticholinergic therapy: comparison of two doses. *Eur Urol* 2010; 58: 759–766.
- Sahai A, Dowson C, Khan MS, Dasgupta P. Repeated injections of botulinum toxin-A for idiopathic detrusor overactivity. *Urology* 2010; 75: 552–558.
- Del Popolo G, Filocamo MT, Li Marzi V, Macchiarella A, Cecconi F, Lombardi G, *et al.* Neurogenic detrusor overactivity treated with English botulinum toxin a: 8-year experience of one single centre. *Eur Urol* 2008; 53: 1013–19.
- Chancellor MB. Ten years single surgeon experience with botulinum toxin in the urinary tract; clinical observations and research discovery. *Int Urol Nephrol* 2010; 42:383–391.
- Rovner E, Kennelly M, Schulte-Baukloh H, Zhou J, Haag-Molkenteller C, Dasgupta P. Urodynamic results and clinical outcomes with intradetrusor injections of onabotulinumtoxinA in a randomized, placebo-controlled dose-finding study in idiopathic overactive bladder. *Neurourol Urodyn* 2011; 30:556–562.