

The Effect of Intradetrusor Botulinum Toxin Injection in Patients with Idiopathic Detrusor Overactivity

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ABSTRACT:

BACKGROUND:

The overactive bladder (OAB) is extremely common. The treatment of refractory overactive bladder conditions has changed radically over the last decade. The efficacy of OAB treatment protocols in improving patient symptoms are not satisfactory, so new agents such as botulinum-A toxin must be investigated.

OBJECTIVE:

To evaluate the safety and efficacy of intradetrusor botulinum -A toxin injection in patients with idiopathic detrusor overactivity resistant to anticholinergic drugs.

METHODS:

From March 2010 to September 2011, 38 women with refractory idiopathic detrusor overactivity (IDO), from the urologic consultation department in Baghdad Medical City and Al-Ramadi teaching hospital, were included in this prospective study. Their age ranged from 45 to 70 years. Inclusion criteria were women with idiopathic detrusor overactivity not responding to different anticholinergic treatments. Patients with urinary tract infection, mixed incontinence, bladder stone, hematuria, neurogenic detrusor overactivity, high postvoiding residual urine volume (more than 50 ml) and history of bladder tumour were excluded from this study. Full clinical and urodynamic evaluations were done before intradetrusor injection of 300 units of botulinum-A toxin and at 2 weeks and 24 weeks after injection.

RESULTS:

Thirty six patients achieved urinary continence (94.7%). The age ranged from 45 to 70 years (mean 56.67 ± 7.34). There was significant clinical improvement after botulinum toxin injection at both 2 weeks and 24 weeks of follow up as reflected by statistically significant decrease in the daytime frequency, nocturia and the incontinence episodes (p value < 0.05).

There was significant urodynamic improvement after botulinum toxin injection at both 2 weeks and 24 weeks of follow up as reflected by statistically significant increase in the maximum cystometric bladder capacity and the bladder compliance and by statistically significant decrease in the detrusor pressure at maximum flow rate (p value < 0.05). Postvoiding residual urinary volume shows statistically significant increase at both 2 weeks and 24 weeks of follow up (p value < 0.05).

CONCLUSION:

The use of intradetrusor injection of botulinum toxin-A (BTX A) in refractory idiopathic detrusor overactivity was well tolerated and demonstrated clinically meaningful and statistically significant improvement in the clinical and urodynamic parameters of the patients. The effect was durable for the period of study which is 6 months.

KEY WORDS: botulinum toxin-A, idiopathic detrusor overactivity, overactive bladder

INTRODUCTION:

The overactive bladder (OAB) is a prevalent problem, with considerable effects on the quality of life of affected individuals and substantial health economic costs. The condition is symptom based and defined by the International Continence Society (ICS) standardization

committee as urgency, with or without urgency incontinence, usually with frequency and nocturia, if there is no proven infection or other obvious pathology. Crucially, the current definition of OAB is based on symptoms; in contrast, detrusor overactivity (DO) is a urodynamic observation, characterized by involuntary detrusor contractions during the filling phase, which may be spontaneous or provoked. OAB and DO are thus not

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interchangeable terms, and the clinician must be specific in their use.⁽¹⁾

DO is described as neurogenic DO(NDO) when associated with a relevant neurologic condition and as idiopathic DO(IDO) when there is no such association. Patients with OAB are often found to have DO when studied, but this is not a requirement for diagnosis. Thus OAB is a condition and DO is a urodynamic finding.⁽²⁾

The OAB often results in poor bladder control causing complications such as increasing risk of falls/fractures in the elderly, depression, vulvovaginitis and skin infections.^(3,4)

Pharmacologic treatment of overactive bladder syndrome (OAB) and detrusor overactivity (DO) has centered around blocking post-synaptic muscarinic receptors on the detrusor muscle, thus preventing or decreasing involuntary detrusor contractions. Antimuscarinic agents are effective in this regard; however, approximately 25% to 40% of patients fail to get adequate symptom relief when incontinence is the primary outcome variable. In addition, because these medications are not uroselective, antimuscarinic side effects, especially dry mouth and constipation, limit their usefulness and result in relatively high discontinuation rates outside large-scale clinical trials. Thus, there is a need for treatments other than systemic antimuscarinic agents and behavioral modification to treat this highly prevalent condition.⁽⁵⁾

The International Consultation on Incontinence (ICI) states that when the first-line therapy is not fully satisfactory or fails after 8-12 weeks, alternative therapies including surgical management options should be considered.⁽⁶⁾

Botulinum toxin (BTX) is a potent natural neurotoxin. It was first isolated in 1897 by Van Ermengem who described the side effects of flaccid paralysis.⁽⁷⁾ It was first approved by the FDA in 1989 to treat strabismus, benign essential blepharospasm, and disorders of cranial nerve VII. The toxin is derived from a gram-positive coccus *Clostridium Botulinum*. Several distinct structural serotypes of BTX have been identified (A, B, C, D, E, F, and G).⁽⁵⁾ Types A and B have been most widely used for medicinal purposes.⁽⁸⁾

BTX inhibits the release of acetylcholine at the presynaptic cholinergic junction, hence inducing muscle relaxation.⁽⁹⁾

This study was carried out to evaluate the effect of Botulinum toxin (BTX) in patients with intractable idiopathic detrusor overactivity.

METHODS:

From March 2010 to September 2011, we observed 100 patients, from the urologic consultation department in Baghdad Medical City and Al-Ramadi teaching hospital, with overactive bladder (OAB) symptoms. Of them 38 women with refractory overactive bladder (OAB) were included in this prospective study. Their age ranged from 45 to 70 years. Inclusion criteria were women with idiopathic detrusor overactivity not responding to different anticholinergic treatments including oxybutinin 5mg three times per day and tolterodine 4mg per day for more than six months. Patients with urinary tract infection, mixed stress and urge incontinence, bladder stone, hematuria, neurogenic detrusor overactivity, high postvoiding residual urine volume (more than 50 ml) and history of bladder tumour were excluded from this study, also patients with suspected carcinoma in situ at the time of endoscopy were excluded and multiple biopsies were taken. Complete voiding diary was obtained from each patient and the baseline daytime frequency, nocturia and the number of incontinence episodes were recorded. Complete neurological examination was carried out to exclude any neurological defect and gynecological examination to exclude pelvic organ prolapse. Full urodynamic evaluation was carried out for each patient and the baseline maximum cystometric bladder capacity, bladder compliance and maximal detrusor pressure were recorded. Postvoiding residual urinary volume was measured by urethral catheterization at the end of urodynamic study. In surgical specialties hospital and under cystoscopic guidance a total of 300 U of botulinum-A toxin were injected into the detrusor muscle at 20 to 30 sites (10 units per ml per site), sparing the trigone, all procedures were carried out under general anesthesia. Most investigators use 200 or 300 U botulinum-A toxin for detrusor injection in IDO. Because the bladder wall is very thin at full capacity (around 2-3 mm), it is possible that much BoNT-A solution is injected too deep and outside the bladder wall when performing detrusor injection, inadequate distribution and diffusion of BoNT-A solution might necessitate a larger dose for effective treatment of IDO.⁽¹⁰⁾ Full clinical and urodynamic evaluations were done at 2 weeks and 36 weeks after injection.

The present study was approved by ethical committee and all participants read and signed an informed consent form.

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The statistical test used was one way ANOVA, using the Statistical Package for Social Sciences (SPSS version 17.0) software. All P values less than 0.05 were considered to indicate significance.

RESULTS:

Thirty six patients achieved urinary continence (94.7%). The age ranged from 45 to 70 years (mean 56.67). There was significant clinical improvement after botulinum toxin injection at both 2 weeks and 24 weeks of follow up as reflected by statistically significant decrease in

the daytime frequency from 12.2 ± 0.31 at baseline to 4.8 ± 0.23 at 2 weeks (p value < 0.05) and to 5.1 ± 0.32 at 24 weeks (p value < 0.05), statistically significant decrease in the nocturia from 5.3 ± 0.24 at baseline to 1.3 ± 0.32 at 2 weeks (p value < 0.05) and to 1.4 ± 0.26 at 24 weeks (p value < 0.05) and by statistically significant decrease in the incontinence episodes from 6.8 ± 0.41 at baseline to 0.4 ± 0.26 at 2 weeks (p value < 0.05) and to 0.5 ± 0.39 at 24 weeks (p value < 0.05). Table (1)

Table 1: Clinical improvement after botulinum toxin injection.

Variable	Baseline	2 weeks	P value	24 weeks	P value
Daytime frequency	12.2 ± 0.31	4.8 ± 0.23	0.0001	5.1 ± 0.32	0.0002
Nocturia	5.3 ± 0.24	1.3 ± 0.32	0.0003	1.4 ± 0.26	0.0004
Incontinence episodes	6.8 ± 0.41	0.4 ± 0.26	0.0001	0.5 ± 0.39	0.0002

There was significant urodynamic improvement after botulinum toxin injection at both 2 weeks and 24 weeks of follow up as reflected by statistically significant increase in the maximum cystometric bladder capacity from 244.2 ± 132.4 ml at baseline to 485.4 ± 129.4 ml at 2 weeks (p value < 0.05) and to 478.7 ± 125.8 ml at 36 weeks (p value < 0.05), statistically significant increase in the bladder compliance from 19.98 ± 5.65 ml/cm H₂O at baseline to 59.65 ± 10.45 ml/cm H₂O at 2 weeks (p value < 0.05) and to $52.74 \pm$

11.87 ml/cm H₂O at 36 weeks (p value < 0.05) and by statistically significant decrease in the maximal detrusor pressure from 42.23 ± 14.3 cm H₂O at baseline to 16.14 ± 12.56 cm H₂O at 2 weeks (p value < 0.05) and to 18.34 ± 13.98 cm H₂O at 24 weeks (p value < 0.05). Postvoiding residual urinary volume increased from 15.4 ± 5.5 ml at baseline to 87.65 ± 13.63 ml at 2 weeks (p value < 0.05) and to 79.65 ± 18.62 ml at 36 weeks (p value < 0.05). Table (2)

Table 2: Urodynamic improvement after botulinum toxin injection.

Variable	Baseline	2 weeks	P value	24 weeks	P value
Maximum cystometric capacity	244.2 ± 132.4 ml	485.4 ± 129.4 ml	0.0001	478.7 ± 125.8 ml	0.0002
Bladder compliance	19.98 ± 5.65 ml/cm H ₂ O	59.65 ± 10.45 ml/cm H ₂ O	0.0003	52.74 ± 11.87 ml/cm H ₂ O	0.0002
Maximal detrusor pressure	42.23 ± 14.3 cm H ₂ O	16.14 ± 12.56 cm H ₂ O	0.0002	18.34 ± 13.98 cm H ₂ O	0.0001
Postvoiding residual urinary volume	15.4 ± 5.5 ml	87.65 ± 13.63 ml	0.0001	79.65 ± 18.62 ml	0.0003

Three patients (7.8%) developed temporary urinary retention immediately after injection requiring intermittent catheterization for few days in the current study.

The effect of treatment was durable for the study period which is 6 months. There was no significant side effect that required hospitalization or surgical intervention, only

slight hematuria occurred in 4 patients and simple urinary tract infection (cystitis) occurred in 5 patients.

DISCUSSION:

The pharmacologic treatment of overactive bladder and detrusor overactivity, whether idiopathic or neurogenic, has centered around blocking muscarinic receptors on the detrusor muscle. Although newer agents have been

developed with better tolerability and safety, the basic mechanism by which the “irritable” detrusor is treated has not changed in decades. Although effective in many cases of idiopathic and neurogenic detrusor overactivity and overactive bladder, antimuscarinic agents fall short in many other cases because of lack of efficacy and/or tolerability. For the past several years, there has been increasing evidence to support the use of botulinum toxin for the treatment of detrusor overactivity and overactive bladder syndrome not effectively treated by anticholinergics.⁽⁵⁾

Urologists are familiar with BTX A, having used it in different urologic disorders, such as interstitial cystitis, ureteral stent pain, prostatitis and benign prostatic hyperplasia.^(11,14)

Sahia and colleagues,⁽¹⁵⁾ in a randomized, double-blind placebo control study, demonstrated statistically significant increases in cystometric capacity and reduced frequency, urgency urinary incontinence and urgency with the injection of 200 units of BTX A. The duration of its effect lasted for at least 24 weeks which, incidentally, is longer than most people stay on anticholinergic medication. Other studies have demonstrated similar statistically significant improvement of symptoms with BTX A.^(16,18)

Kuo,⁽¹⁹⁾ studied patients with NDO and IDO and stated that detrusor injection of 200 U of botulinum A toxin is effective in the treatment of detrusor overactivity that is refractory to anticholinergic agents and patients with detrusor overactivity and inadequate contractility should be carefully selected for this procedure because the postvoid residual urine volume may increase after treatment.

Popat R et al,⁽²⁰⁾ compared the response of patients with idiopathic detrusor overactivity and neurogenic detrusor overactivity to the first intradetrusor injection of botulinum-A toxin and stated that patients with intractable IDO respond to intradetrusor BoNT-A with equally significant improvements in urodynamic and lower urinary tract symptom parameters as those with spinal NDO, despite the lower dose of toxin used.

Kessler et al,⁽²¹⁾ assessed and compared the effect of botulinum A toxin (BTX-A) injections into the detrusor in idiopathic and neurogenic detrusor overactivity resistant to anticholinergic treatment and stated that BTX-A injections into the detrusor have a significant and comparable but temporally limited effect in idiopathic and neurogenic detrusor overactivity resistant to anticholinergic treatment.

Werner et al,⁽²²⁾ investigated the efficacy and safety of botulinum-A toxin (BTX-A) treatment for non-neurogenic detrusor overactivity incontinence and stated that BTX-A treatment seems to be a safe and efficacious new treatment option for patients with detrusor overactivity incontinence.

Schmid et al,⁽²³⁾ stated that intradetrusor botulinum-A toxin injections may be an efficient and safe treatment option in patients with severe overactive bladder resistant to all conventional treatments.

In this study, intradetrusor injection of botulinum toxin achieved highly significant clinical and urodynamic improvement in patients with IDO refractory to different types of anticholinergic drugs as reflected by continence rate of 94.7% and statistically significant improvement in daytime frequency, nocturia, incontinence episodes, maximum cystometric capacity, bladder compliance and maximal detrusor pressure (P value < 0.05), these results are compatible with result of the above mentioned studies.

The risk of urinary retention with BTX A injections has been well-established.^(15,18,24) The risk has been shown to be decreased with decreasing doses of BTXA.^[25] Fortunately only three patients developed temporary urinary retention requiring intermittent catheterization for few days in the current study. This temporary effect may be due to urinary tract infection or the pain associated with the procedure.

Distant muscle weakness has definitely been described with BTX A injections. However, the frequency is extremely low (about 20 reported cases in the literature).None of these cases required any intervention and all reports were described in patients with neurogenic detrusor overactivity. Secondary to the small incidence (less than 1%), the association and causation of BTX A in precipitating these events has not been well-established.⁽²⁶⁾ In our study no such side effect had been encountered.

We used botulinum toxin as second line therapy in IDO refractory to different anticholinergic drugs, for the time being, there is no data to support the use of BTX A as a primary treatment for OAB. The long-term success beyond 10 years of BTX A for OAB is unknown. Thus, patients should continue to be treated in a stepwise fashion beginning with lifestyle and behavioural changes, and oral pharmacotherapy.⁽²⁷⁾

CONCLUSION:

The use of intradetrusor injection of botulinum toxin A (BTX A) in refractory idiopathic detrusor

overactivity was well tolerated and demonstrated clinically meaningful and statistically significant improvement in the clinical and urodynamic parameters of the patients. The effect was durable for the period of study which is 6 months, but it well known that the effect of BTX A is temporary up to 9 months so re-evaluation (clinical and urodynamic) is recommended after 1 year from injection.

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