Original Article

Prospective randomized trial of 100u vs 200u botox in the treatment of idiopathic overactive bladder

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Abstract

Aim: To evaluate the clinical outcomes of two different doses of BTX-A in patients with refractory idiopathic overactive bladder.

Patients and Methods: Thirty nine patients with refractory idiopathic overactive bladder from 1/1/2008 till 30/3/2009 were evaluated in a tertiary care hospital. Patients were evaluated using urodynamic studies, voiding diary, UDI-6 and IIQ-7 questionnaires prior to being prospectively randomized (alternate randomization) to the BTX-A applications and three months after treatment. Voiding diary and residual volume were followed two weeks later. All patients received intradetrusorial injections of BTX-A (Botox, Allergan, Irvine, CA) of 100u or 200u under cystoscopic control on an outpatient basis. The primary endpoint was assessed for the improvement of urodynamic parameters and adverse events at three months after the initial treatment. Secondary end points included urinary frequency, urgency and UUI episodes as assessed by voiding diary and QoL.

Results: Eleven patients were enrolled to each arm of the study. There were no significant differences in demographic characteristics between the two groups. Urodynamic assessment at the end of the third month showed significant improvement in urodynamic variables in both groups. There was no statistically significant difference in urodynamic parameters and in the voiding diary between the two groups. QOL was significantly improved in both groups with no statistically significant difference between the different doses. Only three patients developed acute urinary retention.

Conclusion: BTX-A at 100u and 200u appears to improve symptoms, urodynamic parameters and QoL with no statistical significance between the two groups.

Key Words: Botox, idiopathic overactive bladder, refractory

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INTRODUCTION

Overactive bladder (OAB) is a symptom complex described as urgency, with or without urge incontinence, usually with frequency and nocturia. Oral antimuscarinic agents have been widely used as first line treatment for patients with OAB. However, they are ineffective in some patients or can cause troublesome systemic side effects such as dry mouth, constipation, and blurred vision. Some patients may undergo more invasive treatments like sacral neuromodulation[1] or bladder augmentation.[2]

Now botulinum toxin (BTX) is emerging as a treatment option for idiopathic overactive bladder. Botox, first isolated by van

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Ermengem[3] in 1897, is a potent neurotoxin produced by the Gram-positive anerobic bacterium *Clostridium botulinum*. From a structural viewpoint, the toxin is a 150-kD amino acid di-chain molecule consisting of a light (50 kD) and a heavy chain (100 kD), which are linked by a disulfide bond. BTX causes inhibition of acetylcholine neurotransmitter release resulting in striated muscle relaxation.[4] In the bladder, the action of BTX-A at the presynaptic cholinergic junction induces detrusor muscle relaxation, and potentially affects afferent sensory receptors in the urothelium.[5] Emerging data suggests that these sensory effects are probably due to the action of BTX-A on neurotransmitters other than acetylcholine like substance P, calcitonin gene-related peptide, enkephalins.[6]

As is evident from several studies, there is now a significant body of data on the use of BTX-A in idiopathic overactive bladder showing the efficacy of this treatment.[7-13]

The aim of our study is to evaluate the clinical outcome of two different doses of BTX-A in patients with idiopathic over active bladder.

PATIENTS AND METHODS

Thirty nine patients with refractory idiopathic overactive bladder (RI-OAB) from 1/1/2008 till 30/3/2009 were evaluated. Patients with a post void residual (PVR) urine volume of more than 150 ml, neurogenic bladder, bladder outlet obstruction or urinary tract infection were excluded from the study. Refractory idiopathic OAB was defined as failure of symptom control despite use of antimuscarinic treatment using toleterodine 4 mg/day or oxybutanine 15 mg/day during the previous three months.

All patients provided a clinical history, and underwent physical examination, urinalysis, urine culture and appropriate laboratory evaluation when necessary.

All patients were evaluated using urodynamic studies, voiding diary, UDI6 and IIQ-7 questionnaires prior to being prospectively randomized to the BTX-A applications and three months after treatment. Standard urodynamic study was performed using a 6F dual-channel catheter and an 8F rectal balloon catheter. Filling cystometry was performed at a filling rate of 20 to 30 ml/min. All descriptions and terminology in this report are in accordance with the recommendations of the International Continence Society.[1]The institutional review board of our hospital approved this study. Before treatment, each patient was thoroughly informed about the procedure and provided written, informed consent. The information provided to the patients included the possible complications associated with BTX-A injection, such as anaphylaxis, chronic urinary retention, and urinary tract infection. The patients were randomly (alternate randomization) assigned to receive intradetrusor injection of 100u or 200u of BTX-A (Botox, 100 U/vial, Allergan, Irvine, Calif) under intravenous general anesthesia in the operation room. Each BTX-A 100u was diluted with 10 ml normal saline. Intradetrusor injection of BTX-A was performed in the posterior and lateral walls of the urinary bladder, with an equivalent dose (1cc/injection) given at each site, using a rigid cystoscopic injection instrument 22F and a 23-gauge injection needle. The injection needle was inserted and injected directly into the detrusor muscle. After treatment, a 14F urethral Foley catheter was inserted, and oral antibiotics were prescribed for the next five days. Patients were discharged the same day after the procedure catheter free unless developed retention. The patient's voiding condition was followed up at the outpatient clinic two weeks later with residual volume measurement and then after one, three, six and nine months follow-up by voiding diary. If the PVR volume exceeded 200 ml at the follow-up visits, clean intermittent self-catheterization was recommended for evacuation of the bladder at least four times daily. An indwelling Foley catheter was placed for one week if transient urinary retention developed. The use of anticholinergic agents was discontinued one week before BTX-A injection. The use of urodynamic parameters assessed included maximum cystometric capacity (MCC), maximal voiding detrusor pressure, and maximal flow rate during voiding and PVR urine volume. Follow-up urodynamic studies were performed at three months after treatment. Antibiotics were given for urinary tract infection until the urinalysis results became negative. Data on adverse events including acute urinary retention, difficult urination, urinary tract infection and gross hematuria after BTX-A treatment were collected during follow-up examinations.

The primary endpoint was assessed for the improvement of urodynamics parameter, adverse events at three months after the initial treatment and the therapeutic duration, determined as the period between the treatment day and the day of recurrence of lower urinary tract symptoms of similar severity to those at baseline, was compared among the two groups. Secondary end points included urinary frequency, urgency and UUI episodes as assessed by voiding diary, and QoL assessed using IIQ-7 and UDI-6.The therapeutic duration, determined as the period between the treatment day and the day of recurrence of lower urinary tract symptoms of similar severity to those at baseline, was compared among the two groups. The results of the urodynamic studies at baseline and three months, as well as the treatment outcome, were compared among the two groups.

SPSS® was used to perform all statistical analyses. Statistical analysis was performed with the ANOVA test and Student's

t-test for comparing the differences between the botox doses and in each group compared to baseline respectively. A *P* value less than 0.05 was considered as statistically significant.

RESULTS

A total of 22 patients with refractory idiopathic overactive bladder in whom antimuscarinic treatment using toleterodine 4 mg/day or oxybutanine 15 mg/day during the previous three months had failed were recruited and completed this prospective randomized study. Eleven patients were enrolled to each arm of the study. There were no significant differences in demographic characteristics between the two groups. There were also no significant differences at baseline between the two groups with respect to voiding diary and UDI-6, IIQ-7 and urodynamic variables. Urodynamic assessment at the end of the third month showed significant improvement in urodynamic variables in both groups [Table 1]. We found a significant improvement in frequency, urgency and urinary incontinence compared to baseline using both 100u and 200u [Table 2]. There was no statistically significance in *urodynamic parameters* and in voiding diary between the two groups. Dysurea and urinary retention occur more with 200u botox injection [Table 3]. QOL was significantly improved in both groups with no statistically significant difference between the different doses [Figures 1 and 2].

The mean duration of efficacy, defined as the interval until symptoms which were greater than 50% of pretreatment baseline, was 6.3 months (range 5 to 9). However, four patients were symptom free until the end of our study, three of them received 200u and one patient received 100u.

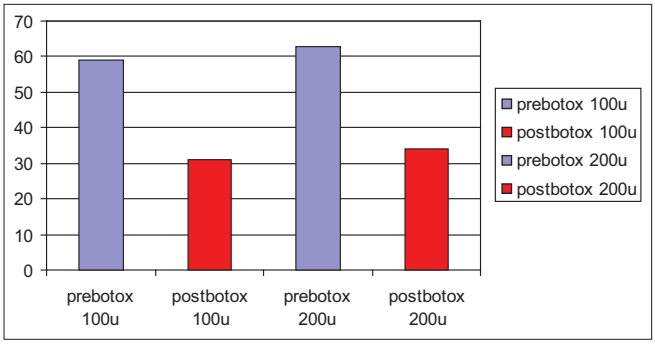

Figure 1: UDI-6

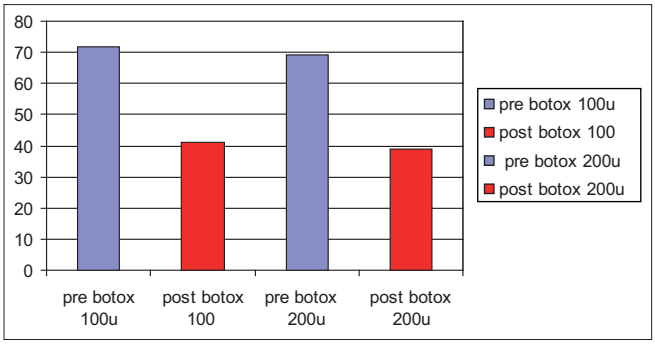

Figure 2: IIQ-7

DISCUSSION

There is now a reasonable amount of published information on the use of BTX-A in the treatment of idiopathic detrusor overactivity. The results suggesting that these patients benefit from BTX-A therapy, with improved continence, reduced

Table 1: Changes in urodynamic parameters in patients receiving 100u, 200u BTX-A injections

UDS	Botox 100u	Botox 200u	*P* value
Mean first sensation bladder filling ml±SD			0.35
Baseline	155±22	153±31	
Three months	188±27	175±12	
Mean MCC ml±SD:			0.70
Baseline	290±30	260±55	
Three months	361±47	392±39	
Mean cm H_2O detrusor pressure±SD			0.53
Baseline	29±11	26±8	
Three months	21±7	19±9	
Mean ml PVR ±SD			0.23
Baseline	33±11	28±9	
Three months	62±49	78±34	
Mean ml/s max flow rate ±SD			0.42
Baseline	14±7	12±8	
Three months	16±8	16±2	

SD: standard deviation, MCC: maximum cystometric capacity, PVR: post void residual

Table 2: Changes in voiding diary in patients receiving 100u, 200u BTX-A injections

symptoms	Botox 100u	Botox 200u	*P* value
Urgency			
Baseline	11.2	9.6	0.25
One month	4.6	3.9	0.07
Three months	3.9	3.2	0.06
Six months	3.3	2.9	0.1
Nine months	8.2	7	0.09
Urge incontinence			
Baseline	4.2	3.8	0.18
One month	2.3	2.6	0.34
Three months	3.7	3.9	0.23
Six months	3.2	3.6	0.4
Nine months	3.7	4.1	0.61
Frequency			
Baseline	15.7	14.2	0.56
One month	8.4	7.3	0.22
Three months	7.9	6.9	0.16
Six months	6.8	7.7	0.33
Nine months	12.4	11.9	0.66

Table 3: Adverse events in patients receiving 100U, 200U BTX-A

Adverse events	100u	200u
Dysuria	2	3
Acute urinary retention	1	2
Urinary tract infections	1	1
Gross hematuria	4	5

urinary frequency and improved quality of life in a high proportion of patients.

International Continence Society recommended that quality of life measures should be included in the lower urinary tract assessment of therapies.[14]

Recent preliminary results of a dose-finding study for botulinum toxin-A in patients with idiopathic overactive bladder of100 versus 150 units showed that 100 U BTX-A and 150 U BTX-A are equivalent in terms of symptom reduction and QOL improvement. [15]

In our study, QOL was significantly improved in both groups with no difference between the different doses. In contrast, quality of life improvement in idiopathic overactive bladder was documented in another study when BTX-A bladder injections at 200 U improved QoL in patients with OAB symptoms and IDO refractory to anticholinergics for at least 24 weeks. [16]

Interestingly, Shahid Khan *et al.* found significant improvement in QOL after BoNT/A injection, which was sustained and reproducible after repeat injections. [17]

With the mean duration efficacy of 6.3 months, our study proved the efficacy of BTX-A in the treatment of refractory overactive bladder. Patient received 200 U BTX-A had less number of urgency and frequency as compared to 100 U BTX-A; however, it was not statistically significant. A second urodynamic testing after six months would have been helpful to evaluate the differences in the duration of the BTX-A different doses.

Patients should be fully counseled on the risks of urinary retention and trained in intermittent catheterization before the procedure. Post-void residual assessment should be part of follow-up and patients should be warned of possible presentations.

BTX-A administration using the dose of 200u can cause significant increases in post void residual volume, that is more than150 ml in 38% of patients [12] or more than 200 ml in 43% of patients.[16]

In this study, only three patients developed acute urinary retention, two after 200u BTX-A and one after 100u BTX-A; they all required clean intermittent catheterization (CIC); however, we used 200cc as an indication for CIC and this might explain the lower rate of urinary retention.

The dosage of 100 u of BTX was chosen in this trial as the control since it has been the standard dose used in many previous studies and determined as a treatment of choice for idiopathic overactive bladder.[14,16-18] To our knowledge, this is the first prospective randomized study using 100u and 200u botox-A in the idiopathic overactive bladder population with comparison of voiding diary data, urodynamic data, and QOL data between patients.

Thirty nine patients were evaluated and after excluding the patients with high post void residual and recurrent UTI and bladder outlet obstruction, only 22 patients were included.

We can clearly say that our study was limited by the less number of patients and the short follow-up period. Placebo-arm would have been warranted in our trial; however, it was rejected by the ethical committee in our hospital.

CONCLUSION

BTX-A at 100u and 200u appears to improve symptoms, urodynamic parameters and QoL. Dose of 200u was insignificantly superior in decreasing urgency for three months. All other parameters show no superiority of 200u when compared to 100u of BTX. However at this time with the limited number of patients, we cannot give a definite conclusion concerning the superiority of one dose versus the other. There is an urgent need for a larger study looking for dose, volume, depth, number and location of injections.

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