Original Article

Time of onset and factors associated with delayed response post intradetrusor injection of onabotulinumtoxin a in patients with neurogenic and idiopathic overactive bladder syndrome

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Abstract

Objective: The objective of this study was to determine risk factors for delayed response in patients with neurogenic and idiopathic overactive bladder (OAB) after intradetrusor onabotulinumtoxin A injection.

Subjects and Methods: This is a retrospective study that included 87 patients who underwent onabotulinumtoxin A intradetrusor injection from October 2011 to November 2019. Patients were followed up at 2, 4, and 12 weeks post intervention in the outpatient clinic and over the phone. The data of patients with early response were compared with those with late response using univariate and multivariate analyses.

Results: The study included 87 patients. The mean age was 41 ± 15.3 standard deviation, and 69% of the participants were female. Fifty-one percent were diagnosed with neurogenic OAB. A median response time to onabotulinumtoxin A injection of 7 days was demonstrated, and patients who responded during the first 7 days post procedure were considered early responders. Independent predictors for late response include diabetes (Relative risk: 3.89, $P = 0.018$, and 95% confidence interval [CI]: 1.26–11.98), >1 BTX-A session (Relative risk: 4, $P = 0.011$, and 95% CI: 1.38–11.6), and wet OAB (RR: 9.94, $P = 0.002$, and 95% CI: 2.31–42.17).

Conclusions: The median time of onset post intradetrusor injection of onabotulinumtoxin A was found to be 7 days. Diabetes mellitus, wet OAB, and <1 Botox sessions were independent risk factors for late onset of response.

Keywords: Botulinum toxin, BTX-A, delayed response, risk factors

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INTRODUCTION

Onabotulinumtoxin A (Botox) has emerged as a treatment modality for patients with overactive bladder (OAB) syndrome.[1] According to the International Continence Society, OAB is defined as 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.[2]

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Another classification for OAB depends on the underlying cause, which can be either neurogenic OAB (N-OAB) or idiopathic OAB (I-OAB). Patients who do not have an obvious underlying cause are considered to have I-OAB.[3]

A stepwise approach in management is discussed with the patient prior to initiating treatment plan. Depending on the patient, conservative methods of management can be initiated with lifestyle changes as well as behavioral and physical therapy approaches. Second-line therapy for patients with OAB includes pharmacotherapy with anticholinergics and the beta-3 adrenoceptor agonist, Mirabegron.[4] However, only a few patients continued on medical treatment mainly due to their side effects.[5]

When conservative management fails, patients are considered eligible for more invasive treatment, including intradetrusor botulinum toxin injections.[4] This neurotoxin affects the motor and sensory pathways and inhibits the release of acetylcholine in the presynaptic nerve terminal.[6,7] The effect is reversible and lasts between 6 and 9 months.[8] BTX-A has been approved by the US Food and Drug Administration in 2011 for the treatment of N-OAB and in 2013 for refractory OAB. Sacral neuromodulation is another treatment option for selected patients refractory to the aforementioned therapies.[7]

Few studies have assessed the long-term outcome of BTX-A along with risk factors associated with its failure and side effects.[9,10] During our literature search, we were unable to identify the risk factors associated with delayed time of onset. It is essential to our clinical practice to predict which patients will be responding later than others for proper counseling and management. Therefore, this study was conducted to determine risk factors for delayed response in patients with N-OAB and I-OAB after BTX-A injection.

SUBJECTS AND METHODS

Study design

In this single-center, retrospective study, we reviewed clinical data of 101 patients who have undergone intradetrusor injection of onabotulinumtoxin A between October 2011 and November 2019 in Kuwait.

Subjects

The inclusion criteria were patients with confirmed diagnosis of either neurogenic or I-OAB, age ≥12 years, and failure of conservative methods and medical treatment for at least 6 weeks. Patients who were on regular clean intermittent catheterization (CIC) and still experienced OAB symptoms and leakage were included in the study. Patients with evidence of bladder outlet obstruction whether mechanical or functional and not on CIC, a postvoid residual (PVR) >100 ml, evidence of stress urinary incontinence as the predominant cause of urinary symptoms, or those who were lost to follow-up were not included in the study. Informed consent was obtained from all patients enrolled.

A renal profile, urine analysis, and cultures were ordered, and patients with UTI were treated prior to intervention. Patients in the study had an office-based flexible cystoscopy and urodynamic study prior to intervention. Interpretation and confirmation of the results were performed by the attending in charge. Wet type of OAB was diagnosed in patients who showed urinary leakage during uninhibited detrusor contractions.

Methods

Anticholinergic treatment was discontinued 14 days prior to intervention. All procedures were done by one urologist in an inpatient setting under anesthesia. After dilution, the toxin was injected into the detrusor muscle via cystoscopy in 20 different sites while avoiding the trigone and visible blood vessels. Patients with N-OAB were injected with 200 U of Botox, and 100 U was given to patients with I-OAB as recommended by the FDA. All patients had a urethral catheter inserted postoperatively, which was removed the next day, and the patient was then discharged once deemed fit.

Patients were followed up at 2, 4, and 12 weeks after intervention at the outpatient department and through phone calls. Further tests such as PVR and urine cultures were ordered according to assessment. Patients were asked to determine when they first noted improvement in either urgency or urge leakage. Although the average effect of BTX-A lasts from 6 to 9 months, some patients experienced longer results. Moreover, some patients with N-OAB required anticholinergic medications to augment the effect of the injections after reporting a decline in response.

RESULTS

Patients' characteristics

During the study period, 101 patients underwent intradetrusor injection of BTX-A. However, 87 patients were included in the study because 10 patients were lost to follow-up and 4 patients did not respond to treatment after 4 weeks of follow-up, and they opted for conservative management. These 14 patients were excluded from statistical analysis. The mean age for patients was 41 ± 15.3

standard deviation, and 68.9% (60/87) of the participants were female. N-OAB was diagnosed in 51.7% (45/87) of the participants as 1.14% had hydrocephalus, 3.44% reported previous back surgery, 12.64% were diagnosed with MS, 5.74% had spina bifida, 21.83% experienced spinal cord injury, and Parkinson's disease, disc prolapse, or an underlying central nervous system tumor was diagnosed in 2.29%, 1.14%, and 3.44%, respectively. The remaining patients did not have any underlying neurological disorder and were included under I-OAB category. Wet OAB was documented in 74.7% (65/87). Thirty-two patients were on CIC prior to intervention. None of the patients enrolled experienced major side effects after the procedure, namely UTI and urinary retention. Side effects of BTX-A injections included high PVR (≥100 ml) requiring CIC for <3 weeks in 3 patients, who showed symptoms of failure to empty, and mild hematuria in 3.4% (3/87) that resolved spontaneously.

Onset of response

The median time to response was 7 days (range = 9). Participants were divided into two groups: early and late responders, with early responders being those who had a decrease in urgency and urge leakage within 7 days or less. Table 1 summarizes the univariate analysis of risk factors for late onset of response. Using multivariate analysis, we have found that the relative risk of late response was 3.8 in diabetic patients, 4 after more than one BTX-A session, and 9.9 for patients with wet OAB [Table 2]. Onset of response did not differ significantly when comparing N-OAB to I-OAB.

Statistical analysis

Statistical analysis was performed using IBM SPSS® Software (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.). Both groups were compared using univariate analysis (Chi-square test, Fisher's exact test, or *t*-test as appropriate). Multivariate logistic regression analysis was performed for detection of independent risk factors. $P < 0.05$ was considered statistically significant.

DISCUSSION

To our knowledge, there are few studies in the literature addressing the time of onset of BTX-A injection in patients with N-OAB and I-OAB.[11-14] A systematic literature review regarding the efficacy of BTX-A injections in patients with N-OAB stated that the time of onset was between 1 and 2 weeks and maximum effect reached was between 4 and 6 weeks.[11] Unlike our study, most of the patients involved in this review received 300 U of BTX-A and it was injected in 30 sites. Another study included 100 patients with I-OAB who received 100 U of BTX-A, and it was noted that urgency completely disappeared in 72% of the patients between 1 and 2 weeks (mean 5 days).[12] Similar to this finding, a study that evaluated the first response to treatment in 35 patients with OAB reported a mean of 5.3 days. These patients received 300 U of BTX-A into 30 different sites and were followed up by quality-of-life questionnaires (IIQ-7 and UDI-6).[13] Kalsi *et al*. demonstrated an improvement in patients with neurogenic detrusor overactivity in terms of urgency, frequency, and nocturia 2 days post injection, and incontinence improved on the 3rd day. However, patients with idiopathic detrusor overactivity had improvement in all symptoms, except nocturia, on day 4.[14] It was noted that urgency was the earliest symptom to improve after BTX-A injection. This has been hypothesized by the anticholinergic

Table 1: Univariate analysis for risk factors of late response after onabotulinumtoxin A injection

Variable	Early response≤7 days (*n*=48), *n* (%)	Late response >7 days (*n*=39), *n* (%)	*P*
Gender			
Female	31 (51.7)	29 (48.3)	0.327
Male	17 (63)	10 (37)	
Smoking			
Yes	6 (46.2)	7 (53.8)	0.478
No	42 (56.8)	32 (43.2)	
Diabetes mellitus			
No	41 (64.1)	23 (35.9)	0.005
Yes	7 (30.4)	16 (69.6)	
OAB type			
Wet	29 (44.6)	36 (55.4)	0.001
Dry	19 (86.4)	3 (13.6)	
Diagnosis			
N-OAB	28 (62.2)	17 (37.8)	0.171
I-OAB	20 (47.6)	22 (52.4)	
Botox session			
1st session	34 (64.2)	19 (35.8)	0.036
>1 session	14 (41.2)	20 (58.8)	
Age (years), mean±SD	40.6±15.56	46±14.85	0.104

OAB: Overactive bladder, N-OAB: Neurogenic OAB, I-OAB: Idiopathic OAB

Table 2: Multivariate analysis for variables affecting time of onset

Variable	*P*	Relative risk	95% CI
Diabetes	0.018	3.89	1.26-11.98
Wet OAB	0.011	4	1.38-11.6
>1 session	0.002	9.94	2.31-42.71

OAB: Overactive bladder, CI: Confidence interval

effect of the toxin via the blockade of release of receptors, which are involved in bladder mechanosensation, hence the early disappearance of urgency was mainly due to its effect on bladder afferent pathways.[11,15] Another important aspect, which was not noted to be significant in our study, was the faster improvement in symptoms in patients with N-OAB when compared to those with I-OAB. This could be attributed to the higher dose of BTX-A (300 U vs. 200 U) in N-OAB patients.[14]

Our aim was to assess the time of subjective improvement in symptoms and factors associated with delayed response. Variables that were associated with a delayed onset for more than 7 days were found to be diabetes, wet OAB, and having undergone more than one session of BTX-A injections. According to our results, diabetes mellitus (DM) was an independent risk factor for delayed response. Different postulations explain the reason for delayed onset of improvement in diabetics. The pathophysiology of OAB caused by DM is multifactorial affecting the detrusor muscle, bladder innervation, extracellular matrix, and urothelial dysfunction.[16] Tanik *et al*. demonstrated a significant correlation between diabetic peripheral neuropathy and OAB. The explanation for this finding was the involvement of small fibers (A-gamma and C-fibers) in early diabetes as well as in OAB. Small fiber neuropathy increases smooth muscle contractions and detrusor overactivity.[16-18] Another hypothesis investigated by Chancellor *et al*. was the progression of compensated bladder function in early DM to decompensated function in late DM.[19] Detrusor hyperactivity with impaired contractility (DHIC) could occur during transition phase from OAB to underactive bladder in diabetics. BTX-A injections were found to be successful in patients with DHIC, however, these patients had a short-term improvement when compared to patients with OAB.[20] Higher glycosylated hemoglobin level was an important predictor of OAB symptoms. Furthermore, male patients with DM were more apt to experience pronounce OAB than controls.[21] Therefore, OAB in DM has been proven to be multifactorial in etiology, and BTX-A may not target all pathophysiological causes, hence the later onset of response in our patient group.

Wet OAB was also associated with a later time of onset. Baseline leakage episodes prior to treatment have been identified as a predictor of poor response following injection for I-OAB.[10] However, no available studies have identified its association with a late onset. On the other hand, Hsiao *et al*. assessed the therapeutic efficacy of BTX-A and found that wet OAB was a predictor of high therapeutic efficacy when compared to other variables on univariate analysis. This was attributed to the high correlation between urgency severity score and wet OAB.[22] The exact cause of this observation is yet to be determined by future studies.

Finally, as regards delayed time of onset in patients with more than one session, it has been shown that repeat injections had a constant effect on urodynamic and clinical parameters in patients with neurogenic detrusor overactivity.[15] Khan *et al*. showed improvement in quality of life after repeat injections in patients with idiopathic detrusor overactivity.[23] However, none of the studies found an association between time of onset and repeated sessions. We hypothesize that this may be secondary to the bladder being habituated to the toxin, hence taking more time to exert the effect, or this could be merely a subjective response.

The first limitation of our study is the retrospective design. Another important caveat is that it is subject to recall bias. Moreover, the lack of use of a standardized questionnaire when assessing patient symptoms is another limitation, which was mainly due to the unavailability of a verified Arabic questionnaire for OAB symptoms at the time of assessment.

CONCLUSIONS

The median time of onset after intradetrusor injection of BTX-A was found to be 7 days. Diabetes mellitus, wet OAB, as well as undergoing more than one BTX-A session were independent predictors for late onset of effect.

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Conflicts of interest

There are no conflicts of interest.

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