Original Article

The effect of spinal cord-injury level on the outcome of neurogenic bladder treatment using OnabotulinumtoxinA

Waleed Al Taweel, Khalil Mohammed Alzyoud[1]

Department of Urology, King Faisal Specialist Hospital and Research Centre, Alfiasal University, Riyadh 11211, [1]Department of Nursing, Prince Sultan Humanitarian City, Riyadh, Saudi Arabia

Abstract

Aim: The aim was to report the effectiveness and safety OnabotulinumtoxinA (Botox, Allergan, Inc., Irvine, CA, USA) intradetrusor injections in spinal cord-injured (SCI) patients with refractory neurogenic detrusor overactivity. And to assess the result based on SCI level.

Materials and Methods: We reviewed the chart of 103 patients with neurogenic bladder secondary to SCI at the rehab center who received OnabotulinumtoxinA in our Neurourology Department for treatment of lower urinary tract symptoms between January 2007 and December 2013. All patients had a clinical examination, urinalysis, and an urodynamic study at baseline and 3 months after treatment as well as a visual analogue scale (VAS; range scale: 0–10) and a bladder diary checked for 3 days. 300 IU of OnabotulinumtoxinA, detrusor muscle injections were performed in 30 sites under cystoscopic guidance. Outcome measures included frequency of urge urinary incontinence collected by bladder diaries; changes in urodynamic parameters such as maximum cystometric bladder capacity, reflex volume, maximum detrusor pressure; side-effects; antimuscarinic drug consumption and quality of life (QOL) measured with VAS.

Results: The study includes 32 female and 71 male with a mean patient age of 29 years (range: 18–56 year). The effect of Botox injection on bladder function was observed within 1–2 week after treatment. The urodynamic parameters were improved significantly after treatment compared with baseline values. There were significant reductions in the frequencies of incontinence episodes after treatment as seen in the voiding diary. A significant improvement in patient satisfaction was found after treatment which was expressed on the VAS assessment, with an improvement of the mean of 3 points. Patients with thoracic and lumbar injury have better result compare to cervical injury patients. The earliest recurrence of clinical symptoms was at 10 weeks. Overall, the mean duration of symptomatic improvement was 8 (2.5–21) months.

Conclusion: Intradetrusor onabotulinumtoxinA injections are an effective and well-tolerated treatment for neurogenic overactive bladder that will increase patient satisfaction and improve QOL with persisted clinical efficacy for more than 8 months.

Key Words: Neurogenic bladder, OnabotulinumtoxinA, overactive, spinal cord-injury

Address for correspondence:
Dr. Waleed Al Taweel, 3353 mbc 83 11211 Riyadh, Riyadh-Saudi Arabia E-mail: drwt1@hotmail.com
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INTRODUCTION

Neurogenic bladder (NB) secondary to spinal cord-injury (SCI) usually associated with symptoms of neurogenic detrusor overactivity (NDO) which include urinary frequency, urgency, and urgency urinary incontinence or urinary incontinence episodes that are not associated with urgency or any other sensation related to bladder filling. NDO usually

impair the quality of life (QOL) and upper urinary tract function.

According to the International Continence Society (ICS), NDO is an urodynamic observation when their underlying neurological condition, characterized by involuntary detrusor contractions during the filling phases that may be spontaneous or provoked.[1]

Antimuscarinics improve bladder compliance, reduce symptoms, prevent upper urinary tract damage and improve QOL. However, treatment with anticholinergic medications may associate with unwanted side-effects and poor compliance.[2-3]

Botulinum toxin inhibit acetylcholine neurotransmitter release by cleaving the snare protein SNAP-25, preventing docking and fusion of vesicles with the nerve terminal resulting in muscle relaxation,[4,5] However it has been found to inhibit the release of a number of neurotransmitters (including acetylcholine, adenosine triphosphate, and neuropeptides such as substance P) and to down-regulate the expression of purinergic and capsaicin receptors on afferent neurons within the bladder.[6]

The detrusor injection of BTX-A in adults with NDO and urinary incontinence who have failed antimuscarinic therapy has beneficial effects both on clinical and urodynamic variables.

Schurch was first to report the effect of injecting BTX-A into the detrusor muscle of patients with NDO.[7] this was followed by numerous studies confirming the benefit of BTXA on NDO.[8-20]

The aim of the study is to report the effectiveness and safety of OnabotulinumtoxinA (Botox, Allergan, Inc., Irvine, CA, USA) intradetrusor injections in SCI patients with refractory NDO.

MATERIALS AND METHODS

After receiving approval from the local Ethics Committee we reviewed the chart of 103 patients with NB secondary to SCI at the rehab center who received OnabotulinumtoxinA in our Neurology Department for treatment of lower urinary tract symptoms between January 2007 and December 2010. Patients were refractory to at least 2 antimuscarinic agents, each ingested for >2 month; All patients had a clinical examination, urinalysis at 3,6,12 months and a urodynamics study at baseline and 3 months after treatment as well as a visual analogue scale (VAS; range scale: 0–10) and a bladder diary checked for 3 days. Clean intermittent catheterization was also performed by all patients before the injection, but they suffered incontinence between catheterizations. All eligible patients provided written informed consent before entering the treatment program. Urodynamic assessments before treatment and 3 months after injections were performed according to the "Good Urodynamic Practice" recommended by the International Continence Society.[21]

Under sedation, we used 300 IU of OnabotulinumtoxinA, detrusor muscle injections were performed in 30 sites under cystoscopic guidance, trigone and bladder neck sparing. Botox was diluted in 30 ml 0.9% NaCl and 1 ml of solution were injected for each site.

Patients were asked to gradually reduce antimuscarinic medication from the Ist week until the complete suspension of the drugs.

Outcome measures included frequency of urge urinary incontinence collected by bladder diaries; changes in urodynamic parameters such as maximum cystometric bladder capacity (MCBC), reflex volume (RV), maximum detrusor pressure; side-effects; antimuscarinic drug consumption and QOL measured with VAS.

Statistical analysis

Statistical analysis was performed with the ANOVA test to compare the change in urodynamic parameters. The *t*-test was also used to compare the changes in the VAS score and the bladder diary after injection. For descriptive purposes, mean and standard deviation (SD) were calculated.

A probability value of $P < 0.05$ was considered statistically significant. The data were analyzed using the SPSS version 14.

RESULTS

In all, 103 patients with drug-resistant NDO and SCI were treated with OnabotulinumtoxinA injection; the patient characteristics are shown in Table 1. Twenty-one of 103 who had an SCI above T5, ASIA A-B, presented a clinically significant autonomic dysreflexia due to neurologic bladder dysfunction. In all patients, the dysreflexia disappeared within 5 days after injection except in one patient.

The study includes 32 female and 71 male with a mean patient age of 29 years (range: 18–56 year). The effect of Botox injection on bladder function was observed within 1–2 week after treatment.

Table 1: Patient's characteristics at baseline

Characteristic	Value
Total number	103
Mean Age (range)	29 (18-56)
Female/male	32/71
Level of injury	
Cervical	10
Thoracic	42
Lumbar	51

The changes in urodynamic parameters (MCBC, RV, and BC) are shown in Table 1. All variables improved significantly after treatment compared with baseline values (ANOVA test, $P < 0.001$).

No significant differences between male and female in urodynamic parameters. ANOVA with Tukey's *post-hoc* test revealed significant differences between the cervical and the other SCI levels, where patient with thoracic and lumbar injury have better result compare to cervical injury patients.

There were significant reductions in the frequencies of incontinence episodes after treatment as seen in the voiding diary. A significant improvement in patient satisfaction was found after treatment which was expressed on the VAS assessment, with an improvement of the mean of 3 points. Before OnabotulinumtoxinA injection, 89 patients used anticholinergic medications. The ranges of the daily doses were oxybutynin 10–30 mg, tolterodine 4–8 mg, and fourteen patients used no drugs. After OnabotulinumtoxinA injection, 55 of these patients remained without anticholinergics. Another twenty patients reduced their daily requirements: Twelve are taking a quarter of their preoperative dose; eight, a half, and fourteen remained on the same dose levels.

Fourteen of 103 patients showed poor clinical improvement (nonresponders). We did not observe any hyposthenia, but we observed mild hematuria in 20 patients and urinary tract infections in 15 patients.

The earliest recurrence of clinical symptoms was at 10 weeks. Overall, the mean duration of symptomatic improvement was 8 (2.5–21) months. There was sustained symptomatic improvement for ≥12 months (mean 14.5 months) in 15 patients [Tables 2, 3, Figures 1 and 2].

Table 2: Urodynamic parameters before and after treatment

Baseline	Before treatment	After treatment	*P*
MCBC			
Mean	223.3 cc	331.5 cc	<0.001
SD	63.6	93.5	
Range	120-360 cc	130-500 cc	
RV			
Mean	178.2 cc	285.2 cc	<0.001
SD	56	87	
Range	50-300 cc	100-450 cc	
MDP			
Mean	31.2 CmH_2O	20.8 CmH_2O	<0.001
SD	8.7	7.3	
Range	14-50 CmH_2O	10-45 CmH_2O	

MCBC: Maximum cystometric bladder capacity, RV: Reflex volume, MDP: Maximum detrusor pressure, SD: Standard deviation

Table 3: Mean urodynamic parameters based on SCI level

Baseline	Before treatment	After treatment	*P*
Cervical			
MCBC	180 cc	217cc	0.07
RV	150 cc	192cc	0.04
MDP	38 CmH_2O	36 CmH_2O	0.3
Thoracic			
MCBC	236 cc	328 cc	<0.001
RV	194 cc	282 cc	<0.001
MDP	33.5 CmH_2O	24 CmH_2O	<0.001
Lumbar			
MCBC	220 cc	353cc	<0.001
RV	169cc	303cc	<0.001
MDP	28 CmH_2O	15 CmH_2O	<0.001

MCBC: Maximum cystometric bladder capacity, RV: Reflex volume, MDP: Maximum detrusor pressure, SD: Standard deviation, SCI: Spinal cord-injured

DISCUSSION

The main goals of treatment for NDO are to protect the upper urinary tract by decreasing bladder pressure, reducing incontinence, and improving QOL.

In addition to significant improvement in the urodynamics bladder capacity and detrusor pressure, voiding diary showed reductions in the frequencies of incontinence episodes. The efficacy results observed in this study are consistent with previous onabotulinumtoxinA studies were within 2 weeks a significant improvement in urgency incontinence episodes was observed, most of which used 300 U.[22-24]

Treatment-related adverse events are few. Most frequent adverse events were localized urologic events (hematuria and UTI). Recurrent urinary tract infections are a significant problem in all patients with NB leading to high morbidity, poor QOL.[25,26] In the current study, 14% of noncomplicated UTI was reported which is within the range of previously reported incidence (2–32%).[8] As previously reported, these results indicate that antibiotic prophylaxis for intradetrusor OnabotulinumtoxinA injections seems necessary.[27]

Patients with Cervical injury have less favorable urodynamic results compared to thoracic and lumber SCI patients, however

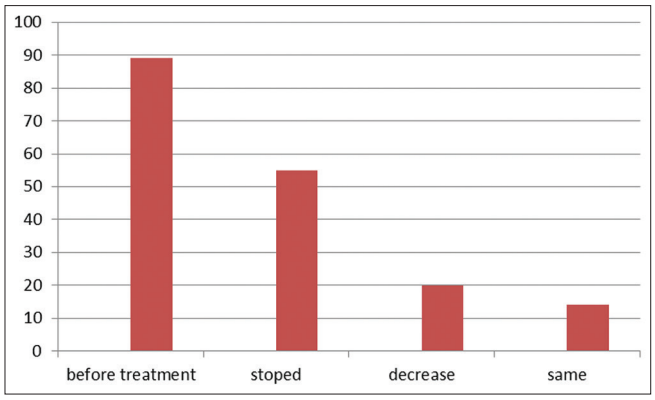

Figure 1: The change in intake of anticholinergic medication in patients after the first OnabotulinumtoxinA injection

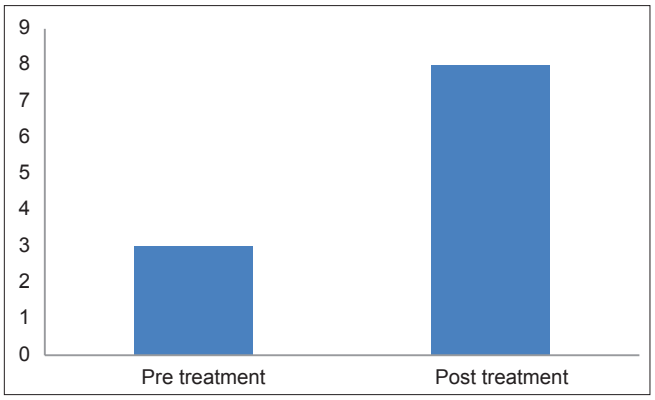

Figure 2: Visual analogue scale

we have small number of patients in this group (10) as compared to thoracic and lumbar SCI patients.

The present study limitation related to the use of concurrent antimuscarinics in some patients.

The current study has shown similar result to Ehren *et al.* with a significant reduction in the need for antimuscarinic therapy after botulinum toxin injections.[28]

The mean duration of symptomatic improvement in the current study was 8 months; however Herschorn *et al.* showed the urodynamic effects were only significant up to 6 months and the median time to request for re-treatment was 9 months.[23]

Significant reductions in weekly UI frequency with OnabotulinumtoxinA were evident within 1–2 week. Several other open-label studies confirmed that these improvements were significant versus baseline at the first assessment after 2 week[15] or even within the 1st week with maximum effects obtained between 1 and 4 week.[16]

The effect is not only reflected in urodynamic studies but also in the subjective patient satisfaction, which was expressed on the VAS assessment. Several studies have shown an improvement in patient satisfaction when compared with baseline.[13,29]

Recently Chancellor *et al.* provides Class I evidence that OnabotulinumtoxinA intradetrusor injections (200 or 300 U) can improve QOL measures in patients with NDO not adequately managed with anticholinergic therapy.[30]

CONCLUSION

Intradetrusor OnabotulinumtoxinA injections are an effective and well tolerated treatment for NDO. It increase patient satisfaction and improve QOL with persisted clinical efficacy for more than 8 months. The effect might be less favorable in cervical SCI patients when compared to thoracic and lumbar SCI patients, however a larger study is required to confirm it.

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