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

Waleed Al Taweel, Khalil Mohammed Alzyoud¹

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

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 1\(^{st}\) 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.

| Characteristic      | Value      |
|---------------------|------------|
| Total number        | 103        |
| Mean Age (range)    | 29 (18-56) |
| Female/male         | 32/71      |
| Level of injury     | Lumbar     |
|                     | Cervical   |
|                     | Thoracic   |
| Lumbar              | 10         |
| Lumbar              | 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, 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 hypoesthesia, 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 \( \geq 12 \) months (mean 14.5 months) in 15 patients [Tables 2, 3, Figures 1 and 2].

**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]

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.

### Table 2: Urodynamic parameters before and after treatment

| Parameter | 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\(_2\)O | 20.8 CmH\(_2\)O |                | <0.001 |
| SD        | 8.7       | 7.3              |                |   |
| Range     | 14-50 CmH\(_2\)O | 10-45 CmH\(_2\)O |                |   |

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

### Table 3: Mean urodynamic parameters based on SCI level

| Level     | Baseline  | Before treatment | After treatment | \( P \) |
|-----------|-----------|------------------|----------------|---|
| Cervical  |            |                  |                |   |
| MCBC      | 180 cc    | 217 cc           |                | 0.07 |
| RV        | 150 cc    | 192 cc           |                | 0.04 |
| MDP       | 38 CmH\(_2\)O | 36 CmH\(_2\)O |                | 0.3  |
| Thoracic  |            |                  |                |   |
| MCBC      | 236 cc    | 328 cc           |                | <0.001 |
| RV        | 194 cc    | 282 cc           |                | <0.001 |
| MDP       | 33.5 CmH\(_2\)O | 24 CmH\(_2\)O |                | <0.001 |
| Lumbar    |            |                  |                |   |
| MCBC      | 220 cc    | 353 cc           |                | <0.001 |
| RV        | 169 cc    | 303 cc           |                | <0.001 |
| MDP       | 28 CmH\(_2\)O | 15 CmH\(_2\)O |                | <0.001 |

**MCBC:** Maximum cystometric bladder capacity, **RV:** Reflex volume, **MDP:** Maximum detrusor pressure, **SD:** Standard deviation, **SCI:** Spinal cord-injured
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 1\(^{st}\) 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 Visual analogue scale (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 persistent 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.

**REFERENCES**

1. Abrams P, Cardozo L, Fall M, Griffiths D, Rosier P, Ulmsten U, et al. The standardisation of terminology in lower urinary tract function: Report from the standardisation sub-committee of the International Continence Society. Urology 2003;61:37-49
2. Yu YF, Nichol MB, Yu AP, Ahn J. Persistence and adherence of medications for chronic overactive bladder/urinary incontinence in the californiap medicaid program. Value Health 2005;8:495-505.
3. Chapple CR, Khullar V, Gabriel Z, Monson D, Bitoun CE, Weinstein D. The effects of antimuscarinic treatments in overactive bladder: An update of a systematic review and meta-analysis. Eur Urol 2008;54:543-62.
4. van Ermengem E. A new anaerobic bacillus and its relations with the botulism. Zeitsch Hyg Infekt 1897;26:1-56.
5. Montecucco C, Schiavo G. Structure and function of tetanus and botulinum neurotoxins. Q Rev Biophys 1995;28:423-72.
6. Chapple C, Patel A. Botulinum toxin – New mechanisms, new therapeutic directions? Eur Urol 2006;49:606-8.
7. Stohrer M, Schurch B, Kramer G, Schmid D, Gaul D, Hauri D. Botulinum A toxin in the treatment of detrusor overactivity in spinal cord injury: A new alternative to medical and surgical procedures? Neurourol Urodyn 1999;18:401-2.
8. Karsenty G, Denys P, Amarenco G, De Seze M, Gamé 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.
9. Giannantoni A, Meaniri E, Di Stasi SM, Costantini E, Zucchi A, Meaniri L, et al. New therapeutic options for refractory neurogenic detrusor overactivity. Minerva Urol Nefrol 2004;56:79-87.
10. Reitz A, Stöhrer M, Kramer G, Del Popolo G, Chartier-Kastler E, Pannek J, et al. European experience of 200 cases treated with botulinum-A toxin injections into the detrusor muscle for urinary incontinence due to neurogenic detrusor overactivity. Eur Urol 2004;45:510-5.
11. Karsenty G, Reitz A, Lindemann G, Boy S, Schurch B. Persistence of therapeutic effect after repeated injections of botulinum toxin type A to treat incontinence due to neurogenic detrusor overactivity. Urology 2006;68:1193-7.
12. Schulte-Baukloh H, Schobert J, Stolze T, Stürzebecher B, Weiss C, Knispel HH. Efficacy of botulinum-A toxin bladder injections for the treatment of neurogenic detrusor overactivity in multiple sclerosis patients: An objective and subjective analysis. Neurourol Urodyn 2006;25:110-5.
13. Kalsi V, Apostolidis A, Popat R, Gonzales G, Fowler CJ, Dasgupta P. Quality of life changes in patients with neurogenic versus idiopathic detrusor overactivity after intradetrusor injections of botulinum neurotoxin type A and correlations with lower urinary tract symptoms and urodynamic changes. Eur Urol 2006;49:528-35.
14. Giannantoni A, Di Stasi SM, Nardicchi V, Zucchi A, Macchioni L, Bini V,

![Figure 1: The change in intake of anticholinergic medication in patients after the first OnabotulinumtoxinA injection](image1.png)

![Figure 2: Visual analogue scale](image2.png)
et al. Botulinum-A-toxin injections into the detrusor muscle decrease nerve growth factor bladder tissue levels in patients with neurogenic detrusor overactivity. J Urol 2006;175:2341-4.

15. Kuo HC. Therapeutic effects of suburothelial injection of botulinum a toxin for neurogenic detrusor overactivity due to chronic cerebrovascular accident and spinal cord lesions. Urology 2006;67:232-6.

16. Smith CP, Nishiguchi J, O’Leary M, Yoshimura N, Chancellor MB. Single-institution experience in 110 patients with botulinum toxin A injection intobladder or urethra. Urology 2005;65:37-41.

17. Hajebrahimi S, Altaweel W, Cadoret J, Cohen E, Corcos J. Efficacy of botulinum-A-toxin in adults with neurogenic overactive bladder: Initial results. Can J Urol 2005;12:2543-6.

18. Gaillet S, Bardot P, Bernuz B, Boissier R, Lenne-Aurier K, Thiry-Escudier L, et al. Five years follow-up study and failures analysis of Botulinum toxin repeated injections to treat neurogenic detrusor overactivity. Prog Urol 2012;22:1064-70.

19. Sussman D, Patel V, Del Popolo G, Lam W, Globe D, Pommerville P. Treatment satisfaction and improvement in health-related quality of life with onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity. Neurol Urodyn 2013;32:242-9.

20. Krhut J, Samal V, Nemec D, Zvara P. Intradetrusor versus suburothelial onabotulinumtoxinA injections for neurogenic detrusor overactivity: A pilot study. Spinal Cord 2012;50:904-7.

21. Schäfer W, Abrams P, Liao L, Mattiasson A, Pesce F, Spangberg A, et al. Good urodynamic practices: Uroflowmetry, filling cystometry, and pressure-flow studies. Neurol Urodyn 2002;18:261-74.

22. Wefer B, Ehiken B, Bremer J, Burgdörfer H, Domurath B, Hampel C, et al. Treatment outcomes and resource use of patients with neurogenic detrusor overactivity receiving botulinum toxin A (BOTOX) therapy in Germany. World J Urol 2010;28:385-90.

23. Herschorn S, Gajewski J, Ethans K, Corcos J, Carlson K, Bailly G, et al. Efficacy of botulinum toxin A injection for neurogenic detrusor overactivity and urinary incontinence: A randomized, double-blind trial. J Urol 2011;185:2229-35.

24. Cruz F, Herschorn S, Aliotta P, Brin M, Thompson C, Lam W, 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;60:742-50.

25. Bakke A, Vollset SE. Risk factors for bacteriuria and clinical urinary tract infection in patients treated with clean intermittent catheterization. J Urol 1993;149:527-31.

26. Sauerwein D. Urinary tract infection in patients with neurogenic bladder dysfunction. Int J Antimicrob Agents 2002;19:592-7.

27. Mouttalib S, Khan S, Castel-Lacanal E, Guilloreau J, De Boissezon X, Malavaud B, et al. Risk of urinary tract infection after detrusorbotulinum toxin A injections for refractory neurogenic detrusor overactivity in patients with no antibiotic treatment. BJU Int 2010;106:1677-80.

28. Ehren I, Volz D, Farrelly E, Berglund L, Brundin L, Hultling C, et al. Efficacy and impact of botulinum toxin A on quality of life in patients with neurogenic detrusor overactivity: A randomised, placebo-controlled, double-blind study. Scand J Urol Nephrol 2007;41:335-40.

29. Schurch B, de Séze M, Denys P, Chartier-Kastler E, Haab F, Everaert K, et al. Botulinum toxin type a is a safe and effective treatment for neurogenic urinary incontinence: Results of a single treatment, randomized, placebo controlled 6-month study. J Urol 2005;174:196-200.

30. Chancellor MB, Patel V, Leng WW, Shenot PJ, Lam W, Globe DR, et al. OnabotulinumtoxinA improves quality of life in patients with neurogenic detrusor overactivity. Neurology 2013;81:841-8.

How to cite this article: Al Taweel W, Alzyoud KM. The effect of spinal cord-injury level on the outcome of neurogenic bladder treatment using OnabotulinumtoxinA. Urol Ann 2015;7:320-4.

Source of Support: Nil, Conflict of Interest: None.