

Effect of Intravesical Botulinum Neurotoxin-A Injection on Detrusor Hyperreflexia in Spinal Cord Injured Patients

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Key words

- neurogenic detrusor hyperreflexia
- botulinum toxin A
- spinal cord injuries
- urodynamics
- voiding

Abstract



Purpose: To evaluate the effects of Botulinum Toxin A injection into the detrusor muscle on various voiding parameters in spinal cord injured patients with neurogenic detrusor hyperreflexia.

Materials and methods: 24 patients with spinal cord injuries who had detrusor overactivity and urinary incontinence and were refractory to oral medications, were injected 300 IU of BTX-A into the detrusor muscle. The pre-and post-treatment evaluations included determination of bladder urinary continence status, frequency/volume chart of CIC, Incontinence Quality of Life questionnaire (I-QOL) and patient satisfaction. The urodynamic parameters measured included maximum cystometric capacity (MCC), reflex detrusor volume (RDV) and maximum detrusor pressure during bladder contraction (MDP) were

analyzed at the outset and during the follow-up (2, 6, and 24 weeks) examinations.

Results: The evaluation of urodynamic parameters during follow-up examinations (2, 6 and 24 weeks) revealed significant increase in mean reflex volume ($p < 0.05$) and cystometric capacity ($p < 0.05$), on the other detrusor pressure decreased significantly ($p < 0.05$). In majority of patients there was considerable reduction in incontinence episodes and no complications or side effects were reported. Most of the patients were satisfied with the treatment.

Conclusion: The use of Botulinum toxin type A for treatment of neurogenic detrusor overactivity in spinal cord injured patients is safe and efficacious. In our 24-week study period, there was significant improvement in most urodynamic parameters with consistence and subjective satisfaction indicated by the treated patients.

received 09.05.2014

accepted 10.06.2014

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DOI <http://dx.doi.org/10.1055/s-0034-1383573>
Published online:
October 28, 2014
Drug Res 2015;
65: 327–331
© Georg Thieme Verlag KG
Stuttgart · New York
ISSN 2194-9379

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Introduction



Annually there are up to 40 cases per million people of spinal cord injury (SCI) resulting from a range of traumatic and non-traumatic incidents [1]. Neurogenic detrusor hyperreflexia (NDH) is a well-known clinical emergency which appears in 96% of patients with spinal cord injuries [2]. Successful control of (NDH) in spinal cord-injured patients is a major challenge for urologists. Therefore, the primary goal of bladder management is to preserve kidney functions by attaining safe bladder pressures, in addition to achieve acceptable social continence and low urinary tract infection. Spinal cord injuries induce neurogenic detrusor hyperreflexia and simultaneous detrusor sphincter dyssynergia that reduces the storage and emptying functions of the urinary bladder. Anticholinergic medications combined with clean intermittent catheterization (CIC) is

the first line “gold standard” treatment for NDH. However, due to the high incidence of side effect related to their systemic actions, the long-term use of anticholinergic medication and intermittent catheterization is restricted.

Botulinum toxin (BTX), first described by van Ermengem as “sausage poison” in 1895, is probably most potent occurring natural biological toxin that can affect humans [3]. Botulinum toxin was first isolated by Emile Van Ermengem in 1987, from the bacterium *Clostridium botulinum* [3]. Out of the 7 immunologically distinct but structurally similar types of botulinum toxins, types A and B have been used with clinically beneficial effects in various neuromuscular disorders and are commercially available. Botulinum toxin primarily effects on the release of acetylcholine from nerve ending and inhibits parasympathetic neural transmission into the detrusor muscle [4,5]. Initially, clinical trials of botulinum toxin A (BTX-A) started with treatment of bladder overactivity resulting from neurological insult in

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Table 1 Basic demographic data of the patients with spinal cord injury.

Characteristics	Value
Total number of patients	24
Age in years, mean (SD)	42.6 (12.4)
Gender, men/women, n (%)	19 (80%)/5 (20%)
ASIA scale, n (%)	
Grade A	13 (54)
Grade B	3 (12.5)
Grade C	5 (21)
Grade D	3 (12.5)
Injury level, n (%)	
Cervical	14 (58)
Lumbar	6 (25)
Thoracic	4 (17)

SD: standard deviation; ASIA: American Spinal Injury Association [11]

2000. This therapy is a minimally invasive treatment option positioned between oral anticholinergic treatment that was ineffective or not tolerated and invasive surgery [6]. The rapid expansion in the use of BTX-A to treat overactive bladder is due, in large part, to the inadequacy of current standard pharmacologic treatment (i.e., antimuscarinic agents) as well as to the demonstration of the efficacy, and tolerability of BTX in early clinical series. The safety and efficacy have been confirmed in a randomized placebo-controlled study by Schurch et al. [7] and in the local administration of BTX-A into the bladder by Reitz et al. [8], Schurch et al. [6] and Stohrer et al. [9]. The safety profile seen in these studies suggests that this a promising treatment for the management of neurogenic urinary incontinence.

Many studies have appraised the use of botulinum toxin type A injections into the detrusor muscle of SCI patients in order to increase bladder capacity, reduce neurogenic detrusor hyperreflexia, and reduce urge incontinence [6, 7, 10]. In the current study, we have observed differing clinical responses following use of this drug, despite improvement in most urodynamic parameters. In this study, we present the results of the effect of injecting botulinum toxin type A into the detrusor muscle on various voiding parameters for spinal cord injured patients with NDH in China.

Subjects and Methods



Selection of subjects

A total of 24 study subjects with spinal cord injuries (SCI) were admitted in the study which extended from January 2012 to February 2014, the basic demographic data of whose is presented in **Table 1**. Inclusion criteria included detrusor hyperreflexia (DH) and urinary incontinence that proved difficult to treat, despite upon the use of 2 different anticholinergics at maximal doses, patients having intolerable side effects from anticholinergic therapy (e.g., dry mouth, constipation) and patients with poorly compliant bladders. Exclusion criteria included patients with hydronephrosis or renal disease, coagulopathy disease, myasthenia gravis, aminoglycoside treatment, hypersensitivity to BTX-A, previous sphincterotomy, and patients who were unable to perform clean intermittent catheterization. The study was approved by the ethics committee of Jinling Hospital, Southern Medical University. Each patient was fully informed about the procedure and written consent was obtained before the treatment.

Pre-treatment assessment

Patient evaluations included a complete medical history, physical examination, a 3-day voiding diary, a video urodynamic studies, upper tract evaluation, plain abdominal radiograph, an urodynamics assessment 2 week prior to the treatment and a day zero baseline assessment (Multichannel urodynamics studies – Medtronic Duet systems, version 8.20, Minneapolis, MN, USA) before intravesical botulinum neurotoxin A injection. The urodynamic parameters measured included maximum cystometric capacity (MCC), reflex detrusor volume (RDV) and maximum detrusor pressure during bladder contraction (MDP). The standard International Continence Society definitions were used at the time of protocol writing [12]. Reflex volume is the infused volume that induces the first detrusor contraction. Bladder compliance is calculated by the change in volume divided by the change in detrusor pressure. The patients received BTX-A injections in conjunction with clean intermittent catheterization (CIC) to treat detrusor hyperreflexia (DH) and urinary incontinence. DH was diagnosed urodynamically. Incontinence was defined as any episode of urinary voiding between 2 CICs and was quantified with an absorbent pad.

Treatment

All procedures were done on an outpatient basis in the operating room using general anesthesia and vital sign monitoring equipment was set up. Perioperative antibiotics were administered orally for 7 days, according to urine culture, and the botulinum toxin A injection performed on the fifth day of drug administration. Clostridium botulinum toxin type A (commercial grade onabotulinum toxin A, Botox®, Allergan) [13] was diluted in 0.9% preservative-free saline to a final concentration of 10 IU/ml. Shaking of the vial was prevented because this may break the disulfide linkage between the light and heavy chains, rendering the toxin ineffective [13]. Using flexible cystoscope, an ultrafine 4 mm needle (Dasgupta technique) which is less invasive, a total maximal dose of 300 IU (dilution: 10 IU/mL) was injected at 30 detrusor muscle sites in approximately equal aliquots except the trigone as described by Schurch et al. [6]. The sparing of trigone from injection was based on a few facts, including a desire to avoid inducing reflux to the upper tract. Moreover, the injection of the dense trigone innervation from both sensory, adrenergic and non-cholinergic pathways might complicate the efficacy analysis of a cholinergic blockade. No patients were administered with repeated/augmentation doses during the period of study. Patients were instructed to progressively taper and then discontinue their anticholinergic medications within the first week following the procedures.

Post treatment follow-up

A clinical and urodynamic follow-up was obtained and visits occurred at 2, 6, 12, 18 and 24 weeks after treatment and compared to the baseline values. The voiding characteristics were measured and recorded at 2, 6, 12, 18 and 24 weeks and the urodynamic parameters were measured and recorded at 2, 6, and 24 weeks. The urodynamic parameters measured included maximum cystometric capacity (MCC), reflex detrusor volume (RDV) and maximum detrusor pressure during bladder contraction (MDP). Subsequently, the patients returned to our practice if urinary losses reoccurred. All patients were asked to complete a 22-item, domain-specific, validated Incontinence Quality of Life Questionnaire (I-QOL) [10] before and 2 weeks after the injections that detected changes in the self-perceived severity of

Table 2 Results of characteristics from 3-day voiding diary.

Timeline	Baseline	2 weeks	6 weeks	12 weeks	18 weeks	24 weeks
Involuntary urine loss frequency	2.8 (1.55)	1.3 (1.41) P=0.017(S)	1.2 (1.36) P=0.015 (S)	1.2 (1.66) P=0.015 (S)	1.2 (1.39) P=0.016 (S)	1.4 (1.52) P=0.02 (S)
Catheterization frequency	4.7 (1.62)	0.1 (0.76) P=0.0017 (S)	0.1 (0.65) P=0.0019 (S)	0.1 (0.71) P=0.0017 (S)	0.3 (0.78) P=0.008 (S)	0.2 (0.76) P=0.006 (S)
Percentage of patients completely dry over 24 h	0 (0%)	18/22 (82%)	16/21 (76%)	17/22 (77%)	15/20 (68%)	13/22 (59%)

S=Statistically Significant by ANNOVA @ 5% level of significance

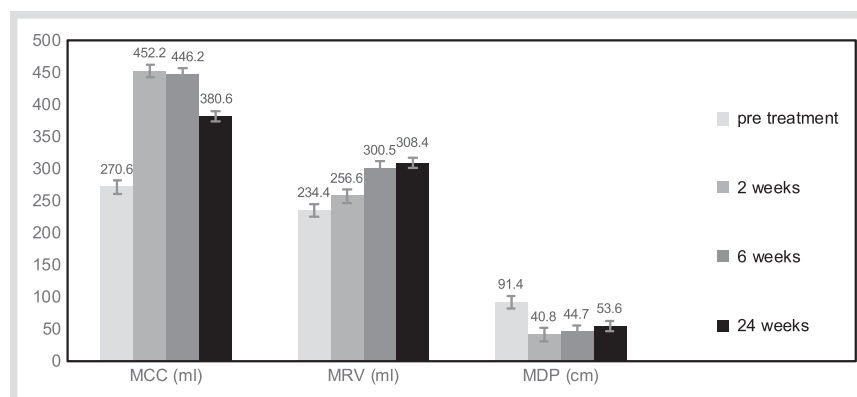


Fig. 1 Plot of Urodynamic measures; cystometric capacity (MCC), reflex detrusor volume (RDV) and maximum detrusor pressure during bladder contraction (MDP) before and 2, 6, and 24 weeks after BTX-A injection therapy ($p < 0.05$), depicting statistically significant decrease in MCC and MDP, and increase in RDV over a 24-week study period.

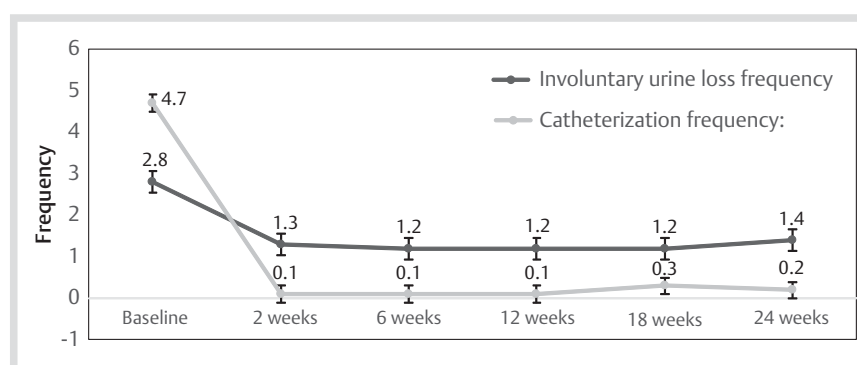


Fig. 2 Representative graph of changes in involuntary urine loss and catheterization frequency at 2, 6, 12, 18, 24 weeks post-treatment, showing significant reduction in involuntary urine loss and catheterization frequency during 24-week study.

incontinence. The QoL index was expressed as a score ranging from 0 (poor self-perceived QoL due to incontinence) to 100 (incontinence does not negatively affect QoL).

Statistical methods

Paired t-test was used to compare urodynamic parameters pre- and post-injection. Repeated measures analysis of variance (ANOVA) were used to analyse longitudinal data. The data was analysed using SPSS (Version 20.0) with statistical significance set at $p < 0.05$.

Results

A total of 24 subjects were selected for the study, out of which 2 were dropped with one showing adverse effects (transient hematuria and mild UTI), which resulted his unwillingness to continue the treatment, and other showed lack of efficacy at 4 weeks. 18 out of the 22 left subjects were men and the other 4 women with a mean age of 42.6 (SD=12.4) ranging from 32 years to 61 years. American Spinal Injury Association (ASIA) scale, were also measured and there were 13 (54%) Grade A, 3 (12.5%) Grade B, 5 (21%) Grade C, and 3 (12.5%) Grade D sub-

jects. No subjects were classified under class E of ASIA scale. The distribution of SCI levels was: 14 (58%) cervical, 4 (17%) thoracic and 6 (25%) lumbar. The basic demographic data are shown in **Table 1**. The results from the 3-day voiding diary after statistical analysis are as shown in **Table 2**. At pre-injection, all patients experienced leakage despite maximal anticholinergic therapy. The percentages of those who achieved complete continence and were completely dry at 2, 6, 12, 18 and 24 weeks post-injection were 82%, 76%, 77%, 68%, and 59%, respectively. The mean number of leakages was reduced from 2.8 ± 1.55 pre-injection to 1.22 ± 1.41 at 2 weeks post-treatment and 1.4 ± 1.52 at 24 weeks post treatment (**Fig. 1**). Compared to the number of leakages pretreatment, the reduction in the amount of leakage was statistically significant. Improvements were demonstrated in the daily frequency of incontinence episodes and urodynamic parameters. Improvements occurred from the first post-treatment evaluation visit at week 2 and were generally maintained for the duration of the 24-week study. No evidence of a treatment by site interaction effect was observed. At baseline the mean daily frequency of incontinence episodes was significantly different from the baseline at 2, 6, 12, 18 and 24 weeks (**Fig. 2**). Following treatment there were significant decreases in incontinence episodes at all-time points however the frequency tended

Table 3 Video urodynamic characteristics pre- and post-treatment.

Timeline	Baseline	2 weeks	6 weeks	24 weeks
Mean cystometric bladder capacity (mL)	270.6±110.5	452.2±130.6 <i>P</i> =0.0012(<i>S</i>)	446.2±188.4 <i>P</i> =0.0015(<i>S</i>)	380.6±168.1 <i>P</i> =0.0019(<i>S</i>)
Mean reflex volume (mL)	234.4±102.2	256.6±118.6 <i>P</i> =0.0011(<i>S</i>)	300.5±130.2 <i>P</i> =0.0009(<i>S</i>)	308.4±136.8 <i>P</i> =0.0007(<i>S</i>)
Maximal detrusor pressure (cmH ₂ O)	91.4±35.8	40.8±39.7 <i>P</i> =0.034(<i>S</i>)	44.7±42.5 <i>P</i> =0.0.029(<i>S</i>)	53.6±50.1 <i>P</i> =0.036(<i>S</i>)

S = Statistically Significant by ANNOVA @ 5% level of significance

to increase at 24 week time point. The decreases represented a reduction in incontinence episodes of approximately 50% despite a lower baseline than anticipated. In terms of urodynamic parameters, maximum detrusor pressure decreased significantly from 91.4±35.8 cmH₂O pre-treatment to 40.8±39.7 and 53.6±50.1 cmH₂O at 2 and 24 weeks post-treatment, respectively. These differences were statistically significant (*P*<0.05) as compared to baseline MDP. The volume at which reflex detrusor contractions first occurred increased from 234.4±102.2 mL pre injury to 256.6±118.6 mL at 2 weeks and 308.4±136.8 mL at 24 weeks post-treatment (*P*<0.05). Pre-injection, all patients had detectable detrusor overactivity during urodynamic study. At 2 weeks post injection, 40% of patients had no detectable detrusor activity during videourodynamic study. This percentage, however, decreased to 9.5% at 24 weeks post-injection, indicating the return of reflex activity. The mean cystometric bladder capacity increased from 270.6±110.5 mL to 452.2±130.6 mL and 380.6±168.1 mL at 2 and 24 weeks, respectively (*P*<0.05 (● Fig. 1)). The results of videourodynamic study are summarized in ● Table 3.

After treatment, the mean QoL index increased from 19.7±15.4 initially to 80.3±21.8 two weeks after injection (*P*=0.001). Most patients were either satisfied or very satisfied with their overall experience with the treatment. Satisfaction levels correlated with fewer leakages per day. Those with a less involuntary urine loss frequency were more satisfied with their voiding pattern. The overall incidence of patients' adverse effects was 40%, who reported condition of dry mouth, UTI and injection site pain. Patients with UTI were successfully treated with oral antibiotics. No cases of autonomic dysreflexia or clinically relevant changes in vital signs, hematology, and ultrasound or cystography observations were recorded during the study.

Discussion and Conclusion

Spinal cord injuries accompany physiological changes that can lead to significant bladder dysfunction, which has major influence on overall morbidity and quality of life [14]. Botulinum toxin injections into the detrusor provide clinically significant improvement in patients with neurogenic detrusor overactivity refractory to antimuscarinics and are very well tolerated [7]. Management strategies for NDH syndrome should meet 3 main objectives: low episodes of leakage per day, maximal voiding volume and adequate reflex volume. However, from the patient's point of view, the most important goals are continence and good tolerability of the therapy [8]. The results of this study indicated that injection of 300 IU botulinum into the detrusor, showed statistically significant effect. The significant effects were observed on the episodes of leakage per day, maximal voiding volume, and urodynamic parameters of reflex volume such as cystometric

capacity and maximal detrusor pressure at 6 and 24 weeks after injection (● Fig. 2). Also, the mean reflex volume remained high after 24 weeks post-injection and 59% of treated patients were completely dry after 24 weeks post-injection. These results are similar to the findings reported in Schurch et al. [6] and Reitz et al. [8]. The results of this study not only indicated significant reduction of detrusor overactivity but also reflected significant improvement on quality of life and patient satisfaction due to reduction in leakage and subsequent improvement of continence (● Fig. 1), which is consistent with results of Stohrer et al. [9] and Schulte-Baukloh et al. [15]. Overall, most of the patients in the present study were satisfied with the BTX-A treatment with an average satisfaction score of 6.9, which is comparable to the previous studies [16, 17].

The most probable reason for elongated effect of botulinum toxin up to 24 weeks, in our research could be because of its effect on smooth muscle as compared to shorter duration of action described in striated muscle. Botulinum toxin inhibits the release of acetylcholine in the synaptic vesicles by binding to the peripheral presynaptic nerve terminals of motor endplates, thus blocking the enzymatic process of ATP dependent exocytosis without affecting membrane transport. It has been shown that there could be differences in the mechanism of action of botulinum toxin in smooth muscles [18]. Khera et al., [19] in an in vitro study on spinal cord injured rats suggested that one mechanism by which BTX-A reduces detrusor overactivity is through impairment of ATP release due to hypo-osmotic stimulation of bladder urothelium markedly caused by administration of BTX-A.

Although there is no consensus regarding the optimal dose of botulinum toxin, most of the studies have suggested and used a maximal dose of 300 IU [6, 20]. However, some studies such as Reitz et al. [8] in randomized placebo controlled study found that both doses of botulinum toxin of 200 and 300 IU showed similar responses. Kuo [21] also reported efficacious results with 200 IU botulinum A toxin in spinal cord injured patients, with improvement of incontinence in 91.6% of patients. These results reflect possible use of 200 IU of botulinum toxin. However, this study was conducted in patients with neurogenic detrusor overactivity and a dose of 300 IU showed statistically significant effect with respect to the episodes of leakage per day, maximal voiding volume, and urodynamic parameters. In addition, as in our study, we recommended botulinum toxin injection in accordance with the clinical response to treatment (incontinence despite anticholinergic in high doses) and urodynamic results. Furthermore, injection technique is an important issue affecting efficacy [22], again there is no consensus regarding a standard injection procedure in the detrusor muscle, most studies have used the technique described by Schurch et al. [6].

In summary, the encouraging results of this study, without any side effects, reflect that use of botulinum toxin in the treatment of neurogenic detrusor hyperreflexia is a safe, valuable and

promising option compared to anticholinergics. From this and other clinical studies, it can be seen that there is definite clinical efficacy, improvement in urodynamic end-point and patient satisfaction with botulinum toxin A injection for treatment of NDH in spinal cord-injury patients, especially those refractory to other treatments. There is a promising role for botulinum toxin A injection into the detrusor in spinal cord injured patients resistant to anticholinergic medications, who do not want invasive reconstructive surgery, or are not fit for surgery.

Acknowledgement

This study was supported by the Medical Foundation of Shanghai Changning Science and Technology Commission (CNKW2013Z04), Nanjing Command (10MA026), Shanghai Changning Health Bureau (20124Y16001); China utility model patent (201320245170.7).

Conflict of Interest

The authors declared no conflict of interests.

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