

Botulinum Toxin Type A for Refractory Neurogenic Detrusor Overactivity in Spinal Cord Injured Patients in Singapore

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Abstract

Introduction: Managing neurogenic detrusor overactivity (NDO) successfully in spinal cord-injured patients is a challenge. The aims of preserving kidney function by achieving safe bladder pressures with anticholinergic medication often leave a significant proportion of patients with side effects. Botulinum toxin type A has been shown to be a promising alternative. **Materials and Methods:** Spinal cord injury patients who had NDO, on clean intermittent self-catheterisation, and were refractory to oral medications, were recruited. Three hundred units of botulinum toxin type A (Botox) in 30 mL NaCl solution were injected under cystoscopic guidance into the bladder. **Results:** Fifteen patients were recruited of whom 9 were tetraplegic and 6 were paraplegic. Eleven (73.3%) had complete injuries. There was a significant reduction in the mean number of leakages from 3.75 ± 1.79 pre-injection to 0.67 ± 1.31 and 1.5 ± 1.5 at 6 and 26 weeks post-injection, respectively ($P < 0.05$). Seventy-five per cent, 37.5% and 50% were completely dry at 6, 26 and 39 weeks post-injection, respectively. The mean maximal catheterisable volume increased from 312.3 ± 145.6 mL pre-injection to 484.6 ± 190 mL, 422.3 ± 157.3 mL and 490.0 ± 230.4 mL at 6, 26 and 39 weeks post-injection, respectively ($P < 0.005$). Maximum detrusor pressure decreased significantly from 66.3 ± 22.6 cmH₂O to 21.2 ± 23.1 cmH₂O and 33.6 ± 30.2 cmH₂O at 6 and 26 weeks post-injection, respectively ($P < 0.05$). The volume at which reflex detrusor contractions first occurred increased from 127.8 ± 57.5 mL pre-injury to 305.7 ± 130.8 mL at 6 weeks and 288.3 ± 13.0 mL at 26 weeks post-injection ($P < 0.05$). Mean cystometric bladder capacity increased from 187.8 ± 69.2 mL to 305 ± 136.4 mL and 288.3 ± 13.0 mL at 6 and 26 weeks post-injury, respectively ($P < 0.05$). Sixty per cent of patients were completely off medications at 6 and 26 weeks post-injection. One patient had urinary tract infection and 1 experienced autonomic dysreflexia during cystoscopy. Satisfaction levels increased from 4.3 ± 2.3 pre-injury to 7.2 ± 1.9 and 7.3 ± 2.3 at 6 weeks and 26 weeks, respectively. This also correlated with fewer leakages. **Conclusion:** Botulinum toxin type A injected into the detrusor is safe and efficacious for spinal cord injured patients with refractory detrusor overactivity. This effect is maintained at 26 weeks post-injection.

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Key words: Anticholinergics, Spinal cord injury, Urodynamics, Voiding

Introduction

Managing neurogenic detrusor overactivity (NDO) successfully in spinal cord-injured patients is a challenge. In addition to the aims of preserving kidney function by achieving safe bladder pressures so as to reduce the likelihood of upper tract deterioration, acceptable social continence and low urinary tract infection also need to be achieved. Current treatment relies on anticholinergic medication to partially block the efferent parasympathetic innervation to the detrusor to attain low bladder pressures

increase storage capacity and achieve continence.¹

In the Spinal Rehabilitation Centre at Tan Tock Seng Hospital, Singapore, a previous study showed that of 47 consecutive patients who had undergone a spinal rehabilitation programme and had had urodynamic studies done, 53% had shown evidence of NDO. Of these, 48% had been managed with anticholinergic medications and intermittent catheterisation upon discharge from rehabilitation.²

Using anticholinergic medications, however, presents

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at least 2 potential problems. Firstly, anticholinergic medications can have significant side effects. Up to 61% of patients on oral oxybutynin report adverse systemic side effects, leading to non-compliance.³ The development of newer anticholinergics with fewer side effects and better tolerance profiles may reduce the non-compliance rate, but there are still some who are refractory.^{4,5} Secondly, the medication at maximal doses may not be sufficiently effective to restore continence or achieve low storage and voiding pressures.

Because of this, there have been various attempts to develop other minimally invasive options for treating NDO resistant or unresponsive to oral anticholinergic or drug treatment. Options that have been considered include intravesical oxybutynin³ and intravesical instillation of vanilloids such as capsaicin and resiniferatoxin.⁶ Sacral neuromodulation can improve urge incontinence, but results are disappointing for neurogenic detrusor lesions, especially complete lesions.⁷ Surgical treatments like sacral anterior root stimulator and clam ileocystoplasty are invasive, require longer hospital stay, and can have long-term morbidity like implant complications and metabolic consequences.^{8,9}

Botulinum toxin is an exotoxin produced by the bacteria *Clostridium botulinum* and is one of the most potent occurring neurotoxins known to man. Out of the 7 distinct but structurally similar types of botulinum toxins, types A and B have been used with clinically beneficial effects in various neuromuscular disorders. Botulinum toxin selectively blocks acetylcholine release from nerve endings and inhibits parasympathetic neural transmission into the detrusor muscle. Early trials with botulinum toxin in patients with NDO indicated promising results.¹⁰⁻¹² The neurotoxin injected into the bladder wall blocked the neuromuscular junction and relaxed the detrusor muscle for 36 weeks. This enabled an increase in cystometric capacity, a decrease in detrusor pressure and a decrease in incontinence episodes. Recently, a multicentre trial involving 10 European centres with 231 patients substantiated the improvement in bladder function with continence, as well as subjective satisfaction.¹³

In this study, we review our preliminary results of the efficiency of injecting botulinum toxin type A into the detrusor muscle and its effects on various voiding parameters for spinal cord injured patients with refractory NDO in Singapore.

Materials and Methods

The trial was a case series of consecutive spinal cord injury patients treated at the Spinal Rehabilitation Centre in Tan Tock Seng Hospital Spinal and Urology Clinic. Fifteen patients with spinal cord injury who had NDO, on clean intermittent self-catheterisation (CISC), and were resistant to or had side effects from oral medication were recruited

over a 24-month period. All patients gave informed consent and were followed up at the Department of Rehabilitation Medicine's combined Spinal Rehabilitation and Urology Clinic.

Inclusion criteria included patients with refractory NDO (i.e., those not responding to maximal doses of oral anticholinergic therapy), patients having intolerable side effects from anticholinergic therapy (e.g., dry mouth, constipation) and patients with poorly compliant bladders. Exclusion criteria included patients with no neurologic deficits, patients with medical complications (e.g., bladder stones and infections, history of myasthenia gravis, pregnancy), and patients or caregivers who were unable to perform clean intermittent catheterisation.

Pre-treatment assessment included a 3-day voiding diary, video urodynamic studies, upper tract evaluation and plain abdominal radiograph. All patients were given a questionnaire with regard to the level of satisfaction with voiding, and whether they had troublesome symptoms (namely, leakage and urgency), as well as troublesome side effects from anticholinergic medications (e.g., dry mouth and constipation).

The injection of botulinum toxin was delivered via cystoscopic guidance. Each patient received 300 units of botulinum toxin type A (Botox, Allergan Inc., Irvine, California) which was diluted in 30 mL of normal saline solution. Thirty injections of 1 mL each were given intramuscularly into the detrusor, sparing the trigone. All but one of the patients was injected without anaesthesia. This patient had developed autonomic dysreflexia during cystoscopic procedure, prior to injection.

After injection, the patients were instructed to reduce anticholinergic drugs immediately after treatment. They were also instructed to keep a 3-day voiding diary at 2 weeks and 6 weeks. Patients who had achieved continence were advised to reduce their anticholinergic medication further and discontinue completely if possible. Post-treatment assessment included the voiding diary, satisfaction scales, medication usage and video-urodynamic studies scheduled at 6 week and 26 weeks after injection. In addition, the following was documented: the number of leakages, dose of anticholinergic medication used, and urodynamic parameters including the volume at which reflex detrusor contraction first occurred, maximum detrusor pressure, duration of contraction and cystometric capacity. Patient satisfaction was measured on a visual analog scale of 0-10, with 10 being the greatest overall satisfaction.

Anticipating that most of the variables were not spherically distributed, signed rank tests were applied to ascertain if they varied significantly at different intervals over the study period. The variables included the number of leakages per day, maximal voided volume, catheterisation frequency,

dose of medication, maximal detrusor pressure, reflex volume, duration of contraction and cystometric capacity. In addition, generalised estimating equations with linear link functions and unstructured correlations were used to identify the factors (completeness of injury, interval since injury and location of injury: cervical versus thoracic injuries) associated with the changes. Analysed with Stata 9.0 (Stata Corporation, Texas, USA), all statistical tests were conducted at 10% level of significance.

Results

Seventeen patients were recruited in the trial. Two dropped out soon after giving initial consent. One patient changed his mind and 1 was discovered to have bladder stones. None of these patients were treated or injected. These patients were therefore not included in the analysis.

There were 10 male and 5 female patients. Eleven patients had complete spinal cord injuries and 4 had incomplete injury. All but 3 were traumatic in origin. Nine were tetraplegics and 6 were paraplegics. The mean age of the subjects was 49.9 ± 11.5 years (range, 31 to 67). The mean time from injury to recruitment was 7.1 ± 7.1 years (range, 1.4 to 26; mean, 4.8).

The results from the 3-day voiding diary are as shown in Table 1. Pre-injection, all patients experienced leakage despite maximal anticholinergic therapy. The percentages of those who achieved complete continence and were completely dry at 6, 26 and 39 weeks post-injection were 75%, 35.7% and 50%, respectively. The mean number of leakages was reduced from 3.75 ± 1.79 pre-injection to 0.67 ± 1.31 at 6 weeks post-injury and 1.5 ± 1.5 at 25 weeks post injury. Compared to the number of leakages pre-injury, the reduction in the amount of leakage was statistically significant. At 39 weeks post-injection, there was a non-statistically significant trend towards an increased

number of leakages; but was still less than that pre-injection.

The mean catheterisable volumes were 312.3 ± 145.6 mL at pre-injection, 484.6 ± 190.5 mL at 6 weeks post-injection, 422.3 ± 157.3 mL at 26 weeks post-injection and 490.0 ± 230.4 mL at 39 weeks post-injection. These differences were statistically significant even up to 39 weeks post-injection. It is interesting to note that the effect of maximal catheterisable volume was maintained and even increased at 39 weeks post-injection.

The mean frequency of catheterisation decreased significantly from 5.80 ± 1.27 at pre-injection to 5.13 ± 0.74 at 6 weeks post-injection ($P = 0.029$). However, at 26 and 39 weeks post-injection, this difference was not statistically significant. Those injured at the cervical level tended to require a greater number of catheterisations per day, compared to those injured at the thoracic level ($P = 0.053$).

In terms of urodynamic parameters, maximum detrusor pressure decreased significantly from 66.3 ± 22.6 cmH₂O pre-treatment to 21.2 ± 23.1 and 33.6 ± 30.2 cmH₂O at 6 and 26 weeks post-injury, respectively. These differences were statistically significant ($P < 0.05$). The volume at which reflex detrusor contractions first occurred increased from 127.8 ± 57.5 mL pre injury to 305.7 ± 130.8 mL at 6 weeks and 288.3 ± 13.0 mL at 26 weeks post-injury ($P < 0.05$). Pre-injection, all patients had detectable detrusor overactivity during urodynamic study. At 6 weeks post-injection, 40% of patients had no detectable detrusor activity during videourodynamic study. This percentage, however, decreased to 12.5% at 26 weeks post-injection, indicating the return of reflex activity. The mean cystometric bladder capacity increased from 187.8 ± 69.2 mL to 305 ± 136.4 mL and 288.3 ± 13.0 mL at 6 and 26 weeks, respectively ($P < 0.05$) (Table 2).

Pre-injection, all patients were receiving anticholinergic medications necessary to control leakage and reduce

Table 1. Results of Characteristics from 3-day Voiding Diary

	Pre-injection	6 weeks post-injection	26 weeks post- injection	39 weeks post- injection
Mean number of leakages/24 hours	3.75 ± 1.79 range, 1.5-9	0.67 ± 1.31 range, 1-4.5 $P = 0.0017$ (SS)	1.50 ± 1.50 range, 1.0-4.5 $P = 0.0109$ (SS)	1.75 ± 3.03 range, 0-8 $P = 0.1755$ (NS)
Maximal catheterisable volume	312.33 ± 145.68 mL range, 150-600	484.67 ± 190.55 mL range, 300-900 $P = 0.003$ (S)	422.31 ± 157.33 mL range, 200-700 $P = 0.006$ (S)	490 ± 230.4 mL range, 250-900 $P = 0.0296$ (S)
Catheterisation frequency	5.80 ± 1.27 range, 4-9	5.13 ± 0.74 range, 4-6.5 $P = 0.029$ (SS)	5.35 ± 0.88 range 4-7 $P = 0.1526$ (NS)	5.72 ± 1.25 range 4-7.5 $P = 0.8077$ (NS)
Percentage of patients completely dry over 24 hours (3-day voiding diary)	0%	75% (10/15)	35.7% (5/14)	50% (5/10)

NS: not statistically significant; SS: statistically significant

Table 2. Video Urodynamic Characteristics Pre- and Post-Injection

	Pre-injection	6 weeks post-injection	26 weeks post-injection
Mean reflex volume (mL)	127.85 ± 57.53.0 range, 50-210	305.73 ± 130.86 range, 80-500 <i>P</i> = 0.0019 (SS)	225 ± 119.34 range, 128-480 <i>P</i> = 0.0172 (SS)
Mean cystometric bladder capacity (mL)	187.8 ± 69.2 range, 50-300	305.7 ± 136.4 range, 100-500 <i>P</i> = 0.0007 (SS)	490.0 ± 230.4 range, 250-900 <i>P</i> = 0.0117 (SS)
Maximal detrusor pressure (cmH ₂ O)	66.3 ± 22.6 range, 15-67	21.2 ± 23.1 range, 0-65 <i>P</i> = 0.0007 (SS)	33.6 ± 30.2 range, 0-75 <i>P</i> = 0.0117 (SS)
Mean duration of contraction (s)	322.7 ± 189.9	141.5 ± 97.2 <i>P</i> = 0.5076 (NS)	142.0 ± 107.7 <i>P</i> = 0.6232 (NS)

NS: not statistically significant; SS: statistically significant

detrusor pressures. Four (26%) were on oxybutynin and 11 (73%) were on tolterodine. The mean dose of oxybutynin was 23.7 mg per day and the mean dose of tolterodine was 6 mg per day pre-injection. This was reduced significantly to 3.75 mg and 0 mg at 6 and 26 weeks post-injection for oxybutynin and to 1.45 mg and 1.5 mg at 6 and 26 weeks post-injection for tolterodine (Table 3).

With respect to side effects of medications, 86% (*n* = 13) had dry mouth. Four patients had problems of urgency despite medications. With the reduction in the dose of anticholinergic medication, the incidence of side effects was reduced to 26.6% and 10% at 6 and 26 weeks post-injection, respectively.

Satisfaction levels increased at 6 and 26 weeks post injury, from 4.3 ± 2.3 pre-injury to 7.2 ± 1.9 at 6 weeks (*P* = 0.074) and 7.3 ± 2.3 at 26 weeks (*P* = 0.121). Satisfaction levels correlated with fewer leakages per day – those with a fewer leakages per day were more satisfied with their voiding pattern (*P* < 0.001)

One patient developed clinical urinary tract infection after injection. This was successfully treated with oral antibiotics. One patient had fever which did not amount to clinical infection. One patient developed autonomic dysreflexia, manifested by high blood pressure and nasal stuffiness, secondary to the cystoscopic procedure, prior to injection. The injection of botulinum toxin was subsequently done under spinal anaesthesia.

Discussion

It can be seen from this study that an injection of 300 units of botulinum toxin A (Botox) into the detrusor has statistically significant effects both on episodes of leakage per day, maximal voided volume, as well as urodynamic parameters of reflex volume, cystometric capacity and maximal detrusor pressure, at both 6 and 26 weeks post-injection. Mean catheterisable volume remained high even

at 39 weeks post-injection. It is also interesting to note that at 39 weeks post-injection, 50% of injected patients were completely dry.

These results are similar to those of other studies in which there were significant improvement in these parameters.¹²⁻¹⁴ It is significant that these results not only translate to the abolishment or reduction of detrusor overactivity, but also have an impact on quality of life and patient satisfaction. In our study, satisfaction with voiding function improved significantly post-injection, and this correlated with frequency of leakage. Reduction in leakage and subsequent improvement of continence was an important factor in the increase in satisfaction and quality of life of patients. Similar results have been reported in other studies.^{10,15}

The fact that the effect of botulinum toxin in our study lasts at least up to 39 weeks and beyond, especially in terms of maximal catheterisable volume, could be attributable to its effect on smooth muscle, compared to the shorter duration of action described in striated muscle.

Botulinum toxin works by binding to the peripheral presynaptic nerve terminals of motor endplates and inhibiting the release of acetylcholine in the synaptic vesicles by blocking the enzymatic process of ATP-dependent exocytosis, without affecting other release mechanisms, e.g., membrane transport. The recent use of botulinum toxin in smooth muscles has shown that there could be differences in the mechanism of action.¹⁶

It has been shown that in rats, botulinum poisoning triggered bladder hypocontractility and a decrease in stimulation-induced acetylcholine release. However, this histological abnormality was not apparent in the smooth fibres of the detrusor muscle of patients treated for overactive neurogenic bladder after spinal cord injury.¹⁶ This lack of axonal reaction could be related to a specific action of the toxin on smooth muscle, or it could be associated

Table 3. Medication Use Pre- and Post-Injection

	Pre-injection	6 weeks post-injection	26 weeks post-injection	39 weeks post -injection
Mean dose of medication per day	Oxybutynin: 23.7 mg range, 15-35	Oxybutynin: 3.75 mg range, 0-15	Oxybutynin: 0 mg	Oxybutynin: 3.75 mg range 0-15
Oxybutynin (n = 4)	<i>P</i> = 0.0021	<i>P</i> = 0.0067	<i>P</i> = 0.2341	
Tolterodine (n = 11)	Tolterodine 6 mg range, 4-8	Tolterodine: 1.45 mg range, 0-8 <i>P</i> = 0.0021	Tolterodine: 1.5 mg range, 0-4 <i>P</i> = 0.0067	Tolterodine: 3.6 mg range, 0-6 <i>P</i> = 0.2341
Number of patients who had reduction of anticholinergics	Nil	73% (11/15)	83% (13/15)	40% (4/10)
Number of patients who were completely off medication	Nil	60% (9/15)	60% (9/15)	40% (4/10)

with an impaired neuronal response in patients with spinal cord injury.¹⁷

It has also been postulated that botulinum toxin could also act on afferent pathways, particularly via subepithelial neuro-mediators. Patients with NDO were found to have increased TRPV-1 and P2X3-immunoreactive suburothelial innervation compared to controls.¹⁸ Biopsies of patients treated with intra detrusor botulinum toxin also showed a progressive decrease and ultimate normalisation of P2X3 and TRPV1 suburothelial nerve immunoreactivity, although there was no change in the overall suburothelial neuronal population. This suggests that botulinum toxin A affects sensory receptors expression in suburothelial fibres.¹⁶ Botulinum toxin A could also induce a phenotypic change of bladder afferents. Bladder levels of neurotrophic growth factor in patients with NDO have been reported to decrease significantly after Botox A treatment.¹⁸ This effect may also explain the absence of significant nerve sprouting in the detrusor after successful botulinum toxin A treatment, unlike in skeletal muscle.¹⁶ Overall, it has been proposed that botulinum toxin A injected into the overactive human bladder has a complex inhibitory effect on the vesicular release of excitatory neurotransmitters and on the axonal expression of other proteins in the urothelium or suburothelium, which are important in mediating those intrinsic or spinal reflexes thought to cause detrusor overactivity, as well as its effects on bladder afferents.

The mechanism of return of detrusor overactivity remains to be determined. Re-innervation of denervated acetylcholine nerve terminals could be a possible reason for the return of reflex activity. Because of this, and the limited duration of effect of botulinum toxin on the bladder, as shown in previous clinical studies, patients will have to undergo repeated injections. Grosse et al¹⁹ showed that repeated injections with botulinum toxin was successful in many patients. Repeat injections were shown to be just as effective as the first treatment. However, there was a trend to a slow decrease in the interval between injections.

Schulte-Baukloh et al²⁰ assessed the long-term success of treatment with repeated botulinum toxin A injections into the detrusor for long-term detrusor overactivity in children. A comparison of the results after the first, third and fifth injections showed that the efficacy remained for both reflex volume, maximum detrusor pressure and maximum cystometric capacity. There was no evidence of drug tolerance.

No side effects related to botulinum toxin have been reported in this study. The development of autonomic dysreflexia is an acceptable complication of cystoscopic procedure in spinal cord injured patients.²¹ Precautions need to be taken to monitor for such an occurrence, for e.g., asking the patient to report symptoms of headache, flushing, as well as blood pressure measured regularly. Preventive measures such as providing adequate analgesia and prevention of excessive nociceptive input should be taken. Wyndale and Van Dromme²² have reported distant muscular weakness as a side effect at 300 U of Botox and 1000 units of Dysport. This could be attributed to the total dose injected, repeat injections being too close together, the total volume injected being too large, or the spread in the nervous system through retrograde axonal transport. One should be aware of this possible complication and avoid high doses or dilution volumes or reduced intervals between injections.²³

The optimal dose of botulinum toxin is yet to be determined. Most studies have used 300 U of botulinum toxin, following the successful use of 300 U of botulinum toxin in initial trials.¹² In a later randomised placebo controlled study, Schurch et al¹⁴ found that both doses of botulinum toxin of 200 and 300 units achieved significant post-treatment decreases in incontinence episodes, urodynamic function and quality of life, compared to placebo. Kuo²⁴ also reported efficacious results with 200 U botulinum A toxin in spinal cord injured patients, with improvement of incontinence in 91.6% of patients. A possible indication for the use of 200 U of botulinum toxin

has also been considered for the reduction; but not abolishment of detrusor contraction so as to allow patients to void via tapping, yet achieve acceptable intravesical pressures during storage and voiding.

Early studies have used Botox to treat neurogenic bladder, although there has been a recent trend towards the use of other preparations. Currently, 3 commercial botulinum toxin preparations are available worldwide. Botox (Allergan, Irvine, Ca, USA) and Dysport (Ipsen, Luxembourg) are botulinum toxin type A toxins, and Myobloc/Neurobloc (Elan, Dublin, Ireland) is a type B toxin. Studies with Dysport have shown almost similar efficacy to Botox.^{25,26} The evidence from studies in skeletal muscle disease suggests an approximate ratio of Botox to Dysport in a ratio of 1:3. The ratio for smooth muscle, however, has not been established.²⁷

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 toxin injection for treatment of NDO in spinal cord-injury patients, especially those refractory to other treatments. There is a 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.

Definitive treatment plans will have to take into consideration the long-term costs and the need for repeat injections for those on botulinum toxin A injections. So far, there have been no long-term studies addressing this question. In addition, there has been concern about the theoretical impact on the bladder of repeated injections – that, with injections over several years, could lead to not only small non-compliant bladders but also tolerance to the treatment. However, there has been no evidence to suggest this so far. Until the long-term effects of optimum number of injections are known, botulinum toxin A injections will have a role in bridging the gap between oral treatment and invasive surgical treatment for drug-resistant NDO secondary to spinal cord injury.

Conclusion

Botulinum toxin type A injected into the detrusor is safe and efficacious for spinal cord-injured patients with refractory NDO. This effect is maintained for at least 26 weeks post-injection. Up to 39 weeks post-injection, botulinum toxin A injection into the bladder caused had significant improvements in maximal catheterisable volume. Future studies will need to be geared towards determining the optimal dose of the medication, and determining the long-term effects of repeated injection as well as assessing the characteristics of patients who will respond better to the treatment.

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