ORIGINAL ARTICLE

Intradetrusor versus suburothelial onabotulinumtoxinA injections for neurogenic detrusor overactivity: a pilot study

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Study design: This was a multicentre, prospective, randomised study.

Objectives: To compare the outcomes of intradetrusor and suburothelial onabotulinumtoxinA injections in patients with spinal cord injury and refractory neurogenic detrusor overactivity (NDO).

Setting: Urology departments of two tertiary hospitals in the Czech Republic.

Methods: A total of 32 spinal cord injury patients with severe NDO refractory to the standard anticholinergic treatment were randomised to receive either intradetrusor or suburothelial 300 IU onabotulinumtoxinA injections. Subjective satisfaction, bladder diary data and urodynamic data were compared in both groups before treatment and at 3 months post treatment.

Results: In all, 64.3% patients in the intradetrusor group and 88.8% patients in the suburothelial group were subjectively satisfied with the treatment. There was a significant post-treatment improvement in both groups regarding the number of catheterisations over 24 h, number of incontinence episodes over 24 h, catheterised volume, cystometric capacity, volume at first involuntary detrusor contraction, maximal detrusor pressure during filling and detrusor compliance. No significant differences between the groups were observed, with the exception of improvement of detrusor compliance, which was better in the intradetrusor group. There was one adverse effect comprising transient muscle weakness that was reported by one patient in the intradetrusor group.

Conclusion: Results in both groups were comparable. The authors favour suburothelial onabotulinumtoxinA injection because this method allows more precise toxin localisation.

Spinal Cord (2012) **50**, 904–907; doi:10.1038/sc.2012.76; published online 17 July 2012

Keywords: urodynamics; neurogenic detrusor overactivity; onabotulinumtoxinA; spinal cord injury; suburothelial injection

INTRODUCTION

Spinal cord injuries are among the most devastating of all injuries, often having life-changing and diverse consequences. Lower urinary tract dysfunction is commonly observed as a result of a spinal cord injury. Neurogenic detrusor overactivity (NDO) is frequently associated with upper motor neuron lesion, and the subsequent increased intravesical pressure may present a potential risk by causing damage to the upper urinary tract.¹ Current standard NDO treatment comprises individualised administration of anticholinergic medication; however, this therapy is inadequate for some patients and is often associated with unacceptable adverse effects.² Treatment with botulinum toxin offers an accepted alternative treatment for those patients in whom anticholinergic treatment has failed.

Botulinum toxin is a neurotoxin produced by anaerobic microorganisms of the *Clostridium* genus. Botulinum toxin acts on the peripheral nervous system where it is responsible for blockade of acetylcholine release from presynaptic nerve endings.³ This process results in blockade of the neuromuscular transfer, with a subsequent loss of muscle cell contractility.

A further effect of botulinum toxin following administration into the urinary bladder wall is an inhibitory influence on neurotransmitters and receptors mediating sensory neurotransmission.^{4,5}

The clinical effect of botulinum toxin injection in the treatment of NDO has been established in several studies.^{6–8} Further aspects of this

form of treatment are currently under discussion, such as optimal dose, optimal dilution of botulinum toxin and the most effective administration technique (for example, bladder trigonum-saving technique versus injection into bladder trigonum).

The lamina propria sensory nerves probably have a key role in the pathophysiology of the detrusor overactivity.⁹ Therefore, the suburothelial injection of the onabotulinumA seems to be the most logical application area. However, most treatment protocols published until now favour intradetrusor application. The aim of this multicentre, prospective randomised trial was to compare the efficacy and safety of intradetrusor and suburothelial injection of onabotulinumtoxinA in a group of patients with NDO caused by a spinal lesion.

MATERIALS AND METHODS

This was a multicentre, randomised, prospective study comprising two groups of patients. Patients in group A received onabotulinumtoxinA injections into the detrusor, whereas patients in group B received onabotulinumtoxinA suburothelial injections. This study was approved by the local Ethics Committee, and all the enrolled patients signed informed consent before any study-specific procedure. All applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during the course of this research.

A total of 32 patients were enrolled into the study (26 males and 6 females), with a mean age of 32.1 years (range: 20–55 years). The main demographic

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Received 21 November 2011; revised 26 April 2012; accepted 27 April 2012; published online 17 July 2012

characteristics of the study population are provided in Table 1. Patient inclusion criteria comprised NDO as evidenced urodynamically. Patients were required to be neurologically stable, with failure of oral anticholinergic treatment due to insufficient efficacy or adverse effects, and the need for urinary bladder evacuation with intermittent catheterisation (that is, auto-catheterisation or catheterisation by another person).

Patients with a history of botulinum toxin treatment, patients with cystolithiasis or previous surgery, or a history of radiation treatment in the pelvic region, together with females of child-bearing potential who were not using reliable methods of contraception, as well as breastfeeding females, were all excluded from the study.

The following parameters were monitored during the course of the study: subjective satisfaction, parameters obtained following analysis of the bladder diary and the results of urodynamic examination. All the parameters were evaluated immediately before treatment and at 3 months post treatment. Patients were then followed-up until symptoms returned to the baseline level.

Urodynamic measurement

Urodynamic evaluation was performed according to the International Continence Society recommendations, with the following additions: (a) volume at first involuntary detrusor contraction (Vol at FC) and (b) maximal detrusor pressure during filling (P_{detF}) representing the highest amplitude of non-voiding contraction.¹⁰ Values were recorded from patients in the supine position using a filling rate of 50 ml min⁻¹.

Injection procedure

Patients were treated with onabotulinumtoxinA (Botox; Allergan Inc., Irvine, CA, USA) at a dosage of 300 IU, diluted in 30 ml of saline. Furthermore, all patients received antibiotic treatment prior to the procedure to ensure urine sterility. The procedure was performed under general anaesthesia, with bladder filling at approximately 200 ml. Sonographic measurement of the thickness of the bladder wall preceded application of onabotulinumtoxinA. OnabotulinumtoxinA was administered with 25 G endoscopic needle into 30 locations so that the whole endoscopically accessible area of the bladder wall was evenly covered. A dose of 1 ml onabotulinumtoxinA was applied with each puncture.

In group A, onabotulinumtoxinA was injected at a depth of approximately 2–4 mm, depending on the thickness of the bladder wall as measured by ultrasound. No visual bulking of the mucosa was observed upon injecting, and muscle tissue resistance was felt during administration. In cases when there was only a slight or no backpressure of the syringe plunger, toxin administration

was discontinued immediately as we suspected possible localisation of the needle tip into the thin paravesical adipose tissue. In these cases, the needle tip was removed from the bladder wall and inserted into a different part of the bladder wall.

Patients in group B received onabotulinumtoxinA injected into the submucosa in such a way that the bulking was clearly visible. A bladder drainage with permanent catheter was maintained for a period of 24 h following toxin administration, after that time the patients continued with evacuation via intermittent catheterisation.

Statistical analysis

The data are expressed as means $\pm$ s.e.m. Statistical analyses were carried out using paired Student's *t*-tests. In cases where data were not normally distributed, a Wilcoxon signed-rank test was used.¹¹ *P*-values ≤ 0.05 were considered statistically significant.

RESULTS

To assess subjective satisfaction, all patients were asked whether they were satisfied with onabotulinumtoxinA treatment to the extent that they would be willing to undergo repeat treatment once all the beneficial effects of the first treatment had diminished. A total of 9 (64.3%) patients in group A requested repeat treatment, 2 (14.3%) patients were undecided and 3 (21.4%) patients stated they would refuse repetition of the treatment procedure. In group B, 16 (88.8%) patients were willing to undergo repeat treatment, 1 (5.6%) patient was undecided and 1 (5.6%) patient would refuse repetition of the treatment.

Based upon the information from bladder diaries, the frequency of urinary bladder catheterisation, the number of incontinence episodes and catheterised volume for each patient was assessed. All these parameters in both study groups were significantly improved after treatment, and the differences observed between groups A and B were not statistically significant.

On the basis of the data obtained from urodynamic examination, cystometric capacity, volume at first involuntary detrusor contraction, maximal detrusor pressure and detrusor compliance were also evaluated. All the parameters in both groups showed a statistically significant improvement following onabotulinumtoxinA treatment. One parameter showed a statistical difference between the two treatment groups, with detrusor compliance being statistically significantly better in group A. No statistically significant difference between the two groups was noted for any of the other parameters (Table 2).

There was no statistically significant difference between the two treatment groups with regard to duration of effect of treatment. Treatment duration was 7.29 ± 1.27 (range 5–9) months in group A and 7.11 ± 1.31 (range 5–9) months in group B ($P = 0.726$).

There was only one treatment-related adverse effect observed in one patient from group A during the study period. The patient complained of a loss of muscle strength for a period of 7 days following onabotulinumtoxinA administration. This adverse effect resolved completely and the patient made a full recovery.

DISCUSSION

OnabotulinumtoxinA injection into the urinary bladder wall presents an effective alternative treatment for NDO refractory to the standard treatment with anticholinergic medication. The effectiveness and safety of this treatment has been assessed in a number of clinical trials.¹²

The clinical effect of botulinum toxin results from a temporary chemical denervation in the target application area.¹³ Axonal resprouting follows after several weeks or months, depending upon

Table 1 Demographic characteristics of the study population

	Group A	Group B
Total number	14	18
Males	9	17
Females	5	1
Age (years)	31.8 (range: 20–48)	32.4 (range: 20–55)
BMI	25.6 (range: 20–32)	25.2 (range: 18–31)
<i>Lesion localisation</i>		
C	8	8
Th	5	9
L	1	1
<i>ASIA</i>		
A	10	14
B	3	3
C	1	1
D	0	0
E	0	0
Time from injury (months)	58.8 (range: 16–154)	60.7 (range: 11–276)

Abbreviations: ASIA: American Spinal Injury Association; BMI: body mass index.

Table 2 Summary of results

	Group A					Group B					Group A vs B		
	Before Tx	After Tx	Diff	Z	P	Before Tx	After Tx	Diff	Z	P	Z	P	P
Frequency of cath/24 ± s.d.	8.71 ± 4.25	6.29 ± 1.27	-2.43 ± 3.55	3.11	0.0019	7.11 ± 1.28	5.89 ± 0.90	-1.22 ± 1.63	2.77	0.0056	-0.97	0.331	
No. of inco ± s.d.	2.50 ± 1.56	0.21 ± 0.43	-2.29 ± 1.54	3.30	0.001	3.00 ± 1.88	0.17 ± 0.38	-2.83 ± 1.86	3.73	0.0002	0.69	0.492	
VV (ml) ± s.d.	199.79 ± 63.16	321.14 ± 57.31	121.36 ± 53.61	3.20	0.0014	189.06 ± 41.14	341.56 ± 59.95	152.50 ± 55.40	3.70	0.0002	-1.14	0.254	
CC (ml) ± s.d.	192.43 ± 71.62	364.57 ± 86.14	172.14 ± 57.58	3.27	0.0011	198.33 ± 84.16	388.28 ± 111.01	189.94 ± 68.58	3.70	0.0002	-1.01	0.314	
Vol. at FC (ml) ± s.d.	148.93 ± 60.73	323.43 ± 90.78	174.50 ± 72.83	3.26	0.0011	141.11 ± 62.85	341.39 ± 115.94	200.28 ± 90.15	3.70	0.0002	-0.70	0.482	
P _{Det} F (cm H ₂ O) ± s.d.	75.29 ± 27.19	27.64 ± 19.56	-47.64 ± 24.01	3.24	0.0012	80.28 ± 22.09	39.28 ± 23.00	-41.00 ± 27.15	3.57	0.0004	-0.57	0.568	
C (ml/cmH ₂ O) ± s.d.	21.57 ± 9.86	52.14 ± 36.60	30.57 ± 28.07	3.27	0.0011	17.94 ± 6.33	34.39 ± 14.59	16.44 ± 12.40	3.70	0.0002	2.30	0.021	

Abbreviations: C, detrusor compliance; CC, cystometric capacity; Frequency of cath/24, number of catheterisations per 24 h; No of inco, number of incontinence episodes per 24 h; P_{Det}F, maximal detrusor pressure during filling; Tx, treatment; Vol at FC, volume at first involuntary detrusor contraction; VV, voided volume.

the dose of botulinum toxin administered. However, according to a study by Haferkamp *et al.*,¹⁴ only a limited resprouting is seen in detrusor biopsies compared with striated muscle. Axonal resprouting was noted in only three axons of 11 detrusor biopsies in patients already experiencing diminished clinical effects of botulinum toxin injections. Thus, the data show that the duration of clinical effect does not depend on the timing of detrusor reinnervation.

Alternative data suggest that the local action of intradetrusor botulinum toxin injection may effect a functional motor inhibition not associated with neuronal death. Furthermore, botulinum toxin has recently been demonstrated to have inhibitory effects on additional neuronal populations (for example, sensory and autonomic) and non-neuronal tissue (for example, urothelium).¹⁵ A number of experimental studies in rodents have provided evidence that the sensory effects of botulinum toxin might be a consequence of a suppression of afferent signalling. When injected into the bladder wall, onabotulinumtoxinA demonstrated inhibition of sensory transmitter adenosine triphosphate release, which is released following stimulation of bladder mechanoreceptors.¹⁶ In addition, afferent nerve-mediated contractions in response to electrical and chemical stimulation were shown to be suppressed in the rat bladder *in vitro* following botulinum toxin treatment.¹⁷ The sensory nerves expressing TRPV1, P2X3, substance P and calcitonin gene-related peptide are most dense in the suburothelial plexus and urothelium.¹⁸

It seems to us that suburothelial injection is the most logical area for onabotulinumtoxinA application. However, most treatment protocols favour administration of onabotulinumtoxinA into the detrusor. The only experience with suburothelial injection of onabotulinumtoxinA was published by Kuo.¹⁹ The author reports treatment doses of 100, 150 and 200 IU of onabotulinumtoxinA administered suburothelially as having identical effects in patients with refractory idiopathic detrusor overactivity. In another study, Kuo²⁰ compared the effect of a 100 IU dose of onabotulinumtoxinA injected into the detrusor, into the base of the bladder and suburothelially in 45 patients with idiopathic detrusor overactivity. A successful result was obtained in 14 (93%) patients with detrusor, 12 (80%) with suburothelial and 10 (67%) with bladder base injection at 3 months. The success rate decreased over time to 10 (67%), 7 (47%) and 2 (13%) at 6 months and 3 (20%), 3 (20%) and 1 (6.7%) at 9 months in the detrusor, suburothelial and bladder base groups, respectively ($P=0.0253$).²⁰

To our knowledge, this study is the first to compare the outcomes of intradetrusor and suburothelial onabotulinumtoxinA administration in patients with NDO. Our results show that both the methods of onabotulinumtoxinA injection have the same effect and duration of clinically beneficial effects.

The subjective satisfaction with the treatment was high in both groups. The use of standardised quality-of-life and treatment impact questionnaires or visual analogue scales was not used in this pilot trial. Although superior in reporting the subjective outcomes, the willingness to undergo a retreatment in the case of this study provides sufficient evidence that most patients in both groups considered the treatment a success. The variance between both the groups is more likely due to small number of enrolled patients and is not of statistical significance.

We observed only one treatment-related adverse effect in one patient assigned to group A, comprising a temporary loss of muscle strength. In our opinion, this event may have been caused by unintentional administration of onabotulinumtoxinA into the perivesical space. This hypothesis is supported by Mehnert *et al.*,²¹ in which the authors examined the distribution of botulinum toxin

labelled with gedopentate using magnetic resonance performed immediately after endoscopic injection. They found 82.4% of the botulinum toxin located in the detrusor, whereas 17.6% was situated in the perivesical fat tissue. Similarly, Boy *et al.*²² found that up to 33% of injected botulinum toxin was not localised in the detrusor.

CONCLUSION

In conclusion, the therapeutic effects and duration of intradetrusor and suburothelial injection of onabotulinumtoxinA in patients with NDO are comparable.

The authors consider that the suburothelial injection technique is at least as safe as intradetrusor injection technique because it enables precise visual monitoring of the area requiring toxin administration.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

Medical writing support for this paper was provided by Debbie Jordan, with funding from Allergan Ltd. Statistical analysis was provided by Josef Tvrdik, Ostrava University.

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