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Success of Repeat Detrusor Injections of Botulinum A Toxin in Patients with Severe Neurogenic Detrusor Overactivity and Incontinence

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Abstract

Objectives: Detrusor injections with botulinum toxin type A are an effective treatment for neurogenic detrusor overactivity, lasting for 9–12 months. When the patients develop botulinum resistance, subsequent injections might be less effective. Repeat injections in patients with severe neurogenic detrusor overactivity and incontinence were studied.

Methods: Patients received Botox® (300 UI) or Dysport® (750 UI) injections. Clinical variables: satisfaction, anticholinergics use, mean and maximum bladder capacity, continence volume. Cystometric parameters: compliance, cystometric capacity, reflex volume. Statistics: Anova, χ^2-tests; *t*-tests and paired *t*-tests ($p = 0.05$).

Results: Forty-three men and 23 women (mean age 38.3 years; mean duration of lesion 9.2 years) were included. The interval between subsequent injections (on average 9–11 months) did not change significantly ($p = 0.5594$). The satisfaction was high and anticholinergics use decreased substantially ($p = 0.0000$). Significant improvements were found in clinical parameters and in cystometric capacity, for compliance only at the second treatment. The incidence of reflex contractions was significantly reduced. Four patients had transient adverse events after Dysport®.

Conclusions: Repeat injections with botulinum toxin type A are as effective as the first one. The cause for repeat treatment is relapse of overactive bladder symptoms.

Keywords: Botulinum; Detrusor injections; Neurogenic detrusor overactivity; Neurogenic urinary incontinence; Spinal cord injury; Aseptic intermittent catheterisation; Botulinum resistance

1. Introduction

The majority of patients with suprasacral spinal cord injury, multiple sclerosis, stroke, or myelomeningocele suffers from lower urinary tract dysfunction: detrusor overactivity and/or low compliance with or without urinary incontinence [1–4].

Anticholinergic treatment is the gold standard for this condition, but many patients with neurogenic detrusor overactivity [5] are refractory to treatment with anticholinergics, mainly because of adverse effects—partly caused by the high dosage needed [6].

In these cases intravesical instillation of vanilloids (capsaicin or resiniferatoxin) can be offered. These drugs cause an irreversible damage of the afferent sensory unmyelinated C-fibres, but their effect is limited and is discussed controversially [7–9].

Alternatively, invasive (auto-)augmentation procedures can be used [10,11], but these have various adverse long term effects [12,13]. Sacral rhizotomy causes loss of reflex erections and thus the implantation of a sacral root neurostimulator thus is best restricted to patients with complete suprasacral cord lesions [14].

Single sessions of multifocal injections with botulinum A toxin (BTX-A) into the detrusor were reported

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to offer an effective and relatively non-invasive treatment for patients with refractory neurogenic detrusor overactivity [15,16]. The therapeutic effect lasted for about 11 months, after which the patients might elect a repeat injection.

This ongoing prospective open label study examines the results of repeat detrusor injections in order to discover a possible increase of drug resistance.

2. Methods

Patients with repeat BTX-A injections for neurogenic lower urinary tract dysfunction (detrusor overactivity, low compliance, reduced bladder capacity—with or without incontinence) unmanageable by anticholinergic treatment and able to practice intermittent (self-)catheterisation were included in this study.

Pregnant patients or patients with systemic or neuromuscular disease, coagulation disorders, or patients unable to practice intermittent catheterisation were excluded. Patients with congenital spinal cord conditions were not included in this study, as we have the impression that the results for this group are less positive.

Two BTX-A complex preparations are commercially available (Botox®, Allergan Inc; Dysport®, Ipsen Pharma). The effective toxin equivalence ratio is given as 1:1 to 8:1 [17,18]; based on clinical experience in man an equal effect is accepted for 1 UI Botox® and 3.5–5 UI Dysport® [19–23]. An initial titration phase (last half year of 1998) had learnt us that 200 UI or 250 UI Botox® ($n = 5$) and 500 UI Dysport® ($n = 7$) were less effective, later on 300 UI Botox® and 750 or 1000 UI Dysport® were used.

The current clinical status and patient self-assessment (change in dosage of anticholinergics, subjective outcome, increase of mean and maximum bladder capacity, increase of continence volume—defined as the patient's indication of the bladder volume at which incontinence starts) and the urodynamic status (compliance, cystometric capacity, reflex volume—defined as the filling volume at the start of the first phasic detrusor contraction [5,24]) were used as outcome parameters. Video-urodynamics were performed at baseline, 3 months and 6–12 months after each treatment.

Because of the induced detrusor paresis, it was decided not to use the maximum detrusor pressure during filling or during voiding as urodynamic variables.

At the mentioned follow-up investigations the decision for necessary re-injection was made when objective data (urodynamic or more subjective clinical patterns, or radiological signs of trabeculation, cellules or reflux) deteriorated substantially. It was not possible to use only a single criterion to specify the need for re-injection.

Methods, definitions and units conform to the standards recommended by the International Continence Society, except where specifically noted [5,24].

Statistical comparisons were made with Anova, χ^2-tests, and t-tests, all at a significance level $p = 0.05$.

The transurethral BTX-A injections were performed as an office procedure. General or spinal anaesthesia was applied for tetraplegic or incomplete paraplegic patients to prevent autonomous dysregulation. The bladder was pre-filled with 100–150 ml saline. The BTX-A injections were mapped on the detrusor, sparing the trigone and the bladder neck. Botox® 300 UI was diluted in 15 ml 0.9% NaCl and 30 injections @ 0.5 ml (10 UI/injection) solution were performed, Dysport® 750 or 1000 UI was diluted in 10 ml 0.9% NaCl and 20 injections @ 0.5 ml (37.5 or 50 UI/injection) solution were performed. After 1 March 2002, 750 UI was used, diluted in 5 ml 0.9% NaCl and 25 injections @ 0.2 ml (30 UI/injection) solution were given to minimize the side effects.

3. Results

Since 1 August 1998 BTX-A injections into the detrusor muscle were performed in 187 patients, of whom 66 (43 men and 23 women) had repeat injections (Table 1) and fulfilled our inclusion criteria for this study. The mean age at first BTX-A treatment was 38.5 (14–77) years. Traumatic spinal cord injury existed in 54 patients, multiple sclerosis in 4, myelitis and brain defects in 2, and aneurysm, dysmelia, hernia, iatrogenic, spinal cord tumor, and spinal cord ischemia in 1 each. The extent of the lesions is given in Table 2.

The average duration of the condition at the first BTX-A injection was 9.2 (0.2–39.9) years. Bladder emptying by aseptic intermittent self-catheterisation was practised by 53 patients, 24 of those also had spontaneous or triggered voiding. Eleven patients always voided spontaneously or by triggering, one was catheterised intermittently, and one had an indwelling catheter.

Anticholinergic treatment was used by 53 patients at baseline. Medication was applied as either monotherapy or in combination with other anticholinergics. The daily dosages used were as followed: oxybutinin 10–40 mg, propiverine 30–45 mg, tolterodine 4–8 mg, trospium chloride 30–120 mg. 13 patients did not use anticholinergics because of adverse effects or ineffectiveness.

All patients complained of bladder overactivity and incontinence. The primary treatment indications were reduced bladder capacity in all patients combined with

Table 1
Number and type of injections

Injection sequence	1	2	3	4	5	6	7
Number of patients	66	66	34	17	5	3	1
Botox®	44	42	23	11	0	1	0
Dysport®	22	24	11	6	5	2	1

Table 2
Patient neuropathic characteristics

		Paraplegic		Tetraplegic	
		complete	incomplete	complete	incomplete
Male	43	23	12	2	6
Female	23	6	11	2	4
Total	66	29	23	4	10