European Urology

European Urology 48 (2005) 984–990

Botulinum-A Toxin Detrusor and Sphincter Injection in Treatment of Overactive Bladder Syndrome: Objective Outcome and Patient Satisfaction

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Accepted 30 June 2005

Available online 18 July 2005

Abstract

Objective: We investigated the effect of botulinum-a toxin injections into the detrusor and external sphincter muscle in patients with overactive bladder (OAB) symptoms.

Methods: We included 44 patients - 41 women and three men with a mean age of 66.1 years - who were suffering from OAB symptoms that were refractory to anticholinergic treatment. We injected 200–300 U of BTX-A (Botox®) into the detrusor muscle; 22 patients also received external sphincter injections. For outcome analysis, we used a bladder diary, a urodynamic examination, and a questionnaire that consisted of 27 validated questions.

Results: Changes in the bladder diary 4 weeks and 3, 6, and 9 months after BTX-A injection were as follows: Micturition frequency was reduced by 12%, 16%, 13% and 9%, respectively. Average pad use decreased from 4.2 pads per day to at most 2.4 pads per day after 6 months. Urodynamic changes were most distinct after 4 weeks: the volume when the first uninhibited detrusor contraction occurred increased from 149 ± 18.2 mL to 263 ± 24.2 mL, and maximum cystometric bladder capacity increased from 228 ± 19.2 mL to 305 ± 19.0 mL. Subjectively, 86% of the patients would choose this procedure for their bladder condition again. Residua 4 weeks after additional injection into the sphincter muscle were distinctly smaller than in the ''only detrusor'' group.

Conclusions: BTX-A detrusor and sphincter injection is very effective in treating OAB symptoms. For patients who might be expected to have residual urine after injection only into the detrusor, additional injection of low doses of BTX-A into the external sphincter muscle could be one option to reduce that risk.

Keywords: Detrusor; Detrusor overactivity; Overactive bladder syndrome; OAB; Botulinum toxin; Botox

The International Continence Society (ICS) defines overactive bladder (OAB) syndrome as a medical condition that consists of urinary frequency and urgency with or without urge incontinence in the absence of local pathologic factors [1]. OAB substantially affects quality of life [2]. Large survey studies found the prevalence of OAB in the United states and Europe to be 16–17% [3,4]. Although OAB can occur at any age, its prevalence increases with age and is higher in women than men [4,5]. Various age-related changes in cell function, structural integrity, central nervous control, and hormone balance seem to be contributing factors [6,7]. Besides behavior therapy, biofeedback, and neuromodulation, especially anticholinergics are the mainstay of conservative treatment of OAB [8–12]. However, side effects or lack of effectiveness can lead to discontinuation of treatment in at least 25% of patients [13,14].

Botulinum toxin (BTX) is becoming more and more established in treatment of dysfunctional voiding of

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0302-2838/$ – see front matter
doi:10.1016/j.eururo.2005.06.021

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any origin. Reports of its use in urology date to 1988, when Dykstra et al. first reported the use of BTX-A in treatment of neurogenic detrusor sphincter dyssynergia (DSD) [15], but Schurch et al. [16] were the first to successfully treated neurogenic detrusor overactivity in spinal-cord-injured patients whose condition was refractory to anticholinergic drugs. There have also been reports of BTX detrusor injections in patients who have non-neurogenic OAB [17–22]. It is not uncommon for these patients to build up residual volume after exclusive detrusor injection, sometimes even requiring temporary catheterization [18–21]. Encouraged by our good experience with detrusor injections in children who had neuropathic bladder due to meningomyelocele [23], we conducted this study in adults who had non-neurogenic OAB. We were interested in an extended objective and subjective outcome analysis and an exploration of the benefits of additional external-sphincter injection in these patients.

1. Material and methods

We included 41 women and three men in our 3-year prospective one-center study, which ran from January 2001 to December 2004. Their average age was 66.1 years (range, 30–91 years; median, 67 years). Inclusion criteria were OAB symptoms according to the ICS definition [1], such as increased daytime frequency, nocturia, and urgency with or without urge incontinence. Before inclusion, the symptoms had been shown to be refractory to several anticholinergic drugs and to such therapy as behavior, biofeedback, or neuromodulating therapy. Patients were asked to write in a standardized bladder diary. At the initial visit, we took a detailed history, conducted physical and neurourologic examinations, and performed laboratory studies of urine to exclude urinary infection. Vaginal examination was conducted to exclude anatomic abnormalities, such as pelvic-organ prolapse, and cystoscopy. Postvoiding residual volume was measured by catheterization within the context of the urodynamic examination. During that urodynamic examination, the reflex volume (the volume when the first uninhibited bladder contraction occurred), the volume when a strong desire to void was expressed, the maximum detrusor pressure, and the maximum cystometric bladder capacity were measured. We followed the recommendations of the ICS Standardization Committee [1] regarding urodynamic techniques strictly. Anticholinergic medication were stopped at least 14 days before enrollment except in four patients, in whom this medication had some benefit and who did not want to relinquish on it; the medication then had to be taken by those four patients in the same dosage over the entire study to ensure clear data. For our urodynamic studies, bladder-filling rate was 20 mL/min. We assessed subjective improvement in lower urinary tract symptoms after BTX-A therapy with three validated questionnaires that the patients were given at each visit. The Urogenital Distress Inventory (UDI-6) provides information on OAB symptoms, stress urinary incontinence, and symptoms of bladder outlet obstruction in women; the overall symptom score ranges from 0 (no symptoms) to 18 (very bothersome symptoms) [24]. The Symptom Severity Index (SSI) and the Symptom Impact Index (SII) [25] are valid and reliable instruments for assessing the severity of incontinence and its effect on patient's lives. The SSI investigates symptoms of incontinence itself (frequency, amount of urine leakage, activities that precipitate incontinence, and so on). The SII aims more at the daily activities and social activities that are restricted by incontinence. The SSI score ranges from 0 (no symptoms) to 20 (always symptoms), and the SII score from 0 to 13. To exclude possible influence by a doctor or a nurse, the questionnaires were filled out by the patients alone. For injection therapy, we used 200–300 U of Botox® (Allergan, Irvine, California). The BTX-A was diluted to 20 mL of normal saline. The toxin was injected transurethrally with a rigid cystoscope and a 6 Fr injection needle (Wolf® endoscopes, Germany) into 40–50 sites of the detrusor muscle. Before this study, we were used to sparing the trigone to avoid vesicoureteral reflux [23], as suggested by Schurch et al. [16]. Nowadays, we inject BTX-A into all sites of the detrusor muscle without excluding the trigone, because Chancellor et al. [17] could not find any iatrogenic reflux in OAB patients in whom he had injected BTX-A into the bladder base and the trigone. Patients who had even small amounts of residua ($\geq$15 mL) ($n = 22$) also received a quadrant injection (50–100 U) in the external sphincter to circumvent postoperative urine retention and the need for self-catheterization; patients who we thought were at higher risk for urine retention, in particular because of distinct preoperative residua, received higher doses. Nevertheless, a total of 300 U of Botox® was never exceeded. The procedure was done under general, spinal, or local anesthesia in combination with light sedoanalgesia. The local anesthetic was 50 mL of Lidocain 1%, which was placed in the bladder via a transurethral catheter and stayed there for at least 20 min; under these conditions, the procedure was tolerated without discomfort, but it can be used only for detrusor injections. After injection therapy, a 16 Fr transurethral silicone balloon catheter was placed for at least 6 hours. Patients were discharged from the hospital on the same or the following day. Urodynamic-followup visits took place regularly: at 4 weeks and then 3, 6, and 9 months after BTX-A injection. For every followup visit, the bladder diary had to be used again for 3 days. At the 3-month followup visit, patients were asked to fill out, in addition, a postoperative satisfaction questionnaire as used by Choe et al. [26]. Values are given as means $\pm$ standard error of the means (SEM). For statistical analysis, we used the Wilcoxon pair-difference test, the Mann-Whitney test, and the Pearson chi-square test. We regarded $p < 0.05$ as statistically significant. The study protocol was approved by the local ethics committee of the Free University of Berlin.

2. Results

Results are given as baseline values and the values after 1, 3, 6 and 9 months, respectively.

2.1. Bladder diary

The daytime frequency (or nighttime frequency) changed from 9.67 $\pm$ 0.60 (2.38 $\pm$ 0.41) to 8.52 $\pm$ 0.40 (2.00 $\pm$ 0.24) ($p < 0.05$), 8.09 $\pm$ 0.36 (1.57 $\pm$ 0.18) ($p < 0.05$), 8.42 $\pm$ 0.51 (1.82 $\pm$ 0.35) (not significant), and 8.81 $\pm$ 0.80 (1.75 $\pm$ 0.35) (not significant). Maximum micturition volume increased from 227.03 $\pm$ 25.46 mL to 258.98 $\pm$ 24.22 mL ($p < 0.05$), 269.75 $\pm$