Int Urogynecol J (2008) 19:905–909
DOI 10.1007/s00192-007-0548-9

ORIGINAL ARTICLE

Botulinum toxin-A for idiopathic overactivity of the vesical detrusor: a 2-year follow-up

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Received: 19 June 2007 / Accepted: 12 December 2007 / Published online: 19 January 2008

Abstract The aim of this trial was to examine the effects after 2 years of a single intravesical botulinum toxin-A injection (BTX-A). This prospective, observational study was conducted using urodynamic measurements and quality of life (QoL) assessment to document the effect after 2 years of a single 100 I.U. injection of BTX-A into the vesical detrusor muscle. Twenty-six patients were followed up for 2 years after a first intravesical BTX-A injection. Of these 26 patients, one was a primary failure, three were lost to follow-up, and 11 patients had a repeated injection at 5–26 months (one patient had a third injection). Seven of the remaining 11 patients in the single injection group were recommended repeated injection or another treatment, and four required no other treatment. In conclusion, 2 years after a single BTX-A injection statistically significant differences in urodynamics and an improvement in QoL could still be demonstrated.

Keywords Botulinum toxin · Overactive bladder · Intradetrusoral injections · Nonneurogenic · Intravesical injection · Botox

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Introduction

According to the International Continence Society, overactive bladder (OAB) is characterized by symptoms of urgency with or without incontinence, often associated with frequency and nocturia [1]. It may be neurogenic or non-neurogenic in origin. Anticholinergics are the mainstay of non-invasive treatment for both types. These drugs act by inhibiting acetylcholine-dependent bladder contractions, thereby improving bladder capacity and reducing urgency and urge incontinence. However, their use is limited by side effects, such as dry mouth, blurred vision, constipation, and impaired brain function and, most importantly, limited efficacy [2–5]. Alternative treatment options for OAB patients are therefore required.

Cystoscopically guided injections of botulinum toxin-A (BTX-A) into the vesical detrusor muscle have shown to be efficacious, safe, and well tolerated in patients with neurogenic detrusor overactivity (NDO) and patients with idiopathic detrusor overactivity (IDO) [6–13]. Unfortunately, however, published studies in the IDO population are of small sample size and mostly without level A evidence, and there are no published data on the long-term effects of a single BTX-A injection in IDO patients. One trial with IDO and NDO patients reported a maximum duration of action of 12 months after a single BTX injection, with a range of a mean duration of 3–10.5 months [6, 12, 14, 15]. This study investigated clinical and urodynamic outcomes after 2 years in IDO patients after a single 100 U.I. BTX-A injection.

Materials and methods

The trial was approved by local ethical board. Female patients with urodynamically proven non-neurogenic OAB/

wet resistant to prior antimuscarinic treatment were enrolled in this prospective observational study. Preoperatively, a urodynamic assessment was performed consisting of a detailed medical history, a physical examination, evaluation of a 1-week voiding diary, cystometry, cystoscopy, serum biochemistry, urinalysis, and a urine culture. Only patients with post-void residual (PVR) volumes <100 ml were included in the trial. After a single prophylactic dose of intravenous antibiotic (cephazoline), patients received a single 100 I.U. intravesical injection of BTX-A (Botox, Allergan, AG, Pfäffikon, Switzerland) cystoscopically, using either spinal or general anesthesia. BTX-A was diluted with 30 ml of 0.9% saline and injected into 30 different sites of the vesical detrusor sparing the trigone. We have previously described the reasons for the choice of this dose and dilution scheme [7]. All patients were asked to stop their initial anticholinergic medication 1 week after their botulinum toxin treatment. Postoperatively, patients were asked to reduce their antimuscarinic medication gradually over 7 days and were discharged from the hospital when PVR was <100 ml. Quality of life (QoL) was assessed using the validated German version of the King's Health Questionnaire (KHQ) [16], a disease-specific questionnaire that assesses ten domains linked to health-related QoL. All patients were followed up at 4 weeks, 36 weeks, and 2 years after the first botulinum toxin injection. Outcomes at 36 weeks follow-up have been published previously [7]. Here, we report outcomes at 2 years. Patients with recurrent

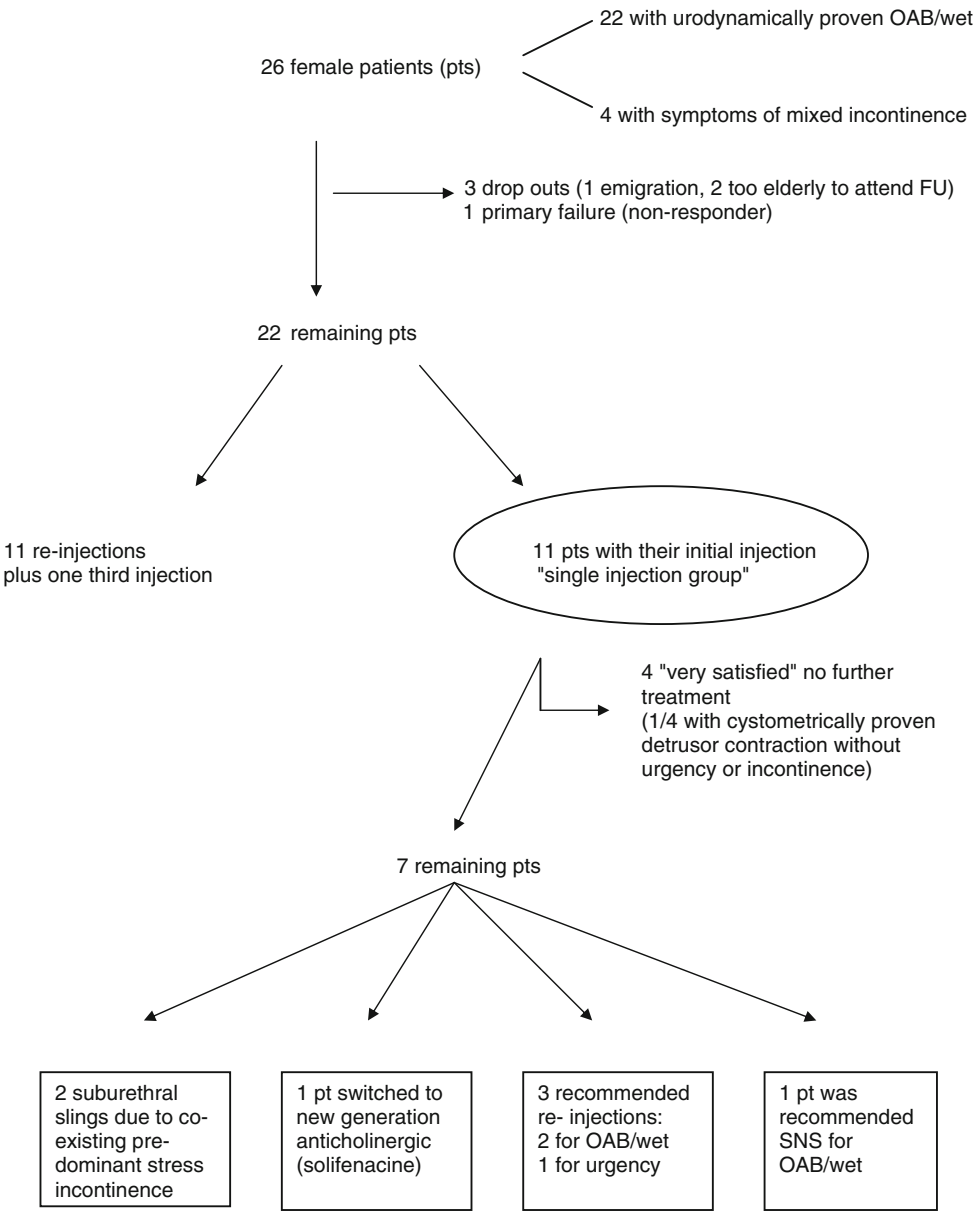

Fig. 1 Follow up and treatment during the 2-year-observation-time

symptoms and recurrent, urodynamic-proven detrusor overactivity were offered a repeated BTX-A injection and excluded from further evaluation, because we intended to study the longevity of a single injection.

Statistical analysis of the KHQ sum score and urodynamic parameters was performed in cooperation with the Institute of Biostatistics of the Zurich University using Wilcoxon-signed ranks test. The program applied was SPSS (SPSS Inc. Chicago, IL, USA). A probability value of $p<0.05$ was considered statistically significant.

Results

Twenty-six female patients (mean age 66 years, range 48–84) who met the entry criteria were enrolled in the trial. Four of these patients had symptoms of mixed incontinence, and one woman had previously received a suburethal sling.

Out of the 26 patients, one patient had no response to BTX-A and was considered a primary failure. Three patients were lost to follow-up over the 2-year follow-up period (one emigrated; two were too elderly to attend follow-up examinations). Therefore, 22 patients could be evaluated at the 2-year follow-up examination (mean age 63.9 years, range 50–86). (Also view Fig. 1).

During the 2-year follow-up period, 11/26 patients had received a second injection at a mean of 14 months after their initial treatment (SD 5, range 5–26 months). (Also view Fig. 2). One of these patients had also received a third BTX-A injection. The remaining 11 patients had only received their single initial injection (which will be referred to as "single injection group"). 7/11 of this single injection group did not show any detrusor contractions, and 4/11 did not request any further treatment. Seven patients had improved and responded to alternative therapy, such as a suburethral vaginal sling procedure because of a predominant pre-existing stress urinary incontinence in two patients and recommendation of a selective oral anticholinergic drug (solifenacine) for urgency in one patient. Three patients were recommended another BTX-A injection, and one patient was offered sacral neuro-modulation, because her insurance was not willing to pay for a repeated BTX-A injection. In the meantime, she was offered behavioral therapy and advised to take desmopressin on demand for rare incontinence episodes.

Objective QoL measures of the 11 patients of the single injection group demonstrated a significant improvement in household and outdoor activities which was reported in 70% and 80%, respectively, ability to travel in 40%, effects on nocturnal sleep in 20%, and necessity of wearing pads in 20% of these patients. The KHQ sum score showed a statistical significant improvement in the following categories: incontinence impact, role limitation, and emotions. Social and physical limitations, sleep, and energy and severity measures showed a trend towards improvement but did not reach a statistical significance, whereas general health perception was unchanged (Fig. 3). The mean maximum cystometric bladder capacity (MCBC) in the single injection group after 2 years was significantly higher than the mean pre-treatment MCBC (360±79 ml vs 238±96 ml ($p<0.005$); Fig. 4). Cystometric filling volumes at first and strong desire to void were elevated compared to the preoperative situation (138.4±53.1 vs 128.9±66.7 ml, 209.2±65.5 vs 198.1±66.4 ml), although the difference was small and therefore not statistically significant. Daytime frequency and nocturia were reduced (9.5±3.0 vs 11.4±2.9, 1.9±0.5 vs 2.1±1) compared to before BTX-A injection,

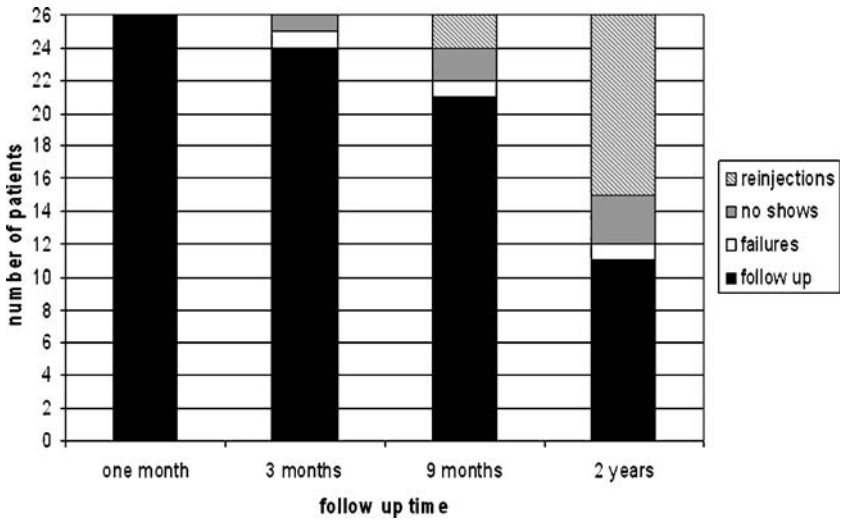

Fig. 2 Reasons for the drop out of the patients during 2 years until the 2-year follow-up examination

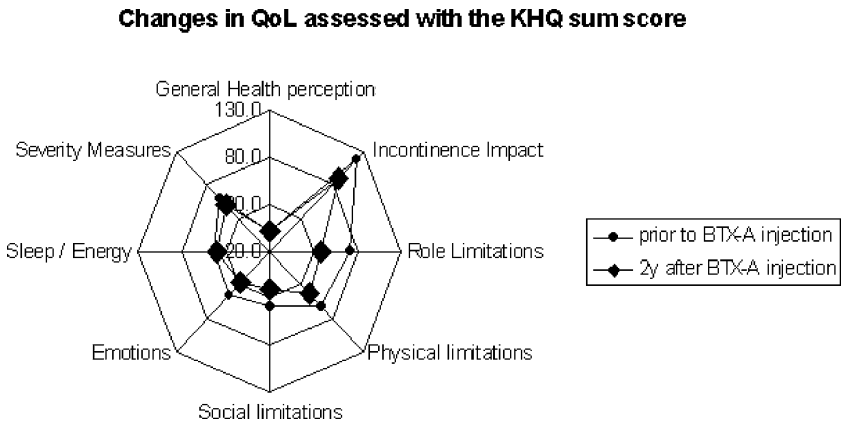

Fig. 3 Changes in the King's health sum score after 2 years

but the difference did not reach statistical significance. Mean PRV at 2 years was 36.4 ml (0–100, 1×50, 1×70, 2×75, 1×100 ml).

Complications

One non-responder, one patient with PVR of 100 ml and recurrent uncomplicated urinary tract infections, and one patient with intermittent high PVR who transiently had to perform clean intermittent self catheterization de novo because of a PVR of 170 ml at one of the follow-up examinations which later resolved spontaneously.

Discussion

This is the first trial showing that a single injection of BTX-A in IDO patients was able to improve QoL and urodynamic parameters after 2 years. Improvements were seen in 7/26 patients, and another 4/26 (15%) of the patients did not require further treatment. Our results indicate that the duration of effect of a single intravesical BTX-A treatment may be longer than initially thought, and that the BTX-A effect outlasts its mere motor-blocking potency, which recovers after several months because of new nerve sprouting. Recently published studies give reason to believe that the neurotoxin affects not only efferent but also afferent pathways and seems to have an additional central modulating effect [17–23], which results in a profound and long-lasting inhibition of pathophysiologic mechanisms that are thought to be the basis for detrusor overactivity [24]. These mechanisms may underlie the observed long-term effects of BTX-A.

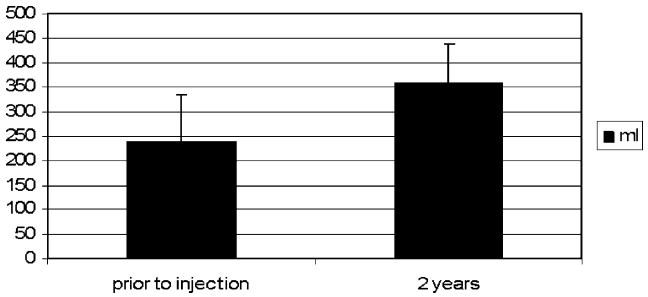

Fig. 4 Comparison of the mean maximum bladder capacity of the patients with a single BTX-A injection (n=11) before injection compared to after 2 years

Urodynamically, this effect was manifested as a significantly increased posttreatment MCBC compared with that before treatment; 8/11 patients had a MCBC of more than 300 ml compared to only 2/11 patients before BTX-A treatment. The increased MCBC was accompanied by a significant improvement in incontinence-related QoL, even though daytime frequency, nocturia, first, and strong desire to void had nearly returned to baseline levels. Interestingly, and contrary to our results, another study in NDO and IDO patients after intravesical BTX-A therapy found a correlation between changes in QoL and changes in 24-h micturition frequency, number of voids associated with urgency, and number of urge incontinence episodes, but not urodynamic parameters [25].

Although there are no published randomized controlled trials to date, available data suggest that intravesical BTX-A injection is an excellent alternative therapeutic option in both NDO and IDO patients who do not respond to, or do not tolerate, anticholinergic medication. Open questions on the adequate dosing, dilution, and injection scheme remain, which will need to be further evaluated.

Despite a small sample size, this study adds to the growing body of evidence of the efficacy for BTX-A as a second line treatment for IDO patients and shows that its duration of action is longer than its mere motor-blocking potency. Contrary to other studies on the same issue, a full postoperative cystometric evaluation was performed, which could demonstrate that the majority of the patients still had no detrusor contractions.

We are aware that the statistical power of our study is restricted by the small number of patients, and that further clinical research in this area is urgently required.

Conflicts of interest None.

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