Efficacy of botulinum-A toxin in the treatment of detrusor overactivity incontinence: A prospective nonrandomized study

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KEY WORDS
Botulinum toxin A
Detrusor overactivity incontinence
King’s Health Questionnaire

Objective: This study was undertaken to investigate the efficacy and safety of botulinum-A toxin (BTX-A) treatment for non-neurogenic detrusor overactivity incontinence.

Study design: This prospective nonrandomized ongoing study was performed in a tertiary referral urogynecology department. In 26 women with urge incontinence and urodynamically demonstrated detrusor overactivity incontinence resistant to conventional treatment 100 units of BTX-A were injected into the detrusor muscle at 30 sites. Clinical and urodynamic evaluations and a quality of life assessment were performed at baseline and 4, 12, and 36 weeks after BTX-A treatment.

Results: Of 26 women, 14 were dry after 4 weeks, 13 of 20 women after 12 weeks, and 3 of 5 women after 36 weeks. Two women failed to respond. Two women were on self-catheterization temporarily. There were no other complications besides 9 urinary tract infections within the 51 follow-up visits.

Conclusion: BTX-A treatment seems to be a safe and efficacious new treatment option for patients with detrusor overactivity incontinence.

Botulinum toxin, first isolated by van Ermengem in 1897,4 is a highly potent neurotoxin for skeletal muscle function. It acts by inhibiting acetylcholine release at the presynaptic neuromuscular junction.5 Its subtype, botulinum-A toxin (BTX-A), has entered clinical practice for treatment of muscle spasticity at various sites.6 This concept was transferred to the smooth muscle of the detrusor vesicae for successful control of reflex incontinence in patients with spinal cord injury and neurogenic detrusor hyperreflexia7,8 and has recently been established based on a large retrospective European multicenter study in 2004.9 Consequently, BTX-A might also be efficacious to inhibit involuntary detrusor contractions in
non-neurogenic detrusor overactivity incontinence. It was the purpose of this study to investigate the efficacy and safety of BTX-A injections into the detrusor muscle in patients with non-neurogenic detrusor overactivity incontinence.

Material and methods

An open label, nonrandomized, prospective study starting from February 2003 was performed after approval was obtained from the Cantonal Institutional Review Board. All eligible patients signed the informed consent form before the treatment. Until March 2004, 26 female patients (mean age 66; range 48-84 years) entered this ongoing study. Patients were recruited from the urogynecology unit of the department of obstetrics and gynecology, Cantonal Hospital Lucerne, Switzerland. Included were women with urge incontinence and urodynamically demonstrable detrusor overactivity incontinence who failed to respond to various antimuscarinics. Exclusion criteria were renal dysfunction, myasthenia gravis, pregnancy, breastfeeding, and neurogenic hyperreflexia. Pretreatment evaluation consisted of medical history, physical examination, full urodynamnic examination, including filling cystometry and uroflowmetry, voiding diary, serum chemistry (leukocytes, urea, creatinine), ultrasound of the upper urinary tract, urinalysis, and urine culture. Urinary tract infections were treated before urodynamic examination or BTX-A injection.

Under spinal or general anesthesia, a total amount of 100 units of commercially available BTX-A (Botox, Allergan AG, Lachen, Switzerland), diluted in 30 mL 0.9% saline solution, were injected into the detrusor muscle while carefully sparing the trigone to avoid iatrogenic reflux. Under video-cystoscopic control, 1 mL was injected at 30 locations covering the inner surface of the bladder by using a 23-gauge Bard injection needle (Bard Medica SA, Oberrieden, Switzerland). Continuous cardiovascular monitoring was ensured in all patients during the procedure. A single dose of cefazolin 2 g (Kefzol, Medika AG, Aesch, Switzerland) was given as a perioperative prophylaxis. After the BTX-A injection, an indwelling catheter was inserted and the bladder drained for 24 hours. All patients were asked to gradually decrease antimuscarinic medication within 1 week after treatment.

Patients were clinically and urodynamically followed up 4, 12, and 36 weeks after BTX-A treatment. Primary outcome measures were safety of BTX-A treatment and maximum cystometric bladder capacity (MCBC), bladder compliance, volume at first, and strong desire to void as well as daytime frequency and nocturia recorded.

Figure  Distribution of MCBC in patients categorized into 5 volume-depended groups before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment.
in voiding diaries. Urodynamic parameters analyzed were defined according to the standardization reports of the International Continence Society.1 The aim during urodynamic studies was to reproduce the patients’ symptoms as recommended by the “Good Urodynamic Practices.”10 MCBC was defined as the volume when urinary leakage caused by detrusor overactivity occurred. In the posttreatment period, MCBC was defined as before treatment or when the patient felt she can no longer delay micturition in the absence of an involuntary detrusor contraction. Secondary outcome measures included subjective cure of urge incontinence episodes, postvoid residual volume (PVR), and a QoL assessment performed by using the King’s Health Questionnaire (KHQ)11 validated in the German language. The KHQ also was used to determine subjective severity of incontinence before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment. If PVR was greater than 100 mL at any follow-up visit, patients were instructed to perform clean intermittent self-catheterization and were followed up in 1-week intervals.

Failures, defined as patients urodynamically and subjectively unchanged after initial BTX-A injection, were offered a second injection after the first follow-up visit. Repeated BTX-A injections were offered if patients experienced a relapse of initially improved symptoms. Statistical analysis was performed with analysis of variance (ANOVA) for repeated measures to compare urodynamic values before and after BTX-A treatment. KHQ data were analyzed with Wilcoxon signed ranks test. Data programs used were SAS (SAS Institute, Cary, NC) and SPSS (SPSS Inc, Chicago, Ill). A probability value of $P < .05$ was considered significant.

**Results**

At baseline 13 of 26 patients (50%) showed a MCBC of less than 200 mL (4 of the patients <100 mL), 7 of 26 (27%) had a MCBC between 200 to 299 mL, 5 of 26 (19%) between 300 to 399 mL, and 1 of 26 (4%) of 428 mL (Figure). Primary outcome measures before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment are presented in Tables I and II. Before BTX-A treatment, assessment of QoL by the KHQ revealed that in 9 of 10 urge-related items, the majority of the items had a score of 1 or 2.

The KHQ also was used to determine subjective severity of incontinence before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment. If PVR was greater than 100 mL at any follow-up visit, patients were instructed to perform clean intermittent self-catheterization and were followed up in 1-week intervals.

### Table I  Urodynamic parameters before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment (n = 26)</th>
<th>Follow-up times after BTX-A treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 wks (n = 26)</td>
</tr>
<tr>
<td>MCBC (mL)</td>
<td>216.0 ± 104.2</td>
<td>345.7 ± 98.4 (P &lt; .0001)</td>
</tr>
<tr>
<td>C (mL/cm H$_2$O)</td>
<td>14.3 ± 9.9</td>
<td>37.9 ± 19.4 (P &lt; .0005)</td>
</tr>
<tr>
<td>Volume at first desire to void (mL)</td>
<td>116.8 ± 69.9</td>
<td>169.1 ± 86.4 (P &lt; .0005)</td>
</tr>
<tr>
<td>Volume at strong desire to void (mL)</td>
<td>176.5 ± 78.7</td>
<td>229.8 ± 89.0 (P &lt; .0236)</td>
</tr>
<tr>
<td>Cystometric detrusor contractions (no. of patients)</td>
<td>26 (100%)</td>
<td>12 (46%)</td>
</tr>
<tr>
<td>PVR (mL)</td>
<td>18.0 ± 22.0</td>
<td>62.5 ± 64.3 (P &lt; .0129)</td>
</tr>
</tbody>
</table>

C, Bladder compliance.

* No statistical analysis was performed due to the small size of the patient group.

† Data are given as mean ± SD.

‡ Significant difference to baseline data (ANOVA for repeated measures).

### Table II  Daytime frequency and nocturia before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pretreatment (n = 26)</th>
<th>Follow-up times after BTX-A treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4 wks (n = 26)</td>
</tr>
<tr>
<td>Daytime frequency</td>
<td>11.7 ± 3.3</td>
<td>7.2 ± 2.5 (P &lt; .0001)</td>
</tr>
<tr>
<td>Nocturia</td>
<td>2.6 ± 1.4</td>
<td>1.2 ± 1.0 (P &lt; .0018)</td>
</tr>
</tbody>
</table>

Data are given as mean ± SD.

* No statistical analysis was performed due to the small size of the patient group.

† Significant difference to baseline data (ANOVA for repeated measures).
patients had the highest impact category on the 4-point scale. The effect of urge incontinence on sleep was evaluated as less disturbing, only 5 patients recorded “all the time” (Table III).

BTX-A treatment was successfully delivered in all 26 patients. There were no injection-related complications or toxin-related side effects. After removal of the indwelling catheter, no acute urinary retention was noted. All patients have been fully evaluated after 4 weeks, 20 patients after 12 weeks, and 5 patients after 36 weeks. The mean posttreatment period for all patients is 27 weeks (minimum 4 weeks, maximum 52 weeks). At each follow-up visit, ultrasound of the upper urinary tract revealed no urinary tract damage and serum chemistry findings were normal.

Significant changes of the primary outcome measures were observed after BTX-A treatment. No patient had a MCBC of less than 100 mL anymore, and the majority of the patients had increased their MCBC to 400 mL or greater (Figure). Urodynamic examinations after 4 and 12 weeks revealed a significant increase in mean MCBC and compliance. In the 5 patients who were evaluated after 36 weeks, the same trend was observed. There were no detrusor contractions associated with urinary leakage demonstrable in 14 of 26 patients (54%) after 4 weeks, in 13 of 20 patients (65%) after 12 weeks, and in 3 of 5 patients (60%) after 36 weeks (Table I). Mean daytime and nighttime frequency decreased significantly after the treatment (Table II).

After 4 weeks, 18 of 26 patients (69%) were subjectively free of urge incontinence episodes, after 12 weeks 16 of 20 patients (80%), and after 36 weeks 1 of 5 patients (20%). Mean PVR was found to be significantly increased only at the 4-week follow-up visit (Table I). QoL assessment at the 4- and 12-week follow-up showed a significant subjective improvement in all urge-related items evaluated by the KHQ (Table III). No statistical analysis was performed for the 5 patients evaluated after 36 weeks because of the small size of the patient group.

Two patients had no benefit in terms of urge incontinence, which was confirmed by urodynamics and QoL assessment. They dropped out after the first follow-up visit. No patient showed acute urinary retention after BTX-A treatment, but 2 patients had a PVR development of 130 and 230 mL after 4 weeks and were on self-catheterization for 1 week until the PVR was less than 100 mL. Within the 51 follow-up visits, 9 urinary tract infections in 8 patients had to be treated. So far, 2 patients were reinjected after the effect of BTX-A treatment had diminished 5 and 10 months after the initial injection. At present all successfully treated patients (24/26 patients) would be willing to undergo a second BTX-A injection if efficacy diminishes.

Comment

On the basis of sequential urodynamic and subjective evaluation, this is one of the first studies indicating that BTX-A injections into the detrusor muscle seem to be a safe and efficacious treatment option in patients with non-neurogenic detrusor overactivity incontinence resistant to conventional treatment. Urodynamic follow-up evaluations revealed significant improvement of all key parameters. Mean maximum cystometric bladder capacity and mean compliance significantly increased 4

**Table III**  Responses to the KHQ incontinence questions before BTX-A treatment and at 4, 12, and 36 weeks after BTX-A treatment

<table>
<thead>
<tr>
<th>KHQ (items)</th>
<th>No. of patients in the highest impact category for each item</th>
<th>No. of patients with subjective improvement of at least 1 category</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 26)</td>
<td>4 wk (n = 26)</td>
</tr>
<tr>
<td>Effect on life†</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td>Role limitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household tasks †</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Daily activities outside the home †</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Physical/social limitations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ability to travel †</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Social life †</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Daytime frequency †</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Urge incontinence †</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td>Effect on sleep †</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Necessity of wearing pads †</td>
<td>18</td>
<td>14</td>
</tr>
<tr>
<td>Embarrassment †</td>
<td>13</td>
<td>6</td>
</tr>
</tbody>
</table>

* No statistical analysis was performed due to the small size of the patient group.
† Response category “a lot” (of “not at all–a little–moderately–a lot”).
‡ Significant difference to baseline data (Wilcoxon signed ranks test).
§ Response category “all the time” (of “never–sometimes–often–all the time”).
and 12 weeks after BTX-A injection and also in the 5 patients seen so far at the 36-week follow-up visit increasing values of both parameters compared with baseline were observed. After BTX-A treatment the majority of the patients showed a normal maximum cystometric bladder capacity. Fourteen of 26 patients after 4 weeks, 13 of 20 patients after 12 weeks, and 3 of 5 patients after 36 weeks were clinically dry without any cystometric detrusor contractions during bladder filling. Mean daytime frequency had decreased significantly at each follow-up visit and mean nocturia 4 and 12 weeks after treatment. All these improvements of bladder function are mirrored by a significant positive impact on QoL, based on the KHQ.

So far, existing experience of application of BTX-A for non-neurogenic detrusor overactivity is scarce and differs in dosage, injection sites, and injection rate. In 3 abstracts all together 49 patients have been treated. With 30 patients, the study by Loch et al\textsuperscript{13} is the largest evaluating the effect duration and possible complications of BTX-A treatment. Unfortunately, it was a mixture of non-neurogenic and neurogenic detrusor overactivity for which BTX-A is already the treatment of choice\textsuperscript{7,9} and the proportion of the latter group is not mentioned. A significant improvement in urge symptoms was observed 4 weeks after the treatment. The dosage of BTX-A used were 200 units, which may be the reason of acute urinary retention found in 1 patient and a significant increase of mean PVR volume. Zermann et al\textsuperscript{14} reported on a dose titration study (50, 100, and 200 units of BTX-A) in 7 patients. The study group was similar to ours, apart from the fact that each of the patients had failed at least 2 sacral nerve stimulations after unsuccessful antimuscarinic treatment. Initially promising results in 4 of 7 patients, however, lasted for 8 to 20 weeks only. Three patients did not respond at all. Compared with our study, the short duration of efficacy and the poorer results might be a result of the lower dosage used in a few cases (50 units of BTX-A), the different injection sites (trigone and bladder base), and the reduction of injection sites (5 to 7). Radziszewski and Borkowski\textsuperscript{15} reported about the response to BTX-A treatment in 12 patients with non-neurogenic detrusor overactivity. BTX-A of 300 units was injected into the detrusor muscle at 10 to 15 sites sparing the trigone. No change in PVR volume was noted and none of the patients demonstrated detrusor overactivity 4 weeks after treatment. Unfortunately, no further follow-up was reported so far. In summary, to date neither adequate dosage nor injection site is established.

The dosage of 100 units of BTX-A used in our study is considerably less than the 300 units of BTX-A established in a dose finding study in 2000\textsuperscript{7} in patients with neurogenic detrusor overactivity. Our dosage of 100 units of BTX-A so far seems to be similarly effective with regard to total continence rate (80% total continence rate in our study vs 73% in the retrospective European multicenter study in 2004\textsuperscript{9} after 12 weeks) and safe in sustaining detrusor function for micturition: the mean PVR volume was only increased 4 weeks after BTX-A treatment.

Important questions are still open. The dosage of 100 units of BTX-A used in our study was not purely arbitrary. As existing experience of application of BTX-A for non-neurogenic detrusor overactivity is scarce and adequate dosage, injection site, or injection rate are not established so far, we decided to use a “low-risk” dosage of BTX-A to avoid an acute urinary retention directly after the treatment and an increase of mean PVR volume. This was also based on the results observed in the 3 abstracts published so far and in which an acute urinary retention in 1 patient and a significant increase of mean PVR volume was reported after application of 200 units of BTX-A.\textsuperscript{13} What is even more important before routine treatment can be recommended is, how many injections and which dosage of BTX-A could cause irreparable damage to the detrusor muscle. Data from BTX-A treatment in patients with neurogenic detrusor overactivity clearly indicate that reinjections of BTX-A are necessary to maintain continence.\textsuperscript{7} In our series of women with non-neurogenic detrusor overactivity incontinence, 2 of 26 patients had to be reinjected 5 and 10 months after initial BTX-A injection indicating that BTX-A reinjection is also necessary in the majority of patients. Whether the detrusor muscle is gradually damaged by repeated BTX-A injections is of no importance as far as neurogenic detrusor overactivity is concerned because all patients are on intermittent catheterization as a consequence of spinal cord injury. In contrast, patients with non-neurogenic detrusor overactivity incontinence usually have a normal detrusor function during micturition. Any voiding dysfunction as a result of incontinence treatment would have to be estimated as a serious treatment complication.

Larger studies are needed to clarify the future place of this treatment option for patients with detrusor overactivity incontinence. At present, our data imply that injection of 100 units of BTX-A into the detrusor muscle in patients with non-neurogenic detrusor overactivity incontinence after failed conventional treatment may be offered before more invasive treatment options like sacral nerve stimulation are performed.

**Acknowledgments**

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References