Submucosal Administration of OnabotulinumtoxinA in the Treatment of Neurogenic Detrusor Overactivity: Pilot Single-Centre Experience and Comparison with Standard Injection into the Detrusor

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Key Words
Botulinum neurotoxin · OnabotulinumtoxinA · Neurogenic detrusor overactivity · Submucosal administration

Abstract

Introduction: Apart from the standard intramural administration of botulinum neurotoxin A (BoNT/A) to the detrusor, intense research is taking place into new means of administration in view of the complex mechanism of action of BoNT/A. Methods: An open, randomised, prospective study was performed on a total of 23 patients with neurogenic detrusor overactivity. Following randomisation, patients were treated with 300 U of onabotulinumtoxinA (onaBoNT/A) in either the submucosa or the detrusor. Urodynamic examinations were carried out, and a bladder diary was kept both prior to and 12 weeks after the treatment. All patients stopped taking anticholinergics 1 week prior to the treatment. Results: In both the submucosa and detrusor groups, we recorded a significant improvement in the monitored urodynamic parameters and significant decreases in the frequency of urinary incontinence episodes following the treatment. A comparison of the two groups showed no significant difference between the two forms of application, with the exception of voided volume (p = 0.007). Conclusion: A comparison of the two administration methods did not show any significant difference between onaBoNT/A administration to the submucosa and to the detrusor. Thus, the submucosal injection of onaBoNT/A represents an equally effective approach for its administration to patients.

Introduction

Botulinum neurotoxin A (BoNT/A) treatment has become the method of choice for patients with neurogenic detrusor overactivity (NDO) who are refractory to standard anticholinergic therapy.

The application of BoNT/A to the smooth muscle of the detrusor blocks the presynaptic release of acetylcholine and thus results in chemodenervation and paralysis of the muscle. The application of BoNT/A to the submucosa inhibits the vesicular release of acetylcholine, ATP, substance P and the inhibition of TRPV1 receptor expression [1, 2]. The inhibition of ATP release also affects the potential decrease in the excitation of the suburothelial and urothelial P2X\textsubscript{3} receptors and the P2Y receptors of the myofibroblast network. The transfer of afferent signals between the urothelium and the suburothelial nerve endings is thus reduced. This submucosal innervation modulates the activity of the afferent neural pathway.
The afferent neural pathway is most likely responsible for which is used in the treatment of NDO. This influence on inhibition of afferent and efferent neural transmission, combination of these mechanisms leads to a long-term effect of BoNT/A [4].

BoNT/A administration to the detrusor via intramural injection is a standard approach in the treatment of NDO [5]. Novel findings regarding the complex mechanisms underlying the effects of BoNT/A on the bladder led the authors to use a suburothelial method of administration. This approach is easily controlled using an endoscope.

Patients and Methods

A total of 23 patients with NDO after spinal cord injury (SCI) were enrolled in this open, prospective, randomised study. All patients suffered from neurogenic incontinence and were refractory to standard anticholinergic therapy. The group consisted of 2 females and 21 males aged between 20 and 58 years, with a mean elapsed time since occurrence of SCI of 47 months (11–154). In 11 patients, the SCI was localised to the cervical spinal cord and in 12 patients to the thoracic spinal cord. According to the American Spinal Injury Association (ASIA) classification system, 19 patients were in the ASIA A category, 3 patients in ASIA B and 1 patient in ASIA C. The patients were permitted to participate on the following conditions: their neurological condition was stable, a minimum period of 6 months had passed since the SCI, they were able to carry out clean intermittent catheterisation (CIC) and they had more than five incontinence episodes during the monitored 5-day period. Any patients who had bladder stones in the 6-month period prior to the treatment, tumours in organs of the small pelvis or incidences following radical operation in the small pelvis area in the previous year were excluded from the study. The duration of the basic part of the study was 12 weeks, and a urodynamic examination (filling cystometry) was carried out before the start and in the 12th week of the study. The monitored urodynamic parameters included reflex volume (V_{refl}), cystometric capacity (CC), maximal detrusor pressure (P_{max}) and detrusor compliance.

The bladder diary was filled in for the 5 days prior to the start of the study and 6 and 12 weeks following the end of the treatment. The bladder diary was used to evaluate the number of urinary incontinence (UI) episodes, the number of catheterisations during the monitored period and the voided/catheterised volume (V_{cath}).

The treatment using 300 U of onabotulinumtoxinA (onaBoNT/A) was applied to 30 sites (10 U/ml) in the bladder, with the exception of the trigone. Patients were randomised into two groups. The onaBoNT/A was administered to the submucosa in 12 patients and intramurally administered to the detrusor of the bladder in 11 patients. The procedure was performed using a rigid cystoscope and a flexible, endoscopic 23-gauge needle under anti-biotic prophylaxis, with a short general anaesthetic. Anticholinergic therapy was withdrawn at least 1 week prior to the initial urodynamic examination and then for the entire duration of the study. Following the procedure, the permanent urinary catheter was kept in place for a period of 24 h. The patients returned to CIC following removal of the catheter. We assessed the effect of the treatment on the patients’ quality of life based on the standardised Incontinence Quality of Life Questionnaire (I-QOL). The treatment effectiveness was measured by using the change in the monitored urodynamic parameters and the change in the number of UI episodes over the monitored period.

The study was approved by the European Medicines Agency (EudraCT 2009-012431-15) and the local ethics committee (KNL: URO-2009/1).

The Mann-Whitney test was used to monitor changes between individual groups and statistical significance was set at $p < 0.05$.

Results

Following the submucosal administration of 300 U of onaBoNT/A, there was a significant decrease in the number of UI episodes and frequency of catheterisations within a period of 12 weeks after the treatment. An increase in $V_{cath}$ was apparent when evaluating the bladder diary at 6 weeks and remained for a period of 12 weeks following the treatment. A urodynamic control examination 12 weeks following the treatment found significant increases in $V_{refl}$, CC and detrusor compliance, which were accompanied by a statistically significant reduction in $P_{max}$ (table 1). Four patients in this group (33%) showed no involuntary contraction of the detrusor. The mean effectiveness period of the treatment was 7.3 months. None of the patients was entirely continent following treatment. Nine of the 12 patients (75%) stopped wearing incontinence aids.

In the group treated with 300 U of onaBoNT/A to the detrusor, there were significant decreases in UI episodes and in the frequency of bladder catheterisation and a significant increase in $V_{cath}$. A urodynamic control examination after treatment observed significant $V_{refl}$ and CC increases, and we also recorded a significant $P_{max}$ reduction. Only 1 patient in this group showed no involuntary contraction of the detrusor during the course of the urodynamic control examination. The mean treatment effectiveness period was 6 months. Following treatment, 1 patient (9.1%) was entirely incontinent and 8 patients (72%) stopped wearing incontinence aids. During onaBoNT/A administration to the detrusor group, we recorded temporary weakness of the muscles in 1 patient.
Comparing the results of both groups did not reveal any significant difference in the number of UI episodes, urodynamic parameters, number of catheterisations or duration of treatment effectiveness. A significant difference ($p = 0.007$) in $V_{\text{cath}}$ was found between the two groups (fig. 1). In both groups of patients, the treatment was accompanied by a significant increase in quality of life according to the I-QOL score. A comparison of I-QOL scores did not demonstrate any difference between the two groups. There was no significant difference in the duration of effectiveness of treatment between both groups. All patients completed the treatment course according to the clinical protocol.

**Discussion**

The administration of BoNT/A to the detrusor via intramural injection is the standard method to treat NDO, and the majority of authors who report their results use this approach [5–7]. Due to the variable thickness of the bladder wall, there is an increased risk of delivering BoNT/A outside the detrusor if the wall is thin and of systemic administration into a vessel of the musculature (which significantly increases the risk of possible side effects). The bladder wall thickness variability depends mainly on gender, age, bladder fullness, and the presence of neurogenic lesions or obstructions.

Mehnert et al. [8], in their pilot of 6 patients, compiled a morphological evaluation and assessed the distribution of BoNT/A in the detrusor. The BoNT/A treatment used a standard cystoscopic method and included gadopen-

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**Table 1.** Data from the patient bladder diary, urodynamic parameters and I-QOL score at each scheduled visit

<table>
<thead>
<tr>
<th>Parameter/time point</th>
<th>Suburothelial injection (n = 12)</th>
<th>p value</th>
<th>Detrusor injection (n = 11)</th>
<th>p value</th>
<th>Suburothedral vs. detrusor p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incontinence episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.6 ± 4.7</td>
<td></td>
<td>16.9 ± 5.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>−8.3 ± 3.7</td>
<td>0.000</td>
<td>−12.0 ± 5.1</td>
<td>0.000</td>
<td>0.065</td>
</tr>
<tr>
<td>Week 12</td>
<td>−9.3 ± 4.5</td>
<td>0.000</td>
<td>−13.3 ± 5.4</td>
<td>0.000</td>
<td>0.106</td>
</tr>
<tr>
<td>Frequency of catheterisation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>40.7 ± 6.0</td>
<td></td>
<td>41.3 ± 8.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>−11.2 ± 6.7</td>
<td>0.000</td>
<td>−10.5 ± 3.4</td>
<td>0.000</td>
<td>0.820</td>
</tr>
<tr>
<td>Week 12</td>
<td>−12.0 ± 7.3</td>
<td>0.000</td>
<td>−9.8 ± 5.2</td>
<td>0.000</td>
<td>0.683</td>
</tr>
<tr>
<td>Catheterised volume, ml</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>173.5 ± 41.2</td>
<td></td>
<td>182.4 ± 73.3</td>
<td></td>
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</tr>
<tr>
<td>Week 6</td>
<td>162.8 ± 35.8</td>
<td>0.000</td>
<td>82.5 ± 59.0</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 12</td>
<td>175.1 ± 58.9</td>
<td>0.000</td>
<td>93.3 ± 77.3</td>
<td>0.003</td>
<td>0.007</td>
</tr>
<tr>
<td>V$_{\text{refl}}$, ml</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>159.0 ± 44.2</td>
<td></td>
<td>144.0 ± 57.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>216.4 ± 96.2</td>
<td>0.000</td>
<td>155.5 ± 96.5</td>
<td>0.217</td>
<td></td>
</tr>
<tr>
<td>CC, ml</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>230.0 ± 66.3</td>
<td></td>
<td>207.6 ± 96.5</td>
<td></td>
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</tr>
<tr>
<td>Week 12</td>
<td>229.1 ± 54.7</td>
<td>0.000</td>
<td>187.4 ± 77.3</td>
<td>0.000</td>
<td>0.107</td>
</tr>
<tr>
<td>P$_{\text{max}}$, cm H$_2$O</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>85.8 ± 24.8</td>
<td></td>
<td>104.2 ± 43.2</td>
<td></td>
<td></td>
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<tr>
<td>Week 12</td>
<td>−36.3 ± 27.4</td>
<td>0.001</td>
<td>−46.5 ± 28.1</td>
<td>0.000</td>
<td>0.477</td>
</tr>
<tr>
<td>DC, ml/cm H$_2$O</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.0 ± 8.2</td>
<td></td>
<td>20.4 ± 4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>23.0 ± 22.7</td>
<td>0.005</td>
<td>15.8 ± 11.4</td>
<td>0.001</td>
<td>0.596</td>
</tr>
<tr>
<td>I-QOL score</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>59.5 ± 12.6</td>
<td></td>
<td>53.9 ± 17.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 12</td>
<td>18.6 ± 7.4</td>
<td>0.000</td>
<td>18.8 ± 6.5</td>
<td>0.000</td>
<td>0.705</td>
</tr>
</tbody>
</table>

Values represent means ± SD. V$_{\text{refl}}$ is the bladder volume at first involuntary contraction. DC = Detrusor compliance.
tetate, a magnetic resonance imaging contrasting agent. Magnetic resonance imaging was carried out immediately after BoNT/A administration. This test demonstrated that only 82.4% of the agent administered was localised in the detrusor, with the remainder in the perivesical fat tissue. The authors did not find any side effects due to this phenomenon.

BoNT/A can escape following administration at the needle penetration point following needle removal; however, this amount is anticipated to be minimal and corresponds to the small needle diameter. When using methylene blue to colour the medicament solution during photometric evaluation of the lavage fluid following cystoscopic administration, Madersbacher and colleagues [5] recorded a mean loss of 1.96–19.20 U (median 5.5 U) following the delivery of 170–400 U of onaBTA; this value was negligible in view of the administered dose.

Submucosal onaBoNT/A administration is a new alternative to the classic approach to the detrusor. Using this technique, the administration of the agent to the submucosal space is easier to visually control because a typical mucosal bulking can be observed under this technique (fig. 2). The major advantage of this alternative approach is the ease to visually control the target distribution area with practically no loss of the drug. In addition, the risk of accidental administration to minor blood vessels in the detrusor and the potential side effects are eliminated.

In 2006, Kuo [9] was the first to describe the use of submucosal administration for NDO. Following the submucosal application of 200 U of onaBoNT/A (40 injection sites, 5 U/0.5 ml) to 24 patients with SCI or following a brain stroke, CC and $V_{\text{refl}}$ was significantly increased and $P_{\text{max}}$ was significantly decreased 1 month after treatment. Complete continence was achieved in 8.3% of patients, and improved continence was observed in 41.7% of patients in the stroke group. In the group of patients who had suffered from a spinal lesion the equivalent results were 33.3 and 58.3%, respectively. The clinical effect gradually wore off after a period of 3 months, and all patients who had received treatment suffered a relapse within 6 months. Patients with SCI benefited more from the treatment administered as part of this study.

In their study, Krhut et al. [10] described a cohort of 32 patients with NDO following SCI for whom standard treatment with anticholinergics had been unsuccessful. Following randomisation, treatment with 300 U of onaBoNT/A was applied to 30 sites on the detrusor, with the exception of the trigone, via either intramural injection or submucosal administration. Following treatment, there was a major reduction in UI episodes per day for both groups of patients, from a mean of 2.5 incontinence episodes to 0.2 for the group treated using detrusor administration, and from 3.0 to 0.17 UI episodes for the group treated using submucosal administration. A significant improvement in the monitored urodynamic parameters was observed in both groups of patients. A repeat course of treatment was required for 64.3% of patients in the detrusor group and 88.8% of patients whose treatment had been administered via injection to the submucosal space. No significant differences were found when comparing the results of both groups.

Santaniello et al. [11] studied a cohort of 25 patients with NDO following SCI. Following randomisation, the first group received a 300-unit dose of onaBoNT/A, administered to the submucosal layer, including injection to the trigone area. The second group received the same dose but administered to the detrusor. Urodynamic control examinations were carried out 1–3 months following treatment. A significant reduction in UI episodes and catheterisations, as well as an increase in $V_{\text{refl}}$ and CC and a significant reduction in $P_{\text{max}}$, was observed after both 1 and 3 months in the group which had received treatment via submucosal administration. The same results were recorded for the group which had received treatments via injections into the detrusor. No significant difference was observed when comparing the two different approaches of administration. Akbar et al. [12] reported results of

**Fig. 2.** Submucosal administration of onaBoNT/A. The needle is inserted tangentially under the bladder mucosa. Typical bulking forms during application as evidence of administration to the submucosal space.
treatment in a group of 44 patients with NDO after SCI or with myelodysplasia where submucosal applications were routinely used. Intradetrusor applications were only used in the cases with small capacity bladders.

Additionally, there are reports with treatment of idiopathic detrusor overactivity. Kuo [13] reported on 20 patients with idiopathic detrusor overactivity who were treated with an injection of 200 U botulinum A toxin into the suburothelial space. Three months after treatment, 9 patients had regained continence (45%) and 8 patients demonstrated improvement (40%), but treatment had failed in 3 patients (15%). At 6 months after treatment, 7 patients remained continent, but treatment had failed in 5 patients. A large postvoid residual urine volume requiring catheterisation was observed in 6 patients (30%).

Okamura et al. [14] published the short-term effects of 9 men and 8 women. A total of 100 U of BoNT/A were injected at 30 submucosal sites of the bladder wall. Daytime UI completely disappeared in 6 subjects. A urodynamic study showed detrusor overactivity disappearance in 8 patients and a decreased overactivity in 5 patients. The maximum bladder capacity significantly increased from 179.9 to 267.3 ml. Postvoid residual urine volume increased to >100 ml in 7 patients and >200 ml in 1 patient after injection; however, none of the patients required CIC. Onyeka et al. [15] achieved similar results. Submucosal treatment of interstitial cystitis has also been reported [16].

Our treatment utilised a 300-unit dose. At the commencement of our study, there was no clear agreement on the recommended treatment dose of onaBoNT/A. Basic conclusions have been drawn by two major recent studies. In the largest randomised study published, Cruz et al. [17] compared 200- and 300-unit doses of onaBoNT/A in the treatment of NDO and found no significant difference in the effects of either dosage. The same result was demonstrated by Ginsberg et al. [18].

We found no difference between the detrusor and submucosal groups in the duration of the effects of therapy. In our cohort, the effectiveness period of treatment was at the lower limit of published data (7.3 months for submucosal administration and 6 months for administration to the detrusor), and the absence of involuntary contractions during the urodynamic control examination occurred in a lower percentage of cases. Cruz et al. [17] demonstrated a treatment effectiveness period of 42.1 weeks, i.e. 9.5 months. The effect was the same for treatment with a 200- and 300-unit dose of onaBoNT/A. Ginsberg et al. [18] demonstrated treatment effectiveness periods of 256 and 254 days (8.5 months) when treating NDO with 200- and 300-unit doses of onaBoNT/A, respectively.

The patients included in our protocol did not use anticholinergics for the entire duration of the study. We believe that this could be one cause for the relatively short, effective treatment period. However, the study by Sievert et al. [19] did not show that anticholinergics had any influence on the outcome.

We only demonstrated the difference between the two groups after comparing the voided volume; this difference could be a result of inaccurate measurements of patients. When comparing the $V_{\text{refl}}$ and CC, this difference was not confirmed (fig. 1). All patients in our study underwent their procedure (except therapy) in an outpatient setting. In the follow-up study, more attention was given to teaching patients how to measure catheterised volume, and we equipped them with a uniform calibrated measuring container.

In our cohort, we recorded a single episode of temporary muscle weakness in a patient who had received treatment administered via injection to the detrusor. This weakness, which subsided spontaneously within 24 h, was of light intensity and did not require treatment. Bauer et al. [20] reported neurological side effects after treatment of idiopathic detrusor overactivity: 7.1% of patients reported leg weakness, 5.4% reported torso weakness and 8.9% reported arm weakness. In general, all side effects were transient and did not require treatment. The most frequent complication in our cohort was urinary tract infection, which occurred in 25% of patients following submucosal administration and in 18% of patients following injection into the detrusor. Similar results were observed in patients following urodynamic examination or in the CIC regimen [21]. There was also a high rate of asymptomatic bacteriuria colonisation of the urinary tract: 66 and 81% in the group with submucosal administration and the group with administration to the detrusor, respectively. However, there is a 21–32% risk of urinary tract infection following the administration of BoNT/A [5], and this reduced incidence of urinary tract infection following treatment with BoNT/A is an additional advantage of this type of therapy [22].

In both groups in our study, the treatment of NDO was accompanied by a significant improvement in the quality of life and was predominantly in direct correlation with the reduced number of catheterisations and incontinence episodes.

Here, we present pilot study data and are aware of a small number of patients used. To compare the efficiency and importantly the safety of both methods of applications, we need to wait for the results of larger trials.
Conclusions

Three months after treatment, we observed a significant improvement in monitored urodynamic parameters and a significant decrease in incontinence episodes and catheterisation frequency in both the submucosal and the detrusor groups of patients. When comparing the results of both application approaches, we did not observe any significant difference between these methods. Therefore, the authors consider that submucosal delivery of onaBoNT/A is an equally effective approach as the detrusor delivery of administration for this agent.

References


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Disclosure Statement

The authors declare no conflicts of interest related to this work.