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ORIGINAL ARTICLE

# A morphological evaluation of botulinum neurotoxin A injections into the detrusor muscle using magnetic resonance imaging

**Ulrich Mehnert · Sönke Boy · Marius Schmid · André Reitz · Alexander von Hessling · Juerg Hodler · Brigitte Schurch**

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**Abstract**
*Objectives* Although botulinum neurotoxin type A (BoNT/A) intradetrusor injections are a recommended therapy for neurogenic detrusor overactivity (NDO), refractory to antimuscarinic drugs, a standardisation of injection technique is missing. Furthermore, some basic questions are still unanswered, as where the toxin solution exactly spreads after injection. Therefore, we investigated the distribution of the toxin solution after injection into the bladder wall, using magnet resonance imaging (MRI).
*Methods* Six patients with NDO were recruited. Three of six patients received 300 U of BoNT/A + contrast agent distributed over 30 injection sites (group 1). The other three patients received 300 U of BoNT/A + contrast agent distributed over 10 injection sites (group 2). Immediately after injection, MRI of the pelvis was performed. The volume of the detrusor and the total volume of contrast medium inside and outside the bladder wall were calculated.
*Results* In all patients, a small volume (mean 17.6%) was found at the lateral aspects of the bladder dome in the extraperitoneal fat tissue, whereas 82.4% of the injected volume reached the target area (detrusor).

In both groups there was a similar distribution of the contrast medium in the target area. A mean of 33.3 and 25.3% of the total detrusor volume was covered in group 1 and 2, respectively. Six weeks after injection, five of six patients were continent and showed no detrusor overactivity in the urodynamic follow-up. No systemic side effects were observed.
*Conclusions* Our results provide morphological arguments that the currently used injection techniques are appropriate and safe.

**Keywords** Botulinum neurotoxin type A · Neurogenic detrusor overactivity · Magnetic resonance imaging · Detrusor muscle · Gadopentate

U. Mehnert (✉) · S. Boy · A. Reitz · B. Schurch
Neurourology, Spinal Cord Injury Center,
Balgrist University Hospital, Forchstrasse 340,
8008 Zurich, Switzerland
e-mail: ulrich.mehnert@paralab.balgrist.ch

M. Schmid · J. Hodler
Department of Radiology, Balgrist University Hospital,
Forchstrasse 340, 8008 Zurich, Switzerland

A. von Hessling
Department of Radiology, Kantonsspital St. Gallen,
Rorschacher Strasse 95, 9000 St. Gallen, Switzerland

## Introduction

Botulinum neurotoxin type A (BoNT/A) injections into the detrusor muscle are a recommended therapy for neurogenic detrusor overactivity (NDO), when antimuscarinic drug therapy failed or is not tolerated [1–4]. BoNT/A injections have been successfully used to treat NDO worldwide and further indications and therapy options are currently explored [5–8]. The toxin is injected into the detrusor muscle via a cystoscopic approach, either flexible or rigid. The injection needle, which can be of different length and diameter, is stabbed into the bladder wall, followed by the injection of the toxin and the retraction of the needle. This is usually performed at multiple sites of the bladder wall, depending on the technique and amount of toxin, chosen for therapy [3, 9]. Target structure of the toxin is the detrusor muscle, as its main mechanism of action is at the neuromuscular junction [10, 11]. However, detrusor thickness is variable and depends on several factors such as gender, age,

bladder filling volume and the presence of neurogenic lesion or obstruction [12, 13]. Although injection is performed under cystoscopic guidance, injection depth can only be estimated by the surgeon. Therefore, it remains difficult to estimate exactly in which layer the toxin is injected and where it spreads out. The sole visual control could be a bulging of the bladder wall after injection. If a big transparent bleb forms, the injection was probably superficial in the muscosa, if a slight bulging of bladder wall tissue can be observed the injection was probably in the detrusor layer. But very often, no bulging can be observed at all and it remains a very insecure sign of a correct injection.

Although the injection of BoNT/A is frequently used to treat NDO, no standardisation of technique exists [9, 14, 15]. There are repeatedly reports of treatment failures, even in those patients, who formerly showed an excellent treatment response to BoNT/A [16–18]. Not all treatment failures can be explained properly and one reason for this might be a variation in the amount of toxin that reaches its target area.

Therefore, it was our purpose to investigate for the first time, the distribution of the toxin solution after injection into the bladder wall, using magnet resonance imaging (MRI). Since we previously investigated the use of two different injection schemes (10 vs. 30 injection sites), which showed similar clinical results [14], we were also interested to observe the morphological outcome of both injection schemes.

Due to our long term experience with the use of BoNT/A in the treatment of NDO and our favourable results in those years [19, 20], we expected most of the toxin to be found in the detrusor. Nevertheless we also expected some toxin outside the detrusor, as perforation can not be completely excluded using the cystoscopic approach. As a secondary outcome measure we evaluated the urodynamical data before and after BoNT/A injection to be able to correlate the clinical outcome with the morphological evaluation of the toxin distribution.

## Materials and methods

After approval of the local ethics committee, a patient sample was recruited in the neurourological out-patient clinic of the spinal cord injury centre at the Balgrist University Hospital.

Inclusion criteria were: urodynamically proven NDO, failure to treatment with antimuscarinic drugs, minimum age of 18.

Exclusion criteria: allergy to BoNT/A or to MRI contrast agents, any existing malignancy in the bladder or urethra, urinary tract infection, pregnancy, breastfeeding, incapability or unwillingness to perform intermittend selfcatheterisation, coagulation disorders or intake of anticoagulant drugs, impaired renal function, myasthenia gravis, pacemaker, Lambert–Eaton syndrome, medication with aminoglycosides (or other drugs with impact upon neuromuscular transmission), any ferromagnetic metal implants or compounds in or at the body.

Prior to inclusion, all patients were informed about the character of the study, both verbally and in writing and each patient had to provide written informed consent.

Pre-treatment evaluation consisted in physical examination, medical history, cystomanometry, blood chemistry, urine sediment and culture. Infections were treated according to germ resistance before examination or injection and all patients received antibiotic prophylaxis for 3 days, starting 1 day before injection and ending 1 day after injection.

Local anaesthesia using electromotive drug administration of 2% lidocain was applied in patient 2 because of preserved bladder sensibility due to an incomplete spinal cord lesion (Table 1) [21].

The BoNT/A injections were performed at the bladder base and dome in a standardised manner by the same surgeon in all patients, using a rigid cystoscope (19 or 22 Fr) and a 22 G (=0.7 mm) needle with a length of 8 mm. Not the full needle length was inserted into the bladder wall during injection. Instead, the needle was retracted up to half its length, depending on the injection angle. The used BoNT/A compound in this study was BOTOX® (Allergan AG, Lachen, Switzerland).

The first group (group 1) of patients received 300 U of BOTOX®, distributed over 30 injection sites each 1 ml BoNT/A solution [3]. A second group (group 2) received 300 U of BOTOX®, distributed over ten injection sites each 1 ml BoNT/A solution [14]. For group 1, 300 U of BOTOX® were diluted in 27 ml 0.9% saline + 3 ml gadopentate. For group 2, 300 U of BOTOX® were diluted in 9 ml 0.9% saline + 1 ml gadopentate. The paramagnetic MRI contrast agent gadopentate (Magnevist®, Schering AG, Berlin, Germany) was mixed into the BoNT/A solutions to detect the distribution of the injections in the following MR-scans, which were performed in a 1.5 T Avanto Siemens Magnetom. Prior to scanning, the bladder of all patients was emptied and filled with 200 ml 0.9% saline to achieve a standardised filling during MR scanning.

A T1 fast low angle shot (FLASH) 3D with fat saturation was used in the MR evaluation including the following specifications: TR: 4 ms, TE: 1.7 ms, flipangle: 12°, matrix: 256 × 256, FOV: 200 mm, slice thickness: 2.9 mm, NEX (Acquisitions): 2.

Using the freehand tool of the MR-software, the following regions of interest (ROIs) were selected: (1) the area of contrast agent within the detrusor muscle, (2) the area of contrast agent outside the detrusor and (3) the whole detrusor itself. Once a ROI was defined, the software automatically

**Table 1** Patients characteristics, urodynamic data before and after treatment, and the data of the magnet resonance imaging analysis of all six patients

| | P 1 | P 3 | P 5 | P2 | P 4 | P 6 |
|---|---|---|---|---|---|---|
| Age | 34 | 34 | 41 | 82 | 67 | 18 |
| Sex | Male | Male | Male | Female | Male | Female |
| Level of SCI | Th11 | Th6 | Th6 | Th7 | Th10 | Th10 |
| ASIA classification | A | A | A | C | A | A |
| Max. bladder capacity before treatment (ml) | 217 | 300 | 222 | 217 | 200 | 249 |
| Max. detrusor pressure before treatment ($cmH_2O$) | 69 | 46 | 41 | 37 | 48 | 27 |
| Incontinence/urine leak | Yes | Yes | Yes | Yes | Yes | Yes |
| Units of Botox® | 300 | 300 | 300 | 300 | 300 | 300 |
| No. injection sites | 30 | 30 | 30 | 10 | 10 | 10 |
| Max. bladder capacity after treatment (ml) | 381 | 500 | 500 | 186 | 500 | 440 |
| Max. detrusor pressure after treatment ($cmH_2O$) | 57 | 10 | 8 | 36 | 11 | 10 |
| Incontinence/urine leak | No | No | No | Yes | No | No |
| Volume detrusor ($cm^3$) | 217.16 | 253.95 | 126.02 | 64.55 | 198.3 | 78.27 |
| Volume contrast medium (total) ($cm^3$) | 101.53 | 61.2 | 57.74 | 14.51 | 56.57 | 38.53 |
| Volume contrast medium inside detrusor ($cm^3$) | 85.6 | 52.97 | 49.76 | 11.52 | 54.08 | 24.11 |
| Volume contrast medium outside detrusor ($cm^3$) | 15.93 | 8.23 | 7.98 | 2.99 | 2.49 | 14.42 |

*P* patient, *SCI* spinal cord injury, *ASIA* American Spinal Injury Association, *Th* thoracic spine

calculated the area in square millimetres. The 3D acquisition technique enabled the generation of volume data by multiplying the previously measured ROIs of each slice with the slice thickness. The distribution of gadopentate after injection was calculated and evaluated by two different radiologists who were blinded to the injection protocol. An urodynamic control visit was scheduled for each patient 3 months after injection and the urodynamic outcome measures were compared with those before BoNT/A injection.

## Results

Six patients with spinal cord injury and subsequent NDO could be included (Table 1). All injections could be performed without any clinically evident adverse events and none of the patients felt discomfort or pain. Only in patient 6, the injection procedure itself was difficult because of an increased spasticity of the lower limb. No systemic side effects were observed in any patient directly after the injection or during follow-up. Bleeding from the injection sites was minimal and stopped shortly after retracting the needle.

The average delay between the end of the BoNT/A injection and the start of the first MR-sequence was 17.5 min, ranging from 10 to 32 min. Mean examination time in the MR-scanner was 25 min, ranging from 17 to 42 min.

In none of the patients, contrast agent could be detected intraperitoneal, which would be highly suspicious for a penetration into the peritoneum. Furthermore, no contrast agent was found in other organs like the rectum or pelvic muscles. In all six patients, fractions of the contrast agent could be detected outside the bladder wall, located in the perivesical fat, mainly at the lateral aspects of the bladder dome either on one or both sides. In one patient contrast agent was also found beyond the bladder base, in another patient beyond the middle part of the bladder dome. The average spreading distance of contrast agent from the outer margin of the detrusor was 16 mm.

The mean total detrusor volume of all subjects was 156.4 $cm^3$. The mean contrast enhanced detrusor volume of all subjects was 46.3 $cm^3$ (29.3% of the mean total detrusor volume). The mean amount of contrast enhanced volume outside the detrusor was 8.7 $cm^3$ (17.6% of the mean total contrast enhanced volume). Accordingly, 82.4% of contrast agent was found within the detrusor (Table 1).

In group 1, the mean total detrusor volume was 199 $cm^3$. The mean volume of detrusor, found to be contrast enhanced, was 62.8 $cm^3$ (33.3% of the mean total detrusor volume in group 1). The mean amount of contrast enhanced volume outside the detrusor was 10.7 $cm^3$ (14.3% of the mean total contrast enhanced volume). Accordingly, 85.7% of contrast agent was found within the detrusor (Table 1).

In group 2, the mean total detrusor volume was 113.7 $cm^3$. The mean volume of detrusor, found to be contrast enhanced, was 29.9 $cm^3$ (25.3% of the mean total detrusor volume in group 2). The mean amount of contrast enhanced volume outside the detrusor was 6.6 $cm^3$ (20.8% of the mean total contrast enhanced volume). Accordingly, 79.2% of contrast agent was found within the detrusor (Table 1).

In five of six patients, the BoNT/A injections showed to be effective. Before treatment, all six patients had NDO in their urodynamic examination. The average volume at which the first detrusor overactivity (DO) could be

observed was 234.2 ml. The maximum detrusor pressure was on average 44.7 $cmH_2O$. Five of six patients had urinary incontinence (Table 1).

After the BoNT/A injections, four of six patients had no DO up to 500 ml and were continent. In patient 1 bladder capacity at least increased from 217 to 381 ml and the maximum detrusor pressure decreased from 69 to 57 $cmH_2O$ (Table 1). Patient 2 showed no improvement in the follow-up cystometry, although he reported improvement. This patient had the lowest percentage of detrusor volume covered by the contrast agent (Table 1).

Due to the spastic limb contractions in patient 6, shifts in the penetration depth of the needle might have incidentally occurred. When analysing this patient's data we found that nearly 40% of the applied contrast agent was located beyond the detrusor (Table 1).

All patients would agree to a second injection, when the effect of the last injection fades.

## Discussion

The aim of this study was to investigate the distribution of the BoNT/A solution, after injection into the bladder wall. Our data show, that using the previously described and most widely used injection technique with 30 or 10 injection sites [3, 14], most of the applied volume spreads inside the detrusor. Only small amounts were found outside the detrusor, almost exclusively in the fat tissue at the lateral aspects of the bladder dome.

That 82.4% (average of all 6 subjects) of the injected BoNT/A-gadopentate solution were detected inside the detrusor, met our expectations. In regard with the clinical improvement of the patients, these results show that the used techniques are accurate and efficient.

Due to the fact, that contrast agent could be detected outside the detrusor, it has to be assumed that the injection needle perforated the detrusor during some of the injections. This is probably not uncommon following detrusor injections via a cystoscopic approach, as the surgeon can only estimate the relation of needle length to detrusor thickness. These two factors, e.g. needle length and detrusor thickness, are most crucial in regard to injection depth. One can now assume that the surgeon could choose the needle length according to the detrusor thickness, which can be measured using ultrasound at a defined filling level [12]. This measurement, however, might not be very reliable during cystoscopic BoNT/A injection, as filling volumes and therefore detrusor thickness is likely to change during cystoscopy due to diuresis and more likely due to the regular use of flushing and draining of saline. Additionally, detrusor thickness might not be the same throughout the bladder, although investigated by Kutzmic [22], who found per individual the same detrusor thickness in all parts of the bladder wall. This is probably true for healthy subjects but might be completely different for patients with NDO.

Perforation might not be the only mechanism contributing to the extravesical amount of contrast medium. A diffusion of the BoNT/A-gadopentate solution outside the bladder can not be excluded in principle. Although one would expect a more homogeneous and broader extravesical accumulation of the contrast medium and not only at certain areas as shown in Fig. 1.

The amount of the injected BoNT/A-gadopentate solution found outside of the bladder wall in the present study seemed to be low enough, not to cause any systemic side effects or to compromise the effect of the toxin on the bladder. Most of the intradetrusor contrast agent was found in the bladder base and dome, since this are the locations we injected. When descriptively comparing the two different treatment modalities (30 vs. 10 injection sites) there was a similar amount of contrast agent found in the target area (85.7 vs. 79.2%) and a similar percentual coverage of detrusor volume with the contrast agent (33.3 vs. 25.3%). Although both groups can not be compared statistically due to the small sample size, this finding can still be seen in agreement with the study from Karsenty et al. [14], who found no difference in clinical efficacy and safety using 10 compared to 30 injection sites with the same amount of BoNT/A.

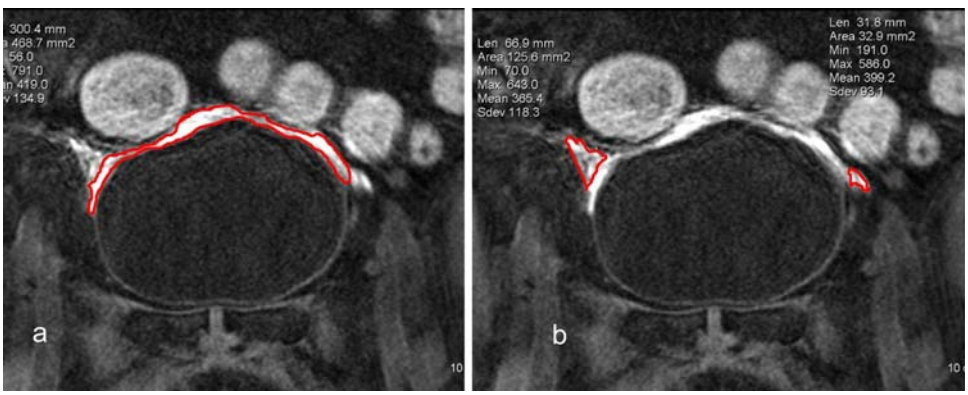


**Fig. 1** An exemplary coronal slice of the magnet resonance imaging of the lower pelvis, showing the urinary bladder in the middle of the image. The contrast agent, appearing in white, can be found for the most part within the detrusor (**a**) and to some extent outside the detrusor in the perivesical fat tissue (**b**) (the areas were encircled in *red* for better visibility)

In general, it remains still unclear, how much detrusor tissue should be covered to gain the best dosage/effect ratio of BoNT/A. One would assume that a distribution of BoNT/A covering most of the detrusor body might cause the greatest effect. In the present study an average of only about 30% (mean of all patients) of detrusor muscle was covered with contrast agent. Nevertheless, a sufficient effect of the BoNT/A treatment could be observed, which is well comparable with the success rates reported in former studies [6, 7]. Therefore, it might not be necessary to cover the whole detrusor with BoNT/A, to achieve good clinical results.

An exact explanation why 30% detrusor coverage with BoNT/A are sufficient enough to produce the reported clinically significant improvements can not be given with this study. A possible reason eventually underlying these results might be areas of detrusor tissue, which are more important for detrusor contraction and increase of local reflex activity than other areas after spinal cord injury [23]. Treatment of those areas with BoNT/A might be sufficient enough to reduce detrusor contractions in NDO patients, regardless of the total amount of detrusor area covered. Experimental studies in neonate and spinal cord injured rats showed that spontaneous contractile activity originated in the urothelium-suburothelium near the bladder dome [23, 24]. This spontaneous activity, unlike activity in normal adult rat bladders, is highly organised, i.e. starting at the dome, followed by the bladder body further contracting towards the bladder outlet. These organised contractions resulted in high amplitudes (10–20 $cmH_2O$). Increased expression of gap junctions seems to play a role in this coordinated contraction in neonate and spinal cord injury bladders, which gives the impression, that the bladder works partially like a "functional syncytium" [24].

In addition, BoNT/A is not only inhibiting the efferent pathway by preventing neuronal acetylcholine release but also modulating the afferent pathway due to its effect on receptors and neurotransmitter release from the urothelium and suburothelium, which probably adds to the efficacy of the toxin in the treatment of DO [25–27].

Disruption of such organised synergic contractions and of the urothelial and suburothelial para- and autocrine signalling by an area of 30% of the total detrusor, due to intradetrusor injection of BoNT/A at and around the bladder dome might not completely abolish detrusor contractions (Table 1), but prevent complete and/or large amplitude contractions arising from the bladder dome. This is probably sufficient enough to prevent incontinence and cause satisfying clinical results. Interestingly, two studies mainly using injections at the bladder base reported a significant lower rate of complete continent patients with NDO compared to other studies injecting BoNT/A in base and dome [7, 28, 29].

Further investigations are necessary to evaluate the degree of detrusor coverage with BoNT/A compared with the clinical outcome. Presumably there is an optimal ratio between the amount and the degree of distribution of BoNT/A inside the detrusor and the clinical outcome, which is worth to be discovered. Using MRI in conjunction with contrast enhanced BoNT/A solution, might be a very useful tool to perform this investigation.

There are, however, limitations of the used investigation method. First limitation is that during the injection procedure there might be some volume leaking out of the injection site into the bladder lumen. We consider this volume as extremely low, as the needle diameter is very small and most injection sites will clot shortly after removing the needle, which is in accordance with the experience of Schulte–Baukloh, who investigated toxin back flow from the injection site using a dye. He found, although not specifically quantified, that none to extremely little dye/toxin is flowing back from the injection sites [30]. Quantification of a dye (e.g. methylene blue) in the bladder irrigation fluid requires at least a photometric device, which was not readily available in our clinic. The group around Helmut Madersbacher and Gustav Kiss from the University of Innsbruck very recently performed such a photometric evaluation and found out that only 1.96–19.2 U (median 5.5 U) of 170–400 U BoNT/A are lost due to back flow after injection (personal communication, annual meeting of the German Urological Association in Stuttgart, 24–27 Sep 2008).

Second limitation might be measurement errors. Although most borders could be clearly distinguished, extravesical fluid may not have perfectly smooth borders. Manual determination of the region of interest introduces an additional small error. These errors were minimised by having two senior radiologists experienced in quantitative assessments of MR images performing the evaluations in consensus. The remaining error is small in comparison to the measured volumes.

Third limitation is the number of six patients, which is too small to receive data for reliable statistics, but besides monetary constraints (expensive MRI-examinations) the focus of this study was to demonstrate morphological aspects of the injection technique for the first time. The used MRI technique is well suited to demonstrate the morphologic situation after injecting the detrusor, but a short delay between injection and obtaining the pictures is mandatory because of fast diffusion and venous backflow of the contrast agent.

At least, it has to be considered that we can not demonstrate the localisation of the BoNT/A itself, but only the localisation of the contrast agent. Although BoNT/A is not residing just at the injection site [31], it probably diffuses much slower and less far as gadopentate, due to the higher

molecular weight of 150 kDa compared to the 835 Da of gadopentate. In our study (with a mean delay of 17.5 min after injection) renal excretion of contrast agent could already be seen in all patients.

## Conclusion

Using the previously described injection techniques, a mean of 82.4% of the injected BoNT/A-gadopentate solution can be found within the detrusor. However, a perforation with the needle tip and injection into the perivesical tissue could not be prevented. Treatment with 10 or 30 injection sites seem similar regarding the distribution of contrast agent in or outside the detrusor. In consideration of the clinical improvements of the patients, our results provide further arguments that the currently used injection techniques are appropriate and safe. Further studies are necessary to explore the optimal ratio between the amount and the degree of dissemination of BoNT/A inside the detrusor and the clinical outcome.

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