ORIGINAL ARTICLE

Factors that influence the urodynamic results of botulinum toxin in the treatment of neurogenic hyperactivity

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KEYWORDS
Botulinum toxin; Urodynamics; Detrusor hyperactivity; Neurogenic bladder; Spinal cord injury

Abstract
Objectives: To determine the urodynamic efficacy and factors that influence the urodynamic results of treatment of neurogenic detrusor hyperactivity with intradetrusor injection of botulinum toxin type A (BTX-A) in patients with spinal cord injury (SCI).

Material and methods: A retrospective study was conducted with a cohort of 70 patients composed of 40 men and 30 women with stable SCI (mean age, 39 ± 13.3 years) who underwent an intradetrusor injection of 300 IUs of BTX-A. A urodynamic study was conducted prior to the injection and 6 ± 4.3 months after the treatment. New urodynamic studies were subsequently performed up to an interval of 16 ± 12.2 months.

Results: The BTX-A significantly increased (p < .05) the cystomanometric bladder capacity, the bladder volume of the first involuntary contraction of the detrusor and the postvoid residue. We observed a decrease that tended toward statistical significance (p < .1) of the maximum detrusor pressure and the maximum urine flow. Neither the bladder accommodation nor the urethral resistance index (bladder outlet obstruction index) varied significantly. The increase in vesical capacity was maintained in 50% of the sample for more than 32 months. Age, sex, anticholinergic treatment and lesion age showed no influence in terms of the increase in bladder capacity. The indwelling urinary catheter (IUC) was the only statistically significant negative factor.

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**Introduction**

Spinal cord injury causes, in most cases, neurogenic lower urinary tract dysfunction (NLUTD). In patients with NLUTD, the main objective is to prevent kidney damage, so urodynamic results turn out to be much more important than the symptoms or impact of neurogenic dysfunction on the quality of life of patients.  

Neurogenic detrusor overactivity (NDO) is a common NLUTD in patients with spinal cord injury. This dysfunction is the leading cause of urinary incontinence in these patients. Furthermore, if it is associated with periurethral detrusor-sphincter dyssynergia (PDSD), it poses a risk of renal impairment due to the functional obstruction it causes. Therefore, proper treatment is essential.  

The initial treatment of NDO is with anticholinergic agents acting on bladder muscarinic receptors. However, this treatment is not as effective in all patients. To date there is no study that analyzes the prognostic factors of the treatment outcome of NDO with BTX-A.  

The main objective of our study is to determine which factors influence the urodynamic result of treatment with BTX-A in a series of patients with spinal cord injury and NDO. As secondary objectives we set to confirm the urodynamic efficacy of BTX-A and the duration of its therapeutic effect in patients with spinal cord injury and NDO.

**Material and methods**

A retrospective study of a cohort of 70 patients with SCI undergoing intradetrusor BTX-A injection was performed for the treatment of NDO. The criteria for the injection of botulinum toxin were urodynamic demonstration of NDO, refractory to anticholinergic treatment at high doses (oxybutynin 15 mg/day) (55 cases) or patient intolerance to anticholinergic treatment due to side effects (15 cases). In all cases, botulinum toxin injection was performed for the first time, and anticholinergic therapy was maintained in patients who were receiving it. In 33 cases, anticholinergics were associated with intermittent bladder catheterization and in 22 cases with permanent bladder catheter.

All patients signed an informed consent. Botulinum toxin being a licensed treatment as compassionate use for NDO,
Factors that influence the urodynamic results

and not being a clinical trial, the study was not submitted to the approval of the scientific committee.

The patients included in the study underwent a medical history where the level and degree of spinal cord injury as well as their evolution time were determined, and then a urodynamic study with a Solar polygraph (MMS, Enschede, The Netherlands), according to the specifications of the ICS and the protocols of the Good Urodynamic Practice.9 In short, patients were placed in the supine position and we proceeded to bladder filling through a two-way 8Fr catheter, inserted transurethrally, with saline at room temperature and a speed of 20 ml/s. The abdominal pressure was recorded using a catheter with transrectal balloon. The filling phase ended when there was an involuntary detrusor contraction.

In this study, the following parameters were determined: cystometric bladder capacity (CBC), the bladder volume at which the first involuntary contraction (ICV) took place, the maximum pressure of the involuntary contraction (IC maxP), the filling pressure (filP), maximum detrusor voiding pressure (maxP), maximum urinary flow (Qmax), post-void residual (PVR), and the index of urethral resistance (BOOI).

From February 2008 to December 2012, a total of 70 patients were treated, of 39 ± 13.3 years of age (mean ± standard deviation). The sample consisted of 40 males and 30 females. The age of the SCI was 167 ± 13.3 months.

The botulinum toxin injection was performed with a dose of 300 IU of onabotulinum toxin A (Botox® Allergan, Inc., Irving, CA, U.S.A.) spread over 30 locations with respect to the trigone.

The patients underwent a second study at 6 ± 4.3 months, after injection of botulinum toxin. After treatment, patients were followed with new urodynamic studies to observe the evolution of urodynamic data for an average of 16 ± 12.2 months (range 3–45 months).

The results were stored in an ACCES® database and exported to the statistical program SPSS® for their analysis. The statistical analysis consisted in applying the Fisher exact test for dichotomous variables, the mean comparison test of Student’s "t"-test for parametric variables, both independent and paired, the Pearson correlation coefficient, and a survival analysis according to the Kaplan–Meier method. The significance level was set at 95% bilateral. 10% bilateral was considered a trend toward significance. The values were expressed as mean ± standard deviation.

Results

The distribution by level and degree of spinal cord injury is shown in Table 1.

The variation of urodynamic parameters following injection of botulinum toxin is shown in Table 2. We observed a significant increase of the CBC, bladder volume at the first involuntary contraction, and PR.

Table 3 analyzed the influence of clinical parameters on CBC after injection of botulinum toxin. It was noted that the only significant difference was the presence of permanent bladder catheter.

Survival analysis showed that the median regarding the time taken for the CBC to return to baseline was 32 months (Fig. 1).

Discussion

In our study, we observed that injection of BTX-A significantly increased both CBC and ICV, in addition to an increase in PR after 6 months of treatment. However, we observed no statistically significant differences from the filP, CI maxP, Qmax, maxP, or BOOI.

In randomized clinical trials (RCTs) on the effectiveness of botulinum toxin in patients with NDO, a significant increase in both CBC and ICV is also observed.10 Moreover, a decrease in detrusor pressure is also demonstrated both during filling (bladder compliance) and during urination.11–13 These results have been corroborated by means of the meta-analysis conducted by Mehta et al.7 Only in two observational studies a significant decrease in detrusor pressure was not evidenced during filling.14,15 In our study, we also observed a decrease in maximum detrusor pressure during voiding and peak urinary flow, although not reaching the proposed level of statistical significance (5% bilateral); in both cases it was below 10% bilateral (p < 0.1), indicating a

<table>
<thead>
<tr>
<th>Level</th>
<th>Degree</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1–C8</td>
<td>10</td>
<td>22</td>
</tr>
<tr>
<td>D1–D4</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>D5–L1</td>
<td>6</td>
<td>22</td>
</tr>
<tr>
<td>L2-cauda equina</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>51</td>
</tr>
</tbody>
</table>

Figure 1 Probability of recovery of basal cystometrographic bladder capacity in terms of follow-up.
tendency of significance, which possibly with an increased sample size would have resulted in statistical significance.

Reduction in the maximum flow and maximum detrusor pressure during the voiding phase, along with increased postvoid residue, clinically confirmed that the mechanism of action of botulinum toxin is exerted on detrusor contractile activity. In our study, we also observed that the rate of urethral resistance did not vary significantly after 6 months of treatment, so it follows that the effects of botulinum toxin on the voiding phase are not due to an increase in urethral resistance.

Regarding the predictors of outcome of botulinum toxin in our study, we observed that both patient age and sex, the age of the injury, or anticholinergic therapy did not influence the outcome of treatment with BTX-A at 6 months on bladder capacity. In an RCT conducted by Neel et al., anticholinergic administration after injection of BTX-A did not significantly improve urodynamic results with respect to patients who were not administered. The efficacy of BTX-A treatment is associated with the elimination or reduction of anticholinergic therapy, so in those patients who need to continue this medication, we should suspect lack of efficacy or partial efficacy of botulinum toxin treatment.

In our study, the only prognostic outcome regarding bladder volume (CBC) of treatment with BTX-A observed was the presence of permanent bladder catheter. This information has not been evaluated in other studies because, in most cases, among the criteria of inclusion, the need for patients to perform or the will to perform ICV is included. The presence of permanent bladder catheter is a known risk factor for the development of urological complications such as infections and urinary stones. Furthermore, it was found that its presence causes a progressive decrease in bladder capacity.

Our study shows that the effect of BTX-A on bladder capacity is maintained in 50% of patients up to 32 months. Most follow-up studies focus on the effectiveness of repeated treatment doses. Schurch et al. calculate that the time after treatment in which bladder capacity remains above that of the control group is more than 24 weeks (6 months). Grise et al. estimate that the median with regard to the reoccurrence of urinary incontinence in patients achieving continence after treatment with BTX-A is 168 days (approximately 6 months). It is possible that the urodynamic effect of BTX-A is longer than its clinical effect. In any case, it would be interesting to design a study to confirm our data.

Among the limitations of our study, there is the fact that it is retrospective, so there could be some bias in information. The absence of a control group has less effect on the main objective, since the study of prognostic factors

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Post treatment</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystomanometric capacity (ml)</td>
<td>188 ± 110.0</td>
<td>247 ± 144.9</td>
<td>0.002*</td>
</tr>
<tr>
<td>Filling pressure (cm H₂O)</td>
<td>8 ± 12.7</td>
<td>7 ± 8.5</td>
<td>0.580</td>
</tr>
<tr>
<td>Volume 1st contraction (ml)</td>
<td>121 ± 70.0</td>
<td>196 ± 117.9</td>
<td>0.003*</td>
</tr>
<tr>
<td>Maximum contraction pressure (cm H₂O)</td>
<td>56 ± 25.3</td>
<td>52 ± 25.1</td>
<td>0.496</td>
</tr>
<tr>
<td>Peak flow (ml/s)</td>
<td>4 ± 6.4</td>
<td>2 ± 3.7</td>
<td>0.057**</td>
</tr>
<tr>
<td>Maximum voiding pressure of the detrusor (cm H₂O)</td>
<td>68 ± 36.6</td>
<td>52 ± 36.2</td>
<td>0.066**</td>
</tr>
<tr>
<td>Post-void residual (ml)</td>
<td>168 ± 106.2</td>
<td>236 ± 149.2</td>
<td>0.002*</td>
</tr>
<tr>
<td>BOOI (cm H₂O)</td>
<td>35 ± 39.8</td>
<td>37 ± 26.5</td>
<td>0.851</td>
</tr>
</tbody>
</table>

BOOI: urethral resistance index.
* Significant differences (p < 0.05).
** Trend to significance (p < 0.1).

Table 3  Relationship between previous clinical parameters and cystomanometric bladder capacity (ml) after the first follow-up after injection of botulinum toxin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (completed years)</td>
<td>$r = -0.125$</td>
<td>0.334</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>244 ± 158.0</td>
<td>250 ± 130.7</td>
</tr>
<tr>
<td>Age of SCI</td>
<td>$r = -0.075$</td>
<td>0.596</td>
</tr>
<tr>
<td>Permanent catheter</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>155 ± 103.8</td>
<td>286 ± 143.2</td>
</tr>
<tr>
<td>Anticholinergic therapy</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td></td>
<td>246 ± 140.4</td>
<td>251 ± 176.3</td>
</tr>
</tbody>
</table>

* Significant differences.
involves analyzing only the population under treatment. Its main strength is that it is the first study that analyzes the prognostic factors of treatment with BTX-A in patients with NDO.

Conflict of interest

The authors declare that they have no conflict of interest.

References