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Groen J[1], Marchand W[2], Blok B[1], Dohle G[1]
1. Dept. of Urology - Sector Furore, Erasmus MC, Rotterdam, The Netherlands, 2. Dept. of Urology, Heilig Hart Ziekenhuis, Roeselare, Belgium

LOW DOSE INTRADETRUSOR INJECTIONS OF BOTULINUM-A TOXIN: CLINICAL RESULTS, URODYNAMIC EFFECTS AND THE NEED FOR A CHANGE

Hypothesis / aims of study

Injection of botulinum-A toxin (BTX-A) into the detrusor muscle is currently widely used in patients with an overactive bladder and, to a smaller extent, in patients with the painful bladder syndrome. The optimal dose is a matter of debate, especially in those patients who void spontaneously, as this treatment option may adversely affect bladder emptying. We evaluated our results with low dose BTX-A intradetrusor injections in women and considered the balance between a clinically successful outcome and the need for clean intermittent catheterisation (CIC).

Study design, materials and methods

Intradetrusor injections of BTX-A (Botox®) are applied at our department since 2004. A dose of 100 U, injected at 20 sites with sparing of the trigone, was chosen in those patients who were able to void spontaneously in order to preserve voiding function. Patients with overactive bladder symptoms, with or without urodynamically proven detrusor overactivity (DO), and patients with symptoms predominated by bladder filling related pain, were eligible if conservative treatment had failed. Clinical success was defined as the choice (by doctor and patient) for re-treatment with the same dose or, if no re-treatment took place yet, as clinical satisfaction for at least 6 months. Other outcomes were considered failures. Satisfied patients with a follow-up shorter than 6 months were not eligible. CIC was considered needed if it was applied at least once per day during any period of time after hospital discharge. Cystometry and pressure-flow studies 3 months after injection were part of the evaluation. Cystometric parameters considered were: maximum cystometric capacity, and, in case of DO (there were no subjects with a low compliance bladder), maximum detrusor filling pressure and threshold volume (the bladder volume at the first involuntary detrusor contraction). As for the pressure-flow studies, bladder contraction strength and urethral resistance were analyzed in addition to the maximum flow rate Q_{max} and the associated detrusor pressure $p_{det.Qmax}$. The bladder contraction strength parameters used were: the Watt's factor w (both its maximum value w_{max} and its value w_{Qmax} at maximum flow rate) and the bladder contractility index BCI. Urethral resistance was characterized by the average pressure $p_{low.ave}$ of the low pressure side of the pressure-flow plot, BOOI and URA. Parametric tests and the chi-square test were used for statistical analysis. Median values and interquartile ranges are given.

Results

From April 2004 to December 2007, BTX-A 100 U was injected in 26 women. 13 Patients had idiopathic DO, 4 had neurogenic DO, 3 had overactive bladder symptoms without urodynamically proven DO and pain was the predominant factor in 6 patients. Median age in the total group was 57 (45 – 63) years. The ages in the DO group were not significantly different from those in the non-DO group. One (satisfied) patient was not eligible due to a too short follow-up. Among the remaining 25 patients, there were 6 (24%) clinically successful outcomes as defined above and 19 failures. No relationship between success rate and diagnostic group (DO: 4/16 = 25% vs non-DO: 2/9 = 22%) could be demonstrated (p=0.876). On average, the successful patients were older than the failures: 63 (60 – 70) vs 56 (49 – 71) years, p=0.022. Considering the DO group only, this finding was reduced to no more than a trend: 67 (61 – 70) vs 63 (54 – 72) years, p=0.064. Success was not correlated with pre-operative cystometric findings. Pre- as well as post-operative cystometric studies were done in 18 women. The results are given in Table I.

Table I. Results of pre- and post-operative cystometric studies in 18 women

	baseline	3 months	p
Capacity (ml) (all; 18 pts)	261 (195 – 399)	345 (258 – 510)	0.020
Capacity (ml) (DO group; 12 pts)	245 (143 – 460)	375 (305 – 548)	0.014
Capacity (ml) (non-DO group; 6 pts)	271 (250 – 384)	265 (241 – 443)	0.825
Maximum pdet (cm H_2O) (DO group; 12 pts)	28 (23 – 39)	20 (13 – 30)	0.042
Threshold volume (ml) (DO group; 9 pts*)	225 (120 – 337)	260 (178 – 530)	0.030

* no DO observed after 3 months in 3 pts

Of the 26 women, 7 (27%) applied CIC after hospital discharge. There was no relationship with clinical outcome (p=0.739) nor with age (p=0.659). A pre-operative pressure-flow study was available in 22 women. Bladder contraction strength parameters were not significantly different between the CIC group and the non-CIC group (all p's > 0.3). As for urethral resistance, results seemed inconsistent. This was however caused by an obstructed outlier in the CIC group. Neglecting this patient, no statistically significant difference was found in any of the urethral resistance parameters (all p's > 0.16).

Pre- as well as post-operative pressure / flow studies were done in 18 women. The results of 16 are given in Table II as two women could not void at the follow-up examination. The table therefore underestimates the true effect of BTX-A 100 U on the voiding function. The difference between the end fill volumes reflects the effect on the filling phase.

Table II. Results of pre- and post-operative pressure / flow studies in 16 women

	baseline	3 months	p
End fill volume (ml)	306 (186 – 423)	445 (214 – 510)	0.009
Voided volume (ml)	256 (140 – 375)	200 (125 – 370)	0.243

Residue (ml)	0 (0 – 38)	155 (26 – 300)	0.000
Voiding efficiency (%)	100 (88 – 100)	62 (40 – 92)	0.000
Q_{max} (ml/s)	15.6 (9.8 – 20.3)	15.7 (10.6 – 17.9)	0.550
$p_{det.Qmax}$ (cm H_2O)	27 (18 – 31)	28 (13 – 36)	0.916
BOOI (cm H_2O)	-3 (-14 – 4)	-6 (-13 – 12)	0.637
URA (cm H_2O)	12 (10 – 15)	11 (10 – 18)	0.959
$p_{low.ave}$ (cm H_2O)	20 (14 – 33)	24 (11 – 30)	0.623
w_{max} (W/m^2)	7.9 (5.6 – 9.3)	6.4 (5.0 – 8.3)	0.031
w_{Qmax} (W/m^2)	6.9 (5.3 – 8.4)	6.0 (4.9 – 7.2)	0.168
BCI	100 (77 – 130)	103 (84 – 117)	0.624
Residue after free uroflow (ml)	0 (0 – 50)	48 (0 – 200)	0.005

Interpretation of results

In our experience, intradetrusor injections of BTX-A 100 U obviously had a beneficial effect on bladder storage function during cystometry in women with DO, but not in women with urgency or pain without DO. The clinical success rate, however, was about the same in both groups and as low as 24% on average. No predictive urodynamic factors could be identified. A considerable decrease of voiding efficiency was found in pressure / flow studies, but this was not mirrored by a similar change in bladder contraction strength parameter values. The median residue after free uroflowmetry was about 50 ml after 3 months. Nevertheless, 27% of the patients needed CIC for some time. Again, no predictive urodynamic factors could be identified.

Concluding message

It was our strategy to inject a low dose (100 U) of BTX-A into the detrusor of those patients who were able to void spontaneously in order to obtain good clinical results with preservation of voiding function. We felt that the observed success rate of 24% unfavourably compared with the need for CIC in 27% of the patients and therefore decided to use 200 U in future patients.

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HUMAN SUBJECTS: **This study did not need ethical approval because it did not concern new indications for application of the drug. and did not follow the Declaration of Helsinki - with approval by the ethics committee - in the sense that no ethics committee approval was asked and no signing of informed consent forms was asked (the study was no trial). The patients were however fully informed on the relative newness of the method and on which results and side effects were to be expected. Informed consent was not obtained from the patients.**