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VIDEO-URODYNAMIC PREDICTIVE FACTORS OF SUCCESSFUL URETHRAL ONABOTULINUMTOXINA TREATMENT OF NEUROGENIC OR NON-NEUROGENIC URETHRAL SPHINCTER HYPERACTIVITY

Hypothesis / aims of study
Voiding dysfunction due to neurogenic or non-neurogenic urethral sphincter hyperactivity is a treatment challenge for urologists. Voiding dysfunction can result from detrusor underactivity, bladder outlet obstruction, urethral sphincter hyperactivity, or inadequate relaxation of the urethral sphincter during micturition. Urethral sphincter dysfunction may be neurogenic or non-neurogenic in origin, with large post-void residual (PVR) volume and upper urinary tract deterioration. In recent decades, urologists have used onabotulinumtoxinA injection into the urethral sphincter to treat such voiding dysfunction. Although onabotulinumtoxinA seems effective in treating voiding dysfunction, not all patients have successful treatment results. Normal voiding requires adequate detrusor contractility and coordinated bladder neck and urethral sphincter relaxation. In patients with non-neurogenic dysfunctional voiding or neurogenic DSD, a decrease in the urethral resistance during voiding is needed for efficient voiding. Injecting onabotulinumtoxinA into the urethral sphincter reduces urethral sphincter resistance, but the treatment is not effective in all such patients. Therefore, we retrospectively analyzed recently treated patients to identify the video-urodynamic predictive factors for the success of onabotulinumtoxinA treatment in patients with voiding dysfunction due to urethral sphincter hyperactivity.

Study design, materials and methods
In this retrospective study, the medical records from 2011 to 2016 were examined for consecutive patients with voiding dysfunction due to urethral sphincter hyperactivity refractory to medical treatment who were treated with 100 U of onabotulinumtoxinA (Allergan, Irvine, CA, USA) injected into the urethral sphincter. Patients underwent video-urodynamic study and cystoscopy before the injections to verify they had no urethral stricture or anatomical bladder outlet obstruction. The patients underwent urethral sphincter onabotulinumtoxinA injections in the operating room under light intravenous general anesthesia. Each 100 U vial of onabotulinumtoxinA was reconstituted to 4 mL with normal saline, making the concentration equivalent to 25 U/mL. The dose of onabotulinumtoxinA was 100 U for patients with DSD, dysfunctional voiding, or a non-relaxing urethral sphincter. The video-urodynamic parameters including bladder neck status during voiding cystourethrography, first bladder sensation of filling, cystometric bladder capacity, detrusor pressure, maximum flow rate (Qmax), PVR, and abdominal pressure to void were recorded and analyzed. Treatment outcomes were assessed 1 month after urethral onabotulinumtoxinA injection. The video-urodynamic variables were compared between patients with good and poor treatment outcomes. The changes of assessment parameters from baseline to post-treatment were also compared between patients with neurogenic and non-neurogenic urethral sphincter hyperactivity.

Results
Of the 95 patients who underwent urethral sphincter onabotulinumtoxinA injection for urethral sphincter hyperactivity, 53 had non-neurogenic and 42 had neurogenic etiologies. Table 1 shows the baseline video-urodynamic characteristics. Treatment outcomes were not related to age, gender, or voiding dysfunction subtype. When we compared the baseline video-urodynamic characteristics between patients with good and poor outcomes. Patients with good outcomes had a significantly smaller volume at the first sensation of filling (122.0 ± 53.2 vs 147.2 ± 67.0 mL, p=0.046), greater detrusor pressure (36.1 ± 27.9 vs 24.2 ± 19.3 cmH_2O, p=0.027), higher Qmax (7.64 ± 5.03 vs 5.16 ± 4.46 mL/s, p=0.017), and smaller PVR (169 ± 130 vs 251 ± 149 mL, p=0.006) than patients with poor outcomes. An open bladder neck during voiding was noted in 87.5% patients with good outcomes but only in 12.5% of patients with poor outcomes (p <0.001). Multivariate analysis revealed that an open bladder neck was the only predictor of a successful therapeutic outcome. There was no significant difference in the improvement of symptom score, Qmax, voided volume or PVR volume between patients with neurogenic and non-neurogenic voiding dysfunction. However, patients with non-neurogenic voiding dysfunction had a significantly longer lasting therapeutic duration than did patients with neurogenic voiding dysfunction (9.55 ± 4.18 vs 7.44 ± 2.91 months, p=0.033). After urethral onabotulinumtoxinA injection, increased urinary incontinence was reported in 18 patients, including 6 with stress urinary incontinence and 12 with urgency urinary incontinence. Patients with neurogenic voiding dysfunction had significantly higher rates of developing *de novo* urinary incontinence. *De novo* urinary tract infection was also observed in 12 (22.2%) patients overall (Table 2).

Interpretation of results
The findings revealed that urethral sphincter onabotulinumtoxinA injection relieved voiding dysfunction in 61.1% of patients regardless of neurogenic or non-neurogenic etiology. Preoperative video-urodynamic studies provide a valuable prognostic indication of treatment success. Patients who had an open bladder neck on voiding cystourethrography had predictably successful therapeutic results. In addition, patients with early bladder sensation of filling, higher detrusor pressure, higher Qmax, and a smaller PVR volume appeared to benefit more from urethral sphincter onabotulinumtoxinA injection than those with lower bladder contractility.

Concluding message
OnabotulinumtoxinA urethral sphincter injection is effective in 61.1% of patients with voiding dysfunction due to neurogenic or non-neurogenic voiding dysfunction refractory to conventional medical treatment. Careful evaluation of the bladder neck

opening at baseline provides predictive value for a successful treatment outcome. However, urinary incontinence might be a *de novo* adverse event after the urethral sphincter onabotulinumtoxinA injections.

Table 1. The patients and baseline video-urodynamic characteristics between patients with good and poor treatment outcomes

	Good outcome (n=58)	Poor outcome (n=37)	Univariate P value
Age (years)	60.2 ± 22.1	59.3 ± 19.4	0.842
Gender Male (n=39)	22 (56.4%)	17 (43.6%)	0.287
Female (n=56)	36 (64.3%)	20 (35.7%)	
Neurogenic (n=42)	27 (64.3%)	15 (35.7%)	0.359
Non-neurogenic(n=53)	31 (58.5%)	22 (41.5%)	
First sensation of filling (mL)	122.0 ± 53.2	147.2± 67.0	0.046
Cystometric bladder Capacity (ml)	309 ± 141	358 ± 126	0.088
Detrusor pressure (cmH_2O)	36.1 ± 27.9	24.2 ± 19.3	0.027
Abdominal pressure (cmH_2O)	24.5 ± 27.3	33.8 ± 28.7	0.117
Maximum flow rate (mL/s)	7.64 ± 5.03	5.16 ± 4.46	0.017
Post-void residual volume (mL)	169 ± 130	251 ± 149	0.006
Open bladder neck	56 (87.5%)	8 (12.5%)	<0.001#

P= 0.0001 in multi-variate analysis

Table 2. Adverse events after urethral sphincter onabotulinumtoxinA injection for patients with urethral sphincter hyperactivity

	Non-neurogenic (n= 53)	Neurogenic (n=42)
Urinary tract infection	8 (15.1%)	4 (9.5%)
Stress urinary incontinence	1 (1.9%)	5 (11.9%)
Urgency urinary incontinence	3 (5.7%)	9 (21.4%)
None	41 (77.4%)	24 (57.1%)

P= 0.028 between groups

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