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BOTULINUM TOXIN A URETHRAL SPHINCTER INJECTION FOR NON-OBSTRUCTIVE VOIDING DYSFUNCTION – A RANDOMIZED, DOUBLE-BLIND, PLACEBO CONTROL, MULTICENTER STUDY

Hypothesis / aims of study
Non-obstructive voiding dysfunction may be due to detrusor underactivity (DU) or dysfunctional voiding (DV). Dysfunctional voiding is characterized with spastic urethra during voiding. The temporary inhibition of external urethral sphincter and/or pelvic floor muscles activation by onabotulinumtoxinA (BoNT-A) can interrupt the cycle of voiding dysfunction. Patients with detrusor underactivity can use less abdominal pressure to void if the urethral sphincter is paralyzed by urethral BoNT-A injection. The aim of study is to assess the efficacy and tolerability of 100U BoNT-A versus placebo to treat voiding dysfunction in patients refractory to previously medical and behavioral treatment.

Study design, materials and methods
A multicenter double-blind randomized, placebo controlled study enrolled patients aged ≥ 20 years of age with voiding difficulty due to DU or DV diagnosed by videourodynamic study. Exclusion criteria included active UTI, neurogenic bladder, abnormal liver or renal function, and patients satisfied with conservative therapy. Patients were randomized by 2:1 to receive a single intraurethral treatment of 100 U BoNT-A (n=49) or placebo (n=25). Primary efficacy end-point was the change from baseline to week 4 in total IPSS. Other endpoints assessed at week 4 included changes from baseline in PPBC, voided volume, PVR and maximal detrusor pressure. Adverse events were also assessed.

Results
The baseline characteristics and urodynamic parameters were comparable in both groups. Follow up data were available in 39 patients receiving BoNT-A and 20 patients receiving placebo. Significant improvements from baseline in IPSS-empty, IPSS-storage, IPSS-total, QOL, PPBC and Qmax were observed in both groups at week 4 ($p<0.05$) (Table 1). Compared with placebo group, patients receiving BoNT-A had significantly less improvement in IPSS-empty, IPSS-total and QOL. Voided volume increased significantly in treatment group and PVR decrease significantly in placebo group. No serious adverse events were found. In the subgroup analysis, 23 patients had Pdet <10 cmH_2O and considered as DU (Table 2). Of them, 9 patients receiving placebo had significantly improvement in IPSS-total, QoL, PPBC, Qmax and PVR. Fourteen patients receiving BoNT-A had significantly improvement in QoL, PPBC and voided volume. Compared with placebo group, patients with DU receiving BoNT-A had significantly less improvement in IPSS-empty and IPSS-total. In the patients with DV, urethral BoNT-A injection did not provide additional therapeutic effect on symptom improvement or uroflow parameters. A high placebo effect was also noted in patients with DV.

Interpretation of results
This randomized placebo-controlled study demonstrated that there was an unexpectedly pronounced placebo response in both DU and DV patients. Surprisingly, the reduction of IPSS in placebo group was higher than that in treatment group. These similar findings were also found both in patients with DU and DV. The reasons for the high placebo effect in this study are not entirely clear, but high placebo response was also noted in other BoNT-A study.

Concluding message
OnabotulinumtoxinA 100 U and placebo both improved IPSS and Qmax. These procedures were well tolerated. Long-term follow-up is still ongoing.

Table. 1. Comparison of IPSS, PPBC, and urodynamic data in overall patients with voiding dysfunction receiving onabotulinumtoxinA versus placebo injection at baseline and 1 month

		Placebo (N=20)	**BOTOX (N=39)**	**P-value**
IPSS-empty	Baseline	14.4±7.0	15.1±5.6	0.001
	1 M	5.8±6.5	12.4±6.9	
IPSS-storage	Baseline	11.0±4.4	10.5±4.2	0.069
	1 M	6.9±4.3	8.7±3.7	
IPSS-total	Baseline	25.1±9.0	25.5±8.2	0.001
	1 M	12.7±9.3	21.1±8.7	
QoL	Baseline	5.5±0.8	4.6±1.8	0.028
	1 M	2.5±1.9	3.0±2.0	
PPBC	Baseline	5.0±1.8	4.8±1.7	0.077
	1 M	2.6±2.0	3.5±2.0	
Qmax	Baseline	6.1±4.2	5.3±5.8	0.955
	1 M	9.8±6.8	8.8±8.7	
Volume	Baseline	95±100	103±112	0.464
	1 M	127±117	161±132	
PVR	Baseline	303±251	297±194	0.185
	1 M	181±189	254±184	
CBC	Baseline	418±228	380±154	0.140
	1 M	365±134	400±152	
Pdet	Baseline	24.8±23.9	22.7±24.8	0.203
	1 M	27.0±21.9	18.0±19.6	

CBC: cystometry bladder capacity, PPBC: patient perception of bladder condition,
PVR: post-void residual urine, Qmax: maximum flow rate, QoL: quality of life.

Table 2. Comparison of IPSS, PPBC, and urodynamic data in patients with dysfunctional voiding (DV) or detrusor underactivity (DU) receiving onabotulinumtoxinA versus placebo injection at baseline and 1 month

		DU			DV		
		Placebo (N=9)	BOTOX (N=14)	P-value	Placebo (N=11)	BOTOX (N=23)	P-value
IPSS-empty	Baseline	15.6±6.8	17.6±3.4	0.004	12.9±7.4	13.6±6.2	0.082
	1 M	5.1±7.3	15.7±5.1		5.5±6.2	10.0±7.1	
IPSS-storage	Baseline	10.1±5.1	10.2±4.6	0.339	12.0±3.0	10.9±4.2	0.029
	1 M	7.1±4.8	9.4±2.9		6.6±4.3	8.8±4.0	
IPSS-total	Baseline	25.1±9.0	27.9±5.5	0.006	25.0±8.9	24.4±9.3	0.021
	1 M	12.2±11.0	25.1±5.7		12.1±8.6	18.8±9.8	
QoL	Baseline	5.1±1.2	4.9±1.4	0.083	5.6±0.8	4.5±1.9	0.123
	1 M	2.1±2.0	3.3±1.9		2.6±2.0	3.0±2.2	
PPBC	Baseline	4.6±1.9	4.9±1.8	0.357	5.1±1.7	4.9±1.6	0.091
	1 M	2.7±1.9	3.7±2.0		2.2±2.1	3.4±2.0	
Qmax	Baseline	3.9±2.7	2.2±5.9	0.103	7.4±4.6	7.1±5.1	0.143
	1 M	12.0±8.7	5.1±7.2		8.0±4.2	11.3±9.0	
Volume	Baseline	64±49	39±101	0.761	97±83	129±90	0.157
	1 M	163±159	120±137		93±59	181±127	
PVR	Baseline	442±290	414±163	0.223	225±157	234±187	0.703
	1 M	208±210	327±165		182±171	214±189	
CBC	Baseline	499±299	407±136	0.258	368±127	363±165	0.395
	1 M	424±161	441±95		335±108	376±189	
Pdet	Baseline	3.0±2.7	1.5±2.0	0.076	40.9±18.6	35.7±23.1	0.788
	1 M	18.0±20.0	5.6±5.0		32.5±22.1	25.4±21.4	

CBC: cystometry bladder capacity, PPBC: patient perception of bladder condition, PVR: post-void residual urine, Qmax: maximum flow rate, QoL: quality of life.

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