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BOTULINUM TOXIN URETHRAL SPHINCTER INJECTION AS TREATMENT FOR NON-NEUROGENIC VOIDING DYSFUNCTION – A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY

Hypothesis / aims of study
Non-neurogenic voiding dysfunction including dysfunctional voiding (DV) and detrusor underactivity (DU) caused by a spastic or non-relaxing external urethral sphincter (EUS) can theoretically be treated by injections of botulinum A toxin (BoNT-A) into the EUS. This randomized, double-blind, placebo-controlled trial was designed to determine the clinical efficacy of BoNT-A EUS injections in patients with DV or DU.

Study design, materials and methods
Patients with medically refractory DV (n=31) or DU (n=31) were randomly allocated in a 2:1 ratio to receive either BoNT-A (100U) (n=38) or placebo (normal saline) (n=24). The primary end-point was change in Patient Perception of Bladder Condition (PPBC) score at 1 mo after the initial injection (success: a reduction in PPBC score ≥2). Patients were assessed with IPSS, QoL-I, and VUDS at baseline and 1 month later. If patients were not satisfied with the treatment result at 1 mo, repeated EUS injection with 100 U BoNT-A was performed regardless of patient allocation.

Results
Overall success rate was 43.5% (BoNT-A 36.8% vs placebo 54.2%, p=0.114). In both BoNT-A and control groups, there were significant improvements in subjective clinical parameters and voiding efficiency in VUDS (Table 1), but no significant difference in subjective or objective parameters between these two groups was noted. The results were similar between the DV and DU subgroups (Table 2). However, a significant reduction in detrusor voiding pressure was only observed in DV patients who received BoNT-A injection. Repeat EUS BoNT-A injections offered greater therapeutic effects in both DV and DU patients.

Interpretation of results
Local EUS injection therapy resulted in significant improvement in all subjective parameters as well as in Qmax and VE, indicating that the action of a local injection itself had a therapeutic effect on the EUS, regardless of the pharmacologic effects of BoNT-A. However, only EUS BoNT-A injection in patients with DV resulted in a reduction in Pdet, which demonstrates the paralytic effect of BoNT-A. Injection of either substance into the EUS might result in reduced spasticity of the EUS in patients with DV and increased relaxation of the EUS in patients with DU, regardless of the pharmacologic effects of BoNT-A (probably due to the insufficient dose).

Concluding message
EUS injection therapy with either BoNT-A 100U or placebo could safely and effectively ameliorate clinical symptoms and improves voiding in patients with DV and in those with DU. We found that the action of local injection itself had a therapeutic effect on the EUS, regardless of the pharmacologic effects of BoNT-A. Increased dose/ or repeat injections may render more benefits to some DV and DU patients.

Table 1. Demographics and the changes of clinical and VUDS parameters in the BoNT-A and placebo groups at baseline and 1 month after the first EUS injection therapy

		BoNT-A (N=38)	Placebo (N=24)	P value$	P value#
Age (yr)		64.7 ±16.2	66.9 ±14.2	0.562	
Gender		9 M, 29 F	5 M, 19F	0.865	
IPSS-V	BL	15.2 ± 5.6	14.5 ± 6.7	0.468	0.002
	1 mo	12.7 ± 7.0*	6.0 ± 6.6*		
IPSS-S	BL	10.7 ± 4.0	11.0 ± 4.3	0.518	0.074
	1 mo	8.5 ± 3.8*	7.1 ± 4.2*		
IPSS-T	BL	25.8 ± 8.2	25.5 ± 8.8	0.776	0.001
	1 mo	21.2 ± 8.6*	13.1 ± 9.5*		
QoL-I	BL	4.5 ± 1.9	5.4 ± 0.9	0.024	0.014
	1 mo	3.0 ± 1.9*	2.4 ± 1.9*		
PPBC	BL	4.8 ± 1.7	5.0 ± 1.7	0.761	0.066
	1 mo	3.4 ± 2.0*	2.7 ± 2.1*		
CBC (mL)	BL	378.9 ± 154.2	397.8 ± 223.5	0.585	0.201
	1 mo	404.6 ± 182.4	360.0 ± 140.7		
Pdet (cmH_2O)	BL	22.7 ± 24.7	25.3 ± 24.6	0.444	0.161
	1 mo	19.2 ± 19.6	30.5 ± 25.1		
Qmax (mL/s)	BL	5.3 ± 5.7	6.3 ± 5.1	0.344	0.558
	1 mo	9.8 ± 9.5*	9.5 ± 6.6*		
Vol. (mL)	BL	104.8 ± 112.2	102.4 ± 101.4	0.942	0.627
	1 mo	170.7 ± 140.5*	148.5 ± 144.7		
PVR (mL)	BL	295.7 ± 194.1	279.3 ± 246.9	0.965	0.141
	1 mo	251.7 ± 214.0	146.6 ± 160.5*		
VE (%)	BL	29.6 ± 28.3	34.4 ± 34.2	0.530	0.336
	1 mo	44.1 ± 35.3*	56.1 ± 36.4*		

Table 2. The changes of Clinical and VUDS parameters in the BoNT-A and placebo groups at baseline and 1 month after the first EUS injection therapy within DV and DU patients

		DV			DU		
		BoNT-A (N=16)	Placebo (N=15)	P value#	BoNT-A (N=22)	Placebo (N=9)	P value #
IPSS-V	BL	12.7 ± 6.6	14.1 ± 5.8		17.0 ± 3.8	15.1 ± 8.4	
	1 mo	8.3 ± 7.6*	5.7 ± 5.8*	0.089	16.0 ± 4.3	6.6 ± 8.2*	**0.036**
IPSS-S	BL	11.4 ± 4.3	12.1 ± 4.0		10.1 ± 3.8	9.8 ± 4.5	
	1 mo	8.5 ± 3.7*	6.3 ± 3.9*	0.089	8.5 ± 3.9	8.4 ± 4.5	0.831
IPSS-T	BL	24.1 ± 10.3	26.2 ± 7.8		27.1 ± 6.2	24.3 ± 10.7	
	1 mo	16.8 ± 10.4*	12.0 ± 8.0*	0.026	24.4 ± 5.2*	15.0± 11.8*	0.002
QoL-I	BL	4.4 ± 1.7	5.4 ± 1.0		4.6 ± 2.0	5.4 ± 0.9	
	1 mo	2.8 ± 2.1*	2.4 ± 2.1*	0.089	3.0 ± 1.9*	2.4 ± 1.8*	0.107
PPBC	BL	4.8 ± 1.4	5.4 ± 1.4		4.7 ± 1.9	4.4 ± 1.9	
	1 mo	3.3 ± 1.9*	2.5 ± 2.2*	0.085	3.5 ± 2.1*	3.0 ± 1.8*	0.814
CBC (mL)	BL	359 ± 172.6	334 ± 176		393.9 ± 141	497± 262.5	
	1 mo	365 ± 154.4	354 ± 125.7	0.860	434.7± 199.4	369 ± 169.2	0.042
Pdet (cmH_2O)	BL	40.3 ± 23.0	35.6 ± 25.1		9.2 ± 16.4	9.1 ± 12.8	
	1 mo	31.6 ± 22.3*	32.1 ± 22.6	0.473	9.8 ± 10.0	27.9 ± 30.0	0.070
Qmax (mL/s)	BL	6.4 ± 5.4	7.9 ± 5.2		4.5 ± 6.0	3.4 ± 3.7	
	1 mo	11.1 ± 10.1*	8.9 ± 4.7	0.099	8.8 ± 9.1*	10.6 ± 9.2*	0.445
Vol. (mL)	BL	119.9 ± 82.2	136.3 ± 109		93.9 ± 130.9	45.9 ± 54.9	
	1 mo	191 ± 140.1*	117.5 ± 63.7	0.020	155 ± 142.0	200 ± 219.7	0.182
PVR (mL)	BL	225 ± 200.7	198 ± 168.2		350 ± 174.6	415 ± 304.0	
	1 mo	198 ± 179.1	156 ± 160.5	0.770	293 ± 233.1	131 ± 169.1*	0.046
VE (%)	BL	42.1 ± 27.8	44.9 ± 32.2		20.8 ± 28.5	17.0 ± 31.5	
	1 mo	50.5 ± 34.6	52.8 ± 34.6	0.969	39.4 ± 36.0*	61.6 ± 40.7*	0.094

$: p value between the baseline data of BoNT-A and placebo groups
#: p value between the changes of the parameters after EUS injection therapy in BoNT-A and placebo groups
*: p value < 0.05 versus baseline

Disclosures
Funding: none **Clinical Trial:** Yes **Registration Number:** NCT01733290 **RCT:** Yes **Subjects:** HUMAN **Ethics Committee:** Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation **Helsinki:** Yes **Informed Consent:** Yes