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INTRAVESICAL INSTILLATION OF LIPOSOME ENCAPSULATED ONABOTULINUMTOXINA FOR PATIENTS WITH OVERACTIVE BLADDER – A PILOT CLINICAL STUDY

Hypothesis / aims of study:
Intradetrusor onabotulinumtoxinA (BoNT-A) injection benefits overactive bladder (OAB) patients, but increased post-void residual (PVR) urine volume and urinary tract infection (UTI) remain risks. Intravesical instillation of liposomal BoNT-A instead of injection could prevent such adverse events. In this proof-of-concept study, we tried to evaluate that liquid liposomal delivery of BoNT-A (Liposome-BoNT-A, Lipotoxin) could penetrate the bladder urothelium without injection in patients with refractory OAB. With limited penetration depth in human bladder, Lipotoxion might have a similar effect of BoNT-A on urothelium without affecting detrusor contractility.

Study design, materials and methods:
This pilot study was designed as a randomized, double-blind, parallel, controlled trial. Patients with confirmed OAB were randomly assigned to receive intravesical instillation of either Lipotoxin (treatment group) or normal saline (N/S, control group). Both groups were evaluated at the treatment visit and primary end-point evaluation 1 month after treatment by recording symptom scores, adverse events, overall satisfaction assessments, and urodynamic studies. The primary end-point of the study was the net change in total frequency per 3 days from baseline to 1 month after Lipotoxin or N/S treatment. The secondary end-points were the net change of variables from baseline to 1 month after treatment including urgency episodes/3 days, UUI/3 days, overactive bladder symptom score (OABSS), USS, FBC, maximum flow rate (Qmax), PVR, and global response assessment (GRA).

Results:
A total of 24 patients were eligible for the treatment. There were 10 men and 14 women with the mean age of 67 years (ranged 38 to 82 years). At baseline, there was no significant difference of the measured variables between Lipotoxin and N/S groups. The frequency (35.7 ± 10.0 v 25.4 ± 6.17, p=0.008) and urgency (32.7 ± 11.9 v 21.8 ± 5.94, p=0.012) per 3 days were significantly improved in the Lipotoxin group, but only frequency showed significant improved compared to that of the N/S group (p=0.045). The USS and OABSS all showed significant improvement in both groups, but no difference was noted between groups (Table 1). There was no significant change of Qmax, voided volume, PVR and FBC from baseline to 1 month, in Lipotoxin or N/S group. No adverse events were reported by the patients during the follow-up period. A total of 20 patients received the first time Lipotoxin treatment (12 in Lipotoxin and 10 in control group). The changes of all variables showed significant improvement in frequency, urgency, USS, OABSS and GRA at 1 month (Table 2). Among the 12 patients in Lipotoxin group who had follow-up visits at 3 months, the variables at 3 month did not show significant difference compared with the baseline data (Table 3).

Interpretation of results:
In this study, we for the first time demonstrated that liposome is an efficient vehicle for delivering of BoNT-A into urothelium of OAB bladders. The PVR did not increase and all patients were free of UTI after treatment. However, the therapeutic effects did not last up to 3 months.

Concluding message: This pilot study has demonstrated that intravescal Lipotoxin instillation can effectively reduce frequency episodes at 1 month in OAB patients. The PVR did not increase and all patients were free of UTI after the treatment.

Table 1. Changes of voiding diary parameters in Lipotoxin and control groups at 1 month after intravesical treatment

		Lipotoxin (n=12)	N/S (n=12)	P value
Frequency/3D	BL	35.7 ± 10.0	30.2 ± 5.55	0.045
	1M	25.4 ± 6.17 *	29.4 ± 10.4	
Urgency/3D	BL	32.7 ± 11.9	25.7 ± 7.34	0.199
	1M	21.8 ± 5.94 *	21.2 ± 10.1	
UUI/3D	BL	3.58 ± 5.53	7.76 ± 7.28	0.702
	1M	3.08 ± 6.11	8.17 ± 10.8	
USS	BL	3.42 ± 0.52	3.67 ± 0.49 3.08 ± 0.99 *	1.000
	1M	2.83 ± 0.94 *		
OABSS	BL	9.83 ± 2.95	10.1 ± 2.54	0.544
	1M	7.67 ± 3.31	8.08 ± 4.72 *	
FBC/VD (mL)	BL	310 ± 68.0	285 ± 133	0.916
	1M	263 ± 100	241 ± 131	
Qmax (mL/s)	BL	17.9 ± 16.9	13.1 ± 7.93	0.323
	1M	18.0 ± 17.5	10.9 ± 5.37	
Volume (mL)	BL	200 ± 95.3	166 ± 121	0.930
	1M	186 ± 94.4	149 ± 82.8	
PVR (ml)	BL	35.3 ± 34.1	35.6 ± 32.0	0.665
	1M	37.1 ± 28.4	46.2 ± 61.7	
GRA	BL	0.00 ± 0.00	0.00 ± 0.00	1.000
	1M	1.17 ± 0.84 *	1.17 ± 1.34 *	

GRA: global response assessment, N/S: normal saline, OABSS: overactive bladder symptom score, PVR: postvoid residual, Qmax: maximum flow rate, USS: urgency severity scale, UUI: urgency urinary incontinence.

Table 2. Changes of parameters in 20 patients who received the first LPX treatment

	Baseline (n=20)	2 weeks (n=20)	1 month (n=20)	P value
Frequency/3D	32.9±8.17	28.1±8.0*	25.1±7.06*	0.001
Urgency/3D	28.9±10.3	22.6±8.68*	20.0±6.91*	0.001
UUI/3D	4.65± 5.34	4.70±9.19	4.65±8.58	0.884
USS	3.45±0.51	2.90±0.91*	3.90±0.57	0.687
OABSS	10.0±2.73	7.90±4.17*	7.05±4.02*	0.002
FBC/VD (mL)	316±100	273±122	270±116*	0.000
Qmax (mL/s)	16.4±14.2	15.2±13.1	14.7±14.4	0.137
Volume (mL)	202±107	178±83.7	175±108	0.329
PVR (mL)	39.9±33.6	42.4±25.2	57.6±63.4	0.202
GRA	0.00±0.00	0.90±1.37*	1.25±1.07*	0.001

Table 3. Changes of variables of the first time Lipotoxin treated patients at baseline, 1 month and 3 months

	Baseline (n=12)	1 month (n=12)	3 month (n=12)
Frequency/3d	35.5 ± 9.86	28.4 ± 7.51 *	33.8 ± 8.22
Urgency/3d	30.9 ± 11.8	23.9 ± 9.52 *	29.7 ± 13.2
UUI/3d	4.70 ± 6.98	3.08 ± 6.11	4.60 ± 12.9
Day times/3d	27.7 ± 9.58	21.7 ± 6.22 *	24.9 ± 7.93
Night times/3d	9.24 ± 3.36	8.41 ± 3.59	8.87 ± 3.14
Qmax (mL/s)	16.3 ± 9.32	16.9 ± 8.75	14.4 ± 6.61
VOL (mL)	244 ± 135	229 ± 128	272 ± 86.9
PVR (mL)	44.0 ± 37.1	36.1 ± 33.4	37.0 ± 60.3
FBC (mL)	324 ± 120	311 ± 180	271 ± 133
USS	3.65 ± 0.61	3012 ± 0.86 *	3.24 ± 1.03
OABSS	10.2 ± 2.96	8.21 ± 3.96	9.88 ± 2.69
GRA	0.00 ± 0.00	1.21 ± 1.12 *	1.00 ± 0.87
PPBC	5.07 ± 1.14	3.50 ± 1.99 *	4.18 ± 1.85

* P<0.05 compared to the baseline

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