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DETRUSOR ONABOTULINUMTOXINA 200 U INJECTION IMPROVED UROTHELIAL DYSFUNCTION BUT NOT ALTERED UROTHELIAL SENSORY PROTEIN EXPRESSIONS IN SPINAL CORD INJURED PATIENTS

Hypothesis / aims of study

In recent decades, treatment of neurogenic detrusor overactivity (NDO) with onabotulinumtoxinA has emerged as an alternative method for the management of urological complications due to spinal cord injury (SCI) or multiple sclerosis. Injection of 200-300 U of onabotulinumtoxinA into the detrusor muscle can reduce contractility, improve bladder compliance, and restore urinary continence in patients with NDO. Currently, a 200 U single injection of onabotulinumtoxinA into the detrusor has been recommended as standard treatment for NDO. However, the therapeutic duration of this dosage on NDO was shorter than that of a 300 U injection. Most studies of onabotulinumtoxinA on NDO come from animal models, and only a few human studies have been noted. The current study investigated changes in urothelial dysfunction and sensory protein expression in the bladder urothelium with time after a single onabotulinumtoxin injection in SCI patients.

Study design, materials and methods

Twenty-six patients with chronic SCI causing neurogenic detrusor overactivity and urinary incontinence were treated with a single injection of 200 U onabotulinumtoxinA. Video urodynamic studies were performed at baseline, 3 months, and 6 months after treatment. Bladder mucosal biopsy was performed at the same time-point. Treatment outcomes were considered successful if patients had a 50% increase in cystometric bladder capacity and improvement of incontinence. Twenty patients with stress-related urinary incontinence served as controls. Bladder tissues were investigated for E-cadherin, zonula occludens-1 (ZO-1) expression, mast cell activity, and urothelial cell apoptosis. Western blotting was completed to assess expression of sensory proteins [purinergic receptor P2X3, endothelial and inducible nitric oxide synthases (NOS), β3-adrenoceptor, and muscarinic receptors M2 and M3] between controls and SCI patients, as well as successful and failed treatment groups.

Table 1. Changes of urodynamic parameters between spinal cord injured patients with successful and failed treatment outcome

		Baseline	3M	6M	P value
FSF (mL)	Successful	129± 72.5	206± 120 *	214± 112 *	3M 0.126
	Failed	145± 108	141± 84.5	132± 33.1	6M 0.030
FS (mL)	Successful	182± 116	295± 126 *	289± 152 *	3M 0.009
	Failed	218± 145	156± 84.1	175± 77.8	6M 0.016
US (mL)	Successful	199± 134	327± 141 *	293± 150 *	3M 0.007
	Failed	218± 145	174± 129	178± 78.1	6M 0.053
CBC (mL)	Successful	238± 127	435± 109 *	389± 163*	3M <0.0001
	Failed	373± 215	299± 150	214± 118	6M <0.0001
Compliance	Successful	33.5± 20.0	49.8± 45.1	60.8± 86.3	3M 0.312
	Failed	61.5± 95.1	43.2± 51.5	28.5± 22.3	6M 0.236
Pdet(cmH_2O)	Successful	36.3± 23.9	10.9±15.1*	23.3±27.2*	3M 0.032
	Failed	30.6± 15.1	28.1± 15.4	29.7± 15.2	6M 0.270
Qmax(mL/s)	Successful	2.26± 2.54	2.58± 5.37	2.47± 5.51	3M 0.111
	Failed	7.14± 7.29	2.43± 2.88	6.0± 5.33	6M 0.378
PVR (mL)	Successful	204± 135	399± 146 *	337± 179*	3M 0.002
	Failed	259± 156	261± 176	158± 126	6M 0.001
VV (mL)	Successful	34.8± 39.3	50.7± 80.3	52.2± 94.6	3M 0.067
	Failed	114± 137	37.4± 48.8	55.5± 59.4	6M 0.116

*Significant difference compared with the control, p values indicate the difference between groups at 3 and 6 months; FSF: first sensation of filling, FS: full sensation, US: urge sensation, CBC: cystometric bladder capacity, Qmax: maximum flow rate, Pdet: detrusor pressure at Qmax, PVR: post-void residual , VV: voided volume

Table 2. Urothelial dysfunction parameters and sensory protein expressions in the controls and spinal cord injured patients at baseline and at 3 and 6 months after onabotulinumtoxinA injection

	Control	Baseline	3M	6M	P value
E-Cadherin	41.3 ± 8.4	31.3±19.8*	52.9 ±19.6*	43.6 ± 19.9	BL v 3M 0.001
Mast cell	5.9 ± 4.92	16.5± 5.9*	16.1 ± 4.64*	14.5 ± 4.21*	N.S.
TUNEL	1 ± 1.35	3.3 ± 2.14*	4.05 ± 2.16*	4.58 ± 3.03*	3M v 6M 0.047
ZO-1	6.37 ±1.72	6.5 ± 6.35	8.65 ± 3.86*	7.3 ± 4.44	BL v 3M 0.027
M2	1.22 ±0.59	0.8 ± 0.65	0.89 ± 0.81	0.96 ± 0.8	N.S.
M3	1.55 ±1.03	0.37± 0.27*	0.35 ± 0.34*	0.36 ± 0.3*	N.S.
β3-AR	0.57 ±0.48	0.79 ± 0.55	0.77 ± 0.54	0.8 ± 0.44	N.S.
P2X3	1.66 ±1.17	1.51 ± 0.73	1.78 ± 0.91	1.6 ± 0.73	N.S.
iNOS	0.92 ±0.77	0.68 ± 0.66	0.53 ± 0.44	0.46 ± 0.36	N.S.
eNOS	0.34 ±0.17	0.16 ±0.17*	0.15 ± 0.16*	0.1 ± 0.1*	N.S.

*Significant difference compared with the control, p values indicate the difference between different time-point within spinal cord injured patient group. FSF: first sensation of filling, FS: full sensation, US: urge sensation, CBC: cystometric bladder capacity, Qmax: maximum flow rate, Pdet: detrusor pressure at Qmax, PVR: post-void residual, VV: voided volume

Results

The mean age was 42.7 ± 13.1 years in SCI patients and 52.4 ± 10.5 years in controls. After onabotulinumtoxionA injection, successful treatment outcome was noted in 17 (65.4%) patients at 3 months but only 13 (50%) patients at 6 months; 12 patients had a successful outcome lasting up to 6 months. Table 1 shows the urodynamic parameters at baseline and 3 and 6 months after onabotulinumtoxinA injection. As expected, Pdet decreased, while CBC and PVR volume increased at 3 months after treatment. However, these urodynamic changes faded at 6 months. Comparison of urodynamic parameters at baseline to those as 3 and 6 months revealed only the successful treatment group showed these therapeutic effects (Table 1). Compared to controls, urothelial expression of E-cadherin was significantly lower, while mast cell activity and apoptotic cell count were significantly higher in SCI bladders (Table 2). Increased E-cadherin levels were noted 3 months after injection but were reduced at 6 months. Mast and apoptotic cell counts showed no change at 3 or 6 months after treatment. ZO-1 expression was significantly increased at 3 months but returned to baseline levels at 6 months. Among the urothelial sensory proteins, only baseline M3 and eNOS levels were significantly lower in SCI bladders versus controls. Interestingly, there were no significant changes in any of the sensory proteins examined from baseline to 3 or 6 months in SCI patients after onabotulinumtoxinA injection (Table 2). However, M3 receptor density was significantly decreased in SCI patients with successful treatment outcome at 6 months (0.44 ± 0.29 versus 0.35 ± 0.26, $P = 0.01$).

Interpretation of results

The results of the current study revealed that after detrusor injection of 200 U onabotulinumtoxinA, the urothelial levels of E-cadherin and ZO-1 improved after 3 months, but the effect declined 6 months after treatment. Urothelial sensory protein levels were not significantly changed after onabotulinumtoxinA treatment. Improvement of bladder sensation and CBC were noted in 65.4% of SCI patients who had successful outcomes but not in patients who experienced treatment failure. These results imply that the therapeutic effect of 200 U onabotulinumtoxinA might not be adequate for NDO.

Concluding message

A single injection of 200 U onabotulinumtoxinA in SCI patients improved urothelial expression of E-cadherin and ZO-1 at 3 months, but the effect declined 6 months after treatment. Urothelial sensory protein levels did not significantly change after onabotulinumtoxinA treatment. Observed protein changes were in accordance with bladder function improvements in 65.4% of SCI patients with successful outcomes. These results imply that the therapeutic effect of 200 U onabotulinumtoxinA might not be adequate for NDO.

Disclosures

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