

DEFICITS OF UROTHELIAL E-CADHERIN AND ZONULA OCCLUDENS-1 IN CHRONIC SPINAL CORD INJURED BLADDERS IMPROVED AFTER REPEATED DETRUSOR ONABOTULINUMTOXINA INJECTIONS

Hypothesis / aims of study

Chronic spinal cord injury (SCI) induces bladder urothelium dysfunction. This study investigated the therapeutic effects on urothelial dysfunction after repeated detrusor injections of onabotulinumtoxinA in patients with SCI and neurogenic detrusor overactivity (NDO).

Study design, materials and methods

A total of 20 patients with chronic suprasacral SCI and refractory NDO were enrolled. The patients received 300U onabotulinumtoxinA detrusor injection every 6 months for four times. The urothelium was assessed by cystoscopic biopsy at baseline and 6 months after each onabotulinumtoxinA treatment. Immunofluorescence staining of E-cadherin, zonula occludens-1 (ZO-1), and tryptase for mast cell activity were performed. Urothelial apoptosis was also evaluated. The differences in urothelial dysfunction were compared between baseline and every 6 months after treatment. Bladder biopsies from 10 patients undergoing anti-incontinence surgery served as controls.

Results

Repeated 300 U onabotulinumtoxinA injections into the detrusor significantly and consistently increased bladder capacity and decreased detrusor pressure at 6 months after each onabotulinumtoxinA treatment compared with baseline. Significantly lower E-cadherin and ZO-1 expressions, and increased apoptotic cell counts were noted in SCI bladders compared with controls (all $P < 0.05$). After repeated onabotulinumtoxinA injections, significantly greater distributions of E-cadherin ($p = 0.042$) and ZO-1 ($p = 0.003$) expressions were found at 6 months after 3rd onabotulinumtoxinA injection compared with baseline. Besides, after 3rd onabotulinumtoxinA treatment, no significant difference of E-cadherin and ZO-1 were noted compared to the control.

Interpretation of results

This study demonstrated significantly impaired expressions of adhesion protein E-cadherin and tight junction protein ZO-1 and significantly higher cell apoptosis in the urothelium of patients with chronic SCI and NDO. After repeated detrusor onabotulinumtoxinA injections, E-cadherin and ZO-1 expressions recovered, and the therapeutic effects of onabotulinumtoxinA persisted up to 6 months after 3rd treatment. There is limited data focused on urothelial dysfunction after repeated detrusor BoNT-A injections for SCI patients with NDO. This study provides evidence that the repeated detrusor onabotulinumtoxinA injections can improve the impaired adhesive and junction protein of the urothelium in SCI bladders.

Concluding message

Urothelial dysfunction parameters such as adhesive and tight junction protein concentrations in SCI bladders recovered after repeated 3 times of onabotulinumtoxinA treatment. The therapeutic effects also sustained after repeated onabotulinumtoxinA treatment. However, neurogenic inflammation and urothelial cell apoptosis after SCI could not adequately improve after repeated onabotulinumtoxinA injection.

Table 1. Changes of the urodynamic parameters at 6 months after each set of 300U BoNT-A detrusor injections compared with baseline and control

	Control	Baseline 1 st BoNT-A	1 st BoNT-A + 6M	2 nd BoNT-A + 6M	3 rd BoNT-A + 6M
BC (mL)	364±196	163± 97.7*	223±150**	245±137**	239±118**
Pdet (cmH ₂ O)	25.2± 14.5	42.7±12.5*	33.2±28.6**	22.8±16.9**	22.2±19.1**
Qmax (mL/s)	11.9±6.25	6.9± 6.27*	2.61±3.50**	2.75±4.89**	3.15±4.97**
Vol (mL)	302±154	91.4±99.2*	34.9±51.3**	38.6±71.5**	57.7±82.6**
PVR (mL)	93.3±107	118±90.7*	245±179**	343±190**	329±170**
Compliance (mL/cmH ₂ O)	86.3±38.0	25.6±28.3*	30.0±35.1	36.7±32.5	44.5±56.2

Table 2. Changes of the urothelial dysfunction parameters at baseline and 6 months after each set of 300U BoNT-A detrusor injections and compared with control

	Control	Baseline 1 st BoNT-A	1 st BoNT-A + 6M	2 nd BoNT-A + 6M	3 rd BoNT-A + 6M
E-cadherin	41.3±8.40	25.6±21.4*	29.5±28.4	30.9±32.8	<u>42.4±27.0[#]</u>
Mast cell	5.89±4.92	7.51±6.60	9.61±6.92	7.47±6.22	9.87±7.29
TUNEL	1.00±1.35	2.40±4.67*	2.59±2.11*	2.23±1.31*	2.42±2.45*
ZO-1	6.37±1.72	2.77±3.24*	5.08±6.09	<u>6.86±7.25[#]</u>	<u>8.32±6.78[#]</u>

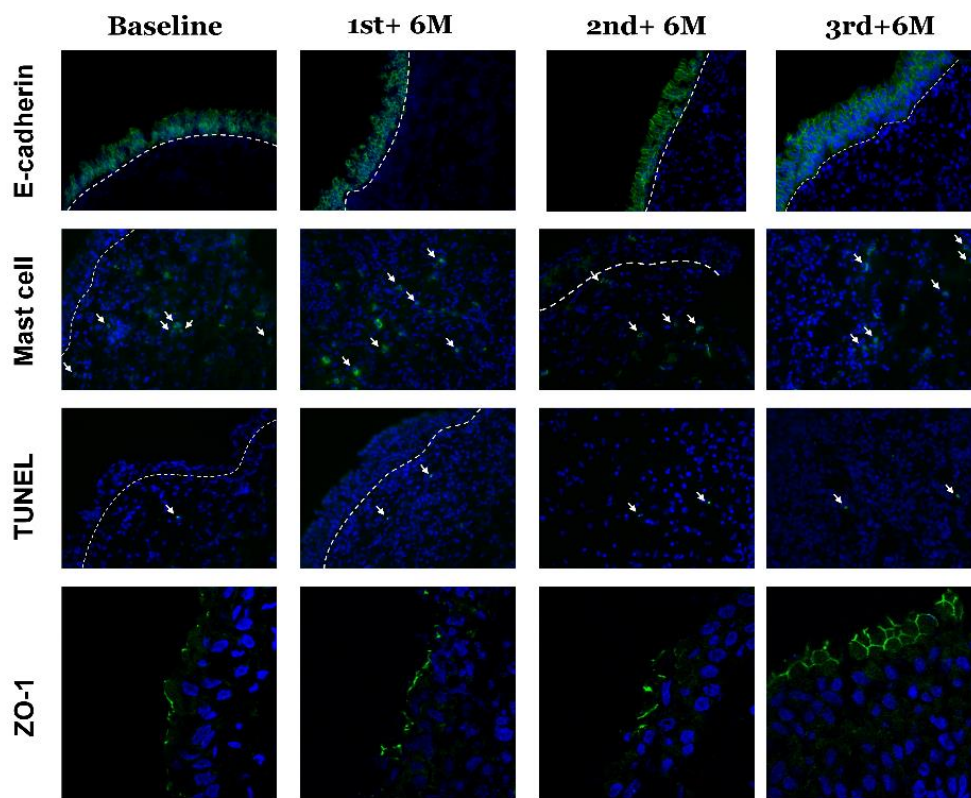


Fig.1. Changes of E-cadherin, mast cell activity, TUNEL and ZO-1 in SCI patients after repeat Botox injections.

Disclosures

Funding: none **Clinical Trial:** Yes **Public Registry:** No **RCT:** No **Subjects:** HUMAN **Ethics Committee:** Research Ethics Committee, Hualien Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation **Helsinki:** Yes **Informed Consent:** Yes