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DOWN REGULATION OF VASCULAR ENDOTHELIAL GROWTH FACTOR AFTER REPEATED INTRAVESICAL BOTULINUM TOXIN A INJECTIONS IS ASSOCIATED WITH IMPROVEMENTS OF CLINICAL SYMPTOMS AND BLADDER CAPACITY IN PATIENTS WITH INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME

Hypothesis / aims of study

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic disease of uncertain etiology that is an unpleasant sensation perceived to be related to the urinary bladder with no reliable biological marker or effective therapy. Recent evidence supports a role for vascular endothelial growth factor (VEGF) signalling in bladder inflammation and is closely associated with the vascular alterations observed in patients with IC/BPS. Other studies suggested that repeated intravesical botulinum toxin A (BoNT-A) injections in patients with IC/BPS have symptomatic improvement and may involve in anti-inflammatory response. The aim of this study was to measure the expression of VEGF in bladder tissue and improvement of clinical symptoms after repeated intravesical BoNT-A injections in patients with IC/BPS.

Study design, materials and methods

Nineteen patients compatible with the NIDDK criteria were included and all patients were not previously treated for IC/BPS before hydrodistention were enrolled in this study. Intravesical BoNT-A injection of 100u was performed and then was repeated every 6 months up to four times. These patients were assessed at baseline and 6 months after three repeated BoNT-A injections by validated questionnaire including O'Leary-Sant Symptom (ICSI) and Problem Index (ICPI), bladder pain visual analogue scale (VAS), functional bladder capacity (FBC), and 3-day voiding diary. Urodynamic parameters were also practiced and the degree of glomerulations and maximal bladder capacity (MBC) under cystoscopic hydrodistention at the intravesical pressure of 80 cm H2O were also measured. The bladder specimens at baseline and after three repeated intravesical BoNT-A injection were investigated by western blotting for the expression of VEGF. Immunohistochemistry staining for TUNEL and mast cell activity (tryptase), western blotting for tryptase and cytokines Bax and p-p38 were also assayed. We compared the clinical results and immunohistochemistry data between baseline and after repeated BoNT-A injections.

Results

Patient demographics showed the average age was 44.8 ±11.1 years old. Subjective symptoms including O'Leary-Sant symptom score and VAS all decreased significantly after repeated intravesical BoNT-A injection compare to baseline, respectively (16.11 ± 8.39 v 21.26 ± 8.14, 3.11 ± 3.07 v 5.16 ± 2.57, p=0.023 and 0.008, respectively). Highly significant increase of functional bladder capacity after repeated intravesical BoNT-A injections compared to baseline was also observed (194.21 ± 117.77 v 134.21 ± 82.75 ml, p=0.037). There were trends that a higher VEGF expression was associated with higher OSS, higher grade of glomerulations, higher VAS, and smaller CBC. A decreased expression of VEGF was significantly negatively correlated with functional bladder capacity after repeated intravesical BoNT-A injections (Table 1). Statistically significant decrease of expression of VEGF in patients with repeated intravesical BoNT-A injections was noted compared to baseline (0.83 ± 0.28 v 1.00, p=0.017). Correlation between different protein expressions also revealed that VEGF was significantly correlated with p-p38 expression (Fig. 1).

Interpretation of results

The results of this study revealed that repeated BoNT-A injection provided both improvement of clinical symptoms including O'Leary-Sant score, VAS, and functional capacity and decreasing chronic bladder inflammation such as expression of VEGF and decreased apoptosis of urothelial cells in IC/BPS. A higher VEGF expression was associated with severe clinical symptoms and bladder inflammation. Although the correlation between the expression of VEGF and the severity of glomerulations was not significant, the trend that after repeated BoNT-A injection the functional bladder capacity could be increased due to improved bladder inflammation in IC/BPS patients was likely.

Concluding message

The increased VEGF expression in IC/BPS can be decreased after repeated BoNT-A injections. Repeated intravesical BoNT-A injections in IC/BPS patients provided the improvement of clinical symptoms with increased functional bladder capacity.

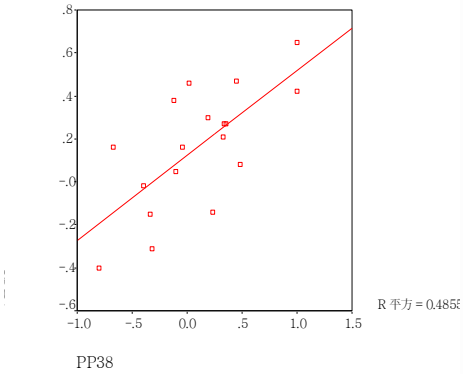
Table 1. The clinical and IHC and western blotting parameters at baseline and 6 months after three repeated BoNT-A injections in 19 IC/BPS patients

Clinical variables	Baseline	6M after BTX-4	p-value
Oleary-Sant Score	21.26 ± 8.14	16.11 ± 8.39	0.023
VAS pain score	5.16 ± 2.57	3.11 ± 3.07	0.008
Frequency	12.32 ± 4.38	11.16 ± 6.34	0.444
Nocturia	3.58 ±1.50	3.74 ±3.03	0.795
Functional bladder capacity	134.2 ± 82.8	194.2 ± 117.8	0.037
Maximum flow rate	12.38 ± 5.63	11.88 ± 6.85	0.739
Voided volume	226.9 ± 102.5	245.5 ± 170.7	0.615
Postvoid residual volume	11.53 ± 26.31	31.18 ± 42.70	0.047

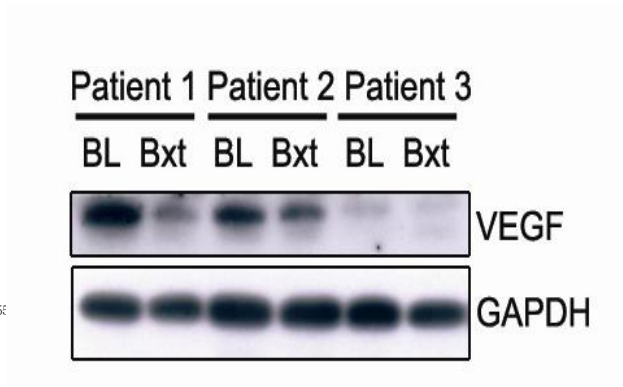
Cystometric bladder capacity	239.1 ± 118.3	278.6 ± 173.6	0.249
Voiding pressure	21.29 ± 6.60	19.50 ± 9.27	0.424
Maximal bladder capacity	628.8 ± 196.0	620.5 ± 220.2	0.803
Glomerulation degree	1.90 ± 1.05	1.47 ± 1.02	0.220
Global response assessment	0.63 ± 0.83	1.79 ± 0.92	0.001
Tryptase	1.00	1.76 ± 2.65	0.459
P-p38	1.00	0.91 ± 0.50	0.866
Bax	1.00	1.02 ± 0.59	0.285
TUNEL	2.30 ± 1.83	0.86 ± 1.00	0.026
VEGF	1.00	0.83 ± 0.28	0.017

Fig. 1. (A) Expression of VEGF was significantly correlated with p-p38. (B) Decrease expression of VEGF after three repeated BoNT-A injections

(A)



(B)



Disclosures

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