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# THE ALTERATION OF GLOMERULATION AND ANGIOGENIC MOLECULES CHANGE AFTER BOTULINUM TOXIN A THERAPY IN INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME

Hypothesis / aims of study

Glomerulation of bladder mucosa after cystoscopic hydrodistention (HD) has been regarded one of the requisite criteria for the diagnosis of interstitial cystitis/painful bladder syndrome (IC/PBS). Previous studies found that botulinum toxin A (BoNT-A) not only inhibit the release of acetylcholine and norepinephrine, but also resolved clinical symptoms of IC/PBS. We have observed the HD induced glomerulation decreased in grade after repeated BoNT-A injection. This study investigated the mechanism of action for IC/PBS patients having symptomatic and cystoscopic improvements after intravesical BoNT-A injections, such as bladder glomerulation and inflammation.

Study design, materials and methods

Twenty-five women with characteristic symptoms of IC/PBS and glomerulation after cystoscopic HD were enrolled in this study. Bladder biopsies at three sites were taken immediately after cystoscopic HD for the diagnosis of IC/PBS. All patients were previously untreated for IC/PBS before the bladder procedure. The bladder specimens with grade 2 to 3 glomerulation without ulceration were used in this study. The bladder tissue specimens at baseline and after intravesical BoNT-A injection were investigated by immunofluorescence, protein array, western blotting and ELISA for the mast cell activity and angiogenic protein expression.

Results

The results of tryptase stain indicated that the inflammation was decreased in the bladder tissue after BoNT-A injection. (Fig.1) We also found that several inflammatory molecules were decreased in the IC/PBS samples, including interleukins and TNF-α signal-related molecule. Beside, the result of angiogenic protein array indicated that VEGF and IL-8 of IC/PBS bladders were reduced after BoNT-A therapy. The alteration of these protein expressions were confirmed by western blotting using bladder tissue specimens of baseline and after intravesical BoNT-A injection. About 92% of the molecules of angiogenesis and vascular inflammation in the array membrane were suppressed after BoNT-A injection, such as VEGF, platelet factor 4, IL-1$\beta$, IL-8, CXCL16, and TIMP-4. The tryptase and IL-8 were found c-localized in IC/PBS bladder mucosa. (Fig.2) Moreover, we found that the decrease of angiogenic and inflammatory molecules were consistent with the glomerulation improved in IC/PBS after BoNT-A therapy. To further prove these angiogenic molecular alterations might be due to inflammatory stimulation, the primary endothelial cell treated with tryptase which derived from human mast cell was analyzed.

Interpretation of results

Our results found that several signal transduction pathway were involved in the pathophysiology of IC/PBS and provided valuable information and signal network of different pathway in IC/PBS, including inflammation, angiogenesis and apoptosis. Our study indicated that glomerulation degree and angiogenic markers could be reduced due to the inflammatory suppression after intravesical BoNT-A injection in a portion of IC/PBS patients. These results could provide evidence for the existing pathophysiology of IC/PBS as well as the possible mechanism of action of BoNT-A in treating IC/PBS.

Concluding message

Intravesical BoNT-A injections in IC/PBS bladders improved clinical symptoms and decreased glomerulation grade. Protein analysis revealed decrease of inflammatory and angiogenic protein expressions in IC/PBS bladders. These findings provides evidence that BoNT-A intravesical injection can decrease inflammation and improved bladder glomerulation in patients with IC/PBS.

**Figure 1. The number of mast cell was decreased after BoNT-A injection**

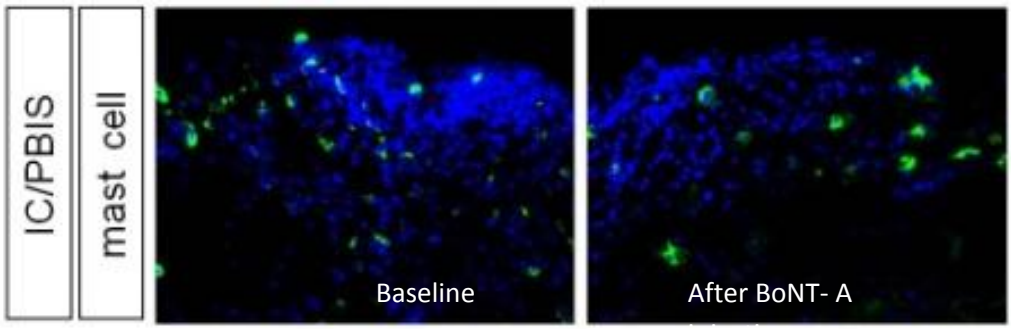
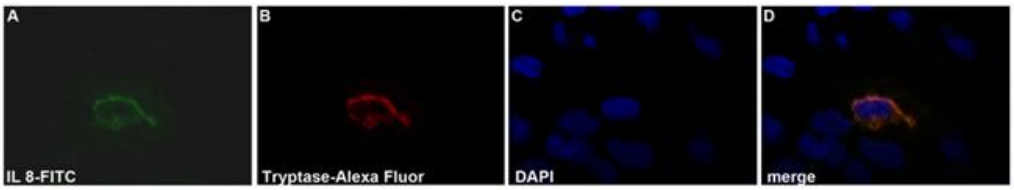


**Figure 2. The co-localization of tryptase and IL-8 in IC/PBS bladder mucosa**

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