TREATMENT OF URETHRAL DYSFUNCTION BY URETHRAL INJECTIONS OF BOTULINUM TOXIN A IN MALE PATIENTS PRESENTED WITH LOWER URINARY TRACT SYMPTOMS BUT WITHOUT BLADDER OUTLET OBSTRUCTION

Hypothesis / aims of study
Male lower urinary tract symptoms (LUTS) in the elderly have been considered to cause by benign prostatic hyperplasia (BPH). However, there are a large part of patients with bothersome LUTS and smaller prostate (less than 40ml) who might not benefit from medical treatment for BPH. The causes for LUTS in these patients could by increased bladder sensation, detrusor overactivity or urethral dysfunction. BTX-A has been demonstrated to have effects on sympathetic activity in urethral smooth muscles. Urethral sphincter injection of BTX-A has been demonstrated to reduce urethral resistance in patients with spastic urethral sphincter or isolated urethral sphincter obstruction. If BTX-A is injected into the urethral muscles, patients with LUTS due to urethral dysfunction might be well treated. This study was designed to treat a group of patients who had bothersome LUTS and refractory to alpha-blocker therapy or combined alpha-blocker and 5ARI therapy with urethral injection of BTX-A. The therapeutic effects might prove the hypothesis that urethral dysfunction could be a pathogenesis of male LUTS without BPH and BOO and BTX-A could be an effective treatment for the urethral dysfunction.

Study design, materials and methods
Thirty patients with LUTS were enrolled in this study. All patients had a moderate LUTS (IPSS greater than 12), maximum flow rate (Qmax) of <15ml/s, and a total prostatic volume (TPV) of less than 40ml. All patients were proven without urodynamically BOO but having a low Qmax with or without large postvoid residual (PVR) were selected in this trial. A total of 100U BTX-A (BOTOX, 100U/vial, Allergan, Irvine, CA, USA) dissolved in 5ml normal saline was injected into 10 sites including trigone, bladder neck, proximal prostatic urethra, distal prostatic urethra and urethral sphincter. Two injections were made at each urethral areas and 0.5 ml of BTX-A solution was injected into each site. Patients were followed up at 1, 3 and 6 months after urethral injection to assess IPSS, QoL index, Qmax, PVR, TPV and general satisfaction scale (0-5) during each follow-up time points. Any adverse events related with urethral injections were recorded including hematuria, miction pain, urinary tract infection or urinary retention. The changes of IPSS, QoL index, Qmax, PVR and TPV at 3 months after urethral botulinum toxin injections were compared.

Results
Patients treated with urethral BTX-A injections had significantly improvement in empty IPSS (11.1±5.7 v 6.9±5.5, p=0.00) and total IPSS (18.8±6.3 v 13.6±6.3, p=0.01), QoL index (4.6±0.93 v 3.1±1.34, p=0.00) and general satisfaction (0.0±0.0 v 1.65±0.59, p=0.00) at 3 months after treatment. The Qmax (9.3±3.9 v 13.8±7.1, p=0.01) and bladder capacity (334.1±146.9 v 415±238, p=0.05) also showed significant improved after urethral Botox injections. However, TPV (34.5±29.0 v 32.1±31.5, p=0.14) and storage IPSS (7.7±3.4 v 6.7±3.7, p=0.16) showed no significant change at 3 months.

Interpretation of results
This study has demonstrated that BTX-A injecting to the urethral muscle is effective in treating patients with urethral dysfunction who presented with low pressure and low flow non-obstructive LUTS. Urethral BTX-A injection is a novel treatment for urethral dysfunction which results in low detrusor contractility and poor relaxation of the urethra. Injection of BTX-A to the trigone can further decrease the hypersensitivity originated from trigonal submucosal sensory afferents. Recovery of detrusor contractility can be observed in half of the patients with low detrusor contractility and voiding dysfunction after urethral sphincter injection of BTX-A. Combined urethral injections to the trigone, bladder neck, urethral smooth muscles and striated sphincter can fully eradicate the normal urethral discharge and resume a normal voiding pattern. Voiding is a complex interaction between detrusor and urethral sphincter. Under guarding reflex due to local inflammation or psychological impact, the normal detrusor contractility can be inhibited. Therefore, we should revisit this subgroup of patients and treat them with appropriate regimen. From the results of this study, male patients who had refractory non-BPH LUTS could be successfully treated, suggesting urethral dysfunction might be an important etiology for the LUTS not related with BPH.

Concluding message
This study has demonstrated that BTX-A injecting to the trigone and urethral muscle is effective in treating patients with urethral dysfunction who presented with low pressure and low flow non-obstructive LUTS.