

Dear Professor,

First of all, thank you for your review on my manuscript. For answer to your questions, I will make the response as follows:

1 The authors also try to review of literature regarding to successful treatment of encrusted cystitis, but there is no data about it.

Response: There is no detailed literature review in the previous manuscript. In the revised manuscript, I have reviewed the literature at the beginning of the discussion section.

2 It is easy to understand about efficacy of HA, on the other hand it is difficult about BoNT/A. It seems to improve after fourth therapy without BoNT/A. It has been improving previous three therapies, why was BoNT/A added?

Response: After treating with mucosal calcification removal surgery, long period of hyaluronic acid and solifenacin therapy, the patient's dysuria and gross hematuria symptoms were relieved. Cystoscopy showed the erosion of bladder mucosa healed well. Nevertheless, the patient still complained of obvious overactive bladder (OAB) symptoms (such as frequency and urgency). Therefore, we sought other methods to treat the patient's OAB symptoms. After consulting the literature of botulinum-A neurotoxin (BoNT/A) in the treatment of refractory OAB^[1], we tried to use BoNT/A for him.

3 The authors described medical effects of BoNT/A, but the authors didn't describe the mechanism why BoNT/A is effect on encrusted cystitis.

Response: The purpose of using BoNT/A for this patient is to treat his residual OAB symptoms. We have consulted some literatures about BoNT/A. The mechanism of BoNT/A reported in the literature was: The primary peripheral effect of BoNT/A is the inhibition of release of acetylcholine, ATP, substance P, and reduction in the axonal expression of the capsaicin and purinergic receptors. This may be followed by central desensitization through a decrease

in central uptake of substance P and neurotrophic factors. The summation of these effects is a profound and long-lasting inhibition of those afferent and efferent mechanisms that are thought to be the pathophysiological basis for DO².

4 How to inject and how dose is BoNT/A used?

Response: BoNT/A was injected into the submucosal tissue of bladder through “COOK” bladder injection needle under cystoscopy. The total dose of BoNT/A was 200U, which was randomly injected into the bladder wall at 40 points.

References:

- 1 **Kumar V, Cross R L, Chess-Williams R, Chapple C R.** Recent advances in basic science for overactive bladder. *Curr Opin Urol* 2005; **15**: 222-6 [PMID: 15928509]
- 2 **Apostolidis A, Dasgupta P, Fowler C J.** Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006; **49**: 644-50 [PMID: 16426734 DOI: 10.1016/j.eururo.2005.12.010]