

Peer Review File

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Reviewer A

This is an informative manuscript that describes the efficacy and safety between bladder auto augmentation transurethral vescomyotomy (BATV) and bladder hydro distention for managing ketamine cystitis (KC). However, there are several points that should be clarified before its consideration of publication.

1. Since there are no definite satisfactory management methods for KC, the management of KC should focus on the fewer side effects and which kind of KC patient will benefit from the management. In that sense, the author should point out what subgroup of patient was suitable for BATV or BH.

Reply 1: We have re-analyzed the data and found the difference between the patients with preoperative MCC < 100 mL and \geq 100 mL. The observed data and clinical significance demonstrated that small bladder with thick fibrous wall may benefit more from BATV than BH.

Changes in the text: We add the results about the subgroup of patients who underwent BATV or BH (see page 10, line 185 - 186 and page 15, line 292 - 296). We also added a new figure 2 containing significant data to explain the choice of the 100 mL cutoff value. Correspondingly, the original Fig. 2 has been changed to Fig. 3. And table 4 was updated with the incidence rate of complications in two subgroups.

2. In case of better outcome of BATV than BH for KC, the surgical procedure should have standard procedure: how long the incision, what the incision of the direction.

Reply 2: The depth of incision varies from 1 - 2.5 mm due to the thickness of the bladder wall. And the direction were longitudinal and latitudinal under resectoscope to create the diverticulum until perivesical fat was vaguely visible (see page 7, line 128 - 131).

Changes in the text: We added the depth of the incision (page 7, line 130 - 131).

3. This is a retrospective analysis; how come the patient numbers are different almost four times and the epidemiology and baseline parameter of the two groups show no significant difference.

Reply 3: The ages are similar in patients with KC because the ketamine abuse happened mostly in young adults (mean 24 - 27 years, see reference [6], [11] and Table 1). The remarkably concentrative distribution of age and addiction time may be the reason for insignificant difference in baseline parameters in two groups.

Changes in the text: None.

4. The author assume that extensive damage to detrusor was the reason of 1.the PVR in the BATV increased significantly at the 12 months not in the 3 months follow up, and 2.the Q max decreased at 12 months not at 3 months. Could the author explain why it did not happen

in the early time?

Reply 4: The increased PVR and decreased Q_{max} at 12 months follow-up may attribute to the increscent width of acquired bladder diverticula and aggravated fibrosis of incisional areas after BATV.

Changes in the text: We added the possible reason for delayed changes in PVR and Q_{max} after BATV (see page 13 - 14, line 256 - 267).

5. Please explain why the subjective parameter (PUF, VAS, ICSI, ICPI, and QoI) did not show difference, while the objective parameter (MCC, Compliance, Pet max PVR) show difference.

Reply 5: The vesicomytomy provided no superiority in remission to subjective symptoms including pelvic pain or urgency to BH. The etiology of KC was unknown, and some theories attributed it to pelvic floor muscle dysfunction, primary neurogenic inflammation and autoimmune disorders. Thus, any surgery can not guarantee symptom relief even after cystectomy. And more long-term follow-up may be necessary to evaluate the post-procedure symptoms as well as the persistent pan-urothelial inflammation.

Changes in the text: We have added some possible reason why two groups show similarity in symptoms relief. (see page14, line 273 - 283)

6. The main drawback of the study is the unequal of two group patients (BH 41 vs. BATV 12). Could it be that the efficacy was due to statistic bias?

Reply 6: We performed a detailed follow-up and statistical analysis. Though the sample size of the two groups was not equal, Levene's test suggested the homogeneity of the variances between the two groups (for example, the Levene's test of MCC volume at 12 months follow-up shows no significance between two groups as $P = 0.121 < 0.05$). However, in spite of the equal variance, Mann-Whitney U test and Fisher's exact test were still used to assess the peri-operative difference of variables in two groups to avoid unequal or small sample size and the corresponding bias. Of course, we are still enrolling patients for follow-up and analysis, and are designing prospective clinical trials for further validation.

Changes in the text: None.

Reviewer B

1. The major concern is that this is a retrospective study. Because the selection criteria of bladder autoaugmentation by transurethral vesicomytomy (BATV) or bladder hydrodistention (BC) are not described and the procedure selection was not randomized, the study design would have been biased. Also three is no information regarding the number of patients who were treated first by BH and, then, later by BATV.

Reply 1: No patients treated firstly by BH then BATV were enrolled in the study. The criteria of enrollment has been described more precisely in our manuscript. The definition of small bladder capacity and low bladder compliance was refer to ICS standards (2020-2021) as well as former study about KC which performed surgical intervention for patients with

capacity < 200 mL, compliance pressures 40cm H₂O or worse and/or upper tract compromise (see reference [7]). A more rigorous standard-setting of inclusion was a more prudent intervention for KC patients. Besides, all patients who underwent surgical intervention were unresponsive to conservative treatment preoperatively. Although the procedure selection was not randomized due to the retrospective design, this study still provided reasonable results based on satisfactory follow-up and systematical data analysis given the fact that there were few KC patients and rare studies worldwide.

Changes in the text: we have modified the selection criteria and add the information about the patients treated firstly by BH then BATV. (see page 6, line 98 - 111)

2. Since ketamine cystitis reportedly shows the condition similar to interstitial cystitis (IC), especially the Hunner lesion subtype with severe inflammation and epithelial denudation, cystoscopic findings such as Hunner-like lesions or neovascularization need to be clarified prior to BH or BATV.

Reply 2: We had carried out the preoperative cysto-urethroscopy and biopsy prior to surgical interventions. All diagnoses were based on the typical pathology as well as exclusion of other diseases such as IC/BPS, neurogenic bladder or tuberculosis affecting the bladder.

Changes in the text: Cystoscopic and histological findings were described in methods and results. (see page 6, line 107 - 111 and page 8, line 157 - 160)

3. Then, the post-procedural changes in bladder inflammation and denudation should be evaluated after each procedure. If the change in these conditions of the bladder are not found, it seems natural that there is no difference in many subjective multifaceted parameters.

Reply 3: We had performed cysto-urethroscopy after surgery in follow-up, while no further biopsy was applied to patients after surgery. The cystoscopic examination showed reduced hypervascular mucosal areas and fibrous scar which means the remission of chronic inflammation of the bladder wall. Besides, the similar subjective symptom score may be the results of partial remission of persistent inflammation in both groups in spite of the significantly improved MCC and other urodynamic parameters. However, the primary purpose of surgical treatment to KC may be improvement of urodynamics and protection of renal function. And the symptom relief may be alleviated by conservative therapy combined with BATV such as pelvic floor relaxation and/or pharmacotherapy.

Changes in the text: We have added the description of post-procedural changes in bladder inflammation and the reason why the two groups show similarity in symptoms relief. (see page 14, line 273 - 283)

4. Without post-procedure evaluation by cystoscopy or histology, no new findings can be obtained in terms of the selection of two different procedures for the treatment of ketamine cystitis.

Reply 4: Post-procedure evaluation by cystoscopy had been performed. The histological assessment after surgery will be made in longer follow-up term and under more comprehensive experimental design.

Changes in the text: We have added the discussion about post-operative cystoscopic evaluation on page 14, line 273 - 283.

