Urological Science 26 (2015) 194–196

Contents lists available at ScienceDirect

Urological Science

journal homepage: www.urol-sci.com

Consensus report

Assessment of ketamine uropathy

Stephen S. Yang [a, *], Chun-Hsien Wu [b], Judy Yi-Ju Chen [a, c], Shang-Jen Chang [a], on behalf of the Team for National Registration of Ketamine Uropathy[x]

[a] Division of Urology, Taipei Tzu Chi Hospital, New Taipei Taiwan and Department of Urology, School of Medicine, Buddhist Tzu Chi University, Hualien, Taiwan
[b] Department of Urology, E-Da Hospital, Kaohsiung, Taiwan
[c] Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan

ARTICLE INFO

Article history:
Received 7 August 2015
Received in revised form
19 August 2015
Accepted 24 August 2015
Available online 1 October 2015

Keywords:
ketamine
ketamine-associated cystitis
ketamine uropathy

ABSTRACT

A group of experts on lower urinary tract dysfunction and cystitis met together to make a consensus report on the assessment of ketamine uropathy (KU) which encompasses ketamine cystitis.

Essential tests, which should be performed in all KU patients, are (1) detailed history taking with structured questionnaire, (2) physical examination, (3) urine tests including test strip biochemistry and sediments analysis, urine culture, and cytology, (4) blood tests including complete blood cell counts with differential counts, liver and renal function tests, IgE, HIV, VDRL, (5) urological tests including uroflowmetry and post void residual urine volume and renosonography.

Optional tests, which will be performed in selective cases, are (1) bladder diary for 48-72 hours, (2) bladder wall thickness by ultrasound, (3) upper tract evaluation with excretory urography, computed tomography of abdomen, diuretic renal scan, (4) lower urinary tract evaluation with cystoscopy, voiding cystography, urodynamics or videourodynamics, (5) bladder and/or ureteral biopsy, (6) abdominal echo and/or gastroendoscope. Optional tests are usually indicated when essential tests disclose abnormal findings.

Using the standardized tools to assess patients with ketamine abuse, patients characteristics can be clarified and different therapeutic strategies for ketamine uropathy can be compared in the future.

1. Introduction

As ketamine uropathy (KU) is a relatively new clinical entity since 2007,[1,2] there is no consensus about the assessment and evaluation for KU to date. Recent publications show that urinary bladder, ureter, and kidney may be damaged in the patients with chronic use of ketamine.[3,4] In addition, brain, liver, upper gastrointestinal tract, and genital tract functions may be also involved.[5–7] Allergic reaction seems to play an important role in the development of KU.[8] A complete evaluation of the aforementioned organ system is mandatory to provide rapid diagnosis and treatment. A group of experts in lower urinary tract dysfunction and cystitis met together several times to discuss optimal assessment for KU. The draft was presented at the consensus meeting held in Taichung, on April 12, 2015. The followings are the consensus from the meeting.

* Corresponding author. Division of Urology, Taipei Tzu Chi Hospital, 289, Jianguo Road, Xindian, New Taipei, 231, Taiwan. Tel.: +886 2 66289779x5708; fax: +886 2 66289009.
E-mail address: urolyang@gmail.com (S.S. Yang).

[x] Members of the team for National Registration of Ketamine uropathy: Jang MY, Wu WJ, Ruan YS (Kaohsiung Municipal Hsiao-Kang Hospital), Li SY (Kaohsiung Municipal Ta-Tung Hospital), Wu JS (I-Dah Hospital), Chung YC, Li WJ (Chang Gung Memorial Hospital, Kaoshiung), Li YH (Kaomei Urologic Clinic), Tang YC (National Cheng Kong University Hospital), Shen KH (Chi-Mei Medical Center), Lin WY, Chen JS (Chang Gung Memorial Hospital, Chia-Yi), Lee MH, Chen MH (Feng Yuan Hospital), Zou JL, Jhang JS (China Medical University Hospital), Syu JS (Tungs' Taichung MetroHarbor Hospital), Yang SS, Chang SJ (Taipei Tzu Chi Hospital), Lin ATL, Fan YH (Taipei Veterans Hospital), Meng E (Tri-Service General Hospital), Syu YJ (Chang Gung Memorial Hospital Linkou), Yu HJ (National Taiwan University Hospital), Guo YC (Taipei City Hospital Yangming Branch), Ye JS (Shin-Kong Wu Ho-Su Memorial Hospital), Wang YJ (Cathy Hospital Si-Ji), Jhang JF, Jiang YH and Kuo HC (Tzu Chi Hospital).

http://dx.doi.org/10.1016/j.urols.2015.08.010

Table 1
Essential tests for ketamine-associated uropathy.

History taking	Structured questionnaire including illicit drug use history, LUTS, pain score, sexual function, mood and quality of life.
Physical examination	Height, weight, and blood pressure. Nostril, and genital skin.
Urine tests	Urine routine, culture, cytology.
Blood tests	BUN/Cr; GOT/GPT, bilirubin, IgE, CBC with differential counts, HIV, VDRL
Urological examinations	Uroflowmetry, PVR and renosonography

LUTS = lower urinary tract symptoms; PVR = post-void residual urine volume.

Because the ketamine cystitis (KC) shares similar clinical symptoms with interstitial cystitis (IC), recommendations of the assessment for IC patients is adopted for KU. Contracted bladder is present in many cases of KU, part of the concept of neurogenic bladder is adopted. In addition, hydronephrosis and ureteral stricture are encountered in severe cases of KU, upper urinary tract evaluation should be performed. Patients also suffer from hepatobiliary problems, epigastralgia, sexual dysfunction, brain dysfunction. Further assessments are mandatory if the patients have symptoms or dysfunction.

2. Essential tests for ketamine uropathy

Table 1 summarizes essential tests for KU. A structured questionnaire is developed to assist history taking (Appendix). Patients should be queried about ketamine use history, including duration, frequency, dosage, and route of ketamine abuse. Whether the patient is an active abuser or ex-abuser should be clarified. The duration of ketamine cessation must be documented for an ex-abuser. Other illicit drugs addiction, smoking, betel nut chewing, and alcohol drinking history should also be asked. Up to date, there is no evidence in the relationship between betel nut chewing history and ketamine uropathy. Since this questionnaire is adopted from the case report form of Taiwan Food and Drug Administration (TFDA), we continue to use this item. In this way, we can compare our data with those already registered on TFDA. Hopefully, the relationship between betel nut chewing, a common behavior in Taiwan, can be illustrated later. The interval between the beginning of ketamine abuse and the occurrence of lower urinary tract symptoms (LUTS) should be noted. The severity of LUTS could be assessed by International Prostate Symptoms Score and the "O'Leary-Sant Symptom and Problem Questionnaire".[9] "Pelvic Pain and Urgency/Frequency (PUF) Questionnaire" has been validated for the evaluation of KU in Hong Kong and was shown to correlate well with cystoscopic change, urodynamic abnormalities, and hydronephrosis in patients with KU.[10] Since PUF was not familiar to most Taiwanese doctors and many experts already used International Prostate Symptoms Score (IPSS) and O'Leary-Sant Symptom and Problem questionnaire, which will be continuously recommended in Taiwan. Mood of the patients should be assessed because KU patients may have suicide idea and attempts. A simple tool is provided in the structured questionnaire. Sexual dysfunction has been reported in female ketamine-abusers,[5] and male patients may share similar symptoms. Erectile dysfunction should be asked in men, while problems of sexual arousal, lubrication, orgasm, and dyspareunia should be evaluated in women.

Though most physical examination will be normal, special attention should focus on the nose to see if there is residual white substance around nostril, which may be a sign of continuing use of ketamine. Basic physical examination, including pelvic examination should be performed to exclude other disorders with similar clinical symptoms. Vaginitis, urethritis, prostatitis, urethral diverticulum, and other potential etiology of pain or infection should be excluded through the evaluation. Genital skin lesions should be recorded for the risk for associated sexually transmitted disease.

Urinalysis is a mandatory examination for KU patients, and urine culture should be performed for those with pyuria. For patients with hematuria, urine cytology should be collected to exclude urothelial carcinoma. Renal and liver function test should be checked for all patients to rule out potential renal and hepatic damages. Complete blood-cell count with differential count is ordered to check the presence of eosinophilia and possible anemia. Immunoglobulin E should be checked to rule to allergic reaction. Patients with ketamine cystitis had higher serum IgE than patients with interstitial cystitis/bladder pain syndrome or acute bacterial cystitis, or controls. Serum IgE and the severity of eosinophil infiltration associated with bladder pain severity and small maximal bladder capacity.[8] HIV and VDRL should be checked to rule out coexisted sexually transmitted diseases such as acquired immunodeficiency disease and syphilis.

Uroflowmetry and post-void residual urine (PVR) should be performed. Voided volume plus PVR can be used as a surrogate of bladder capacity which is an important parameter in managing KU. Renosonography should be performed to rule out hydronephrosis. The grade of hydronephrosis must be documented once it was identified.[11]

3. Optional tests for ketamine uropathy

Table 2 lists the optional tests for KU. A voiding diary can be recorded for 48–72 hours in cooperative patients. Maximal voided volume can be a good surrogate of functional bladder capacity since most of the KU patients have low PVR. However, many patients are uncooperative in recording voiding diary. Bladder sonography can be performed to measure bladder wall thickness which may suggest the presence of bladder fibrosis. However, the technical difficulty in measuring bladder wall thickness in a fixed bladder volume makes this test not easy for the KU patients.

Upper urinary tract evaluation such as intravenous urography or computed tomography should be arranged in the presence of hydronephrosis on renosongraphy.[11] Grade and side of hydronephrosis/ureteral stricture should be recorded. Voiding cystourethrography could be performed once vesico-ureteral reflux was suspected as the etiology of hydronephrosis. Since this is an invasive procedure and may cause severe pain, adequate anesthesia and/or pain killer should be provided.

Lower urinary tract can be assessed by a variety of tools. Cystoscopy is not necessary to reach the diagnosis of KU in all patients. The cystoscopic findings of KU patients are non-specific and

Table 2
Optional tests for ketamine-associated uropathy

Functional bladder capacity/maximal voided volume	Bladder diary for 48–72 hours in cooperative patients.
Bladder fibrosis	Transabdominal ultrasound measuring bladder wall thickness at 1/2-2/3 expected bladder capacity
Upper urinary tract evaluation	Excretory urography, CT of abdomen (Non-contrast CT if impaired renal function), diuretic DTPA
Lower urinary tract evaluation	Cystoscopy, voiding cystography, urodynamics or videourodynamics
Histology	Bladder and/or ureteral biopsy
Gastrointestinal tract	Abdominal echo and/or gastroendoscope for epigastralgia and abnormal liver functions.

provide no benefits in confirming the diagnosis. Cystoscopy could be considered when the diagnosis of KU is in doubt. Disorders such as bladder cancer, bladder stones, urethral diverticula, and intravesical foreign bodies could be identified by cystoscopy and the therapeutic approach would then be changed. The role of cystoscopy in KU may be changed after the first report of bladder cancer in a KU patient.[12] Cystoscopy could also be performed in concomitance with bladder hydrodilatation under regional or general anesthesia because many KU patients could not tolerate the procedure when it is performed under local anesthesia.

Urodynamic study (UDS) is not necessary for the diagnosis of uncomplicated KU The findings of UDS are inconsistent and could not provide further information for diagnosis or guiding therapy. Furthermore, many patients could not tolerate bladder distension or urethral catheterization during the examination. UDS should be considered only when other lower urinary tract dysfunction was suspected and the treatment would be different once it was identified, such as bladder outlet obstruction or detrusor underactivity. Video-UDS could identify VUR and would be beneficial in differentiating the etiology of hydronephrosis. The potassium sensitivity test (or KCl test) is not recommended in the evaluation of IC patients, as it could not provide information for diagnosis and guiding therapy. It is therefore not suggested in KU patients as the same reasons.

Routine bladder biopsy is an issue to be debated. Generally, histology shows denuded epithelium and inflammation with eosinophil infiltration which may be specific. Bladder biopsy should only be performed when bladder cancer and/or urothelial carcinoma in situ are suspected, particularly after the publication of the first ketamine abuse associated bladder tumors was reported in 2014.[12]

Abdominal ultrasonography can be performed in the patients complaining abdominal pain or elevated liver enzymes. Dilatation of bile ducts is quite common. Without knowing the history of ketamine abuse, incision of Sphincter of Oddi had been performed without significant benefits.[7] Panendoscopy may be performed in cases with frequent epigastralgia, though negative findings were usually reported.

4. Conclusions

We recommend essential and options tests to assess patients with ketamine abuse. Hopefully, patient characteristics can be clarified and different therapeutic strategies for ketamine uropathy can be compared in the future. Then we can have a treatment algorithm for ketamine uropathy soon!

Conflicts of interest

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.

Sources of funding

No funding was received for the work described in the article.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.urols.2015.08.010.

References

1. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007;**69**:810–2.
2. Chu PS, Kwok SC, Lam KM, Chu TY, Chan SW, Man CW, et al. 'Street ketamine'-associated bladder dysfunction: a report of ten cases. *Hong Kong Med J* 2007;**13**:311–3.
3. Wei YB, Yang JR, Yin Z, Guo Q, Liang BL, Zhou KQ. Genitourinary toxicity of ketamine. *Hong Kong Med J* 2013;**19**:341–8.
4. Jhang JF, Hsu YH, Kuo HC. Possible pathophysiology of ketamine-related cystitis and associated treatment strategies. *Int J Urol* 2015;**22**:816–25.
5. Jang MY, Long CY, Chuang SM, Huang CH, Lin HY, Wu WJ, et al. Sexual dysfunction in women with ketamine cystitis: a case-control study. *BJU Int* 2012;**110**:427–31.
6. Tan S, Chan WM, Wai MS, Hui LK, Hui VW, James AE, et al. Ketamine effects on the urogenital system–changes in the urinary bladder and sperm motility. *Microsc Res Tech* 2011;**74**:1192–8.
7. Chen JH, Juang GD, Wu CC. Cholangiopathy associated with chronic ketamine abuse (full text in Chinese). *Formosan J Med* 2015;**19**:125–30.
8. Jhang JF, Hsu YH, Jiang YH, Kuo HC. Elevated serum IgE may be associated with development of ketamine cystitis. *J Urol* 2014;**192**:1249–56.
9. Hanno PM, Burks DA, Clemens JQ, Dmochowski RR, Erickson D, Fitzgerald MP, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 2011;**185**:2162–70.
10. Ng CM, Ma WK, To KC, Yiu MK. The Chinese version of the pelvic pain and urgency/frequency symptom scale: a useful assessment tool for street-ketamine abusers with lower urinary tract symptoms. *Hong Kong Med J* 2012;**18**:123–30.
11. Liu DB, Palmer B, Herndon CD, Maizels M. Teaching of the Society for Fetal Urology grading system for pediatric hydronephrosis is improved by e-Learning using Computer Enhanced Visual Learning (CEVL): a multi-institutional trial. *J Pediatr Urol* 2015;**11**:184. e1-8.
12. Mui WH, Lee KC, Chiu SC, Pang CY, Chu SK, Man CW, et al. Primary yolk sac tumour of the urinary bladder: a case report and review of the literature. *Oncol Lett* 2014;**7**:199–202.