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Review article

Ketamine cystitis: Its urological impact and management☆

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ABSTRACT

Ketamine, an N-methyl-D-aspartic acid receptor complex antagonist, has been used as an anesthetic and/or analgesic. However, in the past decade, ketamine has been illegally available as a recreational drug in Asian countries and Taiwan. Due to the characteristic of being short-acting, youngsters widely assume that ketamine is not as harmful as other drugs, such as heroin. Consequently, many young patients used this drug for a longer duration before they presented with severe urinary frequency and urgency symptoms. Subsequently, other cases have been reported in Taiwan, Hong Kong, Singapore, Malaysia, and Europe. Ketamine abuse is increasing, with rates of 0.30% in 2006 to 0.40% in 2007 among those in the 16–59 year age group. In general, affected patients tend to be young with a peak age range of 16–35 years. The incidence of lower urinary tract symptoms in ketamine abuse patients is around 30%. The actual underlying pathomechanism of ketamine cystitis (KC) and associated pelvic pain remains unclear. It is speculated that chronic contact and stimulation to the bladder or ureteral mucosa due to metabolites of ketamine will result in submucosal edema, vascular ectasia, fibrosis, detrusor muscle inflammation, and fibrosis. Presentations of KC include remarkable dysuria, urinary frequency/urgency, urge incontinence, and bladder pain. Urine culture usually fails to yield any microbiology in KC with bladder pain alone. The majority of patients can enjoy clinical improvement after cessation of ketamine and urological treatment similar to interstitial cystitis/bladder pain syndrome (IC/BPS). However, patients who are still abusing ketamine and/or who have a longer duration of ketamine abuse might suffer from severe bladder pain, which does not respond to empirical oral or intravesical treatments such as hyaluronic acid. Among these patients, most have a remarkably impaired quality of life and are at risk of developing upper urinary tract damage, including hydronephrosis and kidney injury. To reduce bladder pain, improve quality of life, and avoid further deterioration of renal function, surgical intervention might be indicated.

1. Introduction

Ketamine, an N-methyl-D-aspartic acid receptor complex antagonist, has been used as an anesthetic or analgesic since the 1960s.[1] It remains the most commonly used anesthetic in veterinary medicine, is an anesthetic agent in children, and is used in chronic pain. The psychosis-like symptoms induced by ketamine have been used as a pharmacological model of schizophrenia.[2] These effects have also led to the recreational use of ketamine. Due to its easy availability and low risk of crime, it has become increasingly used for recreational purposes in Hong Kong, Singapore, Malaysia, Taiwan, and Europe over the past decade.[3–8] The nonmedical use of ketamine has been illegal in Taiwan since it was classified as a class 3 drug in 2003. Ketamine is now the most common illicit drug of abuse detected by the Food and Drug Administration in Taiwan since 2006.

Clinically, the common presentations are transient and self-limiting cardiovascular stimulation, acute psychological experiences, abdominal pain, and lower urinary tract symptoms, including frequency, urgency, suprapubic pain, dysuria, and hematuria.[3] Ketamine cystitis (KC) shares many common histopathological features with interstitial cystitis/bladder pain syndrome (IC/BPS), including urothelial ulceration, inflammatory cell

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infiltration, and varying degrees of bladder wall fibrosis.[9] However, the degrees of bladder wall inflammation and fibrosis are more severe in KC, which results in a contracted bladder and upper urinary tract damage and hydronephrosis, vesicoureteral reflux, and recurrent urinary tract infection.[5] Several treatment modalities have been employed; however, most KC patients cannot achieve symptomatic relief with these treatments. In severe cases, partial cystectomy and enterocystoplasty are necessary to restore normal bladder capacity and normal living activities.[5] In this article, we review the available literature regarding the urological impact of ketamine abuse and its management.

2. Epidemiology

Ketamine is a controlled drug in many countries and is now under international control; however, the precise prevalence of recreational, nonmedical ketamine use is unknown. Several individual country studies revealed that the background population use rates of ketamine are around 0.1–4%.[10–13] Geographically, recreational usage of ketamine is seen across the world, but it appears to be most common in East and Southeast Asia, potentially because of its relatively low price compared to other psychomimetic drugs.[10–13] In Hong Kong, ketamine was the most commonly abused drug.[5] In the United Kingdom, ketamine has been classified as a class C substance since 2006.[12] A survey estimates an increasing number of ketamine abusers from 85,000 in 2006/2007 to 113,000 in September, 2008. The latest data suggests that ketamine is now the fourth most popular drug among UK clubbers. According to the Taiwan Food and Drug Administration's survey, ketamine is the single most common drug of abuse since 2006. The age of young people who tested positive for ketamine was less than a median of 30 years, indicating that the groups abusing ketamine are getting younger in Taiwan.[14] Moreover, the volume of seizures of street ketamine in Taiwan has increased from 916 kg in 2009 to 1187 kg in 2010.

According to a nationwide questionnaire survey in the United Kingdom, 26.6% of regular ketamine users reported experiencing at least one urinary symptom.[3] The symptoms were significantly related to both dose and frequency of ketamine use. Another web-based survey among 18,802 substance users in the United States revealed that the prevalence of Lower urinary tract symptom (LUTS) among ever and recent users of ketamine were 28% and 30%, respectively.[15] However, the associations between ketamine and urological symptoms should be confirmed through longitudinal studies in the future. Whilst some series have reported a slight male predominance, this is insignificant and not universally witnessed. At the present time it would seem that KC does not exhibit any sex bias.

3. Pathophysiology

The exact etiopathological mechanism of disease development of KC remains unknown. Upon histological examination, the urothelium was diffusely denuded. The lamina propria showed prominent granulation tissue with congested vessels, infiltrated predominantly by lymphocytes and a variable number of eosinophils.[5] A number of different postulated mechanisms have been proposed by Chu et al.[5] These include: (1) direct effect of ketamine or its metabolites on bladder interstitial tissues; (2) microvascular changes in the bladder and possibly kidney by ketamine and/or its metabolites; (3) indirect effect of ketamine by causing an autoimmune reaction against the bladder urothelium and submucosa, due to circulating ketamine or urinary ketamine and its metabolites; and (4) bacterial infection.[5]

According an *in vitro* toxicity test of ketamine by Shahzad, (Thesis, University of York, 2011) ketamine is toxic to normal human urothelial cells and the toxicity increases as the concentration of ketamine increases. The toxic effects are a direct result of both itself and its primary metabolite (norketamine) and the effect is more toxic when used daily than a single dose. Jhang et al[16] found that KC patients had higher serum IgE levels than patients with IC/BPS or acute bacterial cystitis or controls. Both the serum IgE levels and the severity of eosinophil infiltration were associated with bladder pain severity in KC patients. In addition, the *in vitro* toxic effect was enhanced by the specific NMDA antagonist MK-801, despite no direct toxicity. A pilot study performed by immunohistochemistry experiments in KC patients revealed that ketamine could lead to reactive urothelial changes that could mimic carcinoma *in situ*.[17] Another pilot study that performed a more detailed immunohistological study in human KC tissue revealed that urothelial damage by ketamine may induce proliferation in the basal and intermediate layers to restore the barrier function (Shahzad K., Thesis, University of York, 2011).The destruction of the superficial layer of urothelium leaves the stroma exposed to toxic metabolites of ketamine, which further induces inflammation of the urothelial tissue and the resultant KC symptoms (Fig. 2).

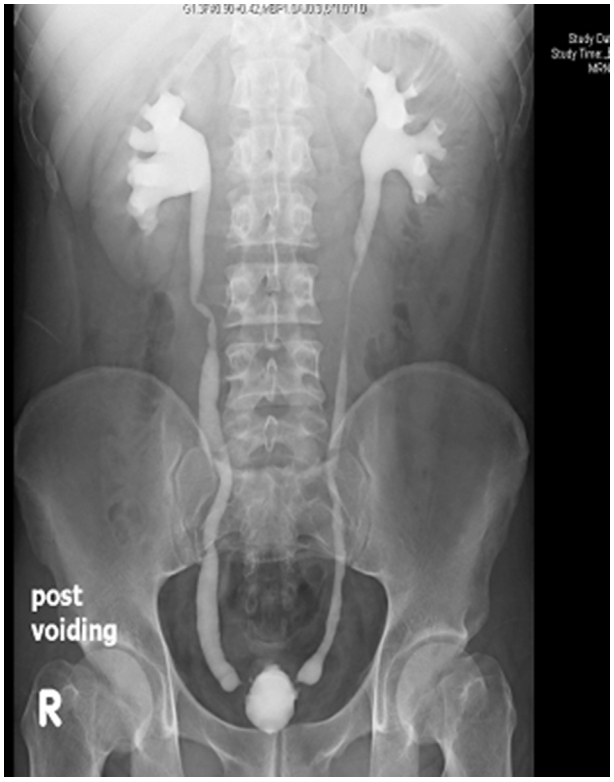

Fig. 1. Intravenous pyelography in a man with ketamine cystitis reveals bilateral hydronephroureters and contracted urinary bladder.

Another interesting finding is that ketamine increased the number of T-cells in the stroma (Shahzad K., Thesis, University of York, 2011). This might suggest that the toxic effects of ketamine on the bladder urothelium are twofold: direct toxic effect on the superficial cells and a receptor-mediated effect to damage the deeper tissue. This might explain why IC/BPS and KC share many clinical and histopathological features, but the degree of bladder wall inflammation and fibrosis are more severe in KC. This finding was also confirmed by another pilot study performed by Lee et al,[18] which revealed that decreased expression of E-cadherin and increased apoptosis were more severe in KC than in IC/BPS and these findings were associated with the clinical symptoms of KC and IC. Urinary epidermal growth factor levels have been found to

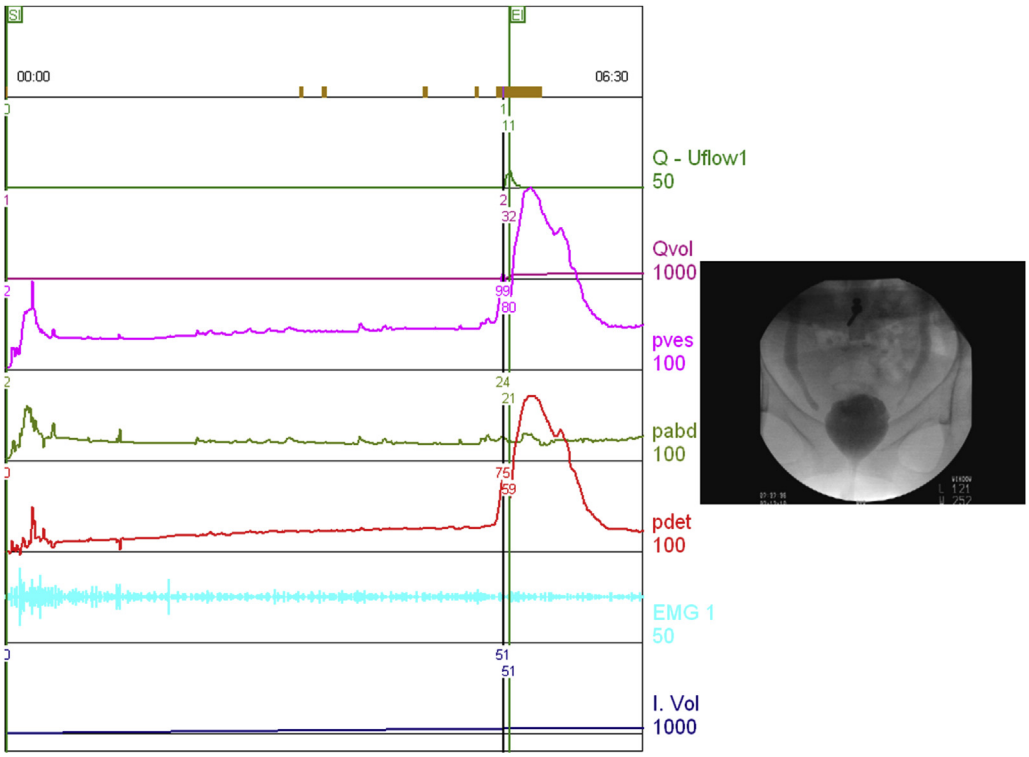

Fig. 2. Videourodynamic findings in ketamine cystitis reveals severe contracted bladder with poor compliance and bilateral vesicoureteral reflux.

be associated with symptomatic ketamine users in a pilot study.[18] In addition, the severe pain induced by KC could be due to a specific neurogenic mechanism in which the lamina propria of KC was replete with fine neurofilament protein nerve fibers and also prominent peripheral nerve fascicle hyperplasia.[19] Enhanced noncholinergic contractions and P2X1 receptor expression in the ketamine bladder may underlie detrusor overactivity of KC.[20] In addition, phosphorylation of transgelin has been identified in long-term ketamine abusers' bladders.[21] In a nutshell, ketamine and its metabolites not only have a direct impact on the urothelium and underline subcutaneous tissues, but also have unexplained direct or indirect impacts on bladder neurological pathways.

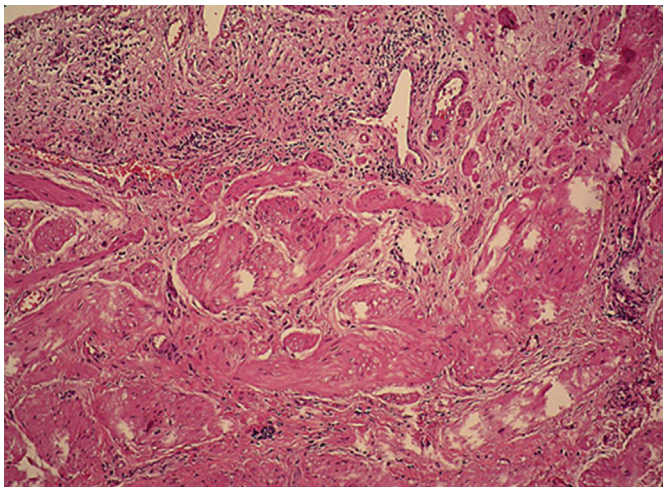

Fig. 3. The bladder histopathology of ketamine cystitis. The lamina propria shows prominent granulation tissue with congested vessels, infiltrated predominantly by lymphocytes (magnification ×100).

4. Clinical presentation

Shahani et al[22] first described the urological presentations in ketamine nonmedical abusers in 2007. After that, several clinical series detailed the clinical pictures of KC. Clinically recreational ketamine users presented with a wide range of LUTS, including urgency, frequency, severe dysuria, urine leakage, and gross hematuria. The time of onset of LUTS after ketamine abuse ranged from a few days to a few years.[2] It is still unclear whether the ingested dosage directly related to the onset time of LUTS. However, it is clear that KC was rarely associated with the medical use of ketamine.[23] The clinical pictures of KC share many common clinical features with IC, thus, the IC questionnaire is the preferred one to record the lower urinary tract symptoms of KC (Fig. 3).

Urine analysis and culture among KC patients always revealed sterile urine or sterile pyuria. Rarely, contaminated growth or bacterial pyuria was presented and mainly in female patients.[5] According to a population-based questionnaire, ketamine users with a more frequent intake (> 2 hits/wk) for at least 1 year had a greater chance of having altered bladder function. In addition, these early changes of KC could be normalized after at least 1 year of abstinence.[24] The typical cystoscopic findings were various degrees of epithelial inflammation neovascularization, ulceration, and petechial hemorrhages in severe cases.[5] The classical computed tomography (CT) findings included generalized bladder wall thickening, small bladder capacity, and perivesical inflammation. Nearly half of the KC patients revealed hydronephrosis on diagnosis. Among them, one third had a ureteral wall thickening and less commonly, a ureteropelvic junction involvement.[25] In extreme cases, ureteral lumen narrowing and strictures could be found under CT and intravenous pyelography (Fig. 1).[26] Thus, in severe cases who initially presented with hydronephrosis, an intravenous pyelography or a CT scan would benefit KC patients to rule out the possibilities of ureteral wall thickening, stricture, and ureteropelvic junction involvement.

Urodynamic study (UDS) typically revealed a reduced bladder capacity (< 100 mL), a reduced bladder compliance, and sometimes combined with detrusor overactivity at a very low bladder infusion volume. Less commonly, vesicoureteral reflux could be identified as a secondary event due to a severely contracted bladder.[5] There were no significant differences in UDS parameters between high dose and low dose abusers, or the long- and short-term abusers. The maximum bladder capacity under anesthesia may be a better predictor of the disease progression of KC when compared with the UDS.[27] Whenever KC patients present with severe frequency, nocturia with a voiding diary of small voiding volume and the possibility of severely contracted bladder with poor compliance cannot be ruled out. A UDS, or even better a Videourodynamic study (VUDS), will provide more information regarding the compliance of bladder and also the possibility of further upper tract damage.

5. Management

Several pathophysiological mechanisms have been postulated, however, the disease development map remains unclear. Hence, no single definite treatment has been reported to date. According to the largest prevalence study in the UK, of the regular ketamine users who reported urinary tract symptoms, 51% reported improvement in urinary symptoms upon cessation of use.[3] In addition, for KC patients who failed to discontinue ketamine addiction, disease progression is always the fate.[5,28,29] Thus, early diagnosis of KC and abstinence are the two most important issues that should be incorporated in every multidisciplinary approach before irreversible bladder and renal function damage occur (Fig. 4).

Several therapeutic agents, mainly symptomatic, have been employed, including antibiotics, nonsteroid antiinflammatory drugs, steroids, and anticholinergics. However, none of the above have achieved a significant and durable effect.[5] IC and KC share many clinical and pathological features, including epithelial inflammation, neovascularization, ulceration, and impaired urothelium impermeability, which has led to the use of urothelium protective agents like chondroitin sulfate, pentosan polysulfate, and hyaluronic acid (Cystistat). One case report illustrates one patient's successful response to chondroitin sulfate 0.2% (Gepan) over a 1 year period.[30] In case series studies, the cessation of ketamine use and the addition of oral pentosan polysulfate or intravesical hyaluronic acid also provided some symptomatic benefit clinically.[31,32] In brief, urothelium protective agents may provide some clinical benefit, mainly symptomatic, in the short-term, but further prospective randomized trials with longer follow up are needed.

Recent evidence suggests that botulinum toxin type A could significantly improve symptoms such as daytime frequency, nocturia, pain, quality of life, and bladder capacity in IC/BPS patients.[33,34] In a pilot study, intravesical injection of botulinum toxin A was shown to be effective in reducing frequency, dysuria, and increasing bladder capacity after 4 weeks of treatment in KC patients.[35] However, another case report revealed ineffective therapy of botulinum toxin in a non-cessation ketamine user.[36] Thus, it is still controversial whether botulinum toxin injection provides clinical benefit to KC patients; further clinical trial investigation is mandatory.

At the end, in severe cases with a small contracted bladder, poor bladder compliance and hydronephrosis, urinary diversion may be the final strategy. In a small case series, augmentation cystoplasty in severely contracted bladders was shown to increase the bladder capacity (from 37 mL to 400–500 mL) dramatically.[37] Although, in this study, the surgical approach is effective in symptomatic relief, further deterioration of renal function could be the consequence of new onset ureteral strictures. Another pilot study in 14 KC patients revealed the most promising results thus far, with significant improvement in LUTS after augmentation cystoplasty. Surprisingly, all hydronephrosis resolved after surgery.[38] Whether the bladder should be totally removed at the time of reconstruction is still controversial.

The goal of treatment for KC related bladder pain is to increase bladder capacity with good compliance, to decrease the detrusor pressure to prevent kidney injury, as well as to eradicate the abnormal painful sensation from the diseased bladder other than the trigone. Our recent study has demonstrated that augmentation enterocystoplasty successfully reduces the bladder pain, improves quality of life, and increases bladder capacity in refractory chronic KC-related bladder pain. Patients after augmentation enterocystoplasty can resume normal life and return to society for work. However, patients with ketamine reuse may have symptom relapse and recurrent urinary tract infection.

In conclusion, KC is an increasing problem among our younger generations due to its recreational usage and easy availability. Unfortunately, a clear pathophysiological mechanism is still not available thus far. In addition, urologists have very limited effective treatment strategies to control the lower urinary tract problem caused by ketamine abuse. One definite thing is that if ketamine cessation is not addressed in the treatment program, further development of LUTS and even upper urinary tract deterioration is always the fate of KC.

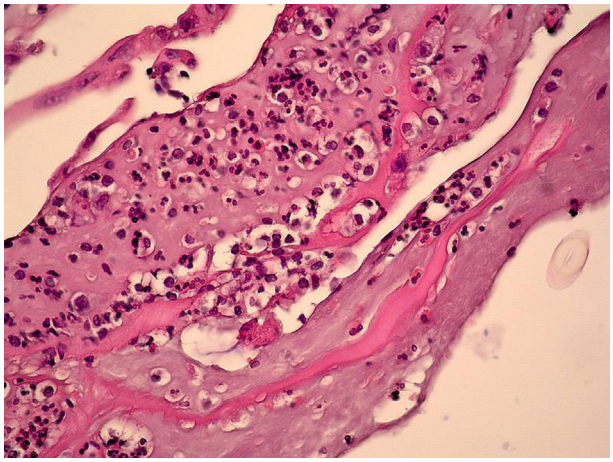

Fig. 4. The ureteral wall was densely infiltrated with inflammatory cells such as mast cells and eosinophils.

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.

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References

1. Lankenau SE, Sanders B. Patterns of ketamine use among young injection drug users. *J Psychoactive Drugs* 2007;**39**:21–9.
2. Middela S, Pearce I. Ketamine-induced vesicopathy: a literature review. *Int J Clin Pract* 2011;**65**:27–30.
3. Winstock AR, Mitcheson L, Gillatt DA, Cottrell AM. The prevalence and natural history of urinary symptoms among recreational ketamine users. *BJU Int* 2012;**110**:1762–6.

4. Tsai TH, Cha TL, Lin CM, Tsao CW, Tang SH, Chuang FP, et al. Ketamine-associated bladder dysfunction. *Int J Urol* 2009;**16**:826–9.
5. Chu PS, Ma WK, Wong SC, Chu RW, Cheng CH, Wong S, et al. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* 2008;**102**:1616–22.
6. Cottrell A, Warren K, Ayres R, Weinstock P, Gillatt DA. The relationship of chronic recreational ketamine use and severe bladder pathology: presentation, management of symptoms and public health concerns. *Eur Urol Suppl* 2009;**8**:170.
7. Lee PY, Ong TA, Chua CB, Lei CCM, Teh GC. Street ketamine-associated bladder dysfunction: an emerging health problem. *Malays Fam Phys* 2009;**4**:15–8.
8. Chen CH, Lee MH, Chen YC, Lin MF. Ketamine-snorting associated cystitis. *J Formos Med Assoc* 2011;**110**:787–91.
9. Wei YB, Yang JR, Yin Z, Guo Q, Liang BL, Zhou KQ. Genitourinary toxicity of ketamine. *Hong Kong Med J* 2013;**19**:341.
10. Australian Institute of Health and Welfare. *2007 National drug survey household survey: detailed findings. Drug statistics series no. 22, Cat No. PHE 107*. Canberra: AIHW; 2008.
11. Paglia-Boak A, Mann RE, Adlaf EM, Rehm J. *Use OSD. Drug use among Ontario students*. Ontario Student Drug Use and Health Survey; 2009.
12. Hoare J, Moon D. *Drug misuse declared: findings from the 2009/10 British crime survey England and Wales*. Home Office Statistical Bulletin. London: Home Office; 2010. p. 1–109.
13. Substance Abuse and Mental Health Services Administration. *The NSDUH report: use of specific hallucinogens 2006*. Rockville, MD. 2008.
14. Meng E, Wu ST, Cha TL, Sun GH, Yu DS, Chang SY. A murderer of young bladders: Ketamine-associated cystitis. *Urol Sci* 2013;**24**:113–6.
15. Pal R, Balt S, Erowid E, Erowid F, Baggott MJ, Mendelson J, et al. Ketamine is associated with lower urinary tract signs and symptoms. *Drug Alcohol Depend* 2013;**1321**:189–94.
16. Jhang JF, Hsu YH, Jiang YH, Kuo HC. Elevated serum immunoglobulin E may be associated to the development of ketamine cystitis. *J Urol* 2014;**192**:1249–56.
17. Oxley JD, Cottrell AM, Adams S, Gillatt D. Ketamine cystitis as a mimic of carcinoma in situ. *Histopathology* 2009;**55**:705–8.
18. Cheung RY, Lee JH, Chan SS, Liu DW, Choy KW. A pilot study of urine cytokines in ketamine-associated lower urinary tract symptoms. *Int Urogynecol J* 2014:1715–9.
19. Baker SC, Stahlschmidt J, Oxley J, Hinley J, Eardley I, Marsh F, et al. Nerve hyperplasia: a unique feature of ketamine cystitis. *Acta Neuropathol Commun* 2013;**1**:64.
20. Meng E, Chang HY, Chang SY, Sun GH, Yu DS, Cha TL. Involvement of purinergic neurotransmission in ketamine induced bladder dysfunction. *J Urol* 2011;**186**:1134–41.
21. Gu D, Huang J, Shan Z, Yin Y, Zheng S, Wu P. Effects of long-term ketamine administration on rat bladder protein levels: A proteomic investigation using two-dimensional difference gel electrophoresis system. *Int J Urol* 2013;**20**:1024–31.
22. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007;**69**:810–2.
23. Morgan CJ, Curran HV, Independent Scientific Committee on Drugs. Ketamine use: a review. *Addiction* 2012;**107**:27–38.
24. Mak SK, Chan MT, Bower WF, Yip SK, Hou SS, Wu BB, et al. Lower urinary tract changes in young adults using ketamine. *J Urol* 2011;**186**:610–4.
25. Huang LK, Wang JH, Shen SH, Lin AT, Chang CY. Evaluation of the extent of ketamine-induced uropathy: the role of CT urography. *Postgrad Med J* 2014;**90**:185–90.
26. Mason K, Cottrell AM, Corrigan AG, Gillatt DA, Mitchelmore AE. Ketamine-associated lower urinary tract destruction: a new radiological challenge. *Clin Radiol* 2010;**65**:795–800.
27. Huang PW, Wu ST, Tsao CW, Tang SH, Cha TL, Sun GH, et al. Is urodynamic study a good witness to the progression of ketamine-associated cystitis? *LUTS: Lower Urinary Tract Symptoms* 2014;**6**:98–102.
28. Tsai JH, Tsai KB, Jang MY. Ulcerative cystitis associated with ketamine. *Am J Addict* 2008;**17**:453.
29. Chen LY, Chen KP, Huang MC. Cystitis associated with chronic ketamine abuse. *Psychiatry Clin Neurosci* 2009;**63**:591.
30. Smart C, Kabir M, Pati J. Treatment of ketamine-associated cystitis with chondroitin sulphate. *Br J Nurs* 2013;**22**. S4,S6,S8–S9.
31. Rohan, et al. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007;**69**:810–2.
32. Lai Y, Wu S, Ni L, Chen Z, Li X, Yang S, et al. Ketamine-associated urinary tract dysfunction: an underrecognized clinical entity. *Urol Int* 2012;**89**:93–6.
33. Kuo HC. Repeated intravesical onabotulinumtoxinA injections are effective in treatment of refractory interstitial cystitis/bladder pain syndrome. *Int J Clin Pract* 2013;**67**:427–34.
34. Jhang JF, Jiang YH, Kuo HC. Potential therapeutic effect of intravesical botulinum toxin type A on bladder pain syndrome/interstitial cystitis. *Int J Urol* 2014;**21**(Suppl. 1):49–55.
35. Shaojun Jiang, et al. Treatment ketamine-related bladder dysfunction by intravesical injection of botulinum toxin A. *J Third Mil Med Univ* 2012;**11**:032.
36. Lieb M, Bader M, Palm U, Stief CG, Baghai TC. Ketamine-induced vesicopathy. *Psychiatr Prax* 2012;**39**:43–5.
37. Ng CF, Chiu PK, Li ML, Man CW, Hou SS, Chan ES, et al. Clinical outcomes of augmentation cystoplasty in patients suffering from ketamine-related bladder contractures. *Int Urol Nephrol* 2013;**45**:1245–51.
38. Chung SD, Wang CC, Kuo HC. Augmentation enterocystoplasty is effective in relieving refractory ketamine-related bladder pain. *Neurourol Urodyn* 2013;**33**:1207–11.