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Ketamine-Associated Uropathy: From Presentation to Management

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Abstract Ketamine consumption as a recreational drug is on an increasing trend. Chronic abuse of ketamine leads to ketamine-associated uropathy, commonly presenting with lower urinary tract symptoms and suprapubic pain. Upper tract involvement is observed in a portion of patients. Inflammatory picture and hypersensitive reaction are observed in the histopathology of ketamine cystitis specimen. Assessment with symptom score questionnaires, imaging assistance and endoscopic examination are essential in the evaluation of patients with ketamine-associated uropathy. While abstinence is the key to alleviate the detrimental impact from ketamine abuse, both medical and surgical options are available to relieve the complications. This review discussed the clinical presentation, pathology, assessment and management strategy of ketamine-associated uropathy.

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Introduction

Ketamine, with its original name "CI581", is a phencyclidine derivative. It has been used for anaesthetic and analgesic purposes since the 1960s [1]. In addition to its role in pain relief, it has been adopted as one of the treatment options for major depression [2], treatment-resistant depression [3] and bipolar affective disorder [4]. However, with properties of a strong psycho-stimulant, ketamine can also be the source of abuse. Ketamine may be consumed via inhalation, smoking or intravenous injection. When it comes to ketamine abuse, snorting is the usual route. The recreational use of ketamine was first reported in 1970s and has become increasingly common in the past 20 years [5]. An increase in ketamine use from 0.8 % in 2007/2008 to 2.1 % in 2010/2011 has been noted among young people aged 16–24 years in the UK [6], and it has been the commonest abusive substance in teenagers since 2005 in Asian cities like Hong Kong [7].

Besides being able to produce a dissociative state and hallucinations, ketamine can also bring toxicity to the urinary tract. Since the initial case series of ketamine cystitis reported by Shahani et al. [8••] and Chu et al. [9••] in 2007, this unique disease entity has been gaining an increasing recognition. The original report by Chu et al. described 59 patients with history of ketamine abuse, presenting with lower urinary tract symptoms (LUTS) [9••]. Their report and other subsequent reports [10, 11] in the literature demonstrated that ketamine-associated uropathy involves both the lower urinary tract and the upper urinary tract. This review presents information on the clinical features, possible mechanisms and the relevant management options on ketamine-associated uropathy.

Clinical Presentation

From an online survey performed in the UK, LUTS were reported in over a quarter of regular ketamine users [12]. Time to symptom onset after ketamine abuse varies from a few days to a few years [13]. In the initial description of ketamine-related LUTS, symptoms include frequency, urgency, nocturia, dysuria, urge incontinence and occasionally painful haematuria [9••]. Table 1 highlighted the available case series and case-control studies in the literature on patients with ketamine-associated uropathy. Yee et al. reported the largest available cohort of patients with ketamine-associated uropathy, in which both active ketamine abusers and ex-ketamine abusers were studied [14•]. Active ketamine abusers exhibited a significantly higher pelvic pain and urgency/frequency (PUF) score than ex-ketamine abusers (23.3 ± 6.7 vs 19.8 ± 7.7; $p < 0.0005$). PUF score has previously been proven useful in detecting interstitial cystitis, and high scores have been found to correlate with symptoms [15]. Ng et al. demonstrated that PUF questionnaire is reliable and valid for assessment in patients with ketamine-related LUTS [16]. The higher PUF score in active ketamine abusers is also in accordance with their poorer quality of life and their smaller functional bladder capacity [14•]. Furthermore, a dose and frequency response relationship was noted by Winston et al. on ketamine use and LUTS [12]. Higher typical doses and a more frequent use of ketamine were both found to be associated with higher rates of lower abdominal pain, frequency of urination and experiencing burning or stinging when passing urine.

Besides symptoms of the lower urinary tract, flank pain associated with upper urinary tract sequelae from ketamine abuse was also reported [17]. Chu et al. found that 51 % of their patients with ketamine-related LUTS had unilateral or bilateral hydronephrosis revealed by ultrasonography [9••]. From our unpublished data on 572 patients with ketamine-related LUTS, 96 (16.8 %) were found to have hydronephrosis on ultrasonography. Very often hydronephrosis was accompanied by varying degrees of ureteral lesions, ureteral wall thickening, ureteral stenosis or vesico-ureteric reflux. A multivariate logistic regression analysis in our cohort revealed that functional bladder capacity (OR 0.997, $p = 0.029$), serum creatinine >100umol/L (OR 1.238, $p = 0.016$) and a deranged serum liver enzymes profile (OR 1.967, $p = 0.006$) are factors predicting the risk of hydronephrosis in patients with ketamine abuse.

While urinary tract symptoms are the prominent features in patients of ketamine abuse, sexual dysfunction is also observed among these patients. In a case-control study by Jang et al., they noted sexual dysfunction in the domains of arousal, lubrication, orgasm, satisfaction and pain among female ketamine abusers [18]. For male ketamine abusers, Tan et al. studied their sperm motility and found that there was a statistically significant difference between the control and ketamine treated groups in the percentages of sperms which were motile [19]. There were also reports on gastrointestinal changes in ketamine abusers including epigastric pain, hepatic dysfunction and impaired gallbladder activity [20]. These are evidence that symptoms of ketamine abuse are more than just a urological problem, and a comprehensive assessment is usually indicated.

Pathology of Ketamine-Associated Uropathy

There is a great variation in the pathological findings of ketamine-associated uropathy and the pathology may change when disease progresses. When patients present with severe LUTS and a small functional capacity on investigation, one may usually find a contracted bladder in these patients with a much thickened bladder wall [21••]. The histopathology of bladder biopsies from ketamine-induced cystitis has features of chronic inflammation similar to those found in interstitial cystitis [8••, 9••]. The urothelial mucosa is substantially denuded. The lamina propria showed granulation tissue and congested vessels. Infiltration of eosinophils, lymphocytes, plasma cells, mast cells and macrophages was observed in the mucosal and submucosal layers [22]. Elevated levels of cyclooxygenase-2 (COX-2), endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS) were found in bladder tissues affected by ketamine, suggesting an inflammatory component of the process [23]. E-cadherin, a calcium-dependent glycoprotein which plays a critical role in cell-to-cell adhesion, was found to express much less in patients with ketamine cystitis than normal subjects [24]. At the same time, the apoptotic cell numbers in ketamine cystitis bladder tissue were higher than that in the control group. Ho et al. also described a proliferation of von Brunn's nests in their case report [25]. Calcification was observed in the bladder tissue from the case series by Lin et al. [26]. From a rat model study, submucosal fibrosis sets in towards the end of the disease process, with muscle hypertrophy and a change in collagen/muscle ratio [23].

The presence of mast cells and eosinohphils infiltrating submucosal tissues suggest a hypersensitive or allergic reaction. In a study by Jhang et al. [27•], patients with ketamine cystitis were found to have a higher serum immunoglobulin E (IgE) level than patients from the control group. It was postulated that ketamine itself might act as a hapten and bind to IgE, inducing hyerpsensitivity reaction in bladder tissue. This hypersensitivity reaction then activates mast cells, which starts a chain reaction that eventually results in inflammation and fibrosis. On the other hand, Shahani et al. [8••] proposed that the high concentration of ketamine and its metabolites in urine might induce significant bladder irritation and cause cystitis due to prolonged contact. Furthermore, they may inflict damage to the microvasculature of the bladder, potentially leading

Table 1 Survey/case series/case-control study in the literature on patients with ketamine-associated uropathy

Study	Number of patients	Significance of the study
Shahani et al. 2007 [8••]	9	Reported on the presentation and outcome of ketamine-associated uropathy
Chu et al. 2008 [9••]	59	Reported on the presentation and outcome of ketamine-associated uropathy
Oxley et al. 2009 [39]	17	Reported on the pathology of ketamine-associated uropathy
Garcia-Larrosa et al. 2012 [40]	13	Reported on the presentation of ketamine-associated uropathy
Jang et al. 2012 [41]	29	A case-control study on the sexual dysfunction in ketamine-associated uropathy
Chang et al. 2012 [42]	20	Reported on the presentation and management of ketamine-associated uropathy
Winstock et al. 2012 [12]	1285	Reported on the result of an online survey among ketamine abusers
Ng et al. 2012 [16]	50	Reported on the use of PUF questionnaire in the assessment of ketamine-associated uropathy
Lai et al. 2012 [43]	6	Reported on the presentation and management of ketamine-associated uropathy
Ng et al. 2013 [36]	4	Reported on the outcome of augmentation enterocystoplasty for ketamine-associated uropathy
Lee et al. 2013 [22]	16	Reported on the pathology of ketamine-associated uropathy
Chung et al. 2014 [35]	14	Reported on the outcome of augmentation enterocystoplasty for ketamine-associated uropathy
Huang et al. 2014 [34]	27	Reported on the use of CT urography in ketamine-associated uropathy
Tam et al. 2014 [30]	318	Reported on the clinical presentation of ketamine-associated uropathy
Huang et al. 2014 [44]	30	Reported on the relevance of urodynamic study in ketamine-associated uropathy
Jhang et al. 2014 [27•]	20	Reported on the immunology and pathology related to ketamine-associated uropathy
Yek et al. 2015 [45]	4	Reported on the presentation and pathology of ketamine-associated uropathy.
Liu et al. 2015 [46]	13	Reported on the pathology of bladder tissues from patients with ketamine cystitis.
Yee et al. 2015 [14]	319	Reported on the management outcome of ketamine-associated uropathy
Lin et al. 2015 [26]	23	Reported on the pathology of bladder tissues from patients with ketamine cystitis.
Wu et al. 2016 [47]	81	Proposed a model to classify ketamine-associated uropathy

to ischaemia and fibrosis. The relationship between ketamine and neural toxic effects was studied by Meng et al. [28]. Immunohistochemical examination revealed increased P2X1 receptor expression in ketamine treated mouse bladders while M2 and M3 receptor expression was unchanged. It indicates that dysregulation of purinergic neurotransmission may underlie detrusor overactivity in cases of ketamine-induced bladder dysfunction.

Assessment of Ketamine-Associated Uropathy

Ma et al. [29] proposed the following to be included in the assessment of ketamine-associated uropathy: questionnaires (PUF symptom scale, visual analogue scale, frequency-volume chart), urine microscopy and culture, urine cytology, urine toxicology screen, serum creatinine, liver function test, c-reactive protein, ultrasonography of the urinary tract, uroflowmetry, urodynamic study and cystoscopy examination. Cystoscopy examination of patients with ketamine cystitis shows various degrees of epithelial inflammation of the bladder and neovascularization. Severe cases may show petechial haemorrhages (Fig. 1).

A similar assessment pathway was adopted by Yee et al. [13]. In their cohort of 319 patients with ketamine-associated uropathy, functional bladder capacity (FBC) was calculated by adding the voided volume to postvoid urine residuals during the uroflowmetry assessment. Mean FBC of the whole cohort was 141.8 ± 120.8 ml, and the FBC of the abstinent group was significantly more than that of the active ketamine abuse group (177.8 ± 122.9 ml vs 125.2 ± 116.4 ml, $p = 0.001$). Tam et al. noted 9.4 % of active ketamine abusers had hydronephrosis on ultrasound, and 6.5 % of active ketamine abusers had abnormal serum creatinine level in their earlier report from the same centre [30].

1Urodynamic study for ketamine-associated uropathy found detrusor overactivity [31]. A bladder with decreased

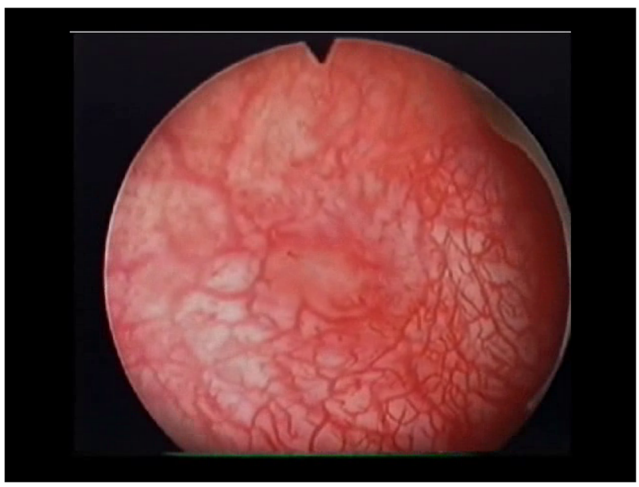

Fig. 1 Petechial haemorrhages

compliance, decreased capacity with or without vesico-ureteric reflux was also noted [9••]. Cystoscopic findings of patients with ketamine-associated uropathy range from a normal looking bladder to a bladder with ulceration [8••], erythema [32], neovascularization or petechial haemorrhages [9••]. There was also a report of mucosal bleeding after hydrodistension [33]. Huang et al. [34] reported the usefulness of CT urography in the assessment of ketamine-associated uropathy. In their case series of 27 patients, CT urography was able to pick up features of bladder wall thickening, ureteral wall thickening, hydronephrosis and vesicovaginal fistula.

Management of Ketamine-Associated Uropathy

Abstaining from ketamine abuse is regarded as the milestone of treating ketamine-related uropathy [16], and with abstinence, symptom resolution has been observed [12, 14•]. In a dedicated clinic for the management of ketamine-associated uropathy, treatment is divided into multiple tiers [14•]. First-line treatment includes nonsteroidal anti-inflammatory drugs (e.g., diclofenac and etoricoxib) and anticholinergic agents (e.g., solifenacin). Phenazopyridine and paracetamol are used for pain control. If first-line treatment could not provide sufficient symptom relief, opioid group of analgesics (e.g., tramadol) and pregabalin are added as second-line treatment. If symptom control is still suboptimal, a third-line treatment with an 8-week course of intravesical instillation of sodium hyaluronate is offered. Fourth-line treatment was defined as any surgical intervention (e.g., augmentation cystoplasty and hydrodistension). They would be performed when indicated, if patients could achieve a 6-month history of abstaining from ketamine abuse. Over the course of almost 3 years, data showed that both nonsteroidal anti-inflammatory drugs and analgesics could effectively alleviate symptoms of ketamine cystitis. Abstinence from ketamine usage and the amount of ketamine consumed have bearings on treatment response and symptom relief.

Chung et al. [35] reported their experience of augmentation enterocystoplasty in patients with ketamine-associated uropathy. Indication of surgery was refractory bladder pain and a small cystometric bladder capacity of less than 100 ml, or low bladder compliance. Concomitant ureteral reimplantation was performed if there was vesico-ureteral reflux or ureteral obstruction. The procedure was performed in an open manner, using 40 cm terminal ileal segment, with the native contracted bladder resected as much as possible. Trigone was preserved with the aim to preserve normal micturition reflex. The group reported that after augmentation enterocystoplasty, bladder pain was immediately relieved in all patients, but frequency, urgency and small functional bladder capacity remained until 1 month after surgery. All patients could void spontaneously without catheterization. A similar strategy, with the exception of using a robot-assisted laparoscopic approach, was reported by Ng et al. [36]. Symptoms and functional outcome was suboptimal due to relapse of ketamine abuse.

Besides ureteral reimplantation, ureteric obstruction secondary to ketamine-associated uropathy has been managed with resonance metallic ureteric stent [37] and autotransplantation [38]. However, these options are limited to case reports and long term outcome is yet to be known.

Conclusions

Ketamine abuse is an increasingly common social and medical problem. It leads to uropathy signified by LUTS and pain, with risk of upper urinary tract involvement. Histopathology and immunochemistry suggest the disease process may have components of hypersensitivity, inflammation, ischaemia and fibrosis. Assessment with urodynamic study and endoscopic investigation found a small contracted bladder with features of that resemble interstitial cystitis. Ultrasonography and CT urography allows the revelation of concomitant hydronephrosis. More commonly adopted management options include anti-inflammatory agents, anti-muscarinic agents, analgesics, intravesical instillation therapy, hydrodistension and augmentation enterocystoplasty. In view of ketamine abuse being an issue that crosses specialties and professions, the optimal strategy to tackle the problem should involve a multidisciplinary approach.

Compliance with Ethical Standards

Conflicts of Interest Drs Yee, Ma, Ng and Chu declare no conflict of interest, including specific financial interests or relationships and affiliations relevant to the subject matter or materials discussed in the manuscript.

Human and Animal Rights and Informed Consent This article does not contain studies with human or animal subjects performed by the author.

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