

# Management of Complications of Ketamine Abuse



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**Abstract** Since 1985, ketamine, a frequently used human and veterinary anaesthetic, has been listed as an essential medicine by the World Health Organization. This *N*-methyl-D-aspartate receptor antagonist has also been used and studied extensively for its role in the treatment of depression. Owing to its potential implications on health when used illicitly, at least 60 countries have already put ketamine under national control. Its illicit use has been reported on a global scale, so are its delirious complications from chronic abuse. The detrimental effects of ketamine abuse encompass different organ systems, where long-lasting complications on the genitourinary, gastrointestinal, hepatobiliary and neuropsychiatric systems stood out. In this relatively new entity of ketamine-associated complications, the importance of proper assessment and building of good rapport is emphasized. Abstinence is the first key for the successful management of its complications. Both medical and surgical management have its role in the multidisciplinary management.

**Keywords** Ketamine · Uropathy · Complications · Cystitis · Management

The detrimental effects of ketamine misuse was only evident to the medical world within the recent decade or so. Despite its initial formal reporting of toxic complications on genitourinary system by Shahani et al. (2007) from Canada and Chu et al. (2008) from Hong Kong, the ketamine abuse problem has gravitated farther and was popularized in Asian countries, particularly in Hong Kong SAR. Ketamine, an *N*-methyl-D-aspartate receptor antagonist, whilst being utilized clinically as an anaesthetic agent, is also being commonly misused as a recreational drug since the late 1990s.

The detrimental effects of ketamine abuse encompass many organ systems, where long-lasting complications on genitourinary, gastrointestinal, hepatobiliary and neuropsychiatric systems stood out. Its alarming burden on health care,

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economic and societal fronts has warranted measures to help cracking down the problem.

## 1 Why Is Managing Complications an Important Topic?

Ketamine-associated complications revealed as a relatively new entity to the medical world. It primarily affects young to middle-aged ketamine abusers, amongst whom they popularized ketamine as a “post-clubbing drug” where you can “sit down and float”. Its handy availability, easy administration and psycho-stimulant properties render it attractive as a recreational drug. The exact pathophysiology and effects of ketamine and its metabolites are yet to be completely dissected and laid out. This poses as both a medical and a social issue to be tackled.

More than 50 countries have reported the presence of ketamine in illicit drug markets from the annual United Nation Office on Drug and Crime World Drug Reports. The 2017/2018 Crime Survey for English and Wales reported a twofold increase in illicit ketamine usage from 0.4 to 0.8% amongst adults aged 16–59 years, equating to 141,000 more using the drug than previous year (Home Office (U.K.) NS 2018). Such estimate of ketamine usage is the highest since survey first began in 2006/07 for this drug. The burden of ketamine abuse lies heavily in the group aged 16–24 years, citing a rise from 1.2 to 3.1%. In Hong Kong, ketamine was the most commonly abused psychotropic drug during 2008–2014. Methamphetamine surpassed ketamine to become the most popular psychotropic substance abused since 2015, followed by triazolam, midazolam, zopiclone and cocaine in 2017 (Narcotics Division SBTGotHKSAR 2019). Over the years, the concerted efforts of governmental officials have helped brought the numbers down by dismantling clandestine ketamine laboratories and decreasing their supply sources, mainly in East and South-East Asia (e.g. China and Malaysia).

Although the number of reported abusers of psychotropic substances is on the fall, the complications are still slowly surfacing. Amongst such young population of ketamine abusers, untreated or suboptimally treated complications will serve as returning patients when their health and quality of life are detrimentally affected.

A vast majority of ketamine abusers are disguised amongst the community snorting the drug undercover for years unnoticed by closed ones. Only by concerted efforts from a dedicated team of clinicians, paediatricians, psychiatrists, psychologists, social workers, teachers, nurses and therapists can we truly evaluate and manage the full spectrum of ketamine-associated complications. Family and parental support, particularly for the teenage abusers, is of paramount importance to keep the ketamine abuser on track, abstaining from the drug and compliant to follow up and treatments. Complications involving genitourinary, hepatobiliary, gastrointestinal and neuropsychiatric systems mark ketamine-associated complications as a complex class of disease entity.

## 2 Pathophysiology

Ketamine is converted to active metabolic norketamine via hepatic biotransformation through the cytochrome P450 and then eliminated via the hepatic route into conjugated hydroxyl metabolites, which is then excreted renally (Dinis-Oliveira 2017). The damage of ketamine and its metabolites on the genitourinary tract is proposed as via direct toxic damage, autoimmune reactions and/or microvascular reactions.

Inflammation of bladder epithelium, denuding of urothelium neovascularization and petechial haemorrhage of the bladder are all reported. However, the exact pathophysiology is not fully known. Histologically, four out of nine Canadian patients in the first series had biopsies revealing denuding of urothelium and inflammation of bladder epithelium with a mild eosinophilic infiltrate (Shahani et al. 2007). The histopathology of bladder biopsies from ketamine cystitis patients shows features of chronic inflammation with strong resemblance to those in interstitial cystitis. The predominant type of infiltrating inflammatory cells is lymphocytes. The severity of histopathology of inflammatory cell infiltration of bladder mucosa is shown to be associated with clinical symptomatology. Patients with moderate or severe neutrophils or lymphocytes infiltration in bladder mucosa had significantly more severe bladder pain and smaller bladder capacity (Jhang et al. 2018). In rat ketamine cystitis models, it is shown that increasing fibrosis and submucosal apoptosis were found according to escalating dose of ketamine. It is postulated that bladder fibrotic change contributes to the manifestation of lower urinary tract symptoms (Song et al. 2016).

## 3 Complications Related to Urinary System: Ketamine-Associated Uropathy

Ketamine abuse may affect both the upper and lower urinary tract. In fact, its effects may go unnoticed until late in stage where irreversible damages have already taken place. Lower urinary tract symptoms, cystitis, bladder dysfunction, contracted bladder, ureteric strictures and secondary renal damage have all been reported in chronic ketamine abusers. The clinical syndrome of ketamine-associated uropathy is described as a small, painful bladder, associated with incontinence, upper tract obstruction with or without papillary necrosis (Shahani et al. 2007; Chu et al. 2008).

## 4 Symptomatology

In the largest online survey to date, more than a quarter of ketamine abusers reported experiencing urinary symptoms to variable extent (Winstock et al. 2012). The onset of symptoms varies from few days to years. From one of the largest reported series, the mean duration of ketamine usage was 81 months prior to the presentation of voiding symptoms (Tam et al. 2014). Ketamine-associated lower urinary tract symptom is recognized as ketamine-induced cystitis. Painful frequent small volume void is a classic chief complaint. Irritative symptoms, such as frequency, urgency, nocturia, dysuria, urge incontinence, pelvic pain and painful hematuria, vary in severity. Symptomatology could be very debilitating to a young individual. Urinary frequency could be down to every quarter of an hour, barring the individual from normal social activities. In more severe cases, the young individuals could be incontinent and dependent on diapers to avoid interruptions to the washroom during work hours. In a 463 patient cohort looking into both active and inactive ketamine abusers by Yee et al. (2015), it was shown that active abusers have significant higher pelvic pain and frequency (PUF) score than inactive ones ( $23.3 \pm 6.7$  vs.  $19.8 \pm 7.7$ ;  $p < 0.0005$ ). Cystitis and bladder dysfunction are the common manifestations. However, its effects are observed to involve organs beyond the bladder.

Upper tract pathologies may be asymptomatic in many ketamine abusers, or may manifest most commonly as loin discomfort. In a cohort of 572 ketamine-associated uropathy patients, up to 16.8% of the patients were found to have unilateral or bilateral hydronephrosis on ultrasonography (Yee et al. 2017), secondary to inflammatory reaction, stricture, vesicoureteric reflux or papillary necrosis (Fig. 1). Functional bladder capacity (OR 0.997,  $p = 0.029$ ), serum creatinine  $> 100 \mu\text{mol/L}$  (OR 1.238,  $p = 0.016$ ) and a deranged serum liver enzyme profile (OR 1.967,  $p = 0.006$ ) are predictive factors of hydronephrosis in ketamine abusers from a multi-variate analysis. Obstructive uropathy, renal impairment and end-stage renal disease are uncommon sequelae of ketamine-associated uropathy.

Symptoms are not confined urologically; they extend to the domains of sexual dysfunction in both female and male patients (Jang et al. 2012; Yang et al. 2018). In a case-control study of female ketamine abusers by Jang et al. (2012), with the exception of the sexual desire domain in female patients, the abusers scored lower on the arousal, lubrication, orgasm, satisfaction and pain domains of the Female Sexual Function Index score ( $17.65 \pm 6.15$  vs.  $25.87 \pm 4.16$  for controls ( $p < 0.001$ )). For the male counterparts, Yang et al. (2018) reported amongst 1056 abusers (993 street ketamine abusers who presented to the urology and 63 who presented to the hospital), erectile dysfunction (30.8%) is frequently observed with International Index of Erectile Function (IIEF-5) score  $\leq 21$ . Multi-variate analysis revealed age is  $\geq 30$  years old (OR = 1.765) as a risk factor for male erectile dysfunction; subgroup analysis revealed abstinence for 3 months or more as a protective factor. A small study evaluated the effects of ketamine on membrane integrity, DNA fragmentation and sperm parameters in humans (Absalan et al. 2014). It is shown to have significantly lower total sperm motility, decreased sperm viability and



**Fig. 1** shows multiple left ureteric strictures and small contracted bladder on antegrade pyelogram

abnormal sperm parameters in progressive motility. Since this is a relatively young patient group where individuals may have not settled down, families may not be completed. Whether infertility will pose an important issue remains a question to be answered. Both urinary symptoms and sexual dysfunction certainly are shown to have adversely impacted on this group of patient's quality of life.

## 5 Assessment, Diagnosis and Investigation

Diagnosis is often easily made clinically.

### 5.1 History Taking

History taking is an important step that should not be underestimated in the management of ketamine abusers. It helps develop doctor–patient rapport, draws patient’s compliance and often reveals the fundamental societal or personal psychological reasons that steer the individual down the illicit substance pathway. A detailed history taking of symptomatology, duration and frequency of recreational ketamine usage, social support and background is an important step of assessment. Of note during history taking, the reported consumption frequency by patients may not be as reliable as the monetary value spent on street illicit ketamine purchase. Misuse of ketamine >3 times per week is associated with significantly lower voided volumes. Pelvic pain, frequency and urgency are reported to be significantly higher in those with chronic ketamine abuse >24 months, compared to those with shorter durations (Mak et al. 2011).

### 5.2 Initial Assessment and Workup

In the largest prospective cohort of ketamine-associated uropathy, Yee et al. (2015) proposed a standardized management protocol at a dedicated urological clinic. Invasive investigations too early on in the assessment process may deter this group of patients from adhering to the programme and follow-up schedules.

#### 5.2.1 Standardized Questionnaire

Apart from the commonly used International Prostate Symptom Score (IPSS), IIEF-5 and frequency/volume charts, symptom assessment can be objectively performed by means of pelvic pain and urgency or frequency (PUF) symptom scale, the EuroQol visual analog scale.

Pelvic pain and urgency/frequency (PUF) symptom scale, a tool initially used in the assessment of interstitial cystitis, correlates with worse symptomatology (Yee et al. 2015). The questionnaire comprises seven questions: daytime and night-time frequency, whether the pain affects or is present during sexual intercourse, pelvic pain and its severity, urgency and its degree of severity. It includes a symptom score and a bother score, totalling 35 points maximum. Its Chinese version has been validated and used in the assessment of patients with ketamine abuse (Ng et al. 2012).

This entity has strong resemblance between interstitial cystitis and ketamine-associated cystitis, hence PUF symptom scale has demonstrated its role in the assessment of such patient groups.

The EuroQol visual analog scale (EQ VAS) is a visual scale marked 0–100 for patients' subjective assessment of own health state. The lower the score, the worse the patients self-perceive their own health state. Such standardized questionnaires are important in the assessment and follow-up of patient's progress.

## 5.2.2 Initial Workup

Initial workup should be kept non-invasive, including uroflowmetry, urine microscopy and culture and serum creatinine, which will help to build the rapport and trust between the patients and the health care providers. As many patients already suffered from painful urination, invasive investigation might frighten them and lead to poor compliance and also delay in treatment. Functional bladder capacity can be calculated by the summation of the voided volume and post-void residual urine volume during uroflowmetry assessment. In a cross-sectional prospective cohort, the mean voided volume of ketamine abusers is reported up to 111.5 mL, with a mean bladder capacity of 152.5 mL (Tam et al. 2014).

Ultrasonography of the urinary system can be performed to screen for any sign of obstructive uropathy. Hydronephrosis can be found in 8.1–51% (Chu et al. 2008; Yee et al. 2017; Tam et al. 2014) amongst which 10.4–30.7% may have concomitant renal impairment. Small bladder volume and wall thickening are also common features (Mason et al. 2010).

Computer tomography with urogram phase is also very useful because upper tract involvement is not uncommon in this group. The common CT findings include diffuse bladder wall thickening, small bladder volume and perivesical inflammation. Moreover, they can also pick up upper tract involvement, such as unilateral/bilateral hydronephrosis and ureteric wall thickening (Huang et al. 2014).

Cystoscopy is invasive and not essential in the diagnosis and initial management of ketamine cystitis, as the diagnosis is based mostly on clinical condition. Unless there are clinical suspicious of other pathology, or failed response to initial therapy, endoscopy might be considered. Endoscopy findings vary from normal-looking bladder mucosa to contracted bladder with erythematous cystitis (Tam et al. 2014), ulceration, neovascularization and petechial haemorrhage (Chu et al. 2008).

Video-urodynamic study can be reserved for patients who require in-depth evaluation of bladder condition and detection of vesicoureteric reflux. It is a particularly useful tool as part of the preoperative planning when all conservative and medical measures fail. Typical findings include diminished bladder compliance or presence of detrusor overactivity with or without urinary leakage when the bladder is filled to a small capacity of 30–50 mL (Chu et al. 2008) (Fig. 2).

With appropriate investigations, prompt detection and management of ketamine-associated uropathy can be carried out.



**Fig. 2** shows small contracted bladder with size of a Foley's catheter balloon and bilateral vesico-ureteric reflux on cystogram

### **Investigations**

- Uroflowmetry, functional bladder capacity
- Urine microscopy and culture
- Serum creatinine
- Liver function test
- Ultrasonography of urinary system
- Computer tomography with urogram phase
- Cystoscopy
- Video-urodynamic study

### **5.3 Management**

Multidisciplinary approach is of paramount importance in successfully treating both the clinical and psychological aspects of the disease entity.



### 5.3.1 Abstinence of Ketamine

First and foremost, abstinence of ketamine is emphasized to patients during their first visit to health care. There is a dose and frequency response relationship between ketamine use and urinary symptoms. Symptomatology score is improved with a direct positive relationship with the length of abstinence from the drug. There is potential to normalize functional damages beyond 1 year of ketamine cessation. More than half reported improvement of urinary symptoms upon abstaining (Winstock et al. 2012). Those abstained have a lower symptom score (19.3 vs. 24.1;  $p < 0.001$ ), a larger voided volume (126 vs. 85 mL;  $p < 0.001$ ) and a larger bladder capacity (204.8 vs. 126.7 mL;  $P < 0.001$ ) compared with active abusers (Tam et al. 2014). Reduced benefits from ketamine abstinence is observed if the drug was misused at higher frequencies or longer duration.

Abstinence is easier said than done. Working hand in hand with a dedicated team of social worker, psychologist, psychiatrist, teacher, parents and family could result in higher rates of success. Local support from drug and addiction services can also play a decisive role in abstinence and treatment success.

### 5.3.2 Treatment Ladder

The four-tier treatment protocol has been developed and implemented at the dedicated Youth Urological Treatment Centre reported by Yee et al. (2015), in hope of offering standardized treatment multidisciplinary care to these batch of patients (Hong et al. 2018). The stepwise approach proposed is as follows:

Tier one: NSAIDs/ COX-2 inhibitors/anti-cholinergics

Tier two: Pregabalin or a short course of opioid analgesics

Tier three: A course of intravesical instillation of sodium hyaluronate

Tier four: Surgical intervention

### 5.3.3 Medical Treatment

Symptoms are often refractory to treatment with antibiotics, simple analgesics and anti-cholinergics alone. First-line oral medications include nonsteroidal anti-inflammatory drugs (e.g. diclofenac and etoricoxib) and anticholinergic agents (e.g. solifenacin). Beta-3 adrenoceptor agonists can be another option.

Phenazopyridine and paracetamol are used for pain control. The aim is to cover the possible increase in pain experienced during the initial abstinence period. If first-line treatment fails to provide sufficient analgesic relief, the second-line treatment is introduced and added onto the cocktail of medications – pregabalin or a short course of opioid group of analgesics (e.g. tramadol). Regular follow-up and reassessments are carried out to ensure abstinence and adherence to the treatment

regime. Outcome is assessed with functional bladder capacity, pelvic pain and urgency or frequency (PUF) symptom scale and the EuroQol visual analog scale.

Both abstinence from ketamine usage and the amount of ketamine consumed are factors predicting the improvement of PUF scores. For patients who required second-line oral therapy in that cohort, 67.7% reported improvement in symptoms.

### 5.3.4 Intravesical Instillation of Sodium Hyaluronate

There have been case reports with complete resolution of symptoms, as well as significant improvement in voided volume for the patients after intravesical treatment with sodium hyaluronic acid.

### 5.3.5 Surgical Treatment

Urinary tract reconstruction has proved a surgical challenge for ketamine-associated uropathy. Even when managed in tertiary high-volume reconstructive units, this group of patients are still at high risk of significant perioperative complications (Sihra et al. 2018). Meticulous preoperative assessment and multidisciplinary approach to optimize treatment strategies are recommended.

Surgical correction is reserved for patients with confirmed abstinence from ketamine use. Whenever indicated, nephrostomy or ureteric stents are inserted to preserve renal function until definitive surgical correction is allowed. There is no optimal time recommended for abstinence from ketamine abuse before major reconstructive use can be carried out.

#### **Common indications for surgical reconstruction include:**

- Small contracted bladder
- Medically uncontrolled pelvic pain or lower urinary tract symptoms
- High-pressure, low-bladder compliance

#### **Reported options for surgical intervention:**

- Intra-detrusor botulinum toxin injection
- Hydrodistension
- Augmentation cystoplasty with or without Mitrofanoff channels
- Ileal conduit urinary diversion
- Cystectomy with neobladder

#### **Ureteric stricture**

- Metallic stents
- Ureteric dilatation
- Ureteric reimplantation
- Autotransplantation

There are reports where intra-detrusor onabotulinum toxin injection was ineffective in symptom relief. Because ketamine cystitis shares similar features with inter-

stitial cystitis, hydrodistension was carried out in small case reports with unsatisfactory outcomes.

Surgical correction was the most commonly reported in the literature with evident outcomes. The number of reported surgical corrections is small, where complication rates are high, even in high-volume tertiary centres. A retrospective cohort where 44 patients spanning over a decade were reviewed at a high-volume tertiary reconstructive unit, 14 patients underwent major reconstruction with indications including intractable symptoms, high-pressure compliance loss with upper tract damage and ureteric obstruction (Sihra et al. 2018). Surgical intervention included ileal conduit urinary diversion, augmentation cystoplasty with or without Mitrofanoff channels, ureteric re-implantation and cystectomy with neobladders. Complications included anastomotic leaks, ureteric strictures, adhesive small bowel obstruction, renal failure and sepsis.

Another cohort of patients where augmentation cystoplasty was performed was reported by Ng et al. (2013), where it reached the same conclusion on high complication rates and the high tendency of resuming ketamine abuse after surgery. Although augmentation cystoplasty is a very effective way of increasing bladder capacity and relieving storage lower urinary tract symptoms (Figs. 3 and 4), it was discussed that the option of simple non-continent urinary diversion (e.g. ileal conduit) may be a better option as it has faster recovery. However, it may not be acceptable and appealing to this young population of patients. The extremely high



**Fig. 3** shows an early post-operative cystogram of a patient who received ileal interposition for right ureteric stricture and augmentation ileocystoplasty



**Fig. 4** is a cystogram revealing a patient who have received augmentation ileocystoplasty

rates of indulging back into ketamine abuse should caution urologists offering surgical definitive treatment in discretely selective groups that have abstained from ketamine abuse and have social support in continuing the abstinence so that all efforts will not go waste.

Ketamine-associated uropathy is an evolving disease entity, patient centred tailored management will provide the best outcomes.

## **6 Complications Involving the Gastrointestinal and Hepatobiliary Systems**

There are also reports on gastrointestinal changes in ketamine abusers including epigastric pain, hepatic dysfunction and impaired gallbladder activity. Many ketamine abusers are often disguised amongst the community. They may not present to clinicians until unbearable symptoms or complications arise. Clinicians may seize the opportunity to identify disguised abusers when being consulted for non-specific symptoms such as epigastric discomfort and lower urinary tract symptoms.

Up to a quarter, amongst 611 patients who have sought medical consultation for ketamine-associated uropathy in a cross-sectional study by Liu et al. (2017), reported upper gastrointestinal symptoms. There may be up to 5 years lag from ketamine abuse to symptoms' onset. Symptomatology may vary from epigastric pain (25.4%), recurrent vomiting (7.9%), anaemia (5.9%) and gastrointestinal bleeding (3.3%). As upper gastrointestinal symptoms usually precede the presenta-

tion of voiding symptom, direct enquiry on substance usage in young non-helicobacter gastritis or ulcer might help to identify potential hidden abuser and allow earlier intervention to them.

Distinct biliary anomalies on magnetic resonance cholangiography patterns have been reported (Seto et al. 2018). Magnetic resonance cholangiography showed biliary tract anomalies in up to 61.9%, where an elevated alkaline phosphatase level was observed. Three distinct radiological patterns were reported: (1) diffuse dilatation of extrahepatic ducts; (2) fusiform dilatation of extra-hepatic ducts with distal tapering and (3) intrahepatic duct dilatation or bleeding and strictures with normal extrahepatic ducts. Elevated alkaline phosphatase level and lack of concomitant drug are predictive of biliary anomalies. Such biliary anomalies are reversible after ketamine abstinence. Biliary sepsis and decompensated cirrhosis are rare sequelae.

Recreational ketamine inhalation serves as a dualistic challenge on health care and social fronts worldwide. Early recognition and detection of ketamine-associated uropathy allows timely management. A combined approach of medical treatment and psychosocial support is of paramount influence in successful abstinence. Surgical intervention is only indicated when abstinence is confirmed and deemed appropriate timing.

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