

Review Article

Ketamine-Associated Uropathy: A Review of Hong Kong Experience

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Abstract

Ketamine had been the most commonly abused drug in Hong Kong from 2006 to 2014. The recognition of ketamine uropathy as a distinct disease entity in Hong Kong began in 2007. Ketamine uropathy included damage to the bladder, ureters and kidneys. Urological evaluation of ketamine abusers began with non-invasive modalities including uroflowmetry and ultrasonography, these investigations served as risk assessment for upper tract damage. Different successful care delivery models - outreach clinic, nurse-led clinic, one-stop clinic, and in-patient program - shared a common core value of patience and care.

ABBREVIATIONS

PUF: Pelvic Pain and Urgency / Frequency

INTRODUCTION

Ketamine, a phencyclidine derivative, was originally discovered and used as an anesthetic and analgesic agent [1]. Ketamine later became popular as a recreational drug owing to its psycho-stimulating effect. When taken, commonly by snorting, the drug produces a dissociative psychedelic state with hallucinations and euphoria. The availability, cheap market price, quick onset time and short half-life added to its popularity among young drug abusers. With a legitimate route of import and lawful use in both human and veterinary medicine, ketamine trafficking was particularly difficult to be controlled.

TREND OF PREVALENCE AND SOCIAL IMPACT

Figure 1 depicted the trend of drug abuse from 2006 to 2015 in Hong Kong [2]. Ketamine had been the most commonly abused drug from 2006 to 2014. In 2015, the popularity of methamphetamine superseded that of ketamine. Probably due to a concerted effort of education and law enforcement, the total number of reported drug abusers had been decreasing steadily since the peak in 2009. The number of reported ketamine users had also plunged to a new low. However, the prior duration of drug abuse in newly reported abusers had increased steadily since 2007 (Figure 2) [2]. The median duration of drug abuse prior to reporting to the Hong Kong Central Registry of Drug Abuse had reached an unprecedented level of 5.8 years in 2015. The increase reflected that despite there was a reduction in total number of reported drug abusers, hidden drug abuse remained a

major concern. In 2015, a total of 4,309 persons were arrested for drug offenses, of which 25.4% was related to ketamine [3].

Apart from a wide range of physical sequelae, the long-term harmful effects of ketamine abuse also included a variety of psychological impairment: poor memory, insomnia, lack of concentration, and increased suspicion. The socio-economic impact of ketamine abuse was estimated based on the cost of treatment, rehabilitation, counselling, preventive education and research. The expenditure was estimated to be HKD 301.42 million for the year 2010 [4]. As some of the physical and psychological impairment were known to persist after years of abstinence, the society would continue to bear this hefty burden even after initial control in number of drug abusers.

HISTORY OF RECOGNITION OF KETAMINE-ASSOCIATED UROPATHY AS A DISTINCT DISEASE ENTITY

The effect of ketamine on the urinary tract was not elucidated before its widespread misuse. In 2008, when the first local case series of 59 patients from Hong Kong was reported [5], the damage of ketamine to the urinary tract started to be acknowledged and ketamine-associated uropathy gained acceptance as a distinct disease entity in other parts of the world.

In January 2007 a young couple, aged 22 and 25, presented with severe dysuria and significant storage symptoms. They were found to have sterile pyuria, and their symptoms persisted after repeated courses of antibiotics. To the surprise of the treating urologist, further investigations showed remarkably similar findings: raised serum alkaline phosphatase and alanine transferase; negative urine culture for acid-fast bacilli

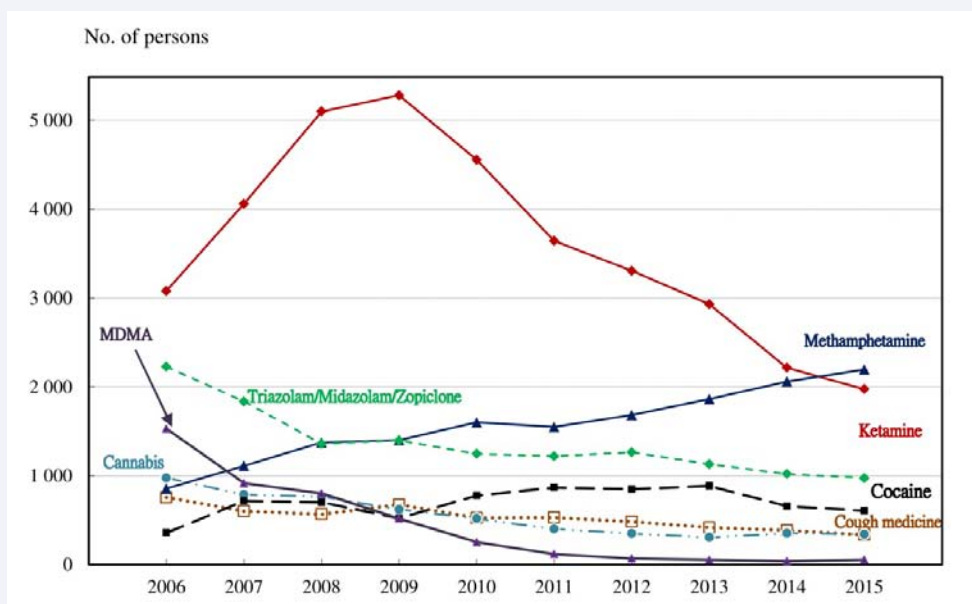


Figure 1 Trend of drug abuse from 2006 to 2015 in Hong Kong.

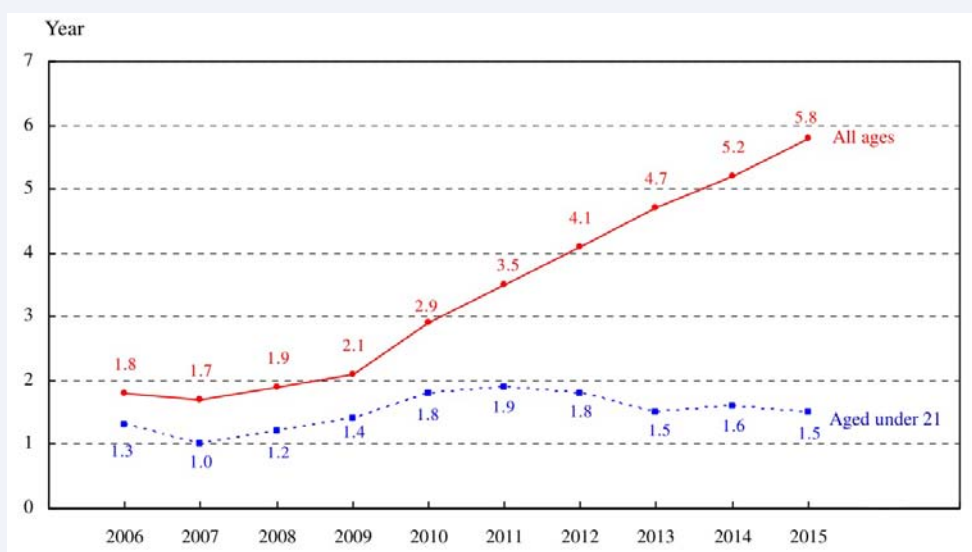


Figure 2 Prior duration of drug abuse in newly reported abusers in Hong Kong.

and negative urine cytology for malignancy; marked detrusor overactivity with leakage and contracted bladder on videourodynamic study; markedly erythematous mucosa with dilated vessels and cystitis on cystoscopic assessment and biopsy. On further detailed history taking, the wife volunteered that it was only after the marriage did she realize that her husband was a regular ketamine abuser for 3 years, and she then started to abuse ketamine as well. The treating urologist then recalled two other male patients both aged 30 years with similar clinical findings who presented around that same period. These patients were subsequently confirmed to be ketamine abusers. The clustering of clinical findings and ketamine exposure rang the bell that ketamine might have led to the damage of the urinary tract. The treating urologists later reported their first 10 patients of street

ketamine-associated bladder dysfunction in August 2007 [6] with the aim to alert medical professionals in Hong Kong.

After gathering more clinical experience and collaborating with various treating institutions in Hong Kong, a larger case series was published in 2008 [5]. The recognition of ketamine-associated uropathy as a distinct disease entity was later echoed by reports from Taiwan [7], United Kingdom [8], Malaysia [9] and Singapore [10].

UROLOGICAL SEQUELAE AND ASSESSMENT

The detrimental effects of ketamine on the urinary tract included small painful bladder, urinary incontinence, upper urinary tract obstruction, and papillary necrosis [6,11,12]. The primary damage was due to the direct toxicity on the urothelium

of the bladder by ketamine metabolites. Histological evaluation indicated mucosal ulceration, striking urothelial reactive atypia, lamina propria inflammation with predominant lymphocyte infiltration, and a variable number of eosinophil cells. This resulted in ulcerative cystitis with submucosal inflammation and fibrosis. Reports had suggested histopathological features mimicking interstitial cystitis [5], or carcinoma in-situ [13]. A patient typically presented with urinary frequency and urgency with small-volume and painful voids [14].

The upper urinary tract damages included ureteric obstruction, reflux nephropathy and papillary necrosis. Hydronephrosis occurred in a significant proportion of chronic ketamine abusers, ranging from 13% to 50% [15-17]. The proposed mechanism included ureteric reflux secondary to detrusor overactivity, poor bladder compliance, and direct detrimental effects of ketamine metabolites on the upper tract urothelium causing ureteric stricture. Histopathological studies demonstrated squamous metaplasia, intestinal metaplasia, nephrogenic metaplasia, and calcification of the ureter [18]. The presence of papillary necrosis in some patients indicated a process of significant ongoing transmural inflammatory changes [5]. Acute renal failure requiring dialysis occurred in severe cases owing to accumulation of ketamine metabolites in both ureters [19]. More sinister disease course with end-stage renal failure was reported in a handful of ketamine abusers in Hong Kong [20].

Urological evaluations of ketamine abusers should start with non-invasive tests. Use of invasive evaluation modalities should be reserved for selected and indicated patients as these would bring considerable discomfort to patients who already had bladder pain to start with. Quantification of baseline voiding function and symptoms should be made by frequency-volume chart and pelvic pain and urgency / frequency (PUF) symptom scale [21]. The Chinese version of PUF symptom scale was validated to be used in ketamine abusers in Hong Kong with proven ease of administration and discriminatory ability [21].

Non-invasive uroflowmetry test served as a valuable

preliminary assessment tool for voiding dysfunction. Mid-stream urine test for bacterial culture would exclude concomitant bacterial infection. Serum renal function test should be mandatory as it would alter the reconstructive management options. Ultrasound scan of the urinary system served as a useful tool for risk stratification, as thickened bladder wall, when accompanied by hydronephrosis of the kidneys might indicate more stringent follow-up schedule and escalation of treatment strategy.

Videourodynamic study combined functional and anatomical evaluation of the urinary tract, but its invasiveness and associated discomfort made it unpalatable to most patients. It should be reserved for selected patients, particularly before offering invasive treatment options. Figure 3 showed the urodynamic tracing of a patient with extremely contracted bladder with poor bladder compliance. The detrusor pressure (Pdet) rose up to 40cm H₂O when the bladder volume was filled to 50ml. The addition of fluoroscopy to urodynamic study provided valuable information regarding the upper tract status. Figure 4 showed the fluoroscopic image of the same patient: an irregularly contracted bladder outline, bilateral vesico-ureteric reflux due to poor bladder compliance, and bilateral distal ureteric stricture with bilateral hydroureters.

RISK ASSESSMENT FOR UPPER TRACT DAMAGE

One of the primary goals of management in ketamine uropathy lied at the prevention of upper urinary tract damage. Convenient and non-invasive means of assessment facilitated acceptable and on-going risk assessment for the upper urinary tract.

The Chinese version of PUF symptom scale was well studied in the local Hong Kong population of ketamine abusers. The scale was proven to be reliable and easy to use. The PUF symptom scale excelled in its discriminatory ability, regarding symptom severity and chance of positive findings in more invasive urological investigations, including hydronephrosis and deranged renal function. A score of 16 or above was shown to have a 100% sensitivity of predicting urodynamic abnormality

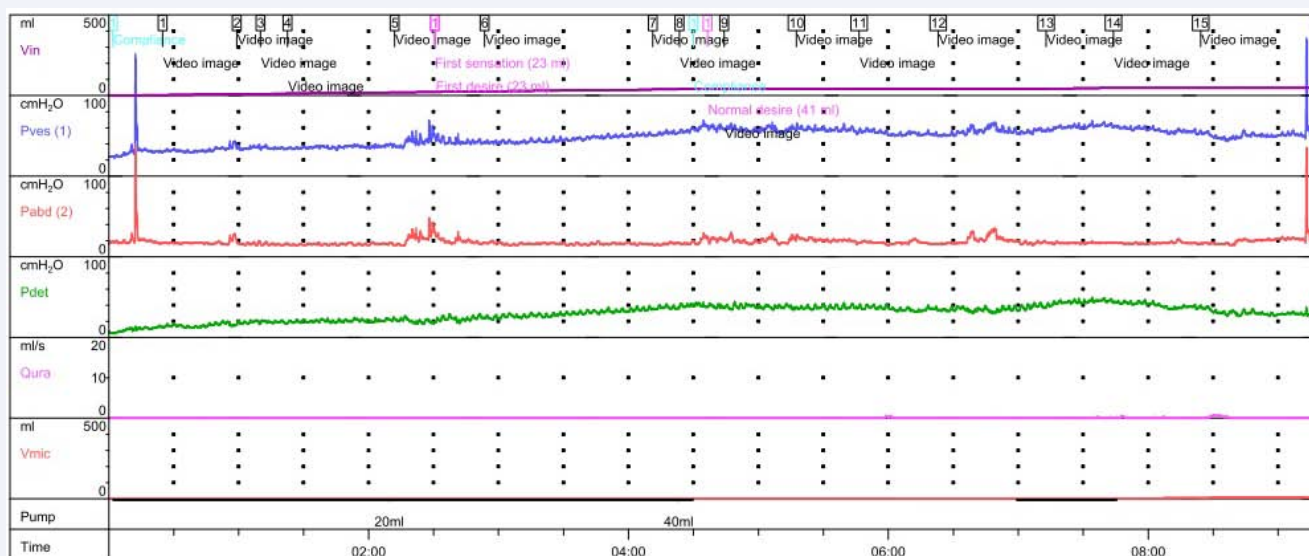


Figure 3 Urodynamic tracing of a patient with extremely contracted bladder with poor bladder compliance.



Figure 4 Fluoroscopic image showing an irregularly contracted bladder outline, bilateral vesico-ureteric reflux due to poor bladder compliance, and bilateral distal ureteric stricture with bilateral hydroureters.

or hydronephrosis [21]. The PUF symptom scale served as a convenient and sensitive initial risk assessment tool before proceeding to more invasive means of evaluation.

A more comprehensive review of local data suggested that parameters pertaining to the presence of hydronephrosis included age, functional bladder capacity, impaired liver enzyme level, and elevated serum creatinine [22]. Presence of one or more of these parameters remained a trigger for early detection of upper urinary tract damage, and early intervention in order to halt the progression of ketamine uropathy.

Contrary to intuitive thinking, the duration of ketamine abuse or expenditure on ketamine acquisition were not accurate in risk assessment for upper urinary tract damage. These parameters were not predictive because of recall error by patients, possibility of individual variation in vulnerability to ketamine metabolites, habit of sharing ketamine among peers and presence of inconsistent impurities in ketamine powder [21].

MANAGEMENT OPTIONS AND DEVELOPMENT OF SUCCESSFUL CARE MODELS

Outreach clinic and community engagement

One of the most difficult aspects in management of ketamine uropathy lied in the hidden nature of drug abusers, and their lack of motivation to seek medical attention. Upon the surge in number of reported drug abusers in 2009, a night outreach clinic was set up to target the young drug abusers. The team comprised urologists, urology nurses, psychiatrists, social workers and other volunteers. The team set out to reach the community of drug abusers from 11pm to 2am. They provided direct conversation and health screening to encountered drug abusers.

The awareness of the detrimental effects of substance abuse motivated abusers to quit and to seek medical care. In 2011, the service expanded to outreach mega-clinics set up at designated community centers conveniently located near various housing estates. At these mega-clinics, more comprehensive assessment was provided, which included body mass index, uroflowmetry, cognitive functioning, urological assessment and psychiatric assessment.

With the success of the outreach clinic, a hospital-based center was established in collaboration with various community-based non-governmental organizations. This hospital-based center served as a bridge between treatment and rehabilitation. While community-based organizations were responsible for identification and referral of drug abusers, the hospital-based center attended to the individual need with specialist-led multi-disciplinary assessment and rehabilitation. The assessment team comprised urologists, hepatobiliary surgeons, urology nurses, and occupational therapists. Intensive counselling and motivational interview were provided. Family members and social workers were engaged to further enhance the continuity of abstinence from drug abuse.

Through an online platform, ex-substance abusers assumed the role as peer counsellors. In collaboration with medical and rehabilitation professionals, these peer counsellors had an indispensable role in uncovering and engaging hidden substance abusers. The keys to success in these community outreach program were accessible care model, territory-wide access points, and service continuity.

Patient empowerment clinic led by urology nurses

Nursing interventions for ketamine abusers complemented medical or surgical intervention for ketamine uropathy. Counselling, care and time devoted by urology nurses, in particular for young ketamine abusers, were just as important as the medication or surgical intervention offered by urologists. A busy general urology clinic was not an ideal setting to facilitate in-depth counselling, patient empowerment and care-giver engagement. The hierarchy of doctor-patient relationship sometimes muted the young and shy patients. Urology nurses, on the other hand, served as amiable, non-judgmental care-givers and friends. Their dedication, patience and support were vital in establishing a trusting and long-lasting relationship between ketamine abusers and healthcare providers.

In a nurse-led clinic set up for ketamine abusers, urology nurses were often the first healthcare providers who would meet the patients. Ample time was allowed to find out their stories and difficulties behind their substance abuse. In-depth counselling and education on harmful effects of drug abuse were provided. Patient empowerment, advice on behavioral modification, psychological support, and care-giver engagement were all key components of nursing interventions. Preliminary investigations including uroflowmetry, ultrasonography, blood and urine analysis were arranged as part of the risk assessment. First-line medical treatment including analgesia and anti-cholinergic medications were also offered. The keys to success of a nurse-led care model were dedicated personnel, early assessment and initiation of treatment, and prioritization of patients to be seen by urologists.

One-stop direct-access clinic

The hassle of having to approach different specialties to get their evaluation and treatment was a major deterrent for ketamine abusers to turn away from medical care. A direct-access one-stop clinic was established in 2011 to address this issue [14]. Direct-access enabled social workers, anti-drug organizations, and patients themselves to arrange an appointment without referral or prior medical assessment. This access model eliminated the barrier for ketamine abusers to seek medical care. The clinic combined the expertise of urologists, pediatric surgeons and internists to enable a comprehensive and non-invasive first-line assessment.

The one-stop clinic adopted a four-tier approach in managing ketamine-related uropathy [23]. First-line treatment included non-steroidal anti-inflammatory drugs, anti-cholinergic medications, phenazopyridine and various analgesic agents. Should their symptoms not be adequately controlled, second-line treatment included opioid analgesics and gabapentinoid agents. For patients who remained refractory to oral medications, third-line treatment with an 8-week course of intravesical instillation of sodium hyaluronate was offered. Fourth-line treatment included surgical interventions such as hydrodistension and augmentation cystoplasty. However, surgical interventions were only considered after 6-month abstinence from ketamine. The key to success of this one-stop clinic was its convenience and uniqueness to suit the behavioral characteristics of young ketamine abusers.

Intensive hospital-based treatment and rehabilitation program

To enhance the motivation and readiness of ketamine abusers for abstinence, a voluntary 5-day in-patient intensive hospital-based treatment and rehabilitation program was devised. During this 5-day program, patients would receive comprehensive urological and hepatobiliary assessment by respective medical professionals, as well as cognitive and emotional assessment by occupational therapists. Care-giver engagements including support to family members were explored. Structured coaching and motivational counselling by experienced occupational therapists were delivered to all patients to enhance their readiness and determination to quit substance abuse. The key to success of this in-patient program lied with its intensiveness and dedication.

CONCLUSION

Ketamine had been the most commonly abused drug in Hong Kong from 2006 to 2014. The recognition of ketamine uropathy as a distinct disease entity in Hong Kong began in 2007. Ketamine uropathy included damage to the bladder, ureters and kidneys. Urological evaluation of ketamine abusers began with non-invasive modalities including uroflowmetry and ultrasonography, these investigations served as risk assessment for upper tract damage. Different successful care delivery models - outreach clinic, nurse-led clinic, one-stop clinic, and in-patient program - shared a common core value of patience and care.

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