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Review article

Burden of ketamine cystitis in Chinese society☆

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ABSTRACT

Ketamine cystitis, also referred to as ketamine-induced uropathy, is a new clinical syndrome affecting primarily young to middle-aged ketamine abusers and has become a global phenomenon since its first reported series in 2007. A spectrum of urological destructions ranging from mild cystitis to severely contracted bladder, ureteric stricture, upper tract damage, and irreversible renal failure has been reported. This review considers the scope and burden of ketamine cystitis in the Chinese population in Asia, stating the current status of management pathway, and reviews our current understanding on the pathophysiology of ketamine-induced uropathy.

1. Prevalence of ketamine cystitis among a Chinese population

Since the first report of street ketamine-associated cystitis involving 10 young Chinese patients by the authors' team from Hong Kong in 2007,[1] more cases of the new clinical syndrome of ketamine cystitis were subsequently reported from other Chinese regions: Taiwan and China.[2,3] The first case series in mainland China was from Nanfong Hospital, Guangzhou, China in 2008.[2] As for Taiwan, the first reported case series was from Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan in 2009.[3] Extremely low market price and easy accessibility to the drug have made ketamine the drug of choice among young people.[4] Furthermore, cracking down of ketamine trafficking is particularly difficult, as it is legally produced and shipped for use in both human and veterinary medicines, which can be easily diverted for illicit purposes.[5] This legal availability may help explain why ketamine came to prominence as a recreational drug in the past number of years.

The exact prevalence of ketamine cystitis, however, is difficult to measure numerically, because many drug abusers are poly-substance abusers and most of them will not seek medical advice until they have severe symptoms. In addition, unless physicians have a high index of suspicion to identify ketamine abuse as a possible cause of lower urinary tract symptoms in young patients, the diagnosis will otherwise be missed. A rough estimation of the prevalence of ketamine cystitis among different Chinese populations, however, may be possible from the statistics published from respective government narcotic bureaus.

In Hong Kong, ketamine was first seized in 1999 and has been on top of the list of commonly abused psychotropic substances since 2001.[6] According to the Hong Kong Central Registry of Drug Abuse Sixty-third Report, which gathered information from various reporting agencies including local law enforcement departments, drug treatment and rehabilitation centers, counseling centers for psychotropic substance abusers, centers for drug counseling of nongovernment organizations, youth outreach teams of nongovernment organizations, and substance abuse clinics under the Hospital Authority, ketamine remained the most popular psychotropic substance being abused from 2004 to 2013, with a peak of > 5000 abusers in 2009 (Fig. 1). When stratified by age, the trend was also similar for young abusers under the age 21 years.[7] The actual number of young ketamine abusers in recent years, however, was not decreasing as it seemed to be, as more abusers are “hidden ketamine abusers”—51% of abusers younger than 21 years have admitted to have abused ketamine at home or at friend's home in 2013, which is a substantial increase from 13% in 2006.[8]

Regarding the proportion of ketamine abusers presenting with lower urinary tract symptoms, a small scale survey conducted by a psychotropic substance rehabilitation center in Hong Kong

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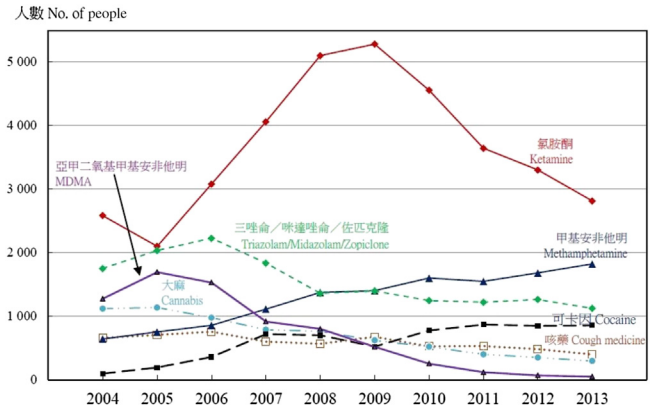

Fig. 1. Reported drug abusers of major types of psychotropic substances in Hong Kong.[7] MDMA = methylenedioxylmethamphetamine.

reported that ~30% of ketamine abusers had lower urinary tract symptoms.[9]

As for Taiwan, according to the National Bureau of Controlled Drugs, the 2014 International Narcotics Central Report, and local Taiwan Bureau, ketamine abuse has been a growing problem in Taiwan since 2008 and remains to be a popular party drug among teenagers because of its low potential for addiction and absence of criminal penalties for possession of a small amount (< 20 g). China is the source of ~76% of the ketamine seized or sold in Taiwan.[10–12]

According to China's National Narcotics Control Commission 2014 Annual Report on Drug Control in China, ketamine is the second most abused drug in China with seizures of 9.7 metric tons of ketamine in 2013, compared to 4.7 metric tons in 2012.[13]

All in all, if 30% of the ketamine abusers in China, Taiwan, and Hong Kong suffer from clinical manifestations of ketamine cystitis, not only does this greatly impair the health conditions of the affected individuals, but also imposes a huge burden on the public health system with increasing numbers of hospital admissions and dialysis requirements for possible upper tract damages.

2. Management of ketamine uropathy in Hong Kong Chinese population

2.1. Investigation pathway

A comprehensive clinical pathway has been established in some urology centers pioneering in the study of this syndrome in the region[9] (Fig. 2). This includes detailed documentation of symptomatology and quantification by questionnaires, blood tests (routine renal and liver function tests), urine tests (culture and toxicology), urinary system ultrasonography, uroflowmetry, flexible cystoscopy, video urodynamic study, and computed tomography for severe cases with possible upper tract involvement.

While pain symptoms can be represented by the widely used visual analog scale (VAS) of 1–10, more comprehensive quantification of the symptoms are documented using standardized frequency/voiding charts and the Pelvic Pain and Urgency/Frequency (PUF) symptom scale. Developed by Parsons et al,[14] the PUF symptom scale questionnaire has been validated and used in screening and diagnosing patients with interstitial cystitis. It comprises seven questions concerning day- and night-time frequency, pelvic/urological pain and its severity, and urgency and its degree of severity. A symptom score and a bother score are included, totaling a maximum of 35 points. In view of the clinical and histopathological resemblance between interstitial cystitis and ketamine cystitis,[15] centers in Hong Kong adopted the PUF symptom scale as an assessment tool for symptom quantification in these patients. A Chinese version of the PUF symptom scale (Fig. 3) has been validated, and correlations with the symptomatology and investigation results were evaluated.[16] In the series comprising 50 patients with a mean age of 24 years and a mean duration of ketamine abuse of 4.7 ± 2.8 years, the prevalence of urinary symptoms was as follows: urinary urgency (46 patients, 92%), frequency (42 patients, 84%), nocturia (44 patients, 88%), dysuria (43 patients, 86%), and hematuria (34 patients, 68%).[16] The same study suggested that higher mean PUF total scores were noted in patients with positive cystoscopic, urodynamic, and ultrasonographic investigation results, and a higher PUF score was associated with smaller bladder capacity. The cutoff value of 17 is suggestive of more serious urological sequelae: endoscopically confirmed cystitis (83% vs. 47%), detrusor instability (48% vs. 0%), vesicoureteric reflux (14% vs. 0%), poor bladder compliance (48% vs. 0%), and hydronephrosis (37% vs. 0%).

In a more recent series from the region involving 318 ketamine abusers with a mean duration of 81 months of ketamine use, the mean voided volume was 111 mL and the mean bladder capacity was 152 mL, with a mean bladder emptying efficiency of 73%.[17] In more severe patients, the typical voided volume can be < 50 mL, and these patients are napkin dependent because of severe urge incontinence. In our earlier series, in which video cystometrogram had been performed in 47 patients, the mean cystometric bladder capacity was 154.5 mL (range 14–600 mL), with 51% ($n = 24$) of the patients having a bladder capacity of ≤ 100 mL.[9] Most of the patients showed decreased bladder compliance and/or detrusor overactivity of different magnitudes at a very low bladder infusion volume (as low as 14 mL). Of the patients, 13% showed vesicoureteral reflux as a secondary event to the severely contracted bladder with high detrusor pressure. This finding correlated well with the symptoms of these patients, in that both functional and cystometric bladder capacities were markedly decreased, causing them to have very frequent small voids.

Cystoscopy examination aims to reveal if there are any inflammatory and cystitis changes and the cause of hematuria, if any. However, because of the small, painful bladder, this procedure is not well tolerated by patients with severe symptoms if performed under local anesthesia. To date, the largest series on cystoscopic findings on ketamine abusers from the region involved 42 patients, in which 30 patients had cystoscopy under local anesthesia, while the others had cystoscopy and transurethral resection biopsy under regional or general anesthesia.[9] All patients showed various degrees of epithelial inflammation of the bladder and neovascularization. Severe cases showed petechial hemorrhages, as classically described in patients with interstitial cystitis. Histologically, there is mucosal ulceration, striking urothelial reactive atypia, lamina propria inflammation with predominant lymphocyte infiltration, and a variable number of eosinophils. Ultrastructural examination by electron microscopy showed querciphylloid muscle cells (vacuoles at the periphery of muscle cells; Fig. 4). This feature has also been found in interstitial cystitis. In another UK series involving 17 patients in whom cystoscopy and bladder biopsies were performed, urothelial atypia with features mimicking carcinoma *in situ* was noted in a significant number of patients.[18] Marked urothelial atypia was seen in the biopsy specimens of 12 patients with nuclear enlargement and loss of polarity. Immunohistochemistry for CK20, p53, and Ki67 was performed in 10 cases, in which high expression of p53 was present in nine cases and that of Ki67 was present in six cases. However, none of the biopsy specimens showed expression of CK20 in the atypical urothelium, which would be against carcinoma *in situ*. In addition, squamous metaplasia, nephrogenic metaplasia, and calcification have been