

One-stop clinic for ketamine-associated uropathy: report on service delivery model, patients' characteristics and non-invasive investigations at baseline by a cross-sectional study in a prospective cohort of 318 teenagers and young adults

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Objective

To describe a service delivery model and report the baseline characteristics of patients investigated by a non-invasive approach for ketamine-associated uropathy.

Patients and Methods

This was a cross-sectional study in a prospective cohort of patients who attended their first visit and underwent non-invasive investigations at a dedicated centre to treat ketamine-associated uropathy in Hong Kong from December 2011 to July 2013. Data on demographics, illicit ketamine use, symptoms scores and voiding function parameters at baseline were prospectively collected. Differences between active abusers and ex-abusers, and risk factors for the most symptomatic group were investigated by univariate and multivariate analysis.

Results

In all, 318 patients completed the non-invasive assessment at their first visit and were eligible for inclusion. In all, 174 were female and the mean (SD) age of the entire cohort was 24.4 (3.1) years. Patients had used ketamine for a mean (SD) period of 81 (36) months. The mean (SD) ketamine use per week was 18.5 (15.8) g. In all, 214 patients were active abusers while 104 were ex-abusers but had persistent lower urinary tract

symptoms. The mean (SD) voided volume, bladder capacity, and bladder emptying efficiency were 111.5 (110) mL, 152.5 (126) mL and 73.3 (26.9)%, respectively. The ex-abusers had 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. Multivariate analysis found female gender was associated with a higher symptom score (odds ratio [OR] 2.39; 95% confidence interval [CI] 1.35–4.23; $P = 0.003$) and a smaller voided volume (OR 1.9; 95% CI 1.1–3.3; $P = 0.02$). Ketamine taken (g/week) was another risk factor for a higher symptom score (OR 1.03; 95% CI 1.01–1.05; $P = 0.002$). Status of ex-abuser was the only protective factor associated with fewer symptoms, larger voided volume and bladder capacity.

Conclusions

An effective service model for recruiting patients with ketamine-associated uropathy is possible. With such a service model as a platform, further prospective studies are warranted to investigate the appropriate choice of treatment for this new clinical entity.

Keywords

ketamine, ketamine-associated uropathy, ketamine-associated cystitis, lower urinary tract symptoms (LUTS)

Introduction

Ketamine has been well known for several decades for its use as a general anaesthetic agent in both human and veterinary

settings. Being a noncompetitive N-methyl-D-aspartic acid receptor antagonist, ketamine is metabolised by hepatic microsomal enzymes with the resultant metabolites being excreted in urine [1]. Ketamine has also been used safely in

chronic neuropathic and malignant pain management [2]. The association of ketamine with urinary tract damage came to light in 2007, when the first report from Canada described a syndrome characterised by severe LUTS in six young patients who had illicitly used ketamine as a recreational drug [3]. Subsequent reports in the following years have confirmed the emergence of this new clinical entity of ketamine-associated uropathy in Asia and the UK [4–8].

The published evidence has established the causal relationship between ketamine recreational use and injury to the urinary tract [5,9]. The urinary bladder is predominantly affected, although concomitant upper tract damage occurs in some patients [4,10]. The exact mechanism for the injury is not fully understood but emerging evidence suggests a receptor-mediated toxic effect of ketamine on the urothelium [11]. Patients present typically with LUTS including severe urgency, urinary frequency, intermittent haematuria, nocturia, dysuria, and bladder pain [3–8]. The typical cystoscopic findings show a contracted bladder with reduced capacity and erythematous cystitis. Bladder biopsies reveal denuded urothelium, reactive urothelial atypia, mixed inflammatory infiltrate rich in eosinophils, and fibrosis in the deeper lamina propria [3,4,12,13]. In Hong Kong, ketamine is the most popular illicitly used psychotropic substance [14]. An increase in ketamine use from 0.8% in 2007/2008 to 2.1% in 2010/2011 has also been noted among young people aged 16–24 years in the UK [11]. It is unquestionable that there is a growing demand for a urology service to manage patients with ketamine-associated uropathy, which may potentially become a heavy burden to the healthcare system. Cystectomy with neobladder construction and augmentation cystoplasty have been reported in extreme cases [5,15]. However, characteristics of patients other than the typical LUTS and cystoscopy findings are largely unknown and evidence-based recommendations on investigations and treatment for such patients are completely lacking in the existing literature, given the paucity of prospective clinical studies and quality data [11]. Prospective studies have been hampered by the difficulty in recruiting the patients who are always hidden youths in the community.

The Youth Urological Treatment Centre (YUTC) in Hong Kong was established in 2011 by the Department of Surgery of the Chinese University of Hong Kong after receiving funding and support from the Hong Kong Government. The mission of YUTC is to provide early urological assessment and treatment to young patients with ketamine-associated uropathy, and to formulate a practical and cost-effective management protocol by concentrating the experience in a single centre. In a national meeting focusing on ketamine-associated uropathy held in the UK in 2011, the attendees expressed their view that cessation is beneficial to patients [11]. A recent on-line survey among non-treatment-seeking ketamine abusers in the UK found

high-dose and frequent users had higher prevalence rates of LUTS [16]. We hypothesised in the present study that the severity of LUTS and voiding dysfunction among patients seeking treatment for ketamine-associated uropathy are associated with the dose and frequency of their ketamine use and their latest status of actively using ketamine or not. This report is the first of the YUTC with the objectives to describe the service delivery model and the baseline characteristics of the patients who were evaluated by a non-invasive approach.

Patients and Methods

The study was a cross-sectional study in a prospective cohort. All the consecutive patients who attended their first visit at the YUTC from December 2011 to July 2013 were recruited into a prospective cohort. The inclusion criteria for the present study were: (i) taking ketamine as a recreational drug for not less than 6 consecutive months and that the typical drug use frequency was not less than twice a month; and (ii) two or more LUTS in the last 3 months prior to the consultation visit. LUTS included haematuria, dysuria, urinary frequency, urgency, nocturia, suprapubic/pelvic/perineal pain. Patients who were known to have lower urinary tract pathology and had been symptomatic before their onset of ketamine abuse were excluded from the study. Active abusers in the present study were defined to be those who were still taking ketamine in the last 4 weeks before their first visit at the YUTC. Ex-abusers were those who had stopped taking ketamine for ≥ 4 weeks before the first visit. Ex-abusers were eligible to be recruited in the study provided that they fulfilled the inclusion criteria and had developed the symptoms before they stopped using ketamine and the symptoms persisted after cessation of ketamine use.

Service Delivery Model: Direct-Access Service

The YUTC works in partnership with other anti-drugs social service organisations in the whole territory. The anti-drugs social work services provide outreaching services and a voluntary residential programme to young ketamine abusers. The YUTC appointments are made through a hotline without the need of medical referrals or prior assessment by medical practitioners. Social workers and patients themselves are both welcome to call the YUTC hotline to make appointments. Social workers are encouraged to accompany their clients during the consultation visits.

Service Delivery Model: One-Stop Non-Invasive Assessment at Baseline

All the new patients were evaluated at their first visit by a standard protocol, which started with scoring the symptoms using the Pelvic pain and Urgency/Frequency (PUF) score questionnaire. The patients completed the questionnaires by themselves after simple explanation and instruction by our

urology nurse. The questionnaire has been validated and used before in evaluating patients with ketamine-associated uropathy [4]. The PUF score ranges from zero to 35, ≥ 15 is considered to represent significant symptoms. After the questionnaire assessment, the patients were asked to drink as much as they could tolerate and instructed to void in the uroflowmetry when they had a strong desire to void. The urology nurse performed the ultrasound (US) bladder scan to estimate the residual urine volume in the bladder immediately after the uroflowmetry test. The bladder capacity was calculated by adding the voided volume and the residual urine volume. Bladder emptying efficiency was estimated by dividing the voided volume over the bladder capacity and expressed as a percentage. The peak urinary flow rate, voided volume, bladder capacity and bladder emptying efficiency were recorded as the baseline voiding function parameters. A mid-stream urine sample was also saved for culture and blood was taken for renal biochemical tests. All the patients were given an appointment for US examination to be performed by two radiologists who were very experienced in urinary tract examination.

Urological Consultation

The patients were seen by one of the urologists who participated in this programme. A full history was taken by the urologist covering questions related to the details of ketamine use and the LUTS. The sequence of self-reporting in the PUF questionnaire by the patient, followed by measurement of voiding function parameters by a nurse, and finally a detailed ketamine use history taken by a urologist was to minimise the potential bias that would have favoured an overestimation of the LUTS severity and abnormal voiding function among those high-dose and frequent ketamine users. The diagnosis of ketamine-associated uropathy was made clinically after history taking, physical examination and interpretation of the voiding function parameters. Patients were counselled in the company of their social workers with regard to the diagnosis, the harmful effects of ketamine on the urinary tract and their abnormal voiding function parameters. The absolute and pressing need to cease ketamine use was emphasised to reduce irreversible urinary tract damage. We prescribed to our patients as first-line treatment an integrated anti-inflammatory therapy which was NSAIDs based. We used diclofenac sodium with histamine H2 blockers to reduce the gastrointestinal side-effects or cyclooxygenase 2 (COX-2) inhibitors as the anti-inflammatory agent. Additional anticholinergic agents and opioid analgesics were prescribed to those patients with more severe LUTS and pain symptoms. Upon follow-up assessment, patients who did not improve with the first-line treatment, despite ketamine cessation or significant reduction in ketamine use would be advised to proceed to further investigations including cystoscopy and urodynamic studies. Such patients were at high risk of having significant

irreversible damage to the urinary bladder. Patients with US evidence of hydronephrosis would undergo further investigation for VUR and ureteric strictures. Details of treatment, additional investigation results and treatment outcomes would be presented in subsequent reports when our on-going longitudinal studies are completed.

Study Variables, Groupings and Main Outcomes

At the first visit, we prospectively collected from each patient the following data: age, gender, duration of ketamine use, frequency and the typical amount of ketamine used per week in last 3 months, duration from the onset of LUTS, history of polysubstance abuse, PUF score, peak urinary flow rate, voided volume, bladder capacity, and bladder emptying efficiency. According to the priori definitions, patients were grouped to either active abusers or ex-abusers for investigating our hypothesis of the benefits of cessation. For ex-abusers the dose and frequency of ketamine use referred to the last 3 months before cessation. A PUF score ≥ 75 th percentile, a voided volume ≤ 25 th percentile and a bladder capacity ≤ 25 th percentile were selected to represent the three worst scenarios to investigate the association with any potential predictors.

Statistical Analysis

Continuous variables are expressed as the mean (SD) and/or median as appropriate. Categorical data are expressed in percentages as frequency/prevalence. The number of missing data for each of the study variables was deducted from the denominator for per protocol analysis. Active abusers were compared with ex-abusers in univariate analysis using the Student's *t*-test for continuous data with normal distribution and Mann-Whitney *U*-test for skewed data. Categorical data were compared using chi-squared or Fisher's exact test or trend test, as appropriate. A multivariable adjusted logistic regression model was used to investigate the association of different clinical parameters with a PUF score ≥ 75 th percentile, a voided volume ≤ 25 th percentile and a bladder capacity ≤ 25 th percentile. The covariates included in the model were duration of ketamine use, amount of ketamine use per week, gender, age, history of polysubstance abuse, the latest status of active abuser or ex-abuser. Independent risk factors are expressed as odds ratio (ORs) with 95% CIs. A $P < 0.05$ was considered to indicate statistical significant.

All the patients provided informed consent to the prospective collection of their data for analysis and the study was approved by the joint ethical committee of the university and the hospital.

Results

In all, 318 patients were prospectively recruited during the study period and were eligible for analysis. All of them took

ketamine by sniffing. In all, 174 (54.7%) were female. The mean (SD) age of the patients was 24.4 (3.1) years and patients had used ketamine for a mean (SD) period of 81 (36) months. The mean (SD) ketamine use per week was 18.5 (15.8) g. In all, 250 (78.4%) patients took ketamine daily and 315 (99%) of the study subjects took ketamine once or more per week. In all, 160 (50.3%) patients admitted a history of polysubstance abuse, although none of them had taken drugs other than ketamine regularly.

All 318 patients at their first visit completed the PUF score questionnaires, the non-invasive measurement of voiding function parameters, the blood tests and saved urine for culture. The patients had had LUTS for a median of 24 months. The mean (SD) PUF score for all the patients was 21.2 (7.8). The mean (SD) voided volume, bladder capacity, and bladder emptying efficiency were 111.5 (110) mL, 152.5 (126) mL and 73.3 (26.9)%, respectively. In all, 5% of patients had a positive urine culture for bacteria and 7.2% had renal impairment with a creatinine level of $>90 \mu\text{mol/L}$. Only 160 patients attended the US examination of the urinary tract by the radiologists. In all, 152 (95%) patients had thick-walled bladders on US and 13 (8.1%) had unilateral or bilateral hydronephrosis. Four of the 13 patients with hydronephrosis had renal impairment compared with only six of 147 patients (4.1%) without hydronephrosis ($P = 0.004$). US revealed calcification of the bladder wall in six patients (Table 1).

Active Abusers vs Ex-Abusers

In all, 214 patients were active abusers while the remaining 104 were ex-abusers according to the priori definition of the study. The ex-abusers had stopped ketamine use for a median period of 4 months. The two groups were comparable for age, gender, dose and frequency of ketamine use. However, the ex-abusers group had a lower mean PUF 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; $P < 0.001$) (Table 2).

Risk and Protective Factors

For all the patients the 75th percentile PUF score was 28, the 25th percentile voided volume was 35 mL and the 25th percentile bladder capacity was 60 mL. Multivariate analysis found female gender was significantly associated with a PUF score of ≥ 28 (OR 2.39; 95% CI 1.35–4.23; $P = 0.003$) and a voided volume of ≤ 35 mL (OR 1.9; 95% CI 1.1–3.3; $P = 0.02$). Ketamine taken per gramme per week (OR 1.03; 95% CI 1.01–1.05; $P = 0.002$) was another risk factor associated with a PUF score of ≥ 28 . On the other hand, status of ex-abuser at baseline was the only protective factor associated with significantly lower risks in developing the three worst scenarios (Table 3).

Table 1 Characteristics of the whole study population at baseline.

Variable	Value
Number of patients	318
Number of female patients (%)	174 (54.7)
Mean (SD, range) age, years	24.4 (3.1, 15–29)
Duration of ketamine use, months	
Mean (SD)	81.1 (36.2)
Median	78
Ketamine use, g/week	
Mean (SD)	18.5 (15.8)
Median	14
Frequency of ketamine use, n (%)	
Daily	250 (78.4)
1–6 days/week	65 (20.4)
< once/week	3 (0.9)
Prevalence of history of polysubstance abuse, n (%)	160 (50.3)
Prevalence of smoking, n (%)	273 (85.8)
Voided volume, mL	
Mean (SD, range)	111.5 (110.5–658)
Median	72
Bladder capacity, mL	
Mean (SD, range)	152.5 (126.9–744)
Median	106
Mean (SD) peak flow rate, mL/s	13.8 (8.3)
Mean (SD) bladder emptying efficiency, %	73.3 (26.9)
Mean (SD) PUF score	21.2 (7.8)
Prevalence of positive urine culture for bacteria, n (%)	16 (5)
*Prevalence of thick-walled bladder on US, n/N (%)	152/160 (95)
*Prevalence of hydronephrosis on US, n/N (%)	13/160 (8.1)
*Prevalence of bladder wall calcification on US, n/N (%)	6/160 (3.8)
Abnormal creatinine level of $>90 \mu\text{mol/L}$	23 (7.2)

*Only 160 patients attended the US examination of the urinary tract performed by radiologists at the time of analysis.

Discussion

The service of the YUTC is unique to fit the behavioural characteristics of young ketamine abusers who are always hidden in the community and passive in seeking help. A recent survey in the UK reported that only 2.9% ketamine abusers symptomatic for LUTS have been referred to urologists [16]. The service delivery model of the YUTC removes the potential barrier due to mandatory assessment by GPs before urological referrals. Encouraging social workers to make appointments for their clients further facilitates identifying the patients and provision of the necessary urological care for them. Existing literature has reported the use of cystoscopy with biopsy and urodynamic studies in investigating these patients [3–8,10,13]. We think that routine use of invasive investigation is not mandatory at the initial assessment when chronic ketamine abusers present with typical LUTS. It has been reported that many patients declined invasive procedures and young ketamine abusers are not reliable attenders at medical appointments [4,5]. We successfully evaluated all the study patients using a one-stop approach with non-invasive investigation tools. The symptom scores and the voiding function parameters were supportive to the diagnosis and useful for comparison upon follow-up. Our

Table 2 Comparison between active and ex-abusers at baseline.

Variable	Active abusers	Ex-abusers	P
Number of patients	214	104	
Number of female patients (%)	119 (55.6)	55 (52.9)	0.65
Mean (SD)			
age, years	24.7 (2.9)	24.4 (3.2)	0.26
duration of ketamine use, months	82.1 (35)	76.1 (40)	0.02
ketamine use, g/week	17.0 (10.1)	22.7 (22.9)	0.10
Frequency of ketamine use, n (%)			0.35
Daily	168 (78.5)	82 (78.8)	
1–6 days/week	46 (21.5)	19 (18.3)	
< once/week	0	3 (2.9)	
Prevalence of history of polysubstance abuse, n (%)	98 (45.8)	62 (59.6)	0.02
Mean (SD):			
Voided volume, mL	85.4 (90.7)	126.5 (97)	<0.001
Bladder capacity, mL	126.7 (105.7)	204.8 (147)	<0.001
Peak flow rate, mL/s	12.6 (8.2)	15.9 (7.4)	<0.001
Bladder emptying efficiency, %	66.2 (29.6)	74.3 (25)	0.09
PUF score	24.1 (6.4)	19.3 (8.2)	<0.001
Prevalence of positive urine culture for bacteria, n (%)	13 (6.1)	3 (2.9)	0.22
*Prevalence of hydronephrosis on US, n/N (%)	10/106 (9.4)	3/54 (2.9)	0.40
Abnormal creatinine level of >90 µmol/L, n (%)	14 (6.5)	9 (8.7)	0.5

*Only 160 patients had attended the US examination of the urinary tract performed by radiologists at the time of analysis.

Table 3 Risk and protective factors in multivariate analysis.

	OR (95% CI); P		
	PUF score ≥28 (75th percentile)	Voided volume ≤35 mL (25th percentile)	Bladder capacity ≤ 60 mL (25th percentile)
Female gender	2.39 (1.35–4.23); 0.003	1.90 (1.10–3.31); 0.02	
Ketamine use, g/week	1.03 (1.01–1.05); 0.002		
Status of ex-abusers at baseline	0.28 (0.13–0.57); 0.001	0.14 (0.06–0.33); <0.001	0.33 (0.17–0.64); 0.001

approach provides excellent comfort and convenience to the patients and is practical to collect useful clinical information at baseline.

A survey among British urologists suggested that LUTS does not always improve after cessation and in some patients symptoms may remain or worsen over time [17]. The finding that one-third of our patients had already ceased ketamine use supports this observation. We think that the LUTS experienced by ketamine abusers are attributable to both the inflammatory process of cystitis and fibrosis as a sequel to inflammation [3,4,9,13,18]. Cessation may partly resolve cystitis. The residual cystitis together with the irreversible fibrotic changes of the bladder wall contributes to the persistent symptoms despite cessation of drug use. Nevertheless, it is reassuring from the present findings that ex-abusers were less symptomatic than active abusers and cessation of ketamine use was an independent protective factor among the symptomatic patients. The prevalence of persistent LUTS among the ex-abusers and its natural course over time of cessation are poorly understood from existing literature. A study of 36 female ex-abusers with LUTS found

spontaneous improvement in urinary frequency at 3 months after study entry, although the voiding functions remained abnormal compared with the non-abusers control group [19]. Further studies are warranted to investigate how the symptomatic ex-abusers benefit from further urological treatment.

The diminished voided volumes and bladder capacities of the present patients as demonstrated by non-invasive tools agree with previously published findings when invasive investigations were used [3,4,6–8]. We have also found that ineffective bladder emptying is another feature of ketamine-associated uropathy, which has not been described previously. In its presence maximal voided volume documented in frequency–volume charts does not reliably reflect the bladder capacity. It may not be realistic to expect young ketamine abusers to return their frequency–volume charts upon follow-up. Measuring the voided volume when the patient experiences a strong desire to void followed by estimating the residual urine volume in each visit appears to be more practical to evaluate the progress of this unique group of patients and their response to treatment. Our

on-going longitudinal studies may provide clues as to whether ineffective bladder emptying can be reversed after treatment and cessation.

The 5% of positive urine cultures in the present patients is consistent with existing knowledge that the uropathy is chemically induced and bacterial infection is likely to be a secondary event. The constant radiological findings of a thickened bladder wall have been demonstrated in the present study and reported by others [10]. We encountered less hydronephrosis than previous a report [4]. Hydronephrosis occurs secondary to reduced compliance of the contracted bladder or ureteric stricture associated with retroperitoneal fibrosis [4,10]. Although only half of the present patients attended the US examination, our finding of the association of hydronephrosis with renal impairment still provides support that its presence may suggest a later stage of the disease. We agree with the postulation that a lower incidence of upper tract involvement is probably a result of early medical attention [10], and in the present study may be attributed to the service delivery model that facilitates identification of the patients at a relatively early stage of their disease. It is interesting that six patients had bladder-wall calcification shown by US, which has not been reported before. Microscopic calcification was found in one bladder biopsy specimen reported in the literature [12]. We think that calcification is another but uncommon event secondary to the ketamine-induced injury of the bladder wall. Further studies are warranted to investigate if the presence of hydronephrosis, bladder-wall calcification and renal impairment at baseline carry any prognostic implications that influence treatment outcomes.

A dose–frequency relationship of ketamine use with LUTS has been suggested previously [16]. To date, the critical amount of ketamine exposure that would result in uropathy is unknown. A systematic review on the use of ketamine on chronic pain management did not find any literature reporting LUTS as side-effects among adult patients receiving orally a daily dose of 30–1000 mg [2]. In a paediatric case report, a 16-year-old girl developed cystitis symptoms after taking ketamine orally at 8 mg/kg body weight for neuropathic pain [20]. The chronic and high-dose consumption of ketamine among the present patients are in marked contrast to the therapeutic dosage used in clinical settings. We found an increase in ketamine use (g/week) was associated with a higher PUF score. The present study is the first to show in a prospective cohort of treatment-seeking patients that the higher the dose and/or frequency of ketamine use the worsening of the LUTS. Together with the finding of cessation of ketamine use being a protective factor, our present results support the rationale that counselling the patients to sustain abstinence from ketamine or at least to reduce drug use should be the mainstay in any urological treatment programme for ketamine-associated uropathy.

It was an unexpected finding in the present study that female gender was associated with more severe LUTS and a smaller voided volume. Existing data, all from small case series, have not reported any gender difference among treatment-seeking patients. A recent survey conducted in the UK of 1285 ketamine abusers did not find any gender difference in the prevalence of LUTS. The present study population was quite different from the UK study, which recruited a self-nominating non-treatment-seeking population [16]. We think our present finding is worthy of note given that the female gender being a risk factor was derived from a large prospective cohort, whether we measured subjectively by the symptoms or objectively by voiding function. It may or may not be a coincidence that females are also more commonly affected by interstitial cystitis/bladder pain syndrome(IC/BPS), which shares similar histological and clinical features with ketamine-associated uropathy but of different aetiology [21,22]. The current theory for the development of IC/BPS is diffusion of toxins from urine to the submucosa after injury or dysfunction of the urothelium resulting in neurogenic inflammation, sensory nerve activation, pain and fibrosis [21]. It is possible that females may be more susceptible to urothelium injury, whether by the toxic effect of ketamine or other unknown aetiological agents in cases of IC/BPS. In Hong Kong, the male-to-female ratio of ketamine abusers has remained at 2–3 to 1 [14]. The fact that we had more female patients might be attributable to both the greater readiness of females to seek medical help and the tendency for female ketamine abusers to develop more bothersome LUTS.

Prior to the present study, the largest published series was a retrospective study describing the clinical presentations of 59 patients [4]. A total of ≈200 cases have been published globally to date [11]. The present study presents the largest patient number ever reported and to the best of our knowledge is the first prospective study on patients seeking treatment for ketamine-associated uropathy in a single centre. We certainly acknowledge the limitations of the present study, including the self-reporting of dose and frequency of ketamine use, uncertainty about the purity of ketamine, and the possibility of confounding effects from polysubstance use. The non-invasive investigation did not provide cystoscopic and histological proof of ketamine-induced cystitis. Our study population may have been biased by having only those who willingly sought urological treatment. The generalisation of our findings is uncertain, as our present study subjects were high-dose frequent ketamine users with a long history and the behavioural patterns of drugs abuse have social, cultural, racial and geographical variations.

The present report illustrates a practical and effective model to evaluate a unique group of young patients with ketamine-associated uropathy. The unprecedentedly large recruitment of patients is encouraging to everyone who is enthusiastic about this topic but has been frustrated by the

difficulty in identifying patients. The one-stop clinic using a non-invasive approach provides the hidden abusers with an easy access service, a comfortable and efficient evaluation at the initial assessment. Our present findings of the protective role of cessation of ketamine use and the association of increase in the amount of ketamine use with more severe lower urinary tract dysfunction support beyond doubt that immediate and sustained cessation of ketamine use is the mainstay in any urological treatment for ketamine-associated uropathy. Nevertheless, difficult questions remain as to what treatment to which patient, whether symptomatic ex-abusers and active abusers respond differently to the same treatment, and what factors would affect the treatment outcomes while awaiting the results of on-going studies by us and other investigators which may provide some clues. To better tackle the challenging issue of ketamine-associated uropathy, continuous efforts are definitely warranted from all stakeholders including the government, the social work services and urological care providers.

Authors Contribution

Y.H.T., C.F.N. and P.B.L. received government funding to establish the centre. Y.H.T. and C.F.N. designed the service model and the study. Y.H.T., C.F.N., P.B.L., G.L.W., V.W.W. and H.L.C. were in the core team for sustainable development of the centre. Y.H.T., C.F.N., K.K.P. and C.H.Y. participated in patient management and data collection. W.C.C. and V.V.L. performed the US examinations. Y.H.T., C.F.N., G.L.W., V.W.W. and H.L.C. interpreted the findings. Y.H.T. wrote the draft of the manuscript. All authors contributed to the critical revision of the manuscript and approved the final version for submission.

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Conflicts of Interest

All the authors declare that they have no competing interests. None of the authors have any financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years. There are no other relationships or activities that could appear to have influenced the submitted work.

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Abbreviations: IC/BPS, interstitial cystitis/bladder pain syndrome; PUF, Pelvic pain, Urgency/Frequency (score); US, ultrasound/ultrasonography; YUTC, Youth Urological Treatment Centre.