

Final Report to the Beat Drugs Fund Association

Project Title

A targeted urological treatment program for secondary school students abusing psychotropic substance and a territory-wide school-based survey of bladder dysfunction symptoms associated with psychotropic substance abuse (BDF101012)

Prepared & Submitted

by

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Executive summary

Ketamine-associated uropathy is an emerging clinical entity characterized by severe lower urinary tract symptoms(LUTS) as a result of illicit ketamine use. Although the exact mechanism of injury to the urinary tract is not fully understood, it is a kind of chemical-induced inflammation predominantly affecting the urinary bladder. Patients usually have severe urinary frequency, urgency, painful haematuria, bladder pain and very small voided volumes. Cystoscopic findings always show a contracted bladder with reduced capacity and cystitis changes. Prospective data on patients seeking treatment for ketamine-associated uropathy is lacking in existing literature. There are no evidence-based recommendations on investigations and treatment for such patients. It has been reported that cessation of ketamine use alone does not improve the symptoms in every patient.

Youth Urological Treatment Centre(YUTC) was established in 2011 by the Department of Surgery of the Chinese University of Hong Kong after receiving the funding support from the Beat Drugs Fund of Hong Kong SAR Government. The mission of YUTC is to provide early urological assessment and treatment to young patients suffering from ketamine-associated uropathy, and to formulate a practical and cost-effective management protocol by concentrating the experience in a single centre. The unique service model of YUTC which collaborates with NGOs has benefited over 300 patients within two years. The non-invasive investigation approach adopted in YUTC is well tolerated by patients and provides useful information both in the initial assessment and after treatment to evaluate outcomes. Our findings suggest that female gender and increase in dose/frequency of ketamine use are associated with more severe LUTS and poorer voiding function before treatment. Almost half of the active abusers who have developed ketamine-associated uropathy symptoms have abnormal liver function. An integrated anti-inflammatory therapy composed of oral medications improves the urological symptoms in more than half of the patients. Cessation of ketamine use significantly enhances the response to treatment and gives the best chance to improve voiding function while the longer history of ketamine use is associated with poor treatment outcomes.

A population-based survey among local secondary school students was also conducted from Jan 2012 to Jan 2014 to investigate the difference in prevalence of LUTS between those with and those without psychotropic substance abuse. 12,350 students from 45 schools participated in the study. The findings suggest a significantly higher prevalence of LUTS among psychotropic substance abusers in comparison to normal control population with no history of substance abuse. Ketamine is the most commonly abused substance among the students and ketamine abusers experience more LUTS than abusers of other psychotropic substances. Female ketamine abusers tend to have more LUTS than male ketamine abusers.

報告摘要

與吸食氯胺酮有關的尿路病變是新興的臨床病症，其特點是由吸食氯胺酮而引起的下尿道症狀。雖然現時尚未能完全了解氯胺酮損害泌尿道的機制，但已知膀胱顯著地被化學物質引致的發炎反應所影響。病人通常會有嚴重的尿頻、尿急、疼痛的血尿、膀胱痛及非常少的排尿量。膀胱鏡檢查發現病人的膀胱收縮而容量減少及有膀胱發炎。現時缺乏文獻刊載關於與吸食氯胺酮有關的尿路病變的病人的前瞻性數據。因此，沒有以數據為基礎的建議可為這類病人提供檢查及治療。曾經有報告指出單單是戒除吸食氯胺酮並未能改善所有病人的症狀。

在香港特區政府轄下的禁毒基金的經濟支持下，香港中文大學外科學系在2011年成立青少年泌尿治療中心（中心）。中心的使命是為年青而患有與吸食氯胺酮有關的尿路病變病人提供早期的泌尿系統檢查及治療，及透過將經驗集中在同一中心來制定一個可行及具成本效益的疾病管理方案。中心與非政府組織合作的獨特模式已在兩年內惠及超過三百名病人。病人能良好地承受中心採用的低介入性檢查方法，此方法同時能提供有用的首次檢查及完成治療後的資料來評估研究成果。我們的研究發現指出女性及增加吸食氯胺酮的劑量 / 次數與較嚴重的下尿道症狀有關以及在治療前排尿功能較差。接近一半有與吸食氯胺酮有關的尿路病變的持續濫藥者肝臟功能異常。由口服藥物組成的綜合消炎治療能改善過半數病人的泌尿系統症狀。戒除吸食氯胺酮能有效地增強病人對治療的反應及給予患者最佳的機會以改善排尿功能。同時，較長時間吸食氯胺酮則與治療效果欠佳有關。

我們在2012年1月至2014年1月期間進行了一項全港性本地中學生問卷調查，調查旨在研究曾濫用及未曾濫用精神毒品人士之間下尿道症狀盛行率的分別。45間學校共12350個學生參與了是次調查。調查數據指出曾濫用精神毒品人士的下尿道症狀盛行率顯著地比未曾濫用精神毒品人士高。氯胺酮是學生之間最常被濫用的毒品及氯胺酮濫用者比其他精神毒品濫用者有更多的下尿道症狀。女性氯胺酮濫用者則傾向比男性氯胺酮濫用者有更多的下尿道症狀。

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 metabolized 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 characterized by severe lower urinary tract symptoms(LUTS) in 6 young patients who had illicitly used ketamine as 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 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 receptor-mediated toxic effect of ketamine on 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. The bladder biopsies reveal denuded urothelium, reactive urothelial atypia, mixed inflammatory infiltrate rich in eosinophils, and fibrosis in deeper lamina propria.[3,4,12,13]

In Hong Kong, ketamine is the most popular psychotropic substance illicitly used.[14] An increase in ketamine use from 0.8% in 2007/8 to 2.1% in 2010/11 has also been noted among 16-24 year-olds in UK.[11] It is unquestionable that there is a growing demand for urology service to manage patients suffering from 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, evidence-based recommendations on investigations and treatment for such patients are lacking in existing literature given the paucity of prospective clinical studies and quality data as hampered by difficulty in recruiting patients.[11]

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 the funding support from the Beat Drugs Fund of Hong Kong SAR Government. The mission of YUTC is to provide early urological assessment and treatment to young patients suffering from ketamine-associated uropathy, and to formulate a practical and cost-effective management protocol by concentrating the experience in a single centre. This report covers both the urological treatment program at YUTC and a population-based survey of LUTS among secondary school students with and without illicit drug use.

Study objectives and Hypotheses

1. To investigate the effectiveness of YUTC service delivery model. We hypothesized that a unique and tailor-made service delivery model which fits the behavioral characteristics of young ketamine abusers is effective in recruiting patients and increases acceptance among patients.
2. To investigate the baseline characteristics of patients with ketamine-associated uropathy who were evaluated by a non-invasive approach. We hypothesized that the severity of LUTS and voiding dysfunction among patients seeking treatment for ketamine-associated uropathy are associated with the duration, dose and frequency of their ketamine use and their status of actively using ketamine or not at baseline.
3. To investigate the response to integrated anti-inflammatory therapy composed of oral medications. We hypothesized that a significant proportion of patients benefit from such therapy and the response to treatment is affected by the duration, dose and frequency of ketamine use and the status of actively using ketamine or not after receiving the treatment.
4. To investigate the difference in the prevalence of LUTS among secondary school students with and without psychotropic substance abuse. We hypothesized that students who have ever abused psychotropic substance have a higher prevalence.

Methods(Urological treatment program at YUTC)

I.Study Design & Participants Recruitment

There were two parallel clinical research projects at YUTC. The first was a cross-sectional study to investigate the patients' characteristics at baseline in a cohort recruited prospectively. The second was a longitudinal observational cohort study to investigate the response to integrated inflammatory therapy. All the consecutive patients who attended their first visit at YUTC were recruited into this prospective cohort. The inclusion criteria for the present study were (i) taking ketamine as recreational drug for not less than 6 consecutive months and the typical drug use frequency not less than twice a month; and (ii) two or more LUTS in the last 3 months prior to the consultation visit. LUTS included intermittent haematuria, dysuria, urinary frequency, urgency, nocturia, suprapubic/pelvic/perineal pain. Patients who were known to have lower urinary tract pathology and had been symptomatic prior to 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 prior to their first visit at YUTC. Ex-abusers were those who had stopped taking ketamine for at least 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.

II.Service Delivery Model: Direct-access service

YUTC works in partnership with other anti-drugs social service organisations in the whole-territory. The anti-drugs social work services provide outreaching service and voluntary residential program to young ketamine abusers. 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.

III. Service Delivery Model: One-stop non-invasive assessment at baseline

All the new cases were evaluated by a standard protocol which started with symptoms assessment by our specialist urology nurse using the Pelvic pain and Urgency/Frequency(PUF) score questionnaire. The questionnaire has been validated and used before in evaluating patients with ketamine-associated uropathy.[4] The PUF score ranges from 0-35, 15 or above is considered to have significant symptoms. The patients were then 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 research nurse performed the ultrasound bladder scan to estimate the residual urine volume in the bladder immediately following 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 in percentage. The voided volume, bladder capacity and bladder emptying efficiency were recorded as the baseline voiding function parameters. 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 ultrasound examination of the urinary tract to be performed by radiologists the other day.

IV. Urological consultation, Integrated Ant-inflammatory therapy and Follow-up assessment

The patients were seen by one of the urologists who participated in this programme. The diagnosis of ketamine-associated uropathy was made clinically following history taking, physical examination and interpretation of the voiding function parameters. Patients were counseled in the company of their social workers with regard to the diagnosis, the harmful effects of ketamine on urinary tract and their abnormal voiding function parameters. The absolute and pressing need to cease ketamine use was emphasized to reduce irreversible urinary tract damage. We prescribed an integrated anti-inflammatory therapy as first-line treatment to patients. The therapy was based on non-steroidal anti-inflammatory drugs(NSAIDs). Additional analgesics and anticholinergic agents were prescribed if clinically indicated at the discretion of the urologists. Selected patients would be advised to proceed to further investigations including cystoscopy, urodynamic studies and CT urogram upon follow-up assessment. Upon follow-up, patients were reassessed clinically for any subjective symptomatic improvement by global response, as well as objectively by repeating PUF score and uroflowmetry assessment. The status regarding the use of ketamine was reassessed. Cessation of ketamine use was defined by stopping use of ketamine for 4 weeks or more prior to the follow-up visit.

V. Study variables, Groupings and Main outcomes

For the cross-sectional study at baseline, we prospectively collected from each patient the following data at their first visit : 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, voided volume, bladder capacity, and bladder emptying efficiency. According to the priori definitions, patients were grouped to either active abusers or ex-abusers. For ex-abusers the dose and frequency of ketamine use referred to the last 3 months prior to cessation. A PUF score $\geq 75^{\text{th}}$ percentile, a voided volume $\leq 25^{\text{th}}$ percentile and a bladder capacity $\leq 25^{\text{th}}$ percentile were selected to represent the 3 worst scenarios to investigate the association with any potential predictors. The data at the latest follow-up were collected and analyzed in the longitudinal cohort study. Main outcomes were urological improvement by a decrease in PUF score from baseline ≥ 1 standard deviation(SD), or increase in voided volume/bladder capacity from baseline ≥ 1 SD. Patients were grouped into either persistent abusers or cessation of ketamine use according to their status at their latest follow-up.

VI. Statistical analysis

Continuous variables were expressed as mean with SD and/or median as appropriate. Categorical data were expressed in percentage as frequency/prevalence. Number of missing data for each of the study variable was deducted from the denominator for per protocol analysis. For baseline study, active abusers were compared with ex-abusers in univariate analysis using 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 $\geq 75^{\text{th}}$ percentile, a voided volume $\leq 25^{\text{th}}$ percentile and a bladder capacity $\leq 25^{\text{th}}$ 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 status of active abuser or ex-abuser. For the longitudinal study, persistent abusers were compared with the cessation group in univariate analysis and multivariable adjusted logistic regression model was used to investigate predictors for urological improvement. The covariates in the model included gender, age, duration of ketamine use, amount of ketamine use per week, history of polysubstance abuse and whether the patients had ceased ketamine use at their latest follow-up. Independent risk factors were expressed in odds ratio with 95% confidence intervals. A p-value of <0.05 was considered to be significant.

All the patients provided the informed consent to the prospective collection of their data for pooled analysis and the study was approved by the Joint CUHK-NTEC Clinical Research Ethics Committee.

Methods(Population-based secondary school survey)

I. Study design, Sample size estimation and Participants recruitment

This was a cross-sectional study which recruited participants from Jan 2012 to Jan 2014. The study sample size was estimated on the basis of the following assumptions derived from the existing literature[16-19]: i)the prevalence rates of LUTS among secondary school students who have and who

have not abused any psychotropic substances are 25% and 15% respectively; ii) the prevalence of psychotropic substance abuse among secondary school students is 4%.[20] An estimate of 5000 participants would be required to detect any difference while allowing a type 1 error of 0.05 and power 0.9. Assuming a response rate of 50%, a potential target of 10,000 participants would be required.

Based on the geographical distribution of the secondary schools serving local residents, 283 schools were randomly selected from Hong Kong Island(HKI), Kowloon(KIn) and New Territories(NT) in an approximate ratio of 1:2:3 in two batches, 142 schools in the first batch and 141 schools in the second batch. School management of each selected school was approached by invitation letters, telephone calls, and emails. School was invited to accept our visits with preventive education to the students and consider participation in the survey after the school visits. Finally 50 schools were visited and 45 agreed to participate in the study (HKI, n=7; KIn, n=13; NT, n= 25) giving a potential target of 16,000 participants.(Flowchart and Table 1)

Flowchart of school recruitment process

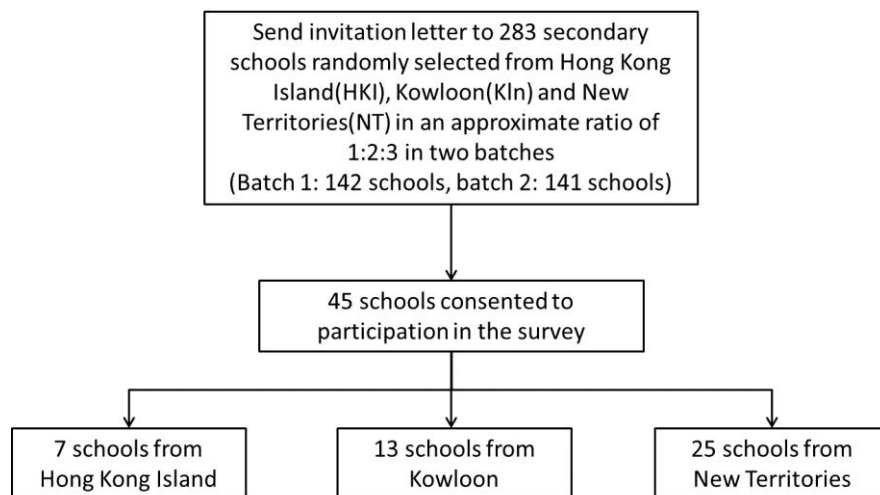


Table 1. Geographical distribution and profiles of participating schools

Geographical distribution	No. of schools
Hong Kong Island	7
Central And Western	1
Eastern	4
Islands	2
Kowloon	13
Wong Tai Sin	4
Yau Tsim Mong	3
Sham Shui Po	3
Kwun Tong	3
New Territories	25
North	3
Sai Kung	1
Sha Tin	9
Tai Po	4
Tuen Mun	8
Total	45

School profiles	No. of schools
Boys school	1
Girls school	2
Co-ed	42
Total	45
Aided	35
Direct Subsidy Scheme	4
Government	6
Total	45
Buddhism	3
Catholicism	6
Protestantism / Christianity	13
Taoism	1
Others	2
Not Applicable	20
Total	45

II. Evaluation instrument and Definitions of positive symptoms

The instrument used for the study was an anonymous self-reported questionnaire. The accompanying invitation letter explained the purpose of the study, the voluntary basis of participation and that participants consented to the study by completing and returning the questionnaire in the accompanying envelope.

There were two questions on participants' demographic data which included gender and age range. 7 questions asked about LUTS including urgency, urinary frequency, feeling of incomplete bladder emptying, straining at urination, intermittent urinary stream, dysuria and daytime urinary incontinence. The LUTS except for urinary incontinence were evaluated in terms of severity on a 6-point scale from i) never happens, ii) happens in <20% of time, iii) happens in 20-50% of time, iv) happens in 50% of time, v) happens in >50% of time and vi) happens in almost every void. Symptom was defined to be positive if it happened in 20-50% of time or more. Daytime urinary incontinence was evaluated by its frequency from i) never happens, ii) 1-3 attacks/month, iii) 1-2 attacks/week, iv) 3-6 attacks/week, v) happens every day. Daytime urinary incontinence was defined to be positive if it happened 1-3 times per month or more.

Regarding the psychotropic substance abuse, participants were asked a yes/no question whether they had ever used drugs illicitly and the types of substance being abused. Participants were allowed to check more than 1 type of commonly-abused substances which included ketamine, ecstasy, crystal methamphetamine(ice), cough mixture, marijuana and others.

III. Statistical analysis

Categorical data were expressed in percentage as frequency/prevalence. Rates of missing data would be calculated and excluded from analysis. Participants with and without psychotropic substances were compared and subgroups were further compared by gender and types of substance abused in univariate analysis using chi-squared or Fisher's exact test or trend test. A p-value <0.05 is considered to be significant.

The study protocol was approved by the Joint CUHK-NTEC Clinical Research Ethics Committee.

Results

I. YUTC patients at baseline

318 new patients were prospectively recruited at their first visit and were eligible for analysis in the cross-sectional baseline study. All of them took ketamine by sniffing. 174 (54.7%) were female. The mean age of the patients was 24.4 years (SD 3.1) and patients had used ketamine for a mean period of 81 months (SD 36). The mean ketamine use per week was 18.5g (SD 15.8). 250 (78.4%) patients took ketamine daily and 315 (99%) of the study subjects took ketamine once or more per week. 160(50.3%) patients admitted history of polysubstance abuse. All 318 patients completed the non-invasive assessment at their first visit. The patients had experienced LUTS for a median of 24 months. 41% had abnormal liver function parameters in biochemical tests, 8.1% had hydronephrosis and 5% patients had a positive urine culture for bacteria.

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 in age, gender, dose and frequency of ketamine use. The ex-abusers group, however, had a lower PUF score ($p<0.0005$), a larger voided volume ($p<0.0005$), a larger bladder capacity ($p<0.0001$) and lower prevalence of abnormal liver function ($p=0.001$)

Multivariate analysis found female gender (OR 2.39; 95%CI:1.35 to 4.23; $p=0.003$) and ketamine taken per gram per week (OR 1.03; 95%CI:1.01 to 1.05; $p=0.002$) were independent risk factors for a PUF score $\geq 75^{\text{th}}$ percentile. Female gender (OR 1.9; 95%CI:1.1 to 3.3; $p=0.02$) was also a risk factor for a voided volume $\leq 25^{\text{th}}$ percentile. Status of ex-abusers at baseline was found to be a protective factor against all 3 most symptomatic parameters (OR 0.14-0.33, $p<0.001$).[21,22]

II. YUTC patients at latest follow-up after integrated anti-inflammatory therapy

271 patients had received integrated anti-inflammatory therapy and returned at follow-up visits and were eligible for analysis in the longitudinal cohort study. Mean follow-up was 10 months(SD 7.8) and none of the patients experienced significant side effects. Overall 67.5% patients showed subjective improvement after integrated anti-inflammatory therapy. 128(47.2%) were persistent abusers and 143(52.8%) had ceased ketamine use. Among the 143 patients in the cessation group, 75(52.4%) were ex-abusers at baseline and represented sustained cessation while 68 patients had converted from active abusers at baseline to cessation at their latest follow-up. The persistent abusers group and cessation group were comparable in age, gender, history of polysubstance use, duration and dose of ketamine use, voiding function parameters and PUF score at baseline. The cessation group, however, had a lower PUF score($p<0.001$), a larger voided volume($p<0.001$) and a large bladder capacity($p<0.001$) in comparison to the persistent abusers after integrated anti-inflammatory therapy at the latest follow-up.(Table 2)

Table 2. Comparison between persistent abusers and those who had ceased ketamine use at their latest follow-up after receiving integrated anti-inflammatory therapy

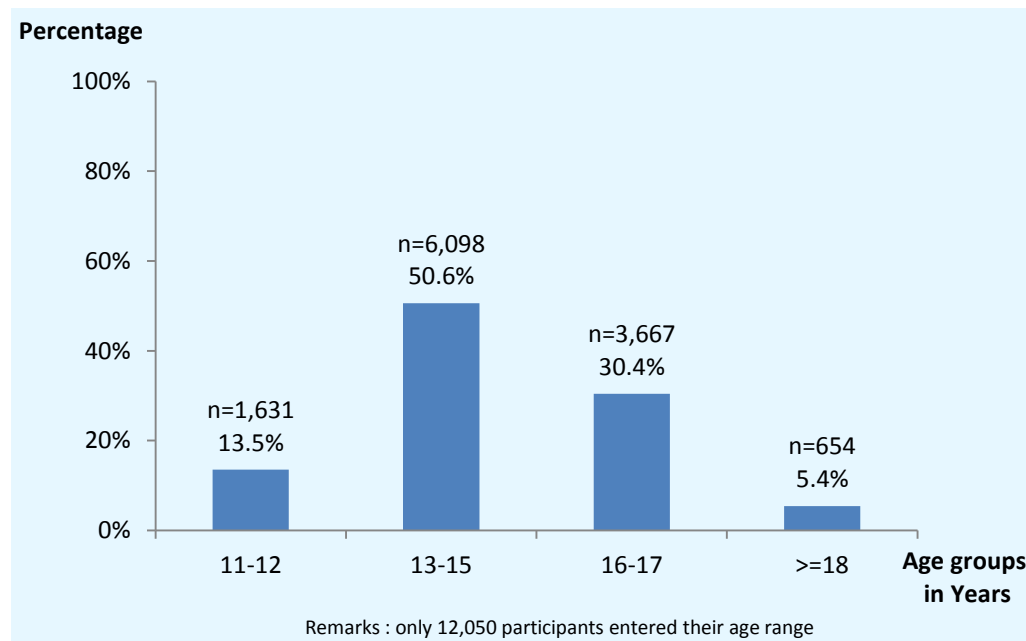
Mean ± SD Median [IQR]	Total no. of patients N=271(%)	Persistent Abusers N=128(%)	Cessation of ketamine use N=143(%)	P-value
Gender – Female	157 (57.9%)	80 (62.5%)	77 (53.8%)	0.175
Age at baseline(years)	25.2 ± 3.8	25.4 ± 3.3	25.0 ± 4.1	0.366
Status of ex-abusers at baseline	93 (34.3%)	18 (14.1%)	75 (52.4%)	<0.001
Polysubstance abuse	129 (42.6%)	59 (46.1%)	70 (49.0%)	0.714
Duration of Ketamine use(months)	80.5 ± 37.1 72 [48 – 120]	79.8 ± 37.7 72 [48 – 120]	81.1 ± 36.7 74 [48 – 120]	0.763
Ketamine use per week(grams) at baseline	18.2 ± 15.8 14 [7 – 24.5]	16.9 ± 11.5 14 [10 – 21]	19.3 ± 18.8 14 [7 – 24.5]	0.195
Baseline voided volume(ml)	100.2 ± 95.9 62.7[33.9-125.5]	92.2 ± 92.8 59.7[35.9-102.7]	107.4 ± 98.4 72.4[33.6-159.7]	0.195
Baseline bladder capacity(ml)	141.3 ± 112.8 98.6 [58 – 189.85]	133.98 ± 105.67 95.35 [58 – 185.2]	147.9 ± 118.9 105 [57.5 – 192.75]	0.316
Baseline bladder emptying efficiency(%)	71.86 ± 27.43	69.61 ± 28.07	73.88 ± 26.77	0.205
Baseline PUF score	22.2 ± 7.3 22.5 [17 – 28]	22.9 ± 6.9 23 [18 – 29]	21.5 ± 7.7 22 [17 – 28]	0.109
Latest PUF score	15.6 ± 7.8 15 [10 – 21]	18.6 ± 6.8 18 [14 – 24]	12.9 ± 7.7 12 [7 – 18.5]	<0.001
Latest voided volume(ml)	134.8 ± 115.7 94.6 [47.7 – 193.7]	92.8 ± 89.6 64.9 [31.3 – 119.6]	171.9 ± 123.6 140 [73.8 – 251.3]	<0.001
Latest bladder capacity(ml)	162.2 ± 125.8 125.9 [69.5 – 233.65]	119.6 ± 95.6 102.8 [51.7 – 156.3]	200.0 ± 137 172.2 [90 – 296.0]	<0.001
Latest bladder emptying efficiency(%)	82.9 ± 22.4	78.0 ± 25.6	87.3 ± 18.2	0.001
Global response at latest FU				<0.001
Improved	183 (67.5%)	64 (50.0%)	119 (83.2%)	
No change	50 (18.5%)	31 (24.2%)	19 (13.3%)	
Worsened	38 (14.0%)	33 (25.8%)	5 (3.5%)	

Multivariate analysis found the duration of ketamine use in months at baseline was negatively associated with improvement in voided volume and bladder capacity at the latest follow-up after treatment (for voided volume, OR 0.99, 95%CI:0.98-0.99, p=0.022; for bladder capacity, OR 0.99, 95%CI 0.98-0.99, p=0.037). Cessation of ketamine use was associated with improvement in voided volume (OR 5.58, 95%CI:2.63-11.85, p<0.0001), improvement in bladder capacity (OR 4.82, 95%CI:2.19-10.59, p<0.0001) and improvement in PUF scores (OR 2.85, 95%CI:1.69-4.80, p<0.0001) after integrated anti-inflammatory therapy.

III. Population-based secondary school survey

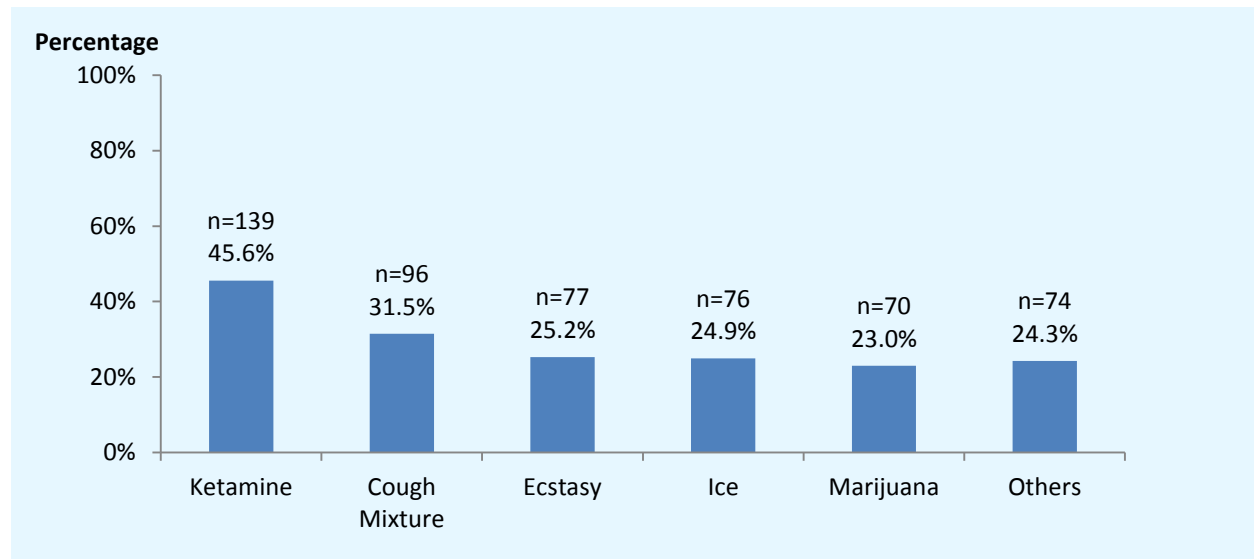
16,000 questionnaires were sent out and we received a return of 12,350 which were considered to be valid for analysis (response rate 77.2%). The participating schools response rate ranged from 68.5% to 100%. The rate of missing data for the questions varied from 0.5 to 5%. Missing data were excluded from analysis. There were similar number of male and female (male, n=6166; female, n=5928; male-to-female ratio 51:49) The age distribution of the participants was presented in Fig 1.

Fig. 1. Age distribution of the whole study population



Among 11,938 participants who had answered the question of “ever use” of psychotropic substances, 321(2.7%) had history of psychotropic substances abuse. 305/321 participants had answered the questions on the types of substance being abused. The most commonly-abused substance was ketamine(45.6%), followed by cough mixture(31.5%) and ecstasy(25.3%)(Fig 2).

Fig.2. Types of psychotropic substances abused among the 305 participants.



Remarks : some participants had abused more than one type of psychotropic substances

Comparing those with and without history of psychotropic substance abuse, participants with abuse history consisted of more males(62.3 vs 50.6%; $p < 0.001$), had a higher proportion of age ≥ 16 years(50.3vs35.8%; $p < 0.001$), and had a higher prevalence rates in all of the LUTS being evaluated($p < 0.001$)(Table 3)

Table 3. Comparison between those with and those without psychotropic abuse. *Missing data excluded from analysis.

	Non-abusers N=11617	Abusers N=321	P-value
*Age Groups			<0.001
11-12	1545 (13.4%)	37 (12.9%)	
13-15	5858 (50.8%)	105 (36.7%)	
16-17	3525 (30.6%)	99 (34.6%)	
>=18	602 (5.2%)	45 (15.7%)	
*Gender			<0.001
Male	5848 (50.6%)	192 (62.3%)	
Female	5703 (49.4%)	116 (37.7%)	
*LUTS			<0.001
No	9570 (84.0%)	175 (56.3%)	
Yes	1825 (16.0%)	136 (43.7%)	
*Incomplete Bladder Emptying			<0.001
No	10943 (94.6%)	224 (71.1%)	
Yes	628 (5.4 %)	91 (28.9%)	
*Urinary Frequency			<0.001
No	10372 (89.8%)	205 (65.5%)	
Yes	1180 (10.2%)	108 (34.5%)	
*Intermittent Stream			<0.001
No	11185 (97.2%)	227 (72.3%)	
Yes	320 (2.8%)	87 (27.7%)	
*Urgency			<0.001
No	11218 (97.1%)	231 (74.0%)	
Yes	338 (2.9%)	81 (26.0%)	
*Straining			<0.001
No	11318 (98.0%)	230 (73.7%)	
Yes	231 (2.0%)	82 (26.3%)	
*Dysuria			<0.001
No	11316 (98.2%)	229 (73.2%)	
Yes	210 (1.8%)	84 (26.8%)	
*Daytime Incontinence			<0.001
No	4142 (96.3%)	103 (81.1%)	
Yes	160 (3.7%)	24 (18.9%)	

Among the 305 participants who had completed the questions on the type of substances being abused, 139 had abused ketamine with or without poly-drug use. Comparing the ketamine abusers with another 166 participants who had abused substances other than ketamine, ketamine users experienced more LUTS except for daytime urinary incontinence($p<0.001$). Comparing female and male ketamine abusers, female had a higher prevalence of one or more LUTS(70.2 vs 42.5%, $p=0.002$).

Discussion

Principal findings

YUTC service delivery model successfully recruited substantial number of patients in a relatively short period and had all the study subjects completed the non-invasive assessment according to protocol. In addition to the diminished voided volume and bladder capacity, impaired bladder emptying was found to be another abnormal voiding function. One third of the patients at baseline had stopped ketamine use but had persistent LUTS. Ex-abusers, however, were less symptomatic with lower PUF scores, larger voided volumes and bladder capacities in comparison to active abusers and status of ex-abusers was an independent protective factor among symptomatic patients before any urological treatment. On the other hand, female gender and an increase in the amount of ketamine use per week were found to be associated with more severe LUTS and poorer voiding function at baseline.[21] Almost half of the active abusers had abnormal liver function at baseline.[22] Almost 70% of patients subjectively improved after integrated anti-inflammatory therapy composed of oral medications only. A shorter history of ketamine abuse and cessation of ketamine use(either sustained cessation or new cessation after urological treatment) were associated with a better response to integrated anti-inflammatory therapy in terms of objective measurement by PUF scores and voiding function parameters by uroflowmetry.

Population-based survey among the secondary school students suggested a significantly higher prevalence of LUTS among psychotropic substance abusers when compared with normal control population with no history of substance abuse. Ketamine was the most commonly abused substance among the students and ketamine abusers experienced more LUTS than abusers of other psychotropic substances. Female ketamine abusers tended to have more LUTS than male ketamine abusers.

Findings interpretation in the context of existing literature

The service of YUTC is unique to fit the behavioral characteristics of young ketamine abusers who are always hidden in the community and passive in seeking help. A recent survey in UK has reported that only 2.9% ketamine abusers symptomatic for LUTS have been referred to urologists.[16] The service delivery model of YUTC removes the potential barrier due to mandatory assessment by general practitioners before urological referrals. Encouraging social workers to make appointments for their clients further facilitates identifying the patients and provision of the necessary urological care to them. Existing literature has reported the use of cystoscopy with biopsy and urodynamic study in investigating the patients.[3-8,10,13] We believe 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 subjects by the 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 to evaluate the progress after treatment. Our approach provides excellent comfort and convenience to the patients and is practical to collect useful clinical information.

A survey among British urologists suggested that LUTS does not always improve following cessation and in some patients symptoms may remain or worsen over time.[23] The finding that one third of our patients at baseline had already ceased ketamine use supports this observation. We believe that the LUTS experienced by ketamine abusers are attributable to both the inflammatory process of cystitis and the fibrosis as a sequel to inflammation.[3,4,9,13,24] Cessation may partly resolve cystitis. The residual cystitis together with the irreversible fibrotic changes of the bladder wall attribute to the persistent symptoms despite cessation of drug use. Nevertheless, it is reassuring from the findings that ex-abusers was an independent protective factor among the symptomatic patients before any urological treatment. The prevalence of persistent LUTS among the ex-abusers and its natural course over time of cessation are poorly understood from the existing literature. A study on 36 female ex-abusers with LUTS found spontaneous improvement in urinary frequency 3 months after study entry although the voiding functions remained abnormal compared with non-abusers control group.[25]

The diminished voided volumes and bladder capacities of our patients as demonstrated by non-invasive tools are in agreement 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 have not been described previously. The 5% positive urine culture of our patients is consistent with existing knowledge that the uropathy is chemically induced and bacterial infection is likely to be a secondary event. We have encountered less hydronephrosis than previous report[4]. Hydronephrosis occurs secondary to reduced compliance of contracted bladder or ureteric stricture associated with retroperitoneal fibrosis.[4,10] We agree with the postulation that a lower incidence of upper tract involvement is likely a result of earlier medical attention.[10]

A dose frequency relationship of ketamine use with LUTS has been suggested previously.[16] To date, the critical amount of ketamine exposure which 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 30-1000mg.[2] In a pediatric case report, a 16-year-old girl developed cystitis symptoms after taking ketamine orally at 8mg/kg body weight for neuropathic pain.[26] The chronic and high-dose consumption of ketamine among our patients are in marked contrast to the therapeutic dosage used in clinical settings. We found an increase in ketamine use per gram per week was associated with a higher PUF score before treatment, and a longer history of ketamine use was associated with a worse response to treatment. Our study is the first to demonstrate in a prospective cohort of treatment-seeking patients that the higher the dose and/or the frequency of ketamine use, the longer the duration of ketamine use, the worse would be the presenting LUTS and the treatment outcomes.

The findings of our longitudinal study suggests that a simple therapeutic regimen using NSAIDs with or without additional analgesics and anticholinergic agents is cost-effective in improving the urological symptoms and well tolerated by patients. The finding of the association of cessation of ketamine use with better response to treatment support the rationale that counseling the patients to sustain abstinence from ketamine or at least to reduce drug use in stepwise fashion with the ultimate goal of cessation should be the mainstay in any urological treatment program for ketamine-associated uropathy.

In our study, female gender was found to be associated with more severe LUTS and a smaller voided volume before treatment although gender did not appear to affect treatment outcomes. Existing literature all from small case series has not reported any gender difference among treatment-seeking patients. A recent survey conducted in UK on 1285 ketamine abusers did not find any gender difference in the prevalence of LUTS and the prevalence of LUTS among those who had used ketamine in last 12 months was 27%. [16] The prevalence of LUTS among our 134 ketamine abusers identified in the secondary school survey appears to be higher than that reported in UK study. The differences in study design, age of study subjects, method of data collection, definitions of positive LUTS and the dose-and-frequency of ketamine use can all be attributed to the different results. [16] We believe our finding that female being a risk factor is worthy of note given that this was derived from a large prospective cohort of treatment-seeking patients at YUTC whether we measured subjectively by the symptoms or objectively by the voiding function, and from non-treatment-seeking population in the school survey. It may or may not be a coincidence that female is also more commonly affected in the interstitial cystitis/bladder pain syndrome(IC/BPS) which shares similar histological and clinical features with ketamine-associated uropathy but of different etiology. [27,28] The current theory for the development of IC/BPS is diffusion of toxins from urine to the submucosa following injury or dysfunction of the urothelium resulting in neurogenic inflammation, sensory nerve activation, pain and fibrosis. [27] It is possible that female may be more susceptible to urothelium injury whether by the toxic effect of ketamine or other unknown etiological 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 more readiness of female to seek medical help and the tendency for female ketamine abusers to develop more bothering LUTS.

Strengths and limitations

Prior to the present study of YUTC patients, the largest series in literature was a retrospective study describing the clinical presentations of 59 patients. [4] A total of around 200 cases have been reported in world-wide literature to date. [11] The present study presents the largest patient number ever reported and to the best of our knowledge is the first well-designed prospective study on patients seeking treatment for ketamine-associated uropathy in a single centre. We certainly acknowledge the limitations of our 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 poly-substance use. The results of non-invasive investigations in bladder functions may have variations even for the same individual at the same point of time if performed repeatedly. Our study population at YUTC may have been biased by having only those who willingly sought urological treatment. The duration course of integrated anti-inflammatory therapy and its components varied among the patients and the

compliance to medications could not be accurately assessed. For the population-based school survey, the response rate of over 70% and the fact that more than 10% of local secondary schools participating in the study was in favor of a good representative of study sample with reliable results. However, the scientific value of anonymous questionnaire survey is always limited by its own intrinsic nature. The accuracy of data entered cannot be proven and dose and frequency of psychotropic substance use were not studied. The overall small number of abusers may affect subgroup analysis.

Conclusions and implications

The present report illustrates a practical and effective model to evaluate and treat a unique group of young patients suffering from ketamine-associated uropathy. The unprecedentedly large recruitment of patients at YUTC is encouraging to all clinical researchers who are enthusiastic about this topic but have been frustrated by difficulty in identifying the patients. The one-stop clinic using a non-invasive approach provides the hidden abusers with an easy-access service, a comfortable and efficient evaluation. Our findings have deepened our knowledge but at the same time have stimulated more questions that have yet to be answered. 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 the urological care providers.

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