

Research report on
Prospective observational study of urinary symptoms, sexual behaviors and psychiatric symptoms in ketamine Misusers

Submitted to Beat Drug Fund Association

Submitted by

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Executive summary

Ketamine has well documented safety in medical and veterinary settings. The recreational use of ketamine gained the popularity in Hong Kong (HK) since 1980s as it is easy to consume and with clear dose response effect. The rising trend of the recreational use of ketamine, especially in the adolescent group, has recently created a large social arousal. Much concern has been put in the acute effect after ketamine intake, while the long term effect is not well known. This will be a heavy medical and socio-economic burden to provide long term care for this group of adolescents.

Urinary symptoms and renal failure has been reported in previous medical case reports. However, the symptom in the people who quitted ketamine is not known. Whether the remaining symptom is related to their previous duration and dosage used or whether these symptoms are reversible or how long they will persist is not clear. This study aims to evaluate the urinary, psychiatric symptoms and sexual attitude in the ex-ketamine user and the relationship of the pattern of previous ketamine use. Also inflammatory markers, cytokines and chemokins, will be tested in the urine sample, which can be a potential new marker to diagnosis ketamine related urinary symptoms in future.

Total of 44 subjects were referred to our Gynaecology specialty clinic in Department of Obstetrics and Gynaecology, Prince of Wales Hospital from November 2009- April 2010 from a local drug rehabilitation centre. All of them had history of ketamine abuse and had stopped using the drug in the centre. They were interviewed and assessed by a gynaecologist and psychiatrist for their urinary and psychiatric conditions respectively. Sexual attitude and behaviors were assessed by special designed questionnaires and appropriate gynaecological examinations were performed accordingly. Urinary symptoms were also assessed by using 3-day bladder diary and validated quality of life questionnaires Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaires Short Form (IIQ-7). Urine samples were saved for laboratory testing of human cytokines and chemokines. Psychiatrist interviewed the subjects using validated Chinese version of the Structured Clinical Interview for the Diagnostic and Statistical manual of Mental Disorders-IV (C-SCID).

Female ketamine misusers had a permissive sexual attitude and had high risk sexual behaviors including accepts one night stand (27.8%), accepts more than one sexual partner at same time (25%), and accepts sex without contraception (52.8%). Results from bladder diary and UDI-6 and IID-7, among those who abused ketamine for 2 years or more, the mean scores of the questionnaires were higher, reflecting their symptoms are more disturbing. When they stopped abusing ketamine for 3 months or more, their mean 24 hour urinary frequency had decreased, the maximum voided volume had increased and the mean UDI-6 and IIQ-7 scores had decreased. Urine analysis found out significant increase in epidermal growth factor (EGF) in ketamine ex-users compared with control. The most common lifetime psychiatric diagnosis obtained from 32 of them was substance-induced mood disorder (47%) and substance-induced psychotic disorder (16%).

In conclusion, female ketamine misusers are rendering for permissive sexual attitude, high risk sexual behaviors, severe lower urinary tract symptoms which affecting their quality of life and also psychiatric morbidity. They are those who warranted special medical attention to screen and treat earlier. Besides, the finding from the urinary symptoms further emphasis the benefit of abstinence from drug use will reduce their symptom, though the urinary symptoms may still persist after cessation.

報告摘要

氯胺酮運用在醫學和獸醫學上的安全性早已獲得確認。但在香港濫用氯胺酮的情況則在 20 世紀 80 年代得以普及，主要因為它是容易服用，並有明顯的劑量反應。濫用氯胺酮的趨勢，尤其是在青少年群中，引起了社會上龐大的迴響。一直備受關注的是服用氯胺酮後的即時影響，而其長期副作用並不為人熟知。長期照顧這一群濫藥少年對社會經濟將會是一個沉重的醫療經濟負擔。

據以往的醫療報告，濫用氯胺酮可引致各種泌尿系統症狀和腎功能衰竭。然而，我們並不清楚在停止服用氯胺酮症狀後，這些症狀會否消失還是會持續；若症狀持續，又將持續多久，而這又與其濫藥的時間和用量是否有關。本研究旨在對一班曾濫用氯胺酮的女青年人之泌尿系統症狀，精神症狀和性態度與以前濫用氯胺酮的情況的關係。並對她們的尿液樣本進行炎症標誌物，細胞因子和趨化因子的測試，這些在未來可望成為診斷氯胺酮相關的泌尿系統症狀的新標誌物。

從 2009 年 11 月 - 2010 年 4 月期間，一共有 44 名從本地一所戒毒康復中心轉介到威爾斯親王醫院婦產科學系專科門診。研究對象都曾濫用氯胺酮，並已停止使用該藥物。他們由一名婦科醫生和精神科醫生進行泌尿系統症狀，性態度和精神狀況的評估。性態度和行方面，我們使用特別設計問卷調查並進行適當的婦科檢查。泌尿系症狀方面，通過 3 天的膀胱排尿日記和生活質量問卷：泌尿生殖系統壓力量表簡表（UDI-6）和尿失禁影響問卷調查短表（IIQ 7）進行了評估。她們的尿液樣本也被送到實驗室作細胞因子和趨化因子的測試。精神科醫生則以中文版 Structured Clinical Interview for the Diagnostic and Statistical manual of Mental Disorders-IV (C-SCID) 作診斷。

本研究顯示曾濫用氯胺酮的女青年人大多有一個開放的性態度和高風險性的行為，包括接受一夜情（27.8%），接受在同一時間有多於一個性伴侶（25%），接受無避孕的性生活（52.8%）。從膀胱排尿日記和 UDI-6 和 IID-7 的結果中顯示，濫用氯胺酮 2 年以上的研究對象，問卷的分數均較高，反映他們的症狀是更令人不安的。當他們停止濫用氯胺酮 3 個月或以上，他們的平均 24 小時尿頻率均較低，他們的排尿量增加，UDI-6 和 IIQ-7 平均分數也較低。尿液分析發現，與對照組相比，表皮生長因子(EGF)顯著在氯胺酮組別中較高。而最常見的精神科診斷為 32 個獲得的藥物引起的情緒障礙（47%）和藥物所致的精神性障礙（16%）。

總括而言，曾濫用氯胺酮的女青年人有較開放的性態度，高風險的性行為；嚴重影響到他們生活質量的泌尿症狀和精神疾病患病率。他們是一班值得特別關注並提供醫療篩查及早期治療的青年人。此外，此項報告確定了泌尿系統症狀於停止服用氯胺酮後仍然存在，但亦進一步強調停藥有利於減低這些泌尿症狀。

Introduction

Ketamine is a noncompetitive glutamate N-methyl-d-aspartate receptor antagonist with well documented safety in medical and veterinary settings. The recreational use of ketamine was first reported in 1971 in North America. Its recreational use gained popularity and overtook ecstasy to be the commonest abused psychotropic drug in Hong Kong (HK) since 2001. Ketamine abusers consider it as a short-acting psychotropic agent, which has a wide margin of safety and low potential for dependence and minimal long term side effect. The major concern has been in the acute effect after ketamine intake, while most reports of long term morbidity have focused on neurological sequelae. Severe lower urinary tracts symptoms including urinary frequency, urgency and dysuria have been reported in active ketamine abusers. Cases of cystitis and contracted bladder have also been reported to be associated with active ketamine user with possible irreversible secondary renal damage including hydronephrosis and deranged renal function. However, whether the severity of these side effects would reverse after cessation of this drug is not clear. The association between the dosage and duration of previous use with these symptoms is also poorly understood. Furthermore, the impact of these symptoms on the quality of life (QoL) of the abusers has not been well evaluated.

Besides, the sexual attitudes in ketamine user have not been much explored before. Another aim of this study is to reveal the magnitude of high risk sexual behaviors and its associated consequences in female ketamine users, which numbers are on the rise locally. This may facilitate the formulation of effective interventions to promote sexual health in this particularly high risk group.

Thirdly, the relatively little is known about the psychiatric co-morbidity of substance abusers in Hong Kong. In a 2005 study of 95 ketamine abusers recruited from nightclubs and drug counseling centres, 26% had lifetime psychiatric diagnoses and substance use disorders. The two most common diagnoses were depressive disorder (13%) and drug-induced psychotic disorder (6%). Data on subjects treated in residential drug treatment centres in Hong Kong are lacking. Furthermore, untreated psychiatric disorders worsen

drug dependence treatment outcomes, the early identification and treatment of psychiatric disorders should be a priority in general and residential substance abuse facilities.

Therefore, one of the aims of this study was to describe the demographic characteristics, pattern of drug abuse, and type of psychiatric co-morbidity in female substance abuse patients treated in a residential setting.

Study Design and methods

This cross-sectional cohort study was conducted in the gynaecology clinic of a tertiary referral center. All women who had previous history of ketamine abuse and had stopped before the consultation were referred to our subspecialty urogynaecology clinic from a local drug rehabilitation centre from November 2009 to April 2010. This is a non governmental welfare organization established in 1961, provides free drug treatment and rehabilitation service. The typical rehabilitation programme consists of 6 to 18 months at the residential treatment centre, followed by 3 to 6 months at a halfway house.

The study protocol and ethical issue approval was granted by the local institution (Reference No. CRE-2009.453). Every subject signed a consent form. Subjects were initially approached by a doctor from the drug rehabilitation centre, who explained the nature of the study. Subjects referred to us were interviewed by a trained research assistant who explained to her about the study protocol in detail again. Then they will be interviewed individually by a gynaecologist for their sexual condition and urinary symptoms, followed by a psychiatrist for their psychiatric condition.

Urinary symptoms assessment

All subjects were invited to complete the validated Chinese version of Urogenital Distress Inventory Short Form (UDI-6) and the Incontinence Impact Questionnaire Short Form (IIQ-7) independently. Urinary Distress Inventory (UDI) and Incontinence Impact Questionnaire (IIQ) are two widely used comprehensive health related quality of life (HRQoL) questionnaires specific to lower urinary tract dysfunction. The total and subscale scores of their short forms UDI-6 and IIQ-7 correlated well with their long-form versions. UDI-6 consists of six items that assess the life impact of urinary symptoms, including irritative symptoms of urgency and urge incontinence, stress incontinence symptoms and obstructive symptoms of difficulty in complete emptying of bladder and

pain or discomfort over lower abdomen. IIQ-7 consists of seven items designed to assess different domains of quality of life, including physical, travel, social and emotional aspects.

Following completion of the HRQoL questionnaires, subjects filled in a special designed 47-item questionnaire concerning their history of ketamine use in a confidential setting. Questions included the age when they started their illicit use of ketamine, duration and dosage of their use, duration of cessation of use and relevant demographic data.

The results obtained from the above questionnaires were blinded to the gynecologist, who subsequently conducted the individual consultation and assessment. Clinical details of urinary symptoms, including urinary frequency, urgency, voiding difficulty, dysuria, stress or urge incontinence were assessed. If any urinary symptom was present, mid-stream urine was sent for culture to exclude urinary tract infection. Urine samples were collected to confirm no continuous use of ketamine and for cytokines testing. Blood test for renal function was performed and transabdominal ultrasonography was done to look for hydronephrosis.

A 3-day bladder diary was completed by all subjects to provide information on the actual drinking and voiding patterns. Two standard measuring cups were provided for each subject. The number of voiding in daytime, bedtime and total 24 hours were recorded as daytime urinary frequency, nocturia and 24-hour frequency. The volume voided was recorded in each micturition. The maximum volume they have voided is defined as the maximum voided volume and the median functional bladder capacity is defined as the median of all the voided volume.

Subjects were confirmed cessation of ketamine abuse and completed a second set of UDI-6 and IIQ-7 and the 3-day bladder diary three months after their first consultation to review their urinary symptoms without giving any active treatment. Urine samples were collected again to confirm cessation of use of ketamine.

An age-matched control group who had never taken any ketamine was selected from the general gynecological clinic of the same unit. UDI-6 and IIQ-7 and the 3-day bladder diary were completed by the control. Their urinary symptoms were also assessed and mid-stream urine culture was sent if any urinary symptom was present. Urine samples were also collected for laboratory testing for cytokines.

Sexual attitude assessment

The participants would then be interviewed by a researcher and asked about gynaecological and obstetrics history, details of sexually transmitted disease (STD) acquired and treatment received. All participants were interviewed by the same investigator who was blinded to the questionnaire results. Screening for STD include hepatitis B surface antigen (HbsAg), anti-hepatitis C virus antibodies (anti-HCV), HIV, Venereal Disease Research Laboratory test (VDRL) and high vaginal swab for bacterial culture, endocervical swabs for gonorrhoea and Chlamydia cultures.

Psychiatric assessment

All subjects were interviewed by a psychiatrist with their age, marital status, educational level, occupation, history of drug-related offences, duration of stay at the centre and the legal status (i.e. if they were under a probation order) were recorded. Each subject's history of psychiatric disorders and their treatment were also recorded. They then were interviewed using the locally validated Chinese version of the Structural Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders-IV (C-SCID). The C-SCID has been shown to have good inter-rater reliability, with a kappa of 0.76 for mood disorder, 0.75 for schizophrenia and other psychotic disorders, and 0.81 for anxiety disorders.

Statistical Analyses

Statistical analysis was performed with the Statistical Package for Social Science version 17.0 (SPSS Inc., IL, USA). Descriptive statistics were used for incidence of urinary symptoms. Chi-square or Wilcoxon Signed Rank Test was used for nonparametric data and Paired-sample t-test was used for parametric data of the paired samples while independent samples t test and Mann-Whitney U test were used for comparison within group. A *p* value less than 0.05 was considered statistically significant.

Results

From December 2009 to April 2010, 44 female ex-ketamine abusers were referred to us, 4 declined and finally 40 (91%) of them consented for this study. 36 of them completed the 47- items questionnaires while 32 of them completed the psychiatric assessment. 40 of them completed the urinary questionnaires and bladder diary. The mean age of the study group was 20.1 years old (range 13-29, SD 3.5).

Table 1: Demographics of all participants

| | Number (%) |
|------------------------------------|------------|
| Age | |
| • ≤15 | 4 (11.2) |
| • >16-20 | 20 (55.5) |
| • >20-25 | 9 (25.1) |
| • >25 | 3 (8.4) |
| Education level | |
| • Grade 7-9 | 20 (55.6) |
| • Grade 10-12 | 16 (44.4) |
| Employment status | |
| • Student | 5 (13.9) |
| • Unemployed | 20 (55.6) |
| • Others | 5 (13.9) |
| • Not answered | 6 (16.7) |
| Monthly family income (HKD) | |
| • ≤\$10000 | 13 (36.1) |
| • >\$10000 to \$20000 | 13 (36.1) |
| • >\$20000 to \$30000 | 6 (16.7) |
| • >\$30000 | 1 (2.8) |
| • Not answered | 3 (8.4) |

Table 2: Pattern of ketamine and other illicit drug use

| | Number (%) |
|---|------------|
| Age of first use | |
| • <10 | 2 (5.9) |
| • 10-12 | 5 (13.9) |
| • 13-14 | 13 (36.1) |
| • 15-16 | 10 (27.8) |
| • 17-18 | 4 (11.1) |
| • >18 | 2 (5.6) |
| Number of years use | |
| • ≤1 year | 6 (16.7) |
| • >1-2 years | 3 (8.3) |
| • >2-3 years | 6 (16.7) |
| • >3-6 years | 16 (44.4) |
| • >6 years | 5 (13.9) |
| Maximum frequency of use (number of times/month) | |
| • ≤10 times | 7 (19.5) |
| • >10-20 times | 5 (13.9) |
| • >20-30 times | 14 (38.9) |
| • >30-100 times | 5 (13.9) |
| • >100 times | 3 (8.3) |
| • Not answered | 2 (5.6) |
| Illicit drug use with sex | |
| • Always | 6 (16.7) |
| • Occasional | 15 (41.7) |
| • Seldom | 3 (8.3) |
| • Rare | 5 (13.9) |
| • Not answered | 7 (19.5) |
| Other illicit drug use | |
| • Cocaine | 26 (72.2) |
| • Benzodiazepine | 24 (66.7) |
| • Methamphetamine | 22 (61.1) |
| • Marijuana | 11 (30.6) |
| • Ecstasy | 8 (22.2) |
| • Heroin | 1 (2.8) |
| Had once consulted doctor for side effects of ketamine | 15 (41.7) |

Sexual attitude assessment

36 of them filled in the questionnaire and were interviewed by the investigator. 35 out of the 36 participants underwent STD screening. STD screening was not performed in one participant because she was not sexually active. Details of sexual behavior and contraception were shown in following tables.

Table 3: Sexual attitude and behaviour

| | Number (%) |
|--|------------|
| Accepts premarital sex | 33 (91.7) |
| Accepts one night stand | 10 (27.8) |
| Accepts > 1 sexual partner at same time | 9 (25.0) |
| Accepts sex without contraception (if not plan for pregnancy) | 19 (52.8) |
| Age of first sex | |
| • ≤13 | 11 (30.6) |
| • 14-15 | 13 (36.1) |
| • 16-18 | 10 (27.8) |
| • Never | 1 (2.8) |
| • Not answered | 1 (2.8) |
| Number of sexual partners altogether | |
| • 1-5 | 14 (38.9) |
| • 6-10 | 16 (44.5) |
| • >10 | 3 (8.4) |
| • Not answered | 3 (8.4) |
| Once had >1 sexual partner at same time | 13 (36.1) |
| Had been involved in prostitution | 1 (2.8) |

Table 4: Contraception

| | Number (%) |
|--|------------|
| Contraception use in sex without illicit drug use | |
| • Always | 11 (30.6) |
| • Occasional | 15 (41.7) |
| • Seldom | 2 (5.6) |
| • Never | 2 (5.6) |
| • Not answered | 6 (16.7) |
| Contraception use in sex with illicit drug use | |
| • Always | 9 (25.0) |
| • Occasional | 14 (38.9) |
| • Seldom | 5 (13.9) |
| • Never | 2 (5.6) |
| • Not answered | 6 (16.7) |
| Contraceptive methods ever used | |
| • Condom | 28 (77.8) |
| • Oral contraceptive pills | 8 (22.2) |
| • Emergency contraceptive pills | 13 (36.1) |
| • Coitus interruptus | 19 (52.8) |
| • Calendar method | 10 (27.8) |
| • Injection | 4 (11.1) |

Table 5: History of STD and termination of pregnancy

| | Number (%) |
|--|------------|
| History of STD | |
| • Chlamydia | 3 (8.3) |
| • Trichomonas | 2 (5.6) |
| • Gonorrhoea | 1 (2.8) |
| • Syphilis | 1 (2.8) |
| • Genital warts | 1 (2.8) |
| • Tuboovarian abscess | 1 (2.8) |
| STD screening results | |
| • Chlamydia | 3 (8.3) |
| • Syphilis | 1 (2.8) |
| History of termination of pregnancy (TOP) | |
| • One TOP | 8 (22.2) |
| • Two TOP | 4 (11.1) |
| • Three TOP | 3 (8.3) |

Table 6: Ketamine use 3 years vs Ketamine use >3 years

| | Ketamine 3 years (n=14) | Ketamine >3 years (n=21) | P value |
|--|-------------------------|--------------------------|---|
| Once had more than 1 sexual partner at same time | 2 (14.3%) | 11 (52.4%) | P < 0.05 OR = 0.136 (CI = 0.024 to 0.775) |
| History of STD | 0 | 9 (43.0%) | P < 0.05 |
| Accept sex without contraception (if not plan for pregnancy) | 5 (35.7%) | 14 (66.7%) | NS |
| Accept one night stand | 2 (14.3%) | 8 (38.1%) | NS |
| Accept pre-marital sex | 12 (85.7%) | 21 (100%) | NS |
| Use of contraception | 11 (78.6%) | 14 (66.7%) | NS |

NS = Not significant

Table 7: Different sexual behaviours in relation to duration of ketamine use and age of first ketamine use

| Duration of ketamine | No. of termination of pregnancy Mean (SD) | No. of sexual partners Mean (SD) | Age of first sex Mean (SD) |
|------------------------------|--|-------------------------------------|-------------------------------|
| ≤1 year (n = 6) | 0.3 (0.8) | 6.0 (3.5) | 13.4 (1.8) |
| >1-2 years (n = 3) | 1.7 (1.2) | 12.5 (10.6) | 14.0 (1.0) |
| >2-3 years (n = 6) | *0.0 (0.0) | 4.7 (1.8) | 15.4 (1.1) |
| >3-6 years (n = 16) | 0.6 (0.8) | 7.3 (2.4) | 14.5 (1.7) |
| >6 years (n = 5) | 1.6 (1.3) | 10.6 (6.6) | 15.4 (2.4) |
| Age of first ketamine | | | |
| <10 (n = 2) | 1.5 (2.1) | 8.5 (6.4) | 15.5 (2.1) |
| 10-12 (n = 5) | 0.2 (0.5) | 8.2 (2.0) | **13.4 (2.7) |
| 13-14 (n = 13) | 1.2 (1.1) | 7.5 (5.2) | 13.9 (1.0) |
| 15-16 (n = 10) | 0.5 (0.7) | 7.3 (5.2) | 14.7 (1.6) |
| 17-18 (n = 4) | 0.0 (0.0) | 7.8 (2.2) | 15.8 (0.5) |
| >18 (n = 2) | 0.5 (0.7) | 4 (1.4) | 17.5 (0.7) |

*P < 0.05 vs duration of ketamine >6 years

** P < 0.05 vs age of first ketamine >18 years old

Urinary symptoms and urine analyses

The mean age of the study group was 20.1 years old (range 13-29, SD 3.5) while the control group was 19.7 years old (range 15-30, SD 3.9). The mean body mass index (BMI) of the study and control groups were 22.3 kg/m² (range 17.2-31.4, SD 3.1) and 22.9 kg/m² (range 17.5-35.1, SD 4.4) respectively. There was no statistical difference of age and BMI in both groups.

In the study group, 8 (20%) of them started abusing ketamine before 13 years of age with the youngest one started at 9 years old; 26 (65%) subjects had their first ketamine experience at age 13-16. None of the subjects is pure ketamine abuser and 34 (85%) of them had abused more than 3 kinds of drugs. In all, 15% used ketamine for less than a year while 62.5% used for ≥3 years. The mean duration of ketamine abuse was 52.9 months (range 6-132 months) and the mean duration of ketamine-abuse cessation was 7.5

months (range 0.5-48 months). There were 18 (45%), 20 (50%) and 2 (5%) have stopped their use for < 6 months, $\geq 6-24$ months, and ≥ 24 months respectively.

In the study group, 36 (90%) had active urinary symptoms, with 21 (52.5%) had urinary frequency, 24 (60%) urinary urgency, 12(30%) urge incontinence, 22 (55%) dysuria and 15(37.5%) had sense of incomplete emptying of bladder. The control group did not report any urinary symptom. There was no positive urinary culture from all subjects. All of them had normal renal function and no hydronephrosis was identified.

Overall, 36 (90%) of the study subjects and all 40 control subjects completed the 3-day bladder diary. Four of the study subjects did not return the bladder diary and no data were available from them for analysis. The daytime, night time and total voiding frequencies were significantly increased, while the maximum voiding volume and the median functional bladder capacity were both reduced in the study group. (Table 8) Two (5%) subjects reported urinary incontinence. The QoL of the study group were significantly impaired as indicated by the significant increase of all subscales and total scores of both UDI-6 and IIQ-7. (Table 8)

The age of the first time of ketamine abuse was not found to be associated with worsened urinary symptoms or UDI-6 or IIQ-7 scoring. Patients stopped using ketamine for ≥ 3 months were found to have significant reduced daytime voiding frequency and higher maximum voiding volume than patients stopped for <3 months. The median functional capacity was also increased but did not reach statistical significance (Table 9). Higher voiding frequency was probably associated with the history of ketamine abuse for ≥ 2 years though statistically not significant.

Ketamine abuse for ≥ 2 years and cessation < 3 months were associated with significant increase in the total scores of UDI-6 and IIQ-7. When comparing the finding of ex-ketamine abusers who had stopped abuse for ≥ 3 months with the control group, there remained significant difference in their result of bladder diary and all the subscales in UDI-6 and IIQ-7 (Table 10).

Bladder diary and the questionnaires of UDI-6 and IIQ-7 were repeated 3 months after the first consultation for the study group. In all, 20 (50%) and 27 (67.5%) of the 40 subjects had completed the 3-day bladder diary and questionnaires respectively. All of them were confirmed to have no recent consumption of ketamine by the absence of ketamine metabolites in their urine samples. There was no significant difference in the age, first bladder diary result and UDI-6 and IIQ-7 scores in those who had or had not complete the second set of results. The day time urinary frequency (8.9 vs 7.6; $p= 0.014$) and 24 hours urinary frequency were significantly reduced (10.0 vs 8.6; $p=0.012$). All the subscales and total scores in UDI-6 and IIQ-7 were improved after 3 months, and with the stress subscale (11.5 vs 8.3; $p= 0.038$) and the total score in UDI-6 (65.6 vs 52.8; $p= 0.037$) reached statistical significance. Comparing the second set of data with the controls, nocturia was still more frequent (1.0 vs 0.01, $p=0.006$), maximum voided volume and the median functional bladder capacity remained significantly lower (315.0ml vs 401.9ml, $p=0.001$ and 175.4ml vs 261.2ml, $p=0.037$ respectively). Both total scores of UDI-6 (52.8 vs 10.0, $p=0.002$) and IIQ-7 (88.9 vs 3.33, $p=0.002$) were also higher. In summary, both the urinary patterns and QoL of the study subjects were improved 3 months after the first consultation. However, after 3 month, they are still with poorer urinary patterns and QoL compared with the control group.

Urine analysis was performed for 40 subjects and 40 controls. Two different commercial urine test kits were used: Human Cytokine/Chemokine Magnetic Bead Panel Kit (Millipore) and Human Cytokine/ Chemokine Magnetic Bead Panel II (Millipore). Total of 19 cytokines were tested with only one single cytokine epidermal growth factor (EFG) was found to be significantly higher in subject group (28184 vs 18058, $p=0.02$). The role of this cytokines in the lower urinary tract symptoms in these subject require further exploration and study to confirm.

Table 8. Result of 3-day bladder diary and UDI-6 and IIQ-7 scores in study group and control group

| | Study group Mean(Standard Deviation) | Control group Mean (Standard Deviation) | <i>p</i> value |
|---|---|--|----------------|
| Bladder diary | (<i>n</i> = 36) | (<i>n</i> =40) | |
| Daytime urinary frequency | 8.9 (5.4) | 5.7 (1.7) | 0.004 |
| Nocturia | 1.0 (0.9) | 0.2 (0.8) | <0.001 |
| 24- hour frequency | 10.0 (6.9) | 5.8 (1.8) | 0.001 |
| Maximum voided volume (ml) | 253.3 (121.0) | 401.9 (126.4) | <0.001 |
| Median Functional bladder capacity (ml) | 195.3 (93.6) | 261.2 (98.5) | 0.011 |
| ¹UDI-6 | (<i>n</i> =40) | (<i>n</i> =40) | |
| Irritative subscale | 26.6 (19.4) | 5.0 (7.8) | <0.001 |
| Stress subscale | 11.6 (14.8) | 2.5 (5.1) | 0.002 |
| Obstructive/discomfort subscale | 27.6 (23.6) | 2.5 (6.0) | <0.001 |
| Total score | 65.6 (50.7) | 10.0 (13.7) | <0.001 |
| ²IIQ-7 | | | |
| Physical Activity subscale | 20.0 (27.3) | 1.1 (4.2) | 0.001 |
| Travel subscale | 30.4 (30.6) | 1.1 (4.2) | <0.001 |
| Social subscale | 28.3 (34.2) | 1.1 (6.1) | 0.001 |
| Emotional subscale | 26.3 (29.4) | 0 | <0.001 |
| Total score | 105.0 (109.9) | 3.3 (13.4) | <0.001 |

¹ UDI-6: Urogenital Distress Inventory Short Form² IIQ-7: Incontinence Impact Questionnaire Short Form

Table 9. Results of 3-day bladder diary in different duration of abuse and cessation of ketamine use

| | Ketamine abuse duration | | <i>p</i> value | Cessation of ketamine | | <i>p</i> value |
|---|---------------------------|--------------------------|--------------------------|---------------------------|---------------|-------------------|
| | Mean (Standard Deviation) | | | Mean (Standard Deviation) | | |
| | <2 years <i>n</i> =7 | ≥2 years <i>n</i> =29 | <3 months <i>n</i> =6 | ≥3 months <i>n</i> =30 | | |
| Daytime urinary frequency | 6.7 (2.6) | 9.43 (5.8) | 0.33 | 15.5 (8.8) | 7.6 (3.3) | 0.04 |
| Nocturia | 0.3 (0.6) | 1.2 (2.1) | 0.13 | 2.6 (4.2) | 0.7 (0.9) | 0.19 |
| 24-hour frequency | 6.5 (2.6) | 10.7 (7.3) | 0.16 | 18.1 (11.8) | 8.3 (4.0) | 0.03 |
| Maximum voided volume (ml) | 255.7 (66.2) | 252.7 (131.7) | 0.88 | 147.8 (122.9) | 274.4 (110.9) | 0.03 |
| Median Functional bladder capacity (ml) | 175.3 (75.0) | 200.2 (98.1) | 0.70 | 142.6 (136.0) | 205.9 (81.9) | 0.06 |

Table 10. Comparison of results in 3-day bladder diary and UDI-6 and IIQ-7 scores in control group versus study group with cessation of ketamine use ≥ 3 months

| | Control group | Cessation of ketamine ≥ 3 months | <i>p</i> value |
|---|---------------------------|--|----------------|
| | Mean (Standard Deviation) | Mean (Standard Deviation) | |
| Bladder Dairy | <i>n</i> =40 | <i>n</i> =30 | |
| Daytime urinary frequency | 5.7 (1.7) | 7.6 (3.3) | 0.001 |
| Nocturia | 0.2 (0.8) | 0.7 (0.9) | 0.004 |
| 24-hour frequency | 5.8 (1.8) | 8.3 (4.0) | 0.001 |
| Maximum voided volume (ml) | 401.9 (126.4) | 274.4 (110.9) | 0.001 |
| Median Functional bladder capacity (ml) | 261.2 (98.5) | 205.9 (81.9) | 0.019 |
| ³UDI-6 | <i>n</i> =40 | <i>n</i> =32 | |
| Irritative subscale | 5.0 (7.8) | 23.8 (18.6) | <0.001 |
| Stress subscale | 2.5 (5.1) | 9.8 (13.4) | 0.010 |
| Obstructive/discomfort subscale | 2.5 (6.0) | 23.4 (22.2) | 0.001 |
| Total score | 10.0 (13.7) | 56.9 (46.5) | <0.001 |
| ⁴IIQ-7 | | | |
| Physical Activity subscale | 1.1 (4.2) | 13.6 (19.6) | 0.002 |
| Travel subscale | 1.1 (4.2) | 25.0 (26.8) | 0.001 |
| Social subscale | 1.1 (6.1) | 20.8 (27.8) | 0.002 |
| Emotional subscale | 0 | 20.3 (26.0) | 0.001 |
| Total score | 3.3 (13.4) | 79.7 (87.8) | <0.001 |

³ UDI-6: Urogenital Distress Inventory Short Form

⁴ IIQ-7: Incontinence Impact Questionnaire Short Form

Psychiatric assessment

32 subjects completed psychiatric assessment. Twenty one (66%) of them had lifetime psychiatric diagnoses, the most common being substance-induced mood disorder (47%), followed by substance-induced psychotic disorder (16%) and specific phobias (13%). 14 out of 15 of those suffering from substance-induced mood disorders were depressive-typed and one was mixed typed. Major depressive disorder, obsessive-compulsive disorder, and post-traumatic stress disorder were all at 3%.

Discussion

Sexual attitude and behaviors

Our study included young female ketamine who had a more permissive sexual attitude. Their acceptance towards premarital sex or having more than one sexual partner were as high as 91.7% and 25% respectively, comparing with 44% and 7% among 14 to 17 years old reported in another local study. This permissive attitude explained their much higher prevalence of sexual activity (97.2%) as compared with 8.2% reported in another local study. The age of first sexual intercourse was significantly lower for those who started taking ketamine at 10 to 12 years of age (mean 13.4 years of age) compared to those who started taking ketamine at >18 years of age (mean 17.5 years). Ketamine user were also more likely to engage in high risk sexual activity with 36.1% having more than one sexual partner at the same time and 52.9% had more than five life time sexual partners, 8.4% even had more than ten lifetime sexual patterns. These results show that ketamine users have much higher risky sexual behaviors and have more consequences of high risk sexual behaviors such as having STD which were shown in the other results of this study. Up to 25% of participants had a history of STD and 11.1% were found to be suffering from STD during our screening. This was much higher than 1.5% to 8.9% in other Asian countries. Less participants in the group of less than or equal to 3 years of ketamine use had history of STD when compared to the group with ketamine use for > 3 years ($P = 0.05$). Duration of ketamine use can be regarded as an indirect reflection of the duration of an individual's overall high risk behavior. Therefore longer duration of ketamine use is

associated with longer exposure to high risk sexual behaviour and its consequences, e.g. STD. Ketamine users are a high risk group from a number of perspectives. Targeting them by offering STD screening or education on STD prevention when they present to medical personnel for other problems allows more effective use of limited resources. Selective screening of Chlamydia infection was shown to be effective in reducing incidence of pelvic inflammatory disease. Some had proposed to include STD screening and treatment in standard treatment programmes. These efforts, from an individual perspective, can promote reproductive health; while, in a global perspective, can reduce the burden of the ever increasing incidence of HIV. However, drug abuse is illegal and this group is difficult to identify. Medical personnel in a primary care setting are in a good position to provide such intervention since drug abuse is associated with various consequences necessitating medical attention. In our study, 41.7% of participants had consulted a doctor for side effects related to ketamine. Appropriate training for general practitioners is important in the delivery of STD prevention information. From previous studies, 27.1% of general practitioners felt there was an inadequate access to counseling and education resources.

The results of this study showed that female ketamine users had more high risk sexual behavior, more liberal sexual attitude, more termination of pregnancy and more STD. Some of the figures were alarmingly high, e.g. 30.6% had first sexual intercourse at ≤ 13 years old. These exposed them to further risks of surgical complications and infertility. Interventions such as STD screening, provision of STD prevention information in a primary care setting may be effective in promoting sexual health in this group. These patients are difficult to identify and even more difficult to recruit for analysis. Our study, although small in number, is the first study to report sexual behavior and STD in this group of subjects in our locality.

Urinary symptoms

Ketamine has been increasingly abused by youngsters over the past 10 years. Its low cost and fast onset of action have resulted in its common abuse around the world in all age groups in 2007-2009. Drug abusers believed that ketamine has low addictive potential and little long-standing harm. They may falsely believe that any adverse physical effect

would resolve after they stopped abusing the drug. Amongst the adverse effects reported are reduced functional bladder capacity, detrusor overactivity, ulcerative cystitis, decreased bladder compliance and vesico-ureteric reflux. Whether the documented urinary side effects will cease after cessation of use remain unclear. The urinary symptoms in the ex-ketamine abusers were investigated in this study with the focus on the impact in their QoL.

Urinary symptoms are influenced by age and BMI, therefore age-matched control group with similar BMI in the current study is important to reflect the significance of urinary symptoms in ex-ketamine abusers. A 3-day bladder diary will generally provide better reflection of the usual voiding pattern and this is especially valuable data to be obtained from this group of young subjects. The high compliance in completing the bladder diary in both groups was also valuable data in studying the urinary problem in this special group.

Urinary symptom scores of the ketamine remained significantly increased when compared with controls. All subscales in the UDI-6 were all more prevalent in the study group. This echoed the findings of moderate to severe lower urinary tract symptoms in the active ketamine abusers in the previous case series. Even after cessation of use, their QoL were still impaired by various urinary symptoms.

The result from this study confirmed that ketamine abuse ≥ 2 years would have a greater extent of impaired QoL as compared to those had taken <2 years. Besides the duration of ketamine use, the longer since last use, the greater is the return to normality in terms of QoL. This was supported by our findings in the ex-ketamine abusers who had stopped for ≥ 3 months. The results from the second set of data collected 3 months later again agreed with this conclusion.

The pathophysiology of the urinary symptoms in ketamine abusers remains unclear. Ketamine has numerous central nervous system actions, and possibly includes neuroinflammation in the urinary tract similar to that occurring in interstitial cystitis.

However, no effective treatment has been identified for this group of patients. Intravesical instillation of hyaluronan solution has been used and reduced their urinary symptoms in some ketamine abusers with hemorrhagic cystitis while they had ceased ketamine abuse at the same time. From our study, cessation of drug and time are proved to be the keys to reverse these symptoms before more severe damage has occurred and more aggressive intervention was introduced. Although complete recovery was not demonstrated after up to 6 months in our subjects compared with the control group, significant progressive improvement was shown. Further research is needed to follow-up their symptoms after longer period of cessation. We may be able to work out the possibility of complete resolution of urinary side effect or the time required for this to happen.

Psychiatric assessment

Psychiatric co-morbidity was much higher in our study than a previously reported local study (66% vs 26%), which suggests that women have higher co-morbidity than men. Another reason for the discrepancy between the results may be due to sampling bias as our subjects were recruited from a residential centre rather than a community based services. Similar to previous Hong Kong survey however, the most common psychiatric diagnosis encountered in our subjects was substance-induced mood disorder.

Limitations of study

Ketamine abuse is limited to a specific population in Hong Kong and it is difficult to find a large sample size of subjects who are willing to participate. To identify them more effectively, healthy promotion, education and collaborations with various organizations which help ketamine users can do. This is also a biased group as they are a hospital clinic-based population. This study is limited by selection bias as they were all female subjects referred from a rehabilitation centre. The conclusion cannot be generalized to the male subjects and it may not reflect the same conditions in all ketamine users in our community. This is a cross-sectional study and cannot address causal relationships between ketamine use and high risk sexual behavior. Results of this study might also be affected by recall bias and under reporting. However, under reporting generally results in fewer positive findings. It is likely that the positive response will likely be even higher than the ones reported here.

Our study was limited by the fact that ketamine abuse is more common in female than in male abusers and only female ketamine abusers were referred and recruited in our study. The results obtained and conclusion drawn is valid for female abusers, but whether they are applicable to male abusers is not clear. It will definitely worthwhile to carry out similar study in male abusers in near future.

Another limitation of this study was a small sample size however, most of the people abusing ketamine are in their teens and they are very reluctant to expose themselves to medical personnel concerning their urinary problems. Either they avoid being labeled as drug abuser or they prefer to tolerate the symptoms and believe the symptoms would resolve spontaneously. Concerning the selected subjects, they are referred from a local drug rehabilitation centre and all of them have used multiple drugs other than ketamine. However, there is no significant associated urinary symptom reported with other common illicit drug. Finally, 30 of the subjects were under probation orders for the possession of dangerous drugs, which constitutes an important selection bias.

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