Risk Factors of Lower Urinary Tract Syndrome among Ketamine Users

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Objective: This study investigated the risk factors of ketamine associated-lower urinary tract symptoms (LUTS), such as duration of use, dosage of ketamine, co-occurring substance use of other psychoactive drugs, comorbidities, and depression.

Methods: This study was a cross-sectional survey. LUTS was assessed with the O’Leary symptom and problem index (OSPI) scores. We included the comorbidities of interstitial cystitis/painful bladder syndrome (IC/PBS) as comorbid factors. Depression was evaluated based on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM 5). Duration of use, dosage of ketamine and the OSPI scores were subjected to log transformation because of the skewed distribution.

Result: Among 143 participating ketamine users, 25 (17.5%) had LUTS. Duration of ketamine use was significantly positively correlated with OSPI scores (adjusted $\beta$ [95% CI], 0.21 [0.06–0.35] in log-log model), which equaled a 10% increase in months of ketamine-use increased OSPI scores by 2.02%. Female and depression were significantly associated OSPI scores (adjusted $\beta$ [95% CI], 0.20 [0.03–0.37], 0.49 [0.29–0.70], respectively in the log-linear model), with OSPI scores being 1.22 times higher in female, and 1.63 times higher in ketamine users with depression. Dosage of use was not significantly associated with OSPI scores (adjusted $\beta$ [95% CI], 0.04 [−0.12 to 0.20], $P = 0.64$ in log-log model), likewise with comorbid diseases (adjusted $\beta$ [95% CI], 0.07 [−0.08 to 0.21], $P = 0.36$ in log-linear model).

Conclusion: Depression and longer duration of exposure to ketamine are significantly associated with the development of LUTS among ketamine users. Early evaluation and intervention of depression should be considered in patients of ketamine-associated LUTS.

Key words ketamine, ketamine cystitis, lower urinary tract syndrome, pain

1. INTRODUCTION

Ketamine alters the feeling of pain and depressive mood. There is marked variation in patterns of ketamine use, including non-dependent ketamine users, who predominantly use on weekends, and frequent users.1 Chronic ketamine users consume ketamine daily or when alone. In the central nervous system, ketamine acts as a noncompetitive glutamate N-methyl-D-aspartate(NMDA) receptor antagonist, an $\alpha$- and $\beta$-adrenergic receptor agonist, an opioid sigma receptor agonist, and a muscarinic receptor antagonist.2

Lifetime use of ketamine was reported by 1% of those 14 years of age or older in an Australian household survey in 2004.3 The lifetime prevalence of ketamine use among regular tobacco and alcohol users among the Asian population is 11.7%.4 Globally 26.6% of ketamine users experience the symptoms of lower urinary tract symptoms (LUTS), including urgency, frequency, and dysuria,5 and secondary renal damage can occur in severe cases.6 The mechanism of lower urinary tract destruction in ketamine users is associated with neuroinflammation and changes in visceral pain transmission.7,8 Patients with ketamine cystitis develop peripheral nerve fascicle hyperplasia in their bladder tissue.9 Recent study reports that excreted ketamine and potentially its metabolites are the main driver of LUTS in ketamine users, by the evidence in a patient undergoing cystectomy for unremitting pain...
following ketamine abuse where near total loss of bladder urothelium was observed from regions in contact with urine, whereas the urachal epithelium (not exposed to urine) remained healthy. These findings lead to ketamine assumedly being the potential direct trigger factor of LUTS in ketamine users.

There can be a potential third variable, such as comorbidity, that is associated with both ketamine use and LUTS. LUTS in ketamine users demonstrates clinical bidity, that is associated with both ketamine use and depression. The high serum IgE levels in ketamine users suggests an underlying immunological pathway. The dysfunction of immune-inflammatory processes and unremitted pain are both common in patients of ketamine-associated LUTS and these comorbid diseases.

The ability of ketamine to produce a rapid antidepressant response may compel users to self-medicate. This effect may account for the association of depression and ketamine use. On the other hand, the rapid antidepressant effect of ketamine is associated with blockade of glutamate NMDA receptor and rapid synthesis of brain-derived neurotrophic factor (BDNF), which can involve neuroprotective pathways or neurotoxic effect. However, the association of depression and ketamine-associated LUTS remains unclear.

In summary, whether ketamine acts as the direct trigger factor of LUTS or there is a potential third variable instead remains unclear. We hypothesize that co-occurring substance use of other psychoactive drugs, depression and IC/PBS comorbidities are correlated with ketamine-associated LUTS, in addition to ketamine’s direct trigger effect. This study investigated whether the duration of ketamine use, dosage of ketamine, co-occurring substance use of other psychoactive drugs, comorbidities of IC/PBS, and depression are correlated with ketamine-associated LUTS.

2. MATERIALS AND METHODS

2.1. Participants

This study consisted of a cross-sectional survey conducted in Taichung City from March 2014 to September 2014. Of 185 ketamine users, 40 were excluded due to age less than 20 years and two were excluded due to psychosis or cognitive impairment. The remaining 143 participants were recruited, including 117 from police detention and 25 from outpatient urology departments, as well as one from a substance abuse service. This study was approved by the Ethics Review Committees of Tau-Yuan Hospital, Ministry of Health and Welfare, Taiwan (project number TYGH102027).

2.2. Measurements

2.2.1. LUTS

Lower urinary tract symptoms were measured with the O’Leary symptom and problem index (OSPI), which was a self-administration instrument designed to analyze the most crucial voiding and pain symptoms of IC/PBS. The scale had a total of nine questions, such as “During the past month, how often have you felt the strong need to urinate with little or no warning?” and “Have you have to urinate less than 2 h after you finished urinating?” The total score is 37, and score ≥ 12 is cutoff point. Previous studies have reported that the mean OSPI score for non-IC/PBS was 4.6 [standard deviation (SD), 0.9], while the mean OSPI score for IC/PBS was 21.1.

2.3. Co-occurring substance use of other psychoactive drugs and dosage of ketamine

Drug use factors included co-occurring substance use of other psychoactive drugs, duration of ketamine use, and dosage of ketamine. This study adapted questions from the Addiction Severity Index, which is a widely used, validated assessment tool for drug abuse. Participants were interviewed regarding other drugs they had used in tandem with ketamine including 3,4-Methylenedioxymethamphetamine (MDMA), amphetamine, marijuana, Gamma-Hydroxybutyrate (GHB), heroin, and hypnotics. We used face-to-face interviews to help participants recall their drug use; the timeline follow back method was used to reduce recall bias. Participants were then asked to select the dosage of ketamine they used during a typical session from several fixed dosage amounts ranging from ≤ 0.125 to ≥ 20 g/day. This question was adapted from an Internet-based global drug survey. Cumulative dosage was calculated as the product of ketamine dosage, frequency of use, and duration of ketamine use (months). Because there is very marked variation in frequency of ketamine use, we adapted a constant frequency of use as “three times per week or 12 times per month”, which is also the definition of frequent ketamine users in previous study.

2.4. Comorbid factors and depression

The comorbid factors in the study included irritable bowel syndrome, migraine, fibromyalgia, Sicca syndrome, atopy, and depression. Their presence was evaluated according to participants’ recollection of the medical diagnosis of any of the comorbidities. The presence of atopy was determined using the following question: “At any time in your life, before the onset of the voiding symptoms, did you have a food allergy, drug allergy, urticaria, allergic rhinitis, or asthma?” The questions evaluating the comorbid factors were created through the consensus of experts, namely a urologist and rheumatologist. Both are authors of the study (Ming-Huei Lee and Tsung-Ching Hu). In this study, depression was defined as being in a depressed mood for most of the day, nearly every day during a 2-week period. Depression was assessed with the face-to-face interview...
by either a psychiatrist or a psychologist. The instrument of assessing depression was based on DSM5 criteria.

2.5. Statistical analysis

With a significance level (α) of 0.05 and power of 85%, the sample size would be 120 in each group. The difference of baseline characteristics was analyzed using independent t-tests for continuous variables with normal distribution, the Mann–Whitney U-test for continuous data with skewed distribution, and Fisher’s exact test for categorical variables. Odds ratio (OR) was estimated by logistic regression analysis. In order to correct non-normality, logarithmic transformation of both the skewed data values in independent variables and dependent variable was performed. Thus duration of use and dosage of ketamine was logarithmically transformed in the independent variable, and the OSPI scores were logarithmically transformed in the dependent variable. The univariate analysis adapted the log-log model for transformed duration of use and transformed OSPI scores (ln Y OSPI scores = α₁ + β₁ln X₁ duration of use + ε₁), the log-log model for transformed dosage of ketamine and transformed OSPI scores (ln Y OSPI scores = α₂ + β₂ln X₂ dosage of ketamine + ε₂), the log-linear model for each remaining independent variable and transformed OSPI scores (ln Y OSPI scores = αₙ + βₙ Xₙ + εₙ). For estimating the adjusted β coefficient, the statistically significant independent variables were assessed through the multivariate regression analysis with the logarithmically transformed model. Change of OSPI scores equaled eβ to under log-linear model, and change of OSPI scores equaled to \([e^{\beta \log(1.1)}]\) % under log-log model. All statistical analyses were performed using SPSS.

3. RESULTS

3.1. Descriptive analysis of demographic characteristics

Among the 143 participating ketamine users (mean ± SD age, 27.1 ± 6.0 years), 25 (17.5%) had LUTS, 35 (24.3%) were women, and 23 (15.5%) were married. In addition, 49 (18.7%) consumed alcohol more than 2 days per week, and 79 (54.9%) smoked more than 11 cigarettes per day (Table 1). Of the 25 participants with LUTS, more than half (14) were women (P < 0.001).

3.2. Univariate analyses

The mean ± SD duration of ketamine use in all participants was 45.2 ± 43.2 months, with median 32 months and interquartile range 58 months. There were statistically significant associations between the logarithmically transformed duration of ketamine use and logarithmically transformed OSPI scores was (β [95% CI] 0.36 [0.20–0.51], P < 0.001). The mean ± SD dosage of use in all participants was 2.2 ± 4.6 g/day, with median 1.0 g/day and interquartile range 1.5 g/day. There were no statistically significant associations between the logarithmically transformed dosage of use and logarithmically transformed OSPI scores (β [95% CI] 0.38 [−0.12 to 0.20], P = 0.64).

Co-occurring substance use of other psychoactive drugs occurred in 44.8% of all participants; the following are the specific drugs used and the percentages of participants using them: MDMA, 39.6%; marijuana, 12.5%; amphetamine, 11.1%; GHB, 21.5%; and hypnotics, 13.9%. MDMA, marijuana, and hypnotic use was significantly associated with LUTS (OR [95% CI]: 6.81 [2.35–19.71], 2.85 [1.12–6.57], and 5.47 [1.96–15.26], respectively) (Table 2).

Comorbid diseases demonstrated significant associations with logarithmically transformed OSPI scores (β [95% CI] 0.20 [0.03–0.37], P < 0.05), which equaled that OSPI scores were 1.22 times in ketamine users with comorbid diseases compared with ketamine users without comorbid diseases. There were also statistically significant association between depression and logarithmically transformed OSPI scores (β [95% CI] 0.69 [0.50–0.88], P < 0.001). Thus OSPI scores were 1.99 times higher in ketamine users with depression than without depression (Table 3).

| TABLE 1. Baseline characteristics of all participants |
|----------------|----------------|----------------|----------------|
| Characteristics | LUTS (n = 25) | No LUTS (n = 118) | Total (n = 143) |
| Age (mean ± SD) | 27.9 ± 4.9 | 26.9 ± 6.2 | 27.1 ± 6.0 |
| Female (N [%]) | 14 (40.0) | 21 (60.0) | 35 (100) |
| Not married (N [%]) | 20 (16.7) | 100 (83.3) | 120 (100) |
| Tobacco smoking (≧11 cigarettes/day) | 13 (16.5) | 66 (83.3) | 79 (100) |
| Alcohol use (≧2 days/week) | 7 (14.3) | 42 (85.7) | 49 (100) |
| Alcohol use (≧2 days/week) | 7 (14.3) | 42 (85.7) | 49 (100) |
| Male | 10 (60.0) | 69 (84.3) | 79 (100) |
| Not married | 20 (16.7) | 100 (83.3) | 120 (100) |
| Tobacco smoking | 13 (16.5) | 66 (83.3) | 79 (100) |
| Alcohol use | 7 (14.3) | 42 (85.7) | 49 (100) |

| TABLE 2. Odds ratios regarding co-occurring substance use of other psychoactive drugs in ketamine-associated LUTS |
|----------------|----------------|----------------|----------------|
| Substance | LUTS (n = 25) | No LUTS (n = 118) | OR† (95% CI) |
| MDMA Yes | 15 | 42 | 6.81 (2.35–19.71) |
| MDMA No | 10 | 76 | 1 |
| Amphetamine Yes | 5 | 11 | 2.43 (0.76–7.58) |
| Amphetamine No | 20 | 107 | 1 |
| Marijuana Yes | 15 | 49 | 2.71 (1.12–6.57) |
| Marijuana No | 10 | 69 | 1 |
| GHB Yes | 6 | 25 | 1.78 (0.42–3.25) |
| GHB No | 19 | 93 | 1 |
| Hypnotics Yes | 9 | 11 | 5.47 (1.96–15.26) |
| Hypnotics No | 16 | 107 | 1 |

†P values were determined using the independent t tests for continuous variables with normal distribution, the Mann–Whitney U-test for continuous data with skewed distribution, and Fisher’s exact test for categorical variables. LUTS, lower urinary tract syndrome.
TABLE 3. Association between duration of use, dosage of ketamine, comorbidity, depression and ketamine-associated LUTS

| Risk factor | Crude β (95% CI) | Adjusted β (95% CI)† | Unit of comparison | Change of OSPI‡ scores |
|-------------|------------------|----------------------|--------------------|-----------------------|
| Sex         | 0.39 (0.21–0.58) | 0.20 (0.03–0.37)     | Female/male        | 1.22 times§           |
| Duration of use, month | 0.36 (0.20–0.51) | 0.21 (0.06–0.35) | 10% increase       | Increase 2.02%††       |
| Dosage of ketamine, g/day | 0.04 (–0.12 to 0.20) | — | —                  | —                     |
| Comorbid diseases | 0.20 (0.03–0.37) | 0.07 (–0.08 to 0.21) | —                 | —                     |
| Depression  | 0.69 (0.50–0.88) | 0.49 (0.29–0.70)     | Yes/no             | 1.63 times§           |

†Adjusted β was estimated by multivariate linear regression model of log transformation (ln Yi OSPI scores = a + β1 Xsex + β4 1 duration of use + β5 Xcomorbid disease + β6 Xdepression + εi). ‡OSPI scores: O’Leary symptom and problem index scores. §Change of OSPI scores equaled to under log-linear model. †Crude β was estimated by linear regression analysis of log-log model (ln Yi OSPI scores = a1 + β1 ln Xduration of use + ε1). ††Change of OSPI scores equaled to [eβ × (log(1.1))])) under log-log model. ♦Crude β was estimated by linear regression analysis of log-log model (ln Yi OSPI scores = a2 + β2 ln Xduration of use + ε2).

3.3. Multivariate analyses

After conducting the multivariate model adjusting for sex, duration of ketamine use, comorbidity and depression, we found that the independent variables significantly associated with logarithmically transformed OSPI scores included sex, logarithmically transformed duration of ketamine use and depression (β [95% CI] 0.20 [0.34–0.37], P < 0.05; 0.21 [0.06–0.35], P < 0.01; 0.49 [0.29–0.70], P < 0.001; respectively). Thus a 10% increase in months of ketamine-use increased OSPI scores by 2.02%. The OSPI scores were 1.22 times higher in females than males, and 1.63 times higher in ketamine users with depression than without depression. Comorbidity was not significantly associated with OSPI scores (β [95% CI] 0.07 [–0.08 to 0.21], P = 0.36) (Table 3).

4. DISCUSSION

The sample size (n = 120) of the study was calculated for equal and balanced groups. Under the number of the two groups were 25 and 118, we calculated the power for unequal sample size and resulted a power 62%. The power 62% should be sufficient to catch the effect and not severely underpowered.

Similar to two studies conducted in Hong Kong,26,27 we observed that the duration of ketamine-use significantly affected LUTS development in ketamine users. Mak et al. reported that people who use ketamine for more than 2 years or more than three times per week experience bladder dysfunction. These ketamine users meet the definition of “frequent users”, although whether they developed ketamine dependence or are “ketamine addicts” is unknown. Tam et al. reported that the patients in the one-stop clinic for ketamine-associated uropathy had ketamine-use for a mean ± SD period of 81 ± 36 months.27 According to the mean ± SD duration of ketamine use in our ketamine users with LUTS (79.6 ± 37.8 months), we hypothesized that long-term ketamine use—for more than 6 years—may associate with lower urinary tract impairment. Early treatment of ketamine-associated LUTS should not be delayed during this period. Thus, the cessation of ketamine use is a milestone of treatment for preventing both deterioration of renal function and remission of symptoms.28

We observed that ketamine dosage was not associated with ketamine-associated LUTS. The mean ± SD dosage of ketamine was 2.2 ± 3.5 g/day and 2.2 ± 4.8 g/day in ketamine users with and without LUTS, respectively. Contrarily, Tam et al. reported that ketamine dosage (g/week) were significantly and moderately associated with LUTS.27 In a study recruiting ketamine users with an average dosage of ketamine of 3 g/day,25 the severity of LUTS was higher than in our study. The average dosage of use in our study (2.2 g/day) was lower compared to the aforementioned study, and so was the severity of LUTS. Thus we argued that the dosage of ketamine 2.2 g/day might not reach the critical point for developing ketamine-associated LUTS. It is very difficult to accurately document the dosage of ketamine use as these abusers do not have a fixed amount of use and tend to change the frequency and amount of use from time to time. As this is a cross-sectional survey, the dosage information gathered at the time of the survey may not be the representative dosage for the abuser and therefore the dosage-symptom relationship is not established.

In this study, although MDMA, marijuana, and hypnotics use was significantly associated with LUTS in the univariate analysis, the association was not observed in the multivariate analysis. Urological complications associated with illicit drug use are being increasingly addressed.29 Furthermore, neurogenic bladder and chronic urine retention were previously reported in a case of chronic MDMA use; the mechanism of the association between chronic MDMA use and neurogenic bladder and chronic urine retention may be chronic upregulation of the sympathomimetic influence on the urinary bladder, inhibition of parasympathetic control, persistent urinary sphincter contraction, and detrusor muscle dysfunction.30 The effect of hypnotics on the lower urinary tract has not been reported. Owing to the small sample in this study, the association between co-occurring substance use of other psychoactive drugs and ketamine-associated LUTS remains unclear and warrants further investigation.

The study found OSPI scores were 1.63 times higher in ketamine users with depression than without depression. However, the causal relationship between depression and LUTS among ketamine users remains unclear. We argued that the users are compelled to self-medicate
with ketamine because the drug produces a fast-acting antidepressant effect; consequently, ketamine users with depression are more vulnerable to LUTS. Recent neurobiological studies have shown that the antidepressant effect of ketamine is associated with rapid synthesis of the brain-derived neurotrophic factor, which is involved in neuro-inflammatory abnormalities and neuro-toxic pathway. This neuro-toxic pathway was reported to lead to depression. Thereby we explained the relationship of depression and ketamine-associated LUTS as followed: patients of ketamine-associated LUTS may pursue rapid-antidepressant effect, which may consequently result in depression. Whether depression was the cause or result of ketamine-associated LUTS remained not clear. A longitudinal study was needed to answer this question.

The clinical picture of IC/PBS is denoted by the comorbidities, including irritable bowel syndrome, migraine, fibromyalgia, autoimmune disease, and atopy. The etiology of IC/PBS is associated with the dysfunction of immune-inflammatory processes and pain regulation. However, the present study did not corroborate the correlation of the preceding comorbidities with ketamine cystitis; hence, the biological mechanisms underlying IC/PBS and ketamine cystitis must be different. Evidence supports that histological changes of ketamine cystitis were quite different from that of IC/PBS.

The OSPI scores were 1.22 times higher in female than male. Another study showed a similar tendency for the female sex. Behavior tendency in dealing with bladder control, voiding, and incontinence: may be the main reason of female aggregation. This study had several limitations. First, frequency, dosage and cumulative dosage of ketamine consumed within a certain period varied considerably among the users. The skew in self-reported dosage could be due to impure drug, lack of ability of users to reliably determine a dosage or route of administration. The self-reported dosage might result in measurement bias and reduce our confidence on the measured value. Similarly, self-reported LUTS might not be an appropriate outcome measure. A diagnosis of LUTS made by a medical professional would provide far more compelling data. The more objective measurements, such as bladder diary, voided volume and functional bladder capacity, could have a more meaningful correlation with the risk factors studied and added literature value to the study. Second, the comorbid diseases were based on participants’ recollection of medical diagnoses; thus, recall bias may have occurred. To overcome this, a biomarker specific to these diseases with sufficient sensitivity and specificity should be included in future studies. Third, we did not ask if the participant had depression symptoms in the past. The temporal relationship between depression and LUTS among ketamine users was not determined. Furthermore, a previous study has verified a Chinese version of the pelvic pain and urgency/frequency (PUF) symptom scale in the evaluation of ketamine abusers and has noted a different cut-off value in these patients for having severe urinary tract damages. Hence, the direct adoption of OSPI score of ≥12 in IC/PBS to ketamine users may not be good enough. Redefining LUTS with the PUF symptom scale may be considered in future studies. Finally, the sampling method of the study did not adapt randomized sampling. The majority of individuals were recruited from police detention. The 25 of a total 143 study subjects were enrolled from hospital, therefore this current series might not be truly representing the incidence of LUTS ketamine-associated in the general population.

5. CONCLUSION

Depression and longer duration of exposure to ketamine are significantly associated with the development of LUTS among ketamine users. Early evaluation and intervention of depression should be considered in patients of ketamine-associated LUTS.

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Disclosure

The authors declare no conflict of interest.

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