

# Epidemiologic characteristics and risk factors in patients with ketamine-associated lower urinary tract symptoms accompanied by urinary tract infection

## A cross-sectional study

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### Abstract

Young adults with longstanding ketamine abuse present with lower urinary tract symptoms (LUTSs), which may be accompanied by urinary tract infection (UTI). However, the morbidity and risk factors for ketamine-associated LUTS accompanied by UTI (KALAUTI) are still unknown. To ascertain these, we surveyed patients with a history of ketamine abuse and LUTS at the time of their initial presentation.

One hundred untreated patients with ketamine-associated LUTS were initially surveyed at 3 medical institutions. The patients' basic demographic and clinical information, KALAUTI status, and possible risk factors were obtained via a questionnaire and analyzed.

Eighty-one patients were finally enrolled. Eight patients (9.88%) had a definitive diagnosis of KALAUTI and 16 (19.75%) had suspected KALAUTI. The diagnosis of KALAUTI was ruled out in the remaining 57 patients (70.37%). Patients with upper urinary tract involvement, longer duration of drug use, or more severe LUTS ( $P < .05$ ), were more prone to KALAUTI. Frequent urine culture and a higher voiding symptom score (VSS) were risk factors for KALAUTI ( $P < .05$ ), increasing the risk of KALAUTI by 44.241- and 1.923-fold, respectively.

The study indicates that frequent urine culture and severe VSS are risk factors for KALAUTI. The possibility of UTI should be considered in ketamine abusers with LUTS in the clinical setting.

**Abbreviations:** IPSS = International Prognostic Scoring System, KAC = Ketamine-associated cystitis, KALAUTI = ketamine-associated LUTS accompanied by UTI, LUTSs = lower urinary tract symptoms, SSS = storage symptom score, UTI = urinary tract infection, VSS = voiding symptom score.

**Keywords:** Cystitis, hydronephrosis, ketamine, lower urinary tract symptoms, urinary tract infection

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WW and WY contributed equally to the study.

The research involves human participants and the study was approved from by the ethics committee of the corresponding author's center. The methods were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Written informed consents were obtained from the guardians of these patients. In addition, identifying information was removed from the study. All data were kept by only the administrator of the study in a confidential manner and was not used by any other purposes.

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## 1. Introduction

Ketamine-associated cystitis (KAC) was 1st reported as a new syndrome in 2007.<sup>[1]</sup> Young adults with longstanding abuse of ketamine, an anesthetic drug and hallucinogen, presented with lower urinary tract symptoms (LUTSs) including frequent micturition, urgent micturition, dysuria, hematuria, or even uroclepsia, which are the typical characteristics of KAC.<sup>[2]</sup> It is challenging to distinguish KAC from acute cystitis because the symptoms of these 2 diseases are notably similar.<sup>[3–5]</sup> The mechanism of KAC is unclear,<sup>[4,6]</sup> although urinary tract infection (UTI) may be involved. Urine culture in patients with KAC is usually negative or only shows microbial contamination.<sup>[1,4,7]</sup> However, unexpectedly, some patients experience relief of symptoms after antibacterial therapy,<sup>[7,8]</sup> and we have commonly observed this phenomenon in our clinical practice. Because of the similarity of symptoms between KAC and acute cystitis, we speculated that some cases of KAC are accompanied by UTI. However, the morbidity and risk factors for ketamine-associated LUTS accompanied by UTI (KALAUTI) are still uncertain. To ascertain these, we surveyed patients with a history of ketamine abuse and LUTS at the time of their initial presentation.

## 2. Methods

### 2.1. Patients

One hundred untreated patients with ketamine-associated LUTS were initially surveyed from March 2013 to March 2014 at 3 medical institutions (Second Xiangya Hospital of Central South University, Brain Hospital of Hunan Province, and Kangda Detoxification Center of Hunan Province). The patients' basic demographic and clinical information, KALAUTI status, and possible risk factors were recorded in a questionnaire. Patients with diabetes mellitus, hypertension, malignant tumor, or other chronic disorders were excluded. The study was approved by the ethics committee of Fujian Provincial Hospital. Written informed consents were obtained from the guardians of these patients.

### 2.2. Questionnaire

The contents of the patient questionnaire included sex, age, educational background, status regarding having a regular sex partner, health history, total consumed dose of ketamine, status of multidrug abuse, duration of ketamine abuse, International Prognostic Scoring System (IPSS), quality of life (QoL), frequency of urine culture, type of bacteria isolated from urine culture, status of upper urinary tract involvement (UUTI, ureter ectasia, or hydronephrosis), and UTI status. The IPSS system includes 7 items, each with a value ranging from 0 to 5 according to symptom severity. Generally, the symptoms were deemed mild, moderate, or severe when the total IPSS range was 0 to 7, 8 to 19, and 20 to 35, respectively. Moreover, in the IPSS system, items 1, 3, 5, and 6 comprise the evaluation for the voiding symptom score (VSS), which was deemed positive for voiding symptoms when the value was 5 or higher. The rest of the items (2, 4, and 7) comprise the storage symptom score (SSS), which was deemed positive for urine storage problems when the value was 4 or higher. A Likert-type questionnaire was used for the QoL evaluation, with items ranging in value from 0 to 6. Generally, a QoL value of 3 or higher indicated a strong impact on the patient's daily life. The patients were interviewed face-to-face and

the clinical information was recorded in the questionnaires by a designated physician. The results of the urine culture and other medical information were also recorded in the questionnaires.

### 2.3. Related definitions and procedures

It was difficult to accurately determine the ketamine dose each patient consumed each time the drug was used. Each patient's dose of consumed ketamine was calculated according to the average dose per use and the frequency of use per week during the 3 months before the patient accepted drug addiction treatment or when the patient 1st presented. The patient's condition was defined as polydrug abuse if the patient combined ketamine with other drugs, such as Ma Gu, ecstasy, or smokable methamphetamine, or as mono-ketamine abuse if only ketamine was used. The midstream 1st morning urine was collected and cultured within 30 minutes of collection. The vulvae were thoroughly cleaned before urine collection in women. The patient was diagnosed with UUTI if unilateral or bilateral upper urinary tract dilatation or hydronephrosis on ultrasonography, abdominal radiography, intravenous pyelography, or computed tomography in the 3 months preceding or on the day of the 1st visit was noted. The UTI diagnostic criteria were in accordance with the diagnosis guideline of the Chinese Urological Association (2014 Edition). The bacteriologic criteria for UTI were definitive diagnosis when the bacterial colonies were greater than 10,000 CFU/mL in urine culture and suspected diagnosis when the bacterial colonies were greater than 1000 CFU/mL but less than 10,000 CFU/mL in urine culture. UTI was ruled out when the bacterial colonies were fewer than 1000 CFU/mL and the patient lacked infection-related symptoms such as fever or percussion tenderness over the kidney region.

### 2.4. Statistical analyses

The measurement data are presented as mean (standard deviation). The independent sample *t*-test was used for continuous variables. Univariate and multivariate logistic regression analyses were performed to determine the risk factors for KALAUTI. The enumeration data are described as ratios and were analyzed with the chi-square test. *P*-values <.05 were considered to indicate statistical significance. IBM SPSS Statistics software ver. 24.0 (IBM Co, Armonk, NY) was used for all calculations.

## 3. Results

### 3.1. Basic clinical data

Nineteen of the 100 preliminarily screened patients were excluded from the study as follows: 7 patients lacked an acceptable urine culture, 4 had urolithiasis, and 8 had a history of significant LUTS before drug abuse (2 patients were diagnosed with benign prostatic hyperplasia and the other 6 received antibacterial therapy before the 1st survey because of a self-diagnosis of prostatitis or UTI). The remaining 81 patients (59 men and 22 women) were enrolled in this study. The average age of these patients was  $28.3 \pm 6.72$  (range, 16–60) years. The average IPSS was  $15.11 \pm 6.72$ . According to the classification method described above, 11 patients (13.58%) had mild symptoms, 46 patients (56.79%) had moderate symptoms, and 24 patients (29.63%) had severe symptoms. The average VSS was  $7.53 \pm 4.29$ . Of the 81 patients, 62 (76.54%) had a VSS of 4 or higher. The average SSS was  $7.58 \pm 2.86$ . Sixty-seven of the

patients (82.72%) had an SSS of 5 or higher. The average QoL was  $3.80 \pm 1.60$ . Sixty-two of the 81 patients (76.54%) had a QoL value of 3 or higher. The average dose of ketamine each patient consumed was  $13.84 \pm 14.9$  (range, 0.17–63.00) g. The average duration of drug use was  $13.84 \pm 14.9$  (range, 1–36) months. Sixty-eight (83.95%) and 13 (16.05%) patients had a history of polydrug and mono-ketamine abuse, respectively.

Twenty-five patients (30.86%) had concurrent UUTI. The frequency of urine culture was once in 41 patients (50.62%) and twice or more in 40 patients (49.38%). Eight patients (9.88%) had a definitive diagnosis of KALAUTI and 16 (19.75%) had suspected KALAUTI. The diagnosis of KALAUTI was ruled out in the remaining 57 patients (70.37%). For comparative purposes, patients with definitive or suspected KALAUTI were categorized as the positive group and patients without a diagnosis of KALAUTI were categorized as the negative group.

### 3.2. Univariate analysis

The susceptibility factors related to the incidence of KALAUTI included age, educational background, status of having a regular sex partner, total consumed dose of ketamine, status of multidrug abuse, duration of ketamine abuse, status of UUTI, and severity of LUTS. Considering these susceptibility factors, the patients were divided into the following groups: younger ( $\leq 28.3$  years) or older ( $> 28.3$  years) age, higher (senior high school education or beyond) or lower (junior middle school education or below) education, with or without a regular sex partner, larger ( $> 13.84$  g) or smaller ( $\leq 13.84$  g) consumed dose of ketamine, mono-ketamine abuse or polydrug abuse, long-term ( $> 12.94$  months) or short-term ( $\leq 12.94$  months) ketamine use, with or without UUTI, and mild (IPSS  $\leq 15.11$ ) or severe (IPSS  $> 15.11$ ) LUTS. Chi-squared testing to determine which factors would be related to a positive incidence of KALAUTI showed no significant relationship between the incidence of KALAUTI and patients' sex, age, educational background, or consumed ketamine dose ( $P > .05$ ). However, patients tended to be positive for KALAUTI if they had UUTI, longer duration of drug use, or more severe LUTS ( $P < .05$ ) (Table 1).

### 3.3. Multivariate logistic regression analyses

We assessed the risk factors for KALAUTI using multivariate logistic regression analyses in which the dependent variables included positive and negative KALAUTI and the independent variables included sex, age, education, status of having a regular sex partner, VSS, SSS, QoL score, mono-ketamine or polydrug abuse, duration of drug use, ketamine dose, status of UUTI, and frequency of urine culture. The results showed that more frequent urine culture and higher VSS were risk factors for positive KALAUTI ( $P < .05$ ), increasing the risk of KALAUTI by 44.241- and 1.923-fold, respectively (Table 2).

### 3.4. Characterization of the bacterial spectrum

At least 1 urine culture was performed for all 81 patients. From the 1st detection in 50 patients (61.7%), 1 type of bacteria was cultured in 16 patients (19.8%), 2 types of bacteria were cultured in 9 patients (11.1%), and 3 or more types of microbial contaminants were cultured in 6 patients (7.4%). From the 2nd detection in 55 patients (67.9%), 1 type of bacteria was cultured in 15 patients (18.5%), 2 types of bacteria were cultured in 7 patients (8.6%), and 3 or more types of microbial contaminants were cultured in 4 patients (4.9%). From the samples of the 24 patients in the positive KALAUTI group, *Escherichia coli* was detected in 13 (54.17%), *Enterococcus faecalis* in 5 (20.83%), *Pseudomonas aeruginosa* in 3 (12.5%), and *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Proteus vulgaris* in 1 (4.17%) patient each.

## 4. Discussion

Our finding suggested that UTI is not rare in KAC patients with LUTS. We found that about 30% of the selected KAC patients with LUTS seemed to have KALAUTI. The incidence of KALAUTI was not related to patients' sex, age, educational background, mono-ketamine or polydrug abuse, or ketamine dose, but was related to the status of UUTI, duration of ketamine use, and severity of LUTS, suggesting that KALAUTI should be suspected in KAC patients with the latter characteristics. In addition, repeated urine culture as well as severe VSS was risk factors for KALAUTI.

**Table 1**  
Univariate Chi-squared analysis in patients with KALAUTI.

Groups	Subgroups	n	UTI (n, %)	$\chi^2$	P-value
Sex	Man	59	18 (30.51)	0.080	.777
	Woman	22	6 (27.27)		
Age	Younger	52	15 (28.85)	0.043	.836
	Elder	29	9 (31.03)		
Sex partner	Yes	44	11 (25.00)	0.990	.320
	No	37	13 (35.14)		
Education	Lower	26	10 (38.46)	1.432	.231
	Higher	55	14 (25.45)		
Drug number	MKA	13	6 (45.15)	2.028	.154
	PDA	68	18 (26.47)		
Duration	Shorter	41	6 (14.63)	8.954	.003*
	Longer	40	18 (45.00)		
Ketamine dose	Smaller	51	12 (23.53)	2.458	.117
	Larger	30	12 (40.00)		
UUTI	Yes	58	13 (22.41)	5.434	.020*
	No	25	12 (48.00)		
LUTS severity	Mild	39	2 (5.13)	21.6	.000*
	Severe	42	22 (52.38)		

KALAUTI=ketamine-associated LUTS accompanied by UTI, LUTS=lower urinary tract symptom, UUTI=upper urinary tract infection.

\*  $P < .05$ .

**Table 2**  
**Logistic regression analysis in patients with KALAUTI.**

	Regression coefficient	Standard deviation	$\chi^2$ value	P-value	OR	95% CI
Sex	0.819	1.069	0.588	.443	2.269	0.279–18.445
Age	−0.056	0.070	0.647	.421	0.945	0.824–1.084
Sex partner	−0.234	1.254	0.035	.852	0.792	0.068–9.248
Education	−0.867	1.278	0.460	.497	0.420	0.034–5.143
QoL	0.352	0.776	0.206	.650	1.422	0.311–6.504
SSS	−0.130	0.322	0.162	.687	0.878	0.467–1.651
VSS	0.654	0.310	4.460	.035*	1.923	1.048–3.527
Frequency of urine culture	3.790	1.307	8.402	.004*	44.241	3.412–573.702
Duration	−0.172	0.248	0.483	.487	0.842	0.518–1.369
Ketamine dose	0.139	0.116	1.423	.233	1.149	0.915–1.443
Status of UUTI	0.663	1.161	0.326	.568	1.940	0.200–18.867
Drug number	−1.716	1.382	1.542	.214	0.180	0.012–2.700
Constant	−8.873	6.087	2.125	.145	0.000	

CI=confidence interval, KALAUTI=ketamine-associated LUTS accompanied by UTI, OR=odds ratio, QoL=quality of life, SSS=storage symptom score, UUTI=upper urinary tract infection, VSS=voiding symptom score.

\*  $P < .05$ .

The incidence of LUTS among individuals with drug-use disorder is significantly higher than in the nondrug using population. It was reported that the incidence of LUTS was increased 2.8-fold in nonketamine substance users and 6.2-fold in ketamine users, especially in female ketamine users (9.9-fold increase), compared with a nondrug using population.<sup>[9]</sup> Another study indicated that more than 80% of ketamine abuse cases in young patients were associated with LUTS.<sup>[4]</sup> The symptoms of LUTS may be relieved in most patients after they undergo ketamine detoxification, but recur when the patients resume ketamine abuse.<sup>[1,10]</sup> However, it should be noted that some patients present with progressively worsening LUTS after quitting ketamine use several years previously.<sup>[11]</sup> In our study, the risk of UTI increased more than 1.9-fold in patients with a high VSS, compared to those with a low VSS, indicating that VSS may be an indicator for KALAUTI and suggesting that KALAUTI should be considered in patients with a history of ketamine use presenting with severe voiding symptoms.

Previous studies found that the results of most of the urine cultures in patients with KAC were negative or only showed contamination, suggesting that the symptoms of LUTS were mostly attributable to worsening KAC and that antibacterial therapy was unnecessary in those patients.<sup>[1,4,7,12–14]</sup> In our study, about 30% of patients were diagnosed with definitive or suspected KALAUTI after they had undergone one or more urine cultures, which differed from the results of previous studies. Furthermore, we identified frequency of urine culture as a risk factor for KALAUTI, in addition to VSS. In another study, moxifloxacin, a quinolone antibiotic, was found to resolve symptoms of LUTS in a patient with KAC, which suggests the possibility of KALAUTI in some patients even with negative cultures.<sup>[8]</sup> The reasons for the different conclusions of previous studies and our current findings include a relatively small sample size<sup>[1]</sup> and lack of routine urine culture.<sup>[9]</sup>

Being aware of the characteristic bacterial spectrum in patients with KALAUTI can guide the selection of appropriate antibiotic therapy. In our study, *E coli* and *E faecalis* accounted for more than half and approximately one-fifth of infections, respectively, in patients with KALAUTI. Thus, further evaluation of pathologic bladder changes and disease progression in patients with KALAUTI is necessary.

Apart from LUTS, ketamine-related hydronephrosis, renal and hepatobiliary dysfunction, gastrointestinal problems, and psychologic problems in patients with KAC have also been described.<sup>[6,15]</sup> Hydronephrosis in patients with KAC, which prevalence varies in different studies, is another important urinary problem that may be misdiagnosed and incorrectly treated.<sup>[4,16]</sup> In a recent study involving 512 individuals with a history of ketamine use, 96 (16.8%) were found to have hydronephrosis.<sup>[17]</sup> The risk factors for hydronephrosis included older age, smaller bladder capacity, abnormal serum creatinine, and abnormal liver enzymes.<sup>[17]</sup> The morbidity of hydronephrosis in our study was more than 30%, which was much higher than previously reported. The greater baseline symptom severity in our patient cohort may account for the higher hydronephrosis morbidity.

One limitation of our study is the absence of follow-up data describing the different outcomes in patients after treatment with appropriate antibiotics, which is an important factor in the management and prognosis of patients with KALAUTI. Another limitation is that the relatively small sample size (81 recruited patients) could have resulted in sampling error.

In this study, we identified the epidemiologic features of KAC patients with LUTS. Frequent urine culture and severe VSS were risk factors for KALAUTI in patients with LUTS. The possibility of UTI should be considered in ketamine abusers with LUTS in the clinical setting.

### Author contributions

LW prepared the draft of manuscript. WJ and WY performed the survey. ZQ, YL and GY reviewed the published articles. LT, HF, and YJ analyzed the data. WW and WY sponsored the study. All authors read and approved the final manuscript.

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