# Magnetic Resonance Imaging in Assessment of Patients with Ketamine-Associated Cystitis

**Bo-Han Chen**
Taoyuan Armed Forces General Hospital
**Ming-Hsin Yang**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**Chien-Chang Kao**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**Chih-Wei Tsao**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**Sheng-Tang Wu**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**Tai-Lung Cha**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**Guang-Huan Sun**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**Dah-Shyong Yu**
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center
**En Meng** ( en.meng@gmail.com )
Division of Urology, Department of Surgery, Tri-Service General Hospital, National Defense Medical Center

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**Research Article**

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# Abstract

**Background:** Ketamine-associated cystitis (KC) is a new entity of disease. Our aim is to compare the magnetic resonance imaging (MRI) appearances of urinary bladder in recreational ketamine users with lower urinary tract symptoms (LUTS) and healthy subjects.

**Materials and Methods:** MRI of pelvis was performed for 10 consecutive ketamine abusers with KC and 16 healthy young adults at a medical center in the northern Taiwan from January to December, 2011. The thickness of the bladder wall was measured and analyzed. All patients with KC had been diagnosed based on their history, clinical features and urodynamic study.

**Results:** The mean bladder wall thickness of KC patients was significantly thicker than the control group (1.45±0.23 cm vs. 0.62 ± 0.50 cm, $p < 0.001$). There is significant positive correlation between the duration of ketamine usage and the thickness of bladder wall ($r = 0.891$, $p = 0.001$); whereas the dosage of ketamine had weak positive correlation with the thickness of bladder wall ($r = 0.413$, $p = 0.235$). Furthermore, the thickness of bladder wall was also strong correlated with maximum urethral closure pressure (MUCP; $r = 0.855$, $p = 0.002$).

**Conclusions:** Ketamine-associated cystitis causes increased bladder wall thickness which may be related to the bladder outlet obstruction. MRI is a useful tool to evaluate the bladder wall thickness and contributes to the diagnosis of ketamine associated cystitis.


# Introduction

Ketamine, which is also known as‘K’, ‘ket’ and ‘special K’, is a derivative of phencyclidine. It is a non-competitive antagonist of the N-methyl-d-aspartate (NMDA) glutamatergic receptor. Approximately 90% of the metabolites are excreted by urine and an elimination half-life of 2-3h in adults is considered to be standard [1]. It is usually used for anesthetic purposes. However, in the past few years, ketamine has become a popular street drug in the UK, Australia, Taiwan and many Asian countries. The effects of ketamine, such as psychotomimetic symptoms, hallucinations, and out-of-body experiences make the drug widely used among young adults in the clubs and pubs for recreational purposes. Within the booming amount of ketamine abusers, about 20-30% of them are suffering from lower urinary tract symptoms (LUTS), such as dysuria, urinary frequency, urgency, bladder pain and incontinence after long-term ketamine use [2-5].

Furthermore, lower urinary tract uropathy, ketamine-induced vesicopathy (KIV), including cystitis, contracted bladder, and secondary vesicoureteral reflux are also reported[6]. The cystoscopic and pathologic findings include ulcerative, hemorrhagic cystitis, epithelial inflammation, neovascularization, eosinophil infiltration, and petechiae[6,7]. Imaging studies often reveal bilateral hydroureteronephrosis, a contracture bladder, and increase wall thickness of bladder [8]. The aim of this study is to compare the

magnetic resonance imaging (MRI) features of patients with ketamine-associated urological symptoms to healthy subjects.

# Materials And Methods

Ten consecutive patients (four female and six male) with KC and 16 healthy subjects (seven female and nine male) were enrolled in this study from January, 2011 to December, 2011. All subjects received non-contrast MRI of pelvis. The study protocol was approved by the institutional research committee (TSGHIRB-20110607, Institutional Review Board of Tri-service General Hospital, National Defense Medical Center, Taiwan, R.O.C.). All participants were at least 18 years old and they all signed the informed consent with full comprehension of the risk and benefits of the following tests, procedures and treatments. The ten ketamine abusers had history of ketamine use by insufflation for 3 months or more. Careful history taking of ketamine use, including mean dose usage per day and duration of drug abuse was performed by one urologist with confidential interviews. They received urodynamic studies and had undergone cystoscopy with bladder wall biopsies, which confirmed the diagnosis of ketamine-associated cystitis. The urine toxicological profiles of these patients were positive for ketamine. Exclusion criteria were LUTS before starting ketamine use, use of urological medications, and positive urine culture. All subjects included were requested to receive the bladder scan examination every ten minutes for evaluating the urine amount in the urinary bladder. When the urine amount in bladder reached 100 mL, the subjects were positioned in a 1.5T MRI scanner (Achieva, Philips) laying in a supine posture and MRI images of pelvis (1.5T, 38 cm DFOV, and 0.5 mm slice thickness) were obtained. The thickest part of the bladder wall was measured and analyzed.

Descriptive statistics were used for patient characteristics and urodynamic data. Values were given as mean (± S.E.M). Independent samples t tests were performed on the variables that evaluated differences between groups as appropriate. Scatterplots and Spearman's correlation coefficients were used to investigate the associations between both bladder thickness and MUCP and the duration or dose of ketamine use. A 0.05 significance level was used for all statistical tests. Statistical analysis was performed by using SPSS version 17 for Windows (SPSS, Chicago, IL, USA).

# Results

The mean age, mean height, mean weight, and BMI of the patients with recreational ketamine abuse with the lower urinary tract symptoms are 21.90 ± 3.11 years, 164.50±3.80 cm, 57.40 ± 8.20 kg, and 20.30 ± 2.40 kg/cm$^2$. The medium dose of taking ketamine is 3.50±0.745 gm, and the medium duration of taking the drug is 30.00 ± 2.79 months. Among the sixteen healthy subjects, mean age 22.21 ± 2.30 years, mean height 165.56±4.62 cm, mean weight 56.76 ± 9.14 kg, and BMI 21.36 ± 2.30 kg/cm$^2$ were recorded. No statistically significant result was found. MRI study revealed mean bladder wall thickness of patients and controls are 1.45 ± 0.23 cm and 0.62 ± 0.50 cm with statistically significant ($P$ < 0.001, Table 1). The patients' bladder walls show low-signal intensity on both T1 and T2-weighted images (Fig. 1). There is significant positive correlation between the duration of ketamine usage and the thickness of bladder wall

($r$ = 0.891, $p$ =0.001); whereas the dosage of had weak positive correlation with the thickness of bladder wall ($r$ = 0.413, $p$ =0.235). (Table 2, Fig. 2A, B). The urodynamic study showed high level of MUCP (114 ± 21.12 cmH2O), and the correlation with bladder thickness is statistically significant ($P$ = 0.002) (Table 2, Fig. 2C). In order to exclude bladder malignancy, all patients underwent cystoscopic bladder biopsies. The histologic finding showed the urothelium was extremely denuded, with submucosal granulation formation and hypervascularity(X200). Higher magnification (X400) revealed intravascular eosinophils, lymphocytes, neutrophils, and plasma cells in the mucosa and submucosal layer of bladder. (Fig. 3 A and B).

# Discussion

The mechanism and etiology of ketamine-associated urinary tract dysfunction remains unclear. Metabolites of ketamine such as norketamine and hydroxynorketamine can be measured in high quantities in the urine of patients with ketamine usage [9]. It is possible that the active metabolites of ketamine cause direct toxic effect and induce significant lower urinary tract symptoms. Current considerations for diagnosis of ketamine-associated cystitis include the history of using ketamine, the lower urinary tract symptoms, image study results or cystoscopic findings, and the discoveries in pathologic report. Wu et. al. reported that contracture of bladder and increase wall thickness of bladder are discovered [8]. In our study, thickness of bladder wall was confirmed thicker in the patients using ketamine compared with healthy subjects (1.45±0.52 cm and 0.62±0.50 cm with statistically significant, p< 0.001). In a normal distended urinary bladder (more than 150cc), the thickness of the bladder wall ranges from 0.3 to 0.5 cm. However, in a non-distended or hypersensitive bladder, the thickness of the bladder wall ranged 0.5 to 0.8cm. The impotence of bladder wall thickness is that the number at cut-point 0.5cm in the normal distended bladder was positive correlation of bladder outlet obstruction. Besides, BWT also found that it was negative correlation to Qmax（$r$= - 20.34，$P$ =0.0001）and positive correlation to PVR（$r$ = 0.33，$P$ = .001）[10]. On T1-weighted MRI images, the normal bladder wall appears as a low-signal intensity band. On T2-weighted MRI images, the normal bladder wall reveals as a low-signal intensity band as well and represents the entire muscular layer [11,12,13]. These findings were certainly detected on our healthy subjects (Fig. 3). There are many differential diagnoses among increase thickness of bladder wall, such as cystitis, granulomatous disease and benign or malignant masses.

The image finding of the bladder wall with cystitis on MRI usually shows low-signal intensity on T1-weighted images and relatively high-signal intensity on T2-weighted images. The result is because of the edematous change in inflammatory lesions [12]. Our patients, however, show low-signal intensity on both T1 and T2-weighted images. In patients with genitourinary tuberculosis, bladder involvement is not uncommon. Focal granulomatous reactions often result in intravesical lesions with high-signal intensity on T2-weighted images [13] . Such finding also does not occur on our patients. Low-signal intensity on T2-weighted images is commonly caused by fibrotic changes or increased cellularity [13,14]. These findings correlated with the pathologic reports of bladder tissue in patients with ketamine associated cystitis. The

pathologic appearances often frequently include inflammatory cells and eosinophils infiltration and a diverse degree of fibrosis which are distinct from typical eosinophilic cystitis [4267].

Differential diagnosis with other benign and malignant tumors is critical for the KC patients. Leiomyoma shows submucosal origin of the mass, but the MRI appearance and enhancement are dependent on the presence of cystic degeneration. The typical bladder leiomyoma has intermediate T1 and low-signal intensity on T2 weighted images. Furthermore, leiomyosarcomas are more heterogeneous with poorly defined margins [15] . In patients with pheochromocytoma of bladder, the lesions often reveal increased signal on T2-weighted images [13] . In cases of hemangiomas and rhabdomyosarcomas of bladder, high signal intensity on T2-weighted images would be detected [13]. Other tumors such as urothelial cell carcinoma, small cell carcinoma, adenocarcinoma, and neurogenic tumors are not specific on non-contrast MRI images. Though we cannot easily distinguish a tumor without the use of intravenous gadolinium contrast agents, which is our limit in this study, several clues can let us exclude the possibility of tumor lesions. Aggressive neoplasm seldom shows the pattern as the near circumferential thickening of the bladder wall and the smooth surface of the bladder mucosa. Inflammatory process would be more favored in our subjects.

Huang et al. [16] have shown that 75% of patients using ketamine had a very high MUCP (MUCP > 90 cmH2 O) in the urethral pressure profilometry. Our patients showed the same results (Table 2). MUCP is correspond to the rhabdosphincter at the level of the midurethra and is a measure for evaluating bladder outlet function. High MUCP may result in high voiding pressures and consequently cause detrusor hypertrophy and increased bladder wall thickness. Furthermore, high MUCP may be associated with urethrovesical reflex [17] . Our patients show the same clinical manifestation, the level of MUCP was high, and the correlation with bladder thickness is statistically significant ($P$ = 0.002) (Table 2, Fig. 2C). The thickness of bladder seems to be caused by smooth muscle hypertrophy or bladder outlet obstruction. Furthermore, the pathologic appearance showed a diverse degree of fibrosis of bladder wall, it might be one of the reasons that made the bladder wall thicker.

Most patients with symptoms reported a correlation between the severity of all lower urinary tract symptoms and the taken dosage and duration. Some even reported that the symptoms relieved when more water intake after using ketamine [18]. It seems that the dose of taken ketamine plays an important role in the process of the symptoms or signs. However, in our study, there was weak relation between the thickness of bladder wall and drug administration dosage. This is probably due to the limited number of cases were included. Moreover, resent study showed the maximal bladder capacity is significant lower in the patients who used ketamine for more than 3 years and who used ketamine more than 5 gm daily [16] . However, in our study, there was 50 percentage of patients with a fewer dosage of ketamine use. It is plausible that the dosage was not high enough to exhibit the correlation with the thickness change of the bladder wall. There are other limitations in this study. The data were collected in a retrospective fashion and a limited number of cases were included. On the other hand, the reliability of the drug histories from confidential interviews is still uncertain, it is not easy to decrease the inherent bias. Furthermore, whether

the thickened bladder wall a reversible phenomenon is still unknown. The available data are scanty for excavating more information. A further study is still required to understand the in-depth relationship between the disease and change of the anatomy of the bladder.

In conclusion, we compared MRI appearances of the urinary bladder in recreational ketamine users with LUTS and healthy subjects. Ketamine-associated cystitis caused increased bladder wall thickness that may be correlated with the symptoms of the patients. The current study demonstrated that MRI may be an optional tool to diagnose ketamine-associated cystitis; however, they may not be useful in determining the severity of the disease. While ketamine-associated cystitis appears to be a relatively new clinical entity, the detrimental effects and results are a phenomenon that all urologists must be aware of.

# Declarations

### Competing interest

The authors declare that they have no conflict of interest.


### Acknowledgements

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### Ethics approval and consent to participate

The study protocol was approved by the institutional research committee (TSGHIRB-20110607, Institutional Review Board of Tri-service General Hospital, National Defense Medical Center, Republic of China). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants were at least 18 years old and they all signed the informed consent with full comprehension of the risk and benefits of the following tests, procedures and treatments. The study protocol was approved by the institutional research committee (TSGHIRB-20110607, Institutional Review Board of Tri-service General Hospital, National Defense Medical Center, Republic of China). All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later

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### Consent for publication

Not applicable.

### Data Availability Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' contributions

BHC and CCK wrote the original draft. MHY, CWT and DSY performed data curation. STW, GHS and TLC were involved in visualization. EM was responsible for project administration. All authors read and approved the final manuscript.

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# Tables

**Table 1. Characteristics of the study population**

| Parameter | Cases(n=10) | Controls(n=16) | p-value |
|---|---|---|---|
| | (Mean ± SD) | (Mean ± SD) | (Student *t* test) |
| Age | 21.2 ± 2.4 | 22.2 ± 2.3 | 0.2 |
| Height (cm) | 164.5 ± 3.8 | 165.6 ± 4.6 | 0.18 |
| Weight (Kg) | 57.5 ± 8.2 | 56.8 ± 9 | 0.32 |
| Bladder wall thickness (cm) | 1.45 ± 0.5 | 0.62 ± 0.5 | <0.001 |

**Table 2. Associations of bladder wall thickness with duration and dosage (n =10)**

| Parameter | Cases(n=10) | p-value |
|---|---|---|
| | (Mean ± SD) | (Student *t* test) |
| Duration of using Ketamine(month) | 37.2 ± 19.34 | 0.001 |
| Ketamine dose usage (gm) | 4.75 ± 2.75 | 0.235 |
| MUCP (cmH2O) | 114.5 ± 21.12 | 0.002 |

# Figures

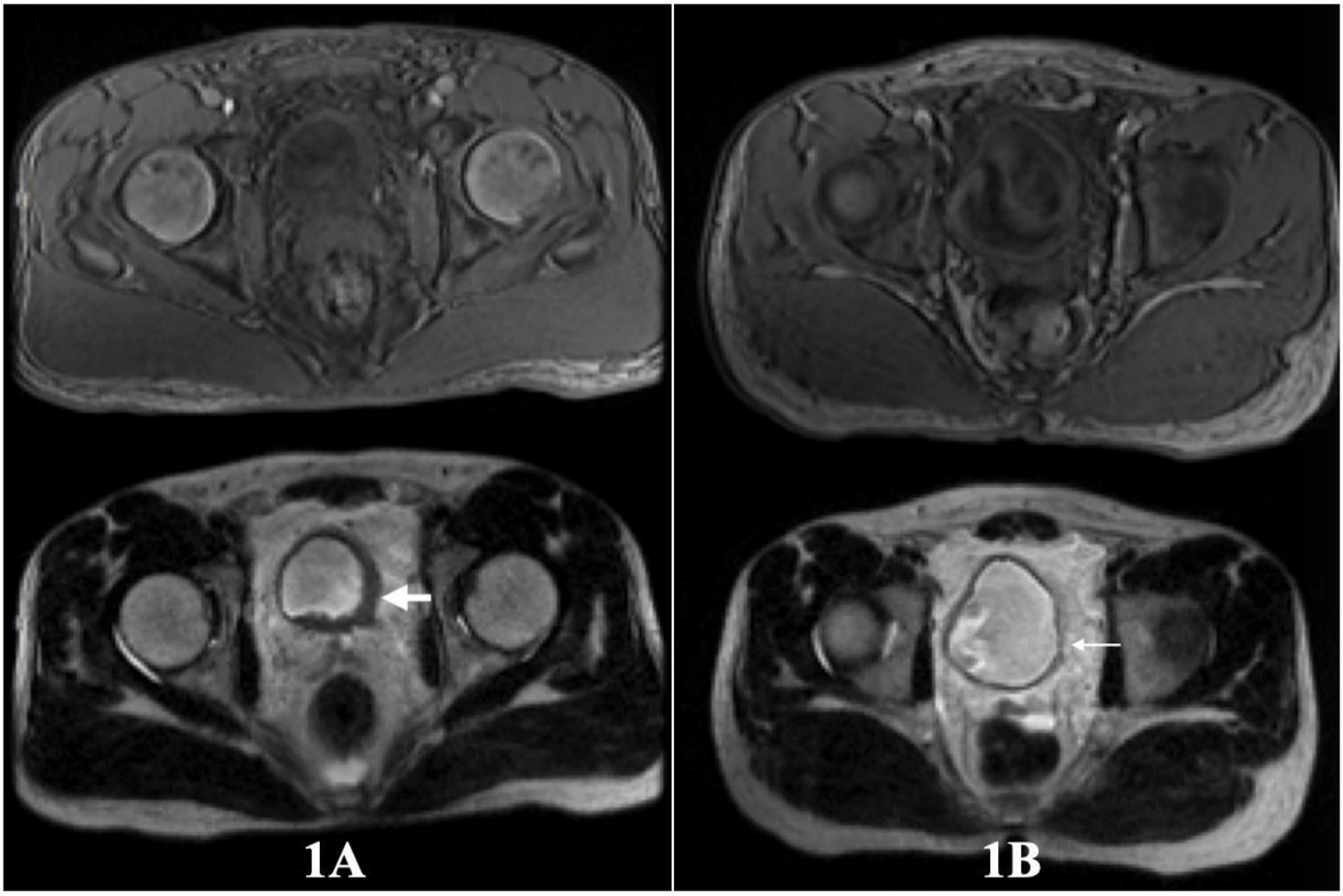
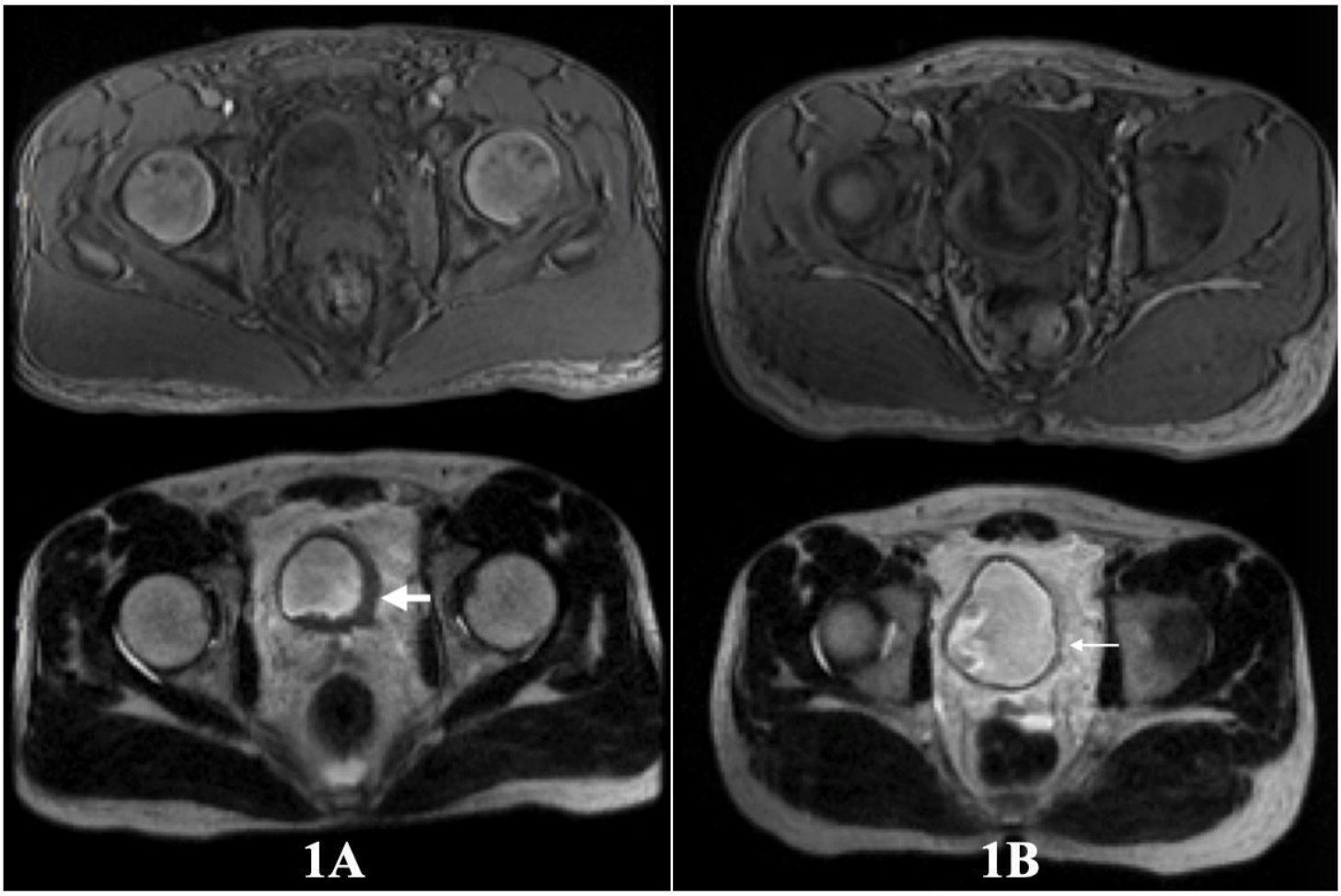



**Figure 1**

(A)MRI imaging demonstration of increase thickness of bladder wall of one of the ketamine using patient (short arrow). The bladder wall shows low-signal intensity on both T1 and T2-weighted images. (B)MRI imaging revealed normal thickness of bladder wall of a healthy subject (long arrow). The bladder wall also showed low-signal intensity on both T1 and T2-weighted images.

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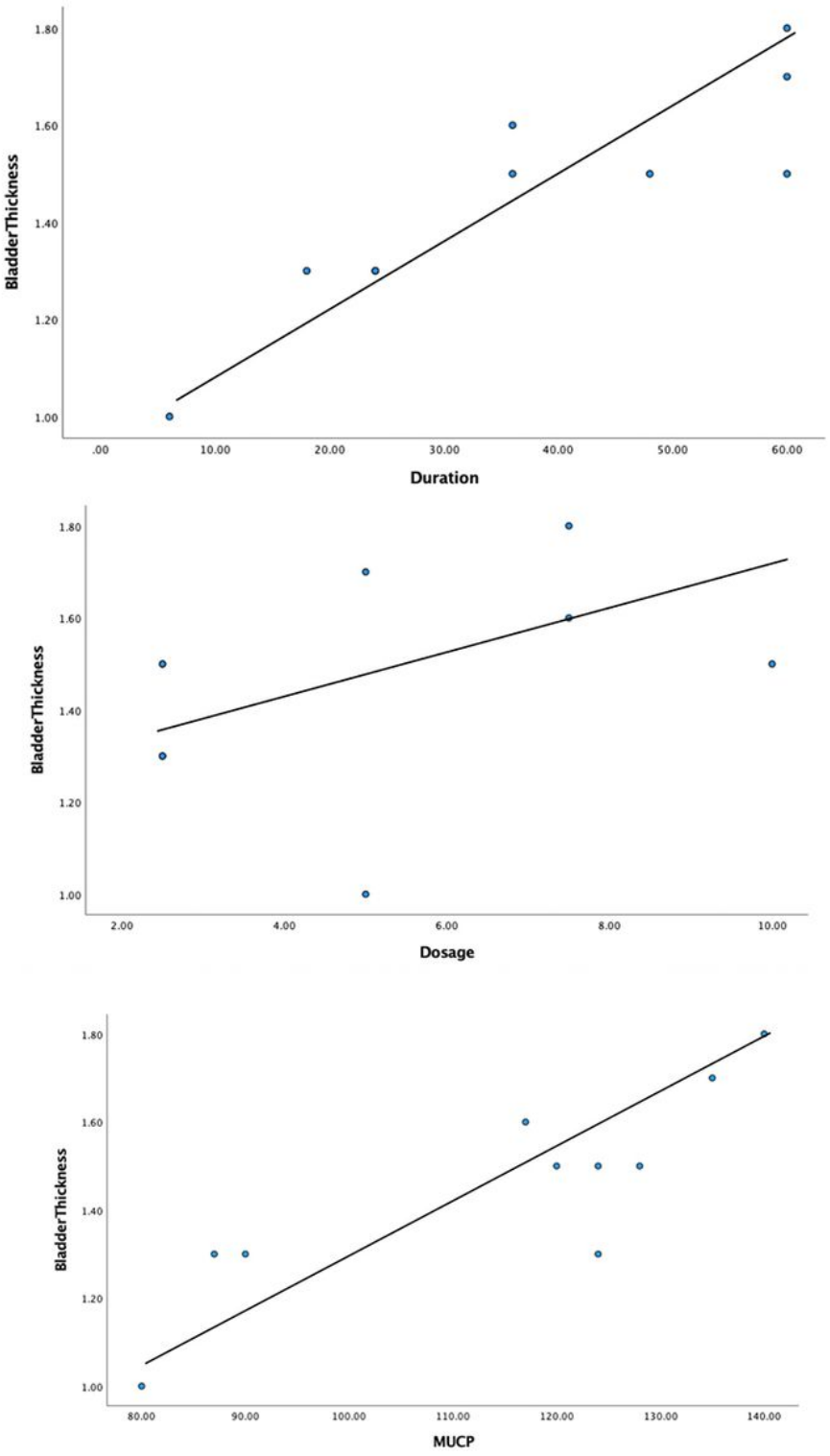
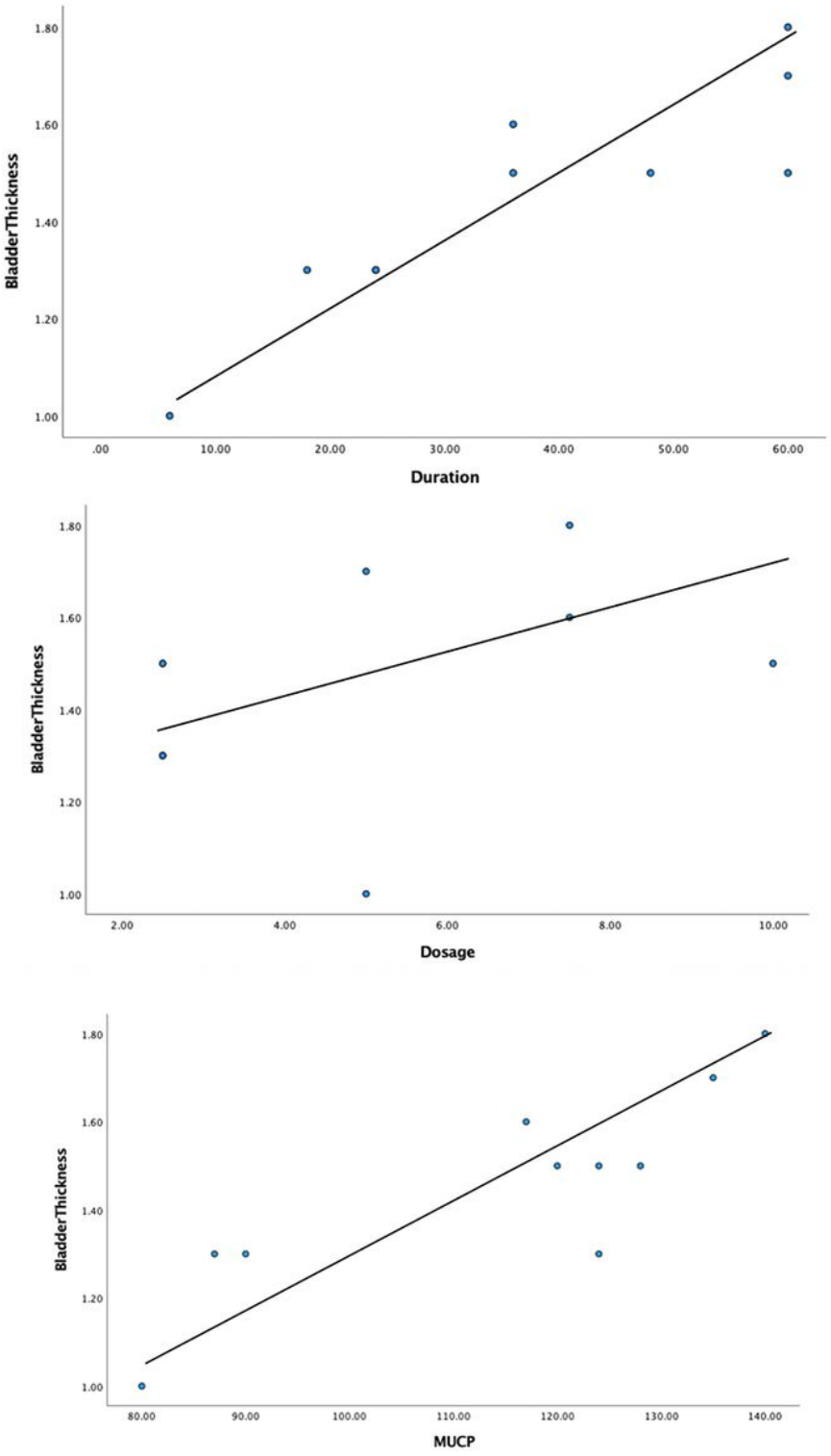



## Figure 2

(A) Correlation between bladder thickness and duration of ketamine use. (B) Correlation between bladder thickness and duration of ketamine use. (C) Correlation between bladder thickness and MUCP.

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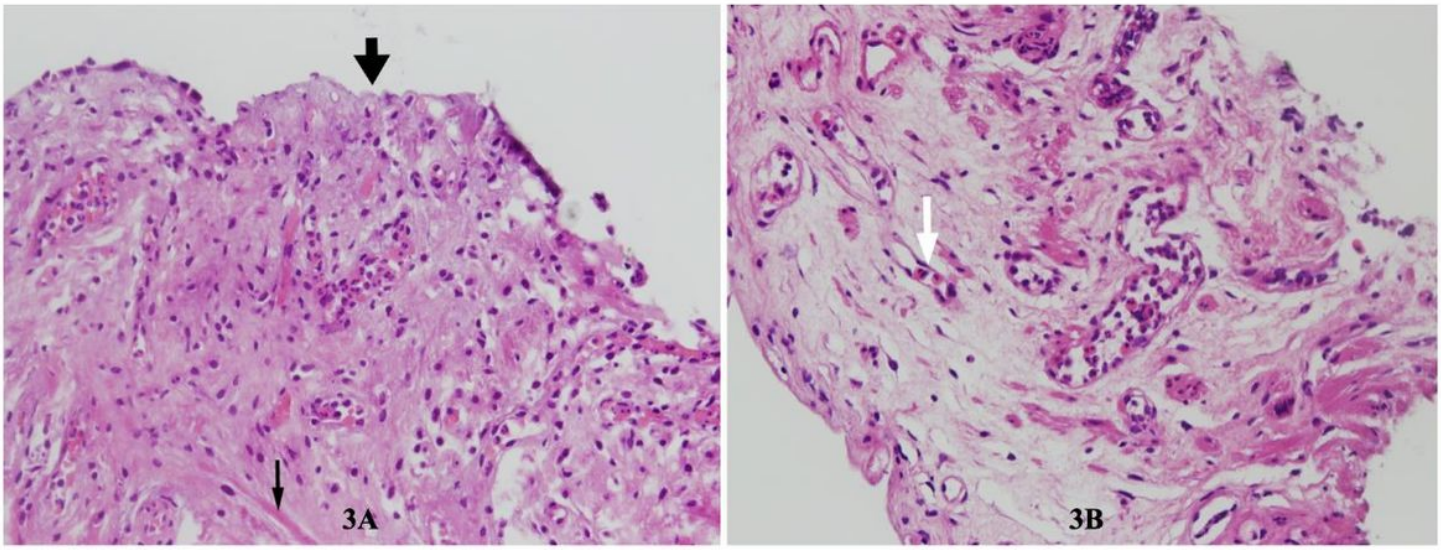
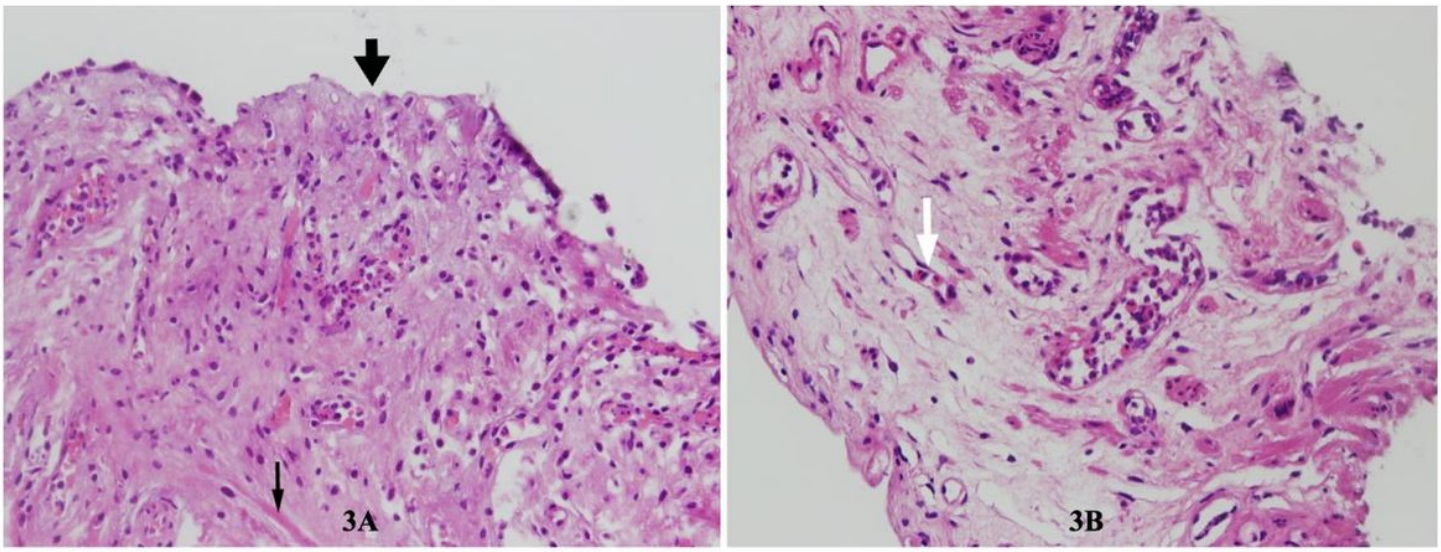



## Figure 3

Histological examination of ketamine cystitis Epithelium is extremely denuded (Short black arrows) with submucosal granulation formation and smooth muscle degeneration (long black arrows) (magnification, ×200). (B) Intravascular eosinophils acumination (white arrows) (magnification, ×400).

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