

Elevated Serum IgE May be Associated with Development of Ketamine Cystitis

Jia-Fong Jhang,* Yung-Hsiang Hsu,* Yuan-Hong Jiang and Hann-Chorng Kuo†

Departments of Urology and Pathology (YHH), Buddhist Tzu Chi General Hospital, Tzu Chi University, Hualien, Taiwan, Republic of China

Purpose: Previous studies revealed bladder mast cell and eosinophil cell infiltration in patients with ketamine cystitis. Due to possible hypersensitivity in those with this condition we investigated the association of serum Ig, histology findings and symptoms in patients with ketamine cystitis.

Materials and Methods: We evaluated patients with ketamine cystitis for maximal bladder capacity, serum IgE, IgG and IgM, and pain visual analog scale score. Bladder biopsies were assessed for mast cells and eosinophils. Patients with interstitial cystitis/bladder pain syndrome, acute bacterial cystitis and controls were also studied. We used the Mann-Whitney U test for nonparametric data to compare serum IgE among groups with $p < 0.017$ considered significant.

Results: Median serum IgE was significantly higher in the 20 patients with ketamine cystitis (205.5 IU/ml, IQR 36.9, 514.0) than in the 10 controls (33.4 IU/ml, IQR 13.5, 71.7, $p = 0.015$) and the 15 with acute bacterial cystitis (34.6 IU/ml, IQR 24.2, 101.9, $p = 0.015$). It was marginally higher than in the 13 patients with interstitial cystitis/bladder pain syndrome (65.8 IU/ml, IQR 11.9, 133.0, $p = 0.029$). Of patients with ketamine cystitis the median visual analog scale pain score was significantly higher in those with serum IgE greater than compared to less than 200 IU/ml. Maximal bladder capacity was significantly less in patients with ketamine cystitis who had higher IgE. Patients with severe or moderate bladder eosinophil infiltration had a greater visual analog scale score, higher serum IgE and smaller maximal bladder capacity than patients with no or mild eosinophil infiltration. Serum IgE and the visual analog scale score correlated significantly ($r^2 = 0.318$, $p = 0.01$).

Conclusions: Patients with ketamine cystitis had higher serum IgE than patients with interstitial cystitis/bladder pain syndrome or acute bacterial cystitis, or controls. Serum IgE and the severity of eosinophil infiltration were associated with bladder pain severity and small maximal bladder capacity.

Key Words: urinary bladder, cystitis, ketamine, substance-related disorders, immunoglobulins

Abbreviations and Acronyms

CBC = cystometric bladder capacity

DO = detrusor overactivity

IC/BPS = interstitial cystitis/bladder pain syndrome

KC = ketamine cystitis

MBC = maximal bladder capacity

VAS = visual analog scale

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* Equal study contribution.

† Correspondence and requests for reprints: Department of Urology, Buddhist Tzu Chi General Hospital, 707 Chung-Yang Rd., Section 3, Hualien, Taiwan 970, Republic of China (telephone and FAX: +886-3-865-1825, extension 2113; e-mail: hck@tzuchi.com.tw or yhhsu@mail.tcu.edu.tw).

THE noncompetitive N-methyl-D-aspartate receptor antagonist ketamine is widely used as an anesthetic agent in humans.¹ It has been increasingly used by young people all over the world as a recreational drug. Recreational use of ketamine might

induce distortion of time and space, hallucinations and mild dissociative effects.¹ Many young patients use the drug for a long duration before they experience urinary frequency, urgency and severe bladder pain, as first described by Shahani et al.² The

number of patients with KC is currently increasing. In the United Kingdom about a quarter of ketamine abusers reported experiencing urinary symptoms.³ KC cystoscopy findings reveal varying degrees of neovascularization, petechial hemorrhage and ulceration.⁴ On histological examination bladder biopsies show denuded urothelial mucosa with focal areas of ulceration and the lamina propria demonstrates granulation tissue and fibrosis, infiltrated mainly by mast cells and a varying number of eosinophils.⁴ Immunofluorescence tryptase assays in our previous study also revealed more activated mast cells in patients with KC than in healthy control patients.⁵

Termination of ketamine use is essential for KC treatment and in most patients symptoms improve after stopping ketamine abuse for 1 year.⁶ Several studies focused on KC pathogenesis but the actual mechanism is still unclear. Chu et al suggested that an immune reaction of bladder urothelium and submucosa might be the possible pathogenesis of KC.⁷ Mast cells and eosinophils infiltrating submucosal tissue suggest a hypersensitive or allergic reaction.⁸ Based on histopathological findings and symptom improvement after stopping ketamine use we hypothesized that bladder hypersensitivity might contribute to the underlying pathogenesis of KC.

Hypersensitivity results in many diseases in the respiratory tract, gastrointestinal tract and vascular system. IgE antibodies were convincingly linked to the pathophysiology of hypersensitivity reactions.⁹ Increased serum IgE correlates with allergic rhinitis and asthma.^{10,11} Patients with eosinophilic esophagitis also have increased serum IgE as well as increased IgE production in the esophageal submucosa.¹²

Since eosinophils and mast cells are highly present in KC bladders, we hypothesized that KC might involve hypersensitivity and serum IgE might be increased in patients with KC. Thus, we investigated the serum Ig profile and bladder biopsy histological findings, and their associations with clinical symptoms in patients with KC.

MATERIALS AND METHODS

From 2011 to 2013 patients admitted to Hualien Tzu Chi General Hospital due to suspected KC were retrospectively recruited for this study. All patients reported previous recreational use of ketamine at least 6 months in duration. The frequency of ketamine use in these patients was at least twice per week and each dose was at least 3 gm. All patients reported lower urinary tract symptoms at least 3 months in duration, including intolerable bladder pain, and severe urinary frequency and urgency. Some patients also complained of hematuria or urinary incontinence. All cases were refractory to oral medication,

including nonsteroidal anti-inflammatory drugs and antimuscarinics. Patients were hospitalized for diagnostic cystoscopic hydrodistention performed using general anesthesia.

Patients with concurrent urological problems such as acute bacterial cystitis, urolithiasis, stress urinary incontinence or neurogenic voiding dysfunction were excluded from study. Those with a history of neoplasms, asthma, collagen vascular diseases or parasitic infections were also excluded. We did not exclude patients with a history of allergic rhinitis due to the 26.3% prevalence in the general population in Taiwan¹³ but those with acute respiratory tract symptoms were excluded.

After study enrollment patients underwent comprehensive medical history reviews and the duration of ketamine abuse was recorded. Patients who had continued to use ketamine in the most recent month preceding hospitalization were considered current drug abusers. Bladder pain was measured using a VAS for the average perception of bladder pain. Videourodynamic studies were performed to investigate CBC, detrusor pressure and presence of DO. Renal ultrasound or excretory urography was done to detect hydronephrosis. Blood samples were collected and sent to the laboratory to measure serum Ig, including IgE, IgM and IgG. Total serum Ig was measured using the Specific Immunoglobulin FEIA solid phase immunoassay (Phadia®) with serum IgE greater than 200 IU/ml considered abnormal.¹⁴ Serum IgA, IgD and light chain were not investigated because they are not conventionally associated with hypersensitivity.

All patients underwent cystoscopic hydrodistention under anesthesia at an intravesical pressure of 80 cm water. Bladder glomerulations and MBC were recorded. Random biopsies of the posterior bladder wall were obtained after cystoscopic hydrodistention. Each specimen was 2 mm in diameter and only bladder mucosa was obtained. Bladder biopsy specimens were sent to the hospital pathology department for investigation. A single pathologist blinded to clinical results reviewed bladder histology and graded bladder inflammation and eosinophil infiltration on a 4-point scale, including 0—none, 1—mild, 2—moderate and 3—severe. If patients still experienced bladder pain and severe urinary frequency, and had CBC less than 150 ml after cystoscopic hydrodistention and conservative treatment, augmentation enterocystoplasty with partial cystectomy was suggested for rapid symptomatic relief and early return to work.¹⁵

Immunohistochemical staining for specific cell infiltrations and mast cells in the whole layer KC bladder was also performed in the partial cystectomy specimen. Immunohistochemistry staining was performed on formalin fixed, paraffin embedded tissues using labeled streptavidin from a complex kit (Dako, Glostrup, Denmark). Individual tissue sections (4 to 5 µm) were deparaffinized. The immunohistochemical technique involved sequential application of antibodies, including primary mouse anti-C-kit antibody (1:100, NeoMarkers, Fremont, California), a biotinylated anti-rabbit antibody and anti-mouse secondary antibodies for a half hour and tertiary streptavidin peroxidase (Dako) for another half hour. Immunoprecipitation sites were identified by light microscopy. Positive and negative control sections were run parallel with each assay. Sections

were also stained with Masson trichrome stain (Dako) using the standard Masson trichrome staining procedure.

Controls were also evaluated for serum IgE, IgM and IgG levels. Controls were recruited without coercion from among hospital employees and research assistants with no history of upper urinary tract infection and no lower urinary tract symptoms. Serum from 11 patients with IC/BPS and 15 with acute bacterial cystitis were also assessed for IgE, IgM and IgG. This study was approved by the Tzu Chi General Hospital ethics committee. Written informed consent was obtained from all patients with KC and healthy controls before enrollment.

Serum Ig was compared in patients with KC, normal controls, patients with IC/BPS and patients with acute bacterial cystitis using the Mann-Whitney U test for nonparametric data with $p < 0.017$ considered statistically significant. Patients with KC were classified into subgroups by IgE level, current ketamine use and severity of eosinophil infiltration. Urodynamic, VAS, MBC and serum Ig findings were compared among subgroups with $p < 0.05$ considered statistically significant. The chi-square test was used to evaluate detrusor overactivity, hydronephrosis and the indispensable augmentation enterocystoplasty rate in patients with KC who had normal or abnormal IgE. Pearson correlation coefficients were calculated to determine correlations of CBC, VAS and MBC with serum IgE. All analysis was done with SPSS® for Windows®, version 12.

RESULTS

Enrolled in the study were 10 women and 10 men with a mean $\pm$ SD age of 25.3 ± 3.48 years who had KC, 7 women and 3 men with a mean age of 27.9 ± 4.01 years who served as controls, 11 women and 2 men with a mean age of 53.8 ± 14.1 years who had IC/BPS and 15 women with a mean age of 61.7 ± 17.6 years who had acute bacterial cystitis. All 20 patients with KC underwent full clinical examination and cystoscopic hydrodistention. Three patients refused bladder biopsy. Table 1 lists clinical information, videourodynamic data, serum Ig levels and histopathology results.

Only patients 6, 10 and 11 with KC had a history of allergic disease (allergic rhinitis) but none had active symptoms. Ten patients with KC had videourodynamic proven DO and 6 had hydronephrosis. A total of 14 patients with KC reported current ketamine use, including 8 who subsequently underwent augmentation enterocystoplasty.

All 17 bladder specimens were histologically reviewed. Histopathology revealed a largely denuded bladder epithelium with or without granulation tissue formation and mild to moderate mast cell predominant inflammatory infiltration. All except 1 bladder specimen showed eosinophil infiltration. Immunohistochemistry staining in 1 partial cystectomy bladder specimen revealed moderate C-kit positive mast cell infiltration (fig. 1, A). Masson

trichrome stain in 1 specimen showed fibrinoid material in the lumen of arterioles, indicating fibrinoid necrosis in the arterioles (fig. 1, B). In the partial cystectomy specimen eosinophil and mast cell infiltration were also found in the muscle layer. Bladder tissue histopathology demonstrated no specific picture but increased mast cells and eosinophil infiltration were identified in almost all specimens.

Median serum IgE in patients with KC was higher than in patients with IC/BPS or acute bacterial cystitis, or normal controls ($p = 0.029$, 0.015 and 0.015 , respectively, table 2 and fig. 2). Median serum IgG was significantly lower than in patients with IC/BPS and normal controls. Of patients with KC those with serum IgE greater than 200 IU/ml had a significantly higher median VAS pain score than those with serum IgE less than 200 IU/ml (table 3). Median MBC in patients with KC and serum IgE greater than 200 IU/ml was also smaller than in those with serum IgE less than 200 IU/ml. Patients who had recently used ketamine had significantly higher serum IgE and IgM, and VAS pain scores than patients without recent ketamine use. Median CBC was also smaller in patients who recently used ketamine than in those who had stopped ketamine use.

Six patients were followed at our clinic 3 months after the initial investigation. Patients 12 and 17 had stopped ketamine. Each had low serum IgE (21.2 and 7.8 IU/ml, respectively) and bladder pain improvement. In contrast, the other 4 patients who continued to use ketamine had persistently high serum IgE (mean 1,865 IU/ml) and complained of severe bladder pain and urinary frequency.

Patients with moderate or severe bladder eosinophil infiltration had greater median VAS pain scores, higher serum IgE and smaller MBC than patients with no or mild eosinophil infiltration. Four of the 9 patients (44%) with serum IgE less than 200 IU/ml had recently used ketamine. In contrast, 9 of the 11 patients (91%) with serum IgE greater than 200 IU/ml had recently used ketamine ($p = 0.05$). All patients who underwent augmentation enterocystoplasty had serum IgE greater than 200 IU/ml. DO and hydronephrosis rates did not significantly differ between patients with serum IgE greater vs less than 200 IU/ml. Serum IgE correlated significantly with VAS pain score ($r^2 = 0.318$, $p = 0.01$) but IgE did not correlate with MBC ($r^2 = 0.099$, $p = 0.176$) or with CBC ($r^2 = 0.122$, $p = 0.132$, fig. 3).

DISCUSSION

To our knowledge we report for the first time significantly increased median serum IgE in patients with KC compared to healthy controls and patients with acute bacterial cystitis. KC bladder

Table 1. Patient details, clinical presentation, serum Ig and ketamine abuse histology findings

Pt—Age—Sex No.	History (mos)		VAS	CBC (ml)	MBC (ml)	Detrusor Overactivity	Hydronephrosis	Ig (IU/ml)			Inflammation*	Eosinophil†	Granulation	Recent Use	Augmentation Enterocystoplasty
	Ketamine Abuse	Lower Urinary Tract Symptoms						E	M	G					
1—21x—M	60	12	8	49	100	Pos	Pos	1,809	106	890	2	3	Pos	Pos	Pos
2—22—F	36	3	8	34	200	Neg	Neg	39.4	166	957	2	1	Neg	Pos	Neg
3—22—M	36	24	3	138	300	Neg	Neg	19.1	62.2	805	1	0	Neg	Neg	Neg
4—22—M	36	24	8	66	150	Pos	Neg	275	47.7	943	3	3	Pos	Pos	Pos
5—22—F	36	12	9	33	100	Pos	Neg	1,833	99.2	1,020	2	2	Neg	Pos	Pos
6—23—F	36	12	7	100	200	Neg	Neg	47.5	129	1,000	3	2	Pos	Pos	Neg
7—23—F	66	24	3	50	200	Pos	Pos	0	109	1,000	2	1	Neg	Pos	Neg
8—24—F	60	24	3	72	100	Pos	Pos	4.62	69.4	697	1	1	Neg	Neg	Neg
9—24—M	60	24	3	268	900	Neg	Neg	29.3	96.3	864	1	1	Neg	Neg	Neg
10—24—F	12	4	7	40	150	Pos	Neg	42.7	103	675	1	1	Pos	Pos	Neg
11—24—F	6	4	9	100	150	Neg	Neg	204	88.3	1,280		Not available		Pos	Neg
12—24—M	24	4	7	78	300	Neg	Neg	445	245	1,330		Not available		Pos	Neg
13—26—F	60	4	3	34	130	Neg	Neg	45.8	83.3	1,740	1	1	Neg	Neg	Neg
14—26—M	72	36	3	157	650	Pos	Neg	18.7	112	1,000	1	1	Neg	Neg	Neg
15—28—F	60	42	6	90	100	Neg	Pos	207	117	1,650		Not available		Pos	Pos
16—28—M	120	12	9	33	100	Pos	Pos	1,008	90.3	1,000	3	3	Pos	Pos	Pos
17—29—F	78	24	9	50	80	Pos	Neg	255	124	1,240	2	2	Pos	Pos	Pos
18—30—M	120	24	9	51	150	Pos	Pos	1,531	97.8	888	1	1	Neg	Pos	Pos
19—30—M	120	36	7	102	200	Neg	Neg	721	68.2	795	2	2	Pos	Neg	Neg
20—34—M	120	60	9	41	100	Neg	Neg	411	177	917	3	3	Pos	Pos	Pos

* Severity 1— mild, 2— moderate and 3— severe.

† Infiltration 0— none, 1—, 2— moderate and 3— severe.

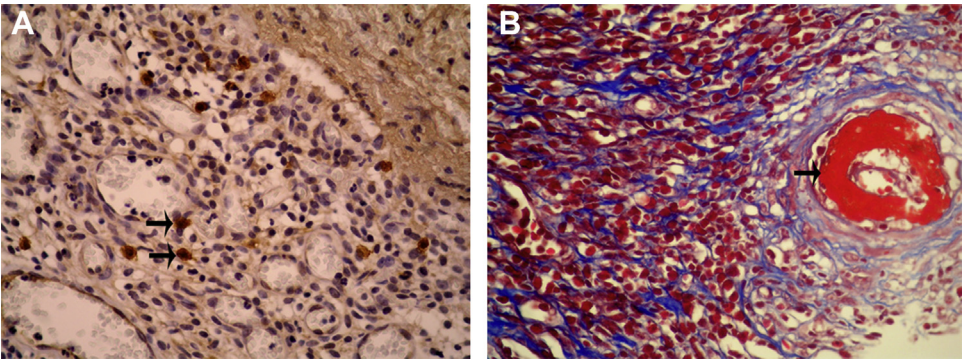


Figure 1. Histology of bladder biopsy of patient with ketamine induced cystitis reveals many eosinophils and mast cells in suburothelial tissue. *A*, moderate amount of C-kit positive mast cells (arrows). Immunohistochemistry stain, reduced from $\times 400$. *B*, 1 specimen showed fibrinoid material in lumen of arterioles, indicating fibrinoid necrosis in arterioles (arrow). Masson trichrome stain, reduced from $\times 400$.

specimens showed predominantly mast cell and eosinophil cell infiltration. Although KC histopathology findings were nonspecific, they were compatible with a picture of hypersensitivity. Patients who had stopped ketamine use for more than 1 month had significantly lower VAS pain scores and a larger CBC than those who continued ketamine use. Median serum IgE and IgM were significantly lower in patients who had stopped using ketamine than in those who did not stop.

Hypersensitivity reactions, which are the result of excessive and inappropriate immune responses, cause many diseases. Hypersensitivity diseases have similar characteristics, including onset after ingesting a substance and symptom relief after avoiding the substance. IgE and mast cells are convincingly linked to the pathophysiology of type 1 hypersensitivity reactions so that it is difficult to think of them in other contexts.⁹ In hypersensitivity reactions the antigen is usually a protein bound to IgE antibody. Some small molecules such as penicillin must attach to a carrier protein to elicit a hypersensitivity reaction and this kind of small molecule is called a hapten.¹⁶ Ketamine is a small molecule and as such it might act as a hapten and bind to IgE, inducing a hypersensitivity reaction in

bladder tissue. This hypersensitivity reaction then activates mast cells, which starts a chain reaction that eventually results in bladder damage such as epithelium denudation, ulceration, submucosal inflammation and fibrosis.

Eosinophilic cystitis was first reported in the 1960s. It has many clinical presentations and histological findings similar to those of KC, including spontaneous bladder contraction, bladder wall thickening, uncontrollable bladder pain, upper urinary tract involvement, severe submucosal eosinophil infiltration and fibrosis.¹⁷ The etiology of eosinophilic cystitis is also associated with hypersensitivity reactions but the precipitating factor is not yet clearly identified.^{17,18}

Although our study shows an association between increased serum IgE and clinical symptoms of KC, the evidence is not strong enough to support the hypothesis that hypersensitivity has a crucial role in KC pathogenesis. In young adults who present with bladder pain, frequent urination and a history of recent ketamine abuse the diagnosis of KC should be considered. The serum IgE level can serve as a biomarker for the differential diagnosis from IC/BPS in this specific patient group and it represents a predictive factor for the severity of disease progression.

Table 2. Serum Ig

Group	No. Pts	Median IU/ml Ig (IQR)		
		E	M	G
KC	20	205.5 (36.9, 514.0)	101.1 (87.1, 118.8)	978.5 (882, 1,075)
Control	10	33.4 (13.5, 71.7)	107.5 (77.1, 141)	1,390.0 (1,242.5, 1,455.0)
IC/BPS	13	65.8 (11.9, 133.0)	85.9 (83.8, 126.0)	1,260.0 (1,080, 1,410)
Acute bacterial cystitis	15	34.6 (24.2, 101.9)	89.5 (77.7, 117.5)	1,220.0 (948, 1,285)
p Value	—	0.015,* 0.029,† 0.015‡	Not significant	0.002,* 0.013,† 0.127‡

* KC vs control.

† KC vs IC/BPS.

‡ KC vs acute bacterial cystitis.

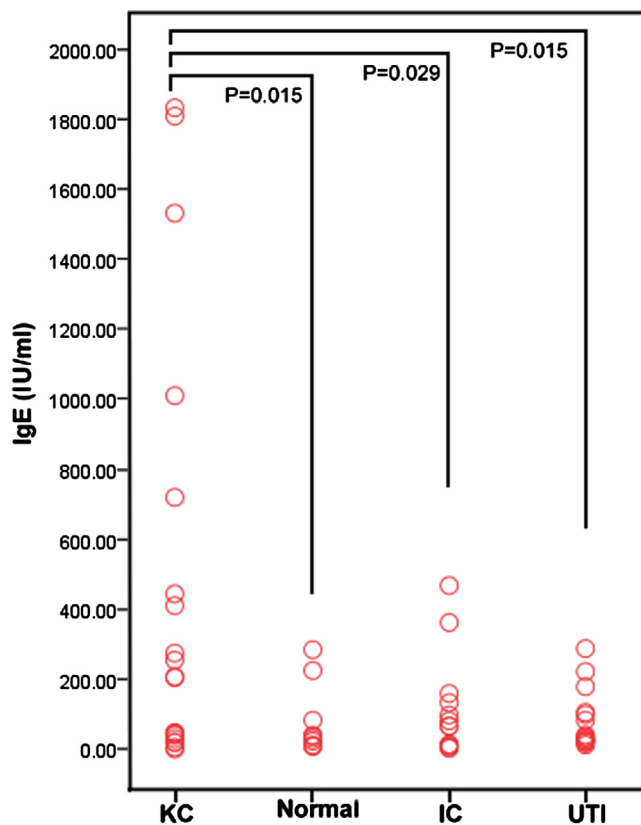


Figure 2. IgE in patients with KC, IC/BPS (IC), acute bacterial cystitis (UTI) and controls (Normal).

Time to symptom onset after ketamine abuse varies from a few days to a few years.¹⁹ In our experience patients with KC generally report urinary frequency or urgency at first. Incontinence or bladder pain begins months later. Because initially mild urinary frequency or urgency might not bother these patients, they do not complain and continue using ketamine until intractable symptoms appear.

We hypothesized that in KC mast cell release of 5-hydroxytryptamine evokes acetylcholine release from cholinergic nerves,²⁰ resulting in involuntary bladder contraction. A previous study also showed that dysregulation of purinergic neurotransmission may underlie DO in an animal model of KC bladder dysfunction.²¹ Apoptosis, eosinophil infiltration and submucosal fibrosis develop progressively after repeated ketamine abuse, eventually resulting in bladder contraction and severe bladder pain. We also found submucosal fibrinoid necrosis of arterioles, suggestive of immune complex accumulation involving a type III hypersensitivity reaction.²² Thus, type III hypersensitivity might also be involved in KC pathogenesis.

Serum IgG in all groups was in the normal range but IgG was significantly lower in patients with KC than in patients with IC/BPS and normal controls.

Table 3. Subgroup symptom history and serum Ig

	No. Pts	Median Mos History (IQR)			Median ml CBC (IQR)	Median ml MBC (IQR)	Median IU/ml Ig (IQR)	E	M	G
		Ketamine Abuse	Lower Urinary Tract Symptoms	Median VAS (IQR)						
IgE (IU/ml):										
Greater than 200	11	60.0 (36.0, 120.0)	24.0 (12.0, 36.0)	9 (7.0, 9.0)	51.0 (41.0, 90.0)	100.0 (100.0, 150.0)	445.0 (255.0, 1531.0)	99.2 (88.3, 124.0)	1,000.0 (890.0, 1,280.0)	
Less than 200	9	60.0 (36.0, 63.0)	24.0 (4.0, 24.0)	3.0 (3.0, 7.0)	72.0 (37.0, 147.5)	200.0 (140.0, 475.0)	29.3 (11.7, 44.3)	103.0 (76.4, 120.5)	957.0 (751.0, 1,000.0)	
p Value		0.333	0.457	0.001	0.424	0.027	0.001	0.849	0.253	
Recent use:										
Yes	14	48.0 (33.0, 88.5)	12.0 (4.0, 24.0)	8 (7.0, 9.0)	50.0 (38.5, 81.0)	150.0 (100.0, 200.0)	265.0 (46.3, 1,138.8)	107.5 (95.9, 138.3)	1,000.0 (910.3, 1,250.0)	
No	6	60 (54.0, 84.0)	24.0 (19.0, 36.0)	6 (3.0, 4.0)	120.0 (62.5, 184.8)	250.0 (122.5, 712.5)	24.2 (15.2, 214.6)	76.4 (66.7, 100.2)	834.5 (770.5, 1,185.0)	
p Value		0.424	0.218	0.002	0.029	0.084	0.039	0.025	0.172	
Eosinophil infiltration:										
2-3	8	69 (36.0, 120.0)	18.0 (12.0, 33.0)	8.5 (7.25, 9.0)	49.5 (35.0, 91.5)	100.0 (100.0, 187.5)	566.0 (260.0, 1,608.8)	102.6 (73.7, 127.8)	971.5 (896.8, 1,015.0)	
0-1	9	60 (36.0, 69.0)	24.0 (4.0, 24.0)	3.0 (3.0, 7.5)	51.0 (37.0, 147.5)	200.0 (140.0, 475.0)	29.3 (11.7, 44.3)	97.8 (76.4, 110.5)	888.0 (751.0, 1,000.0)	
p Value		0.430	0.651	0.009	0.360	0.039	0.004	0.700	0.287	

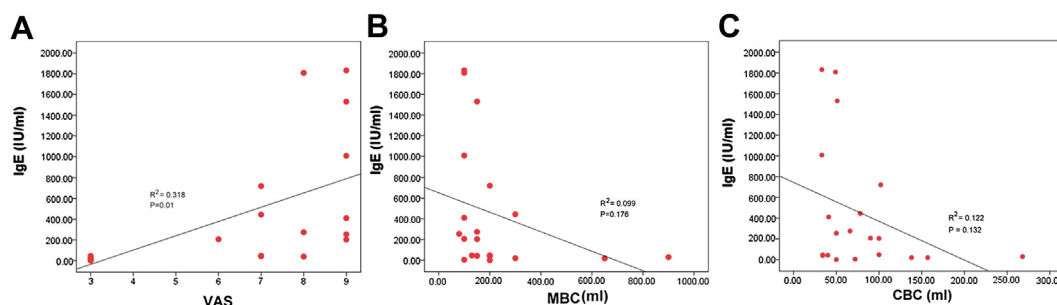


Figure 3. Serum IgE in patients with KC. A, by VAS pain score. B, by MBC. C, by CBC.

This result might be attributable to the fact that there were more male patients in the KC group than in the other groups.²³ The imbalanced gender distribution between the KC group and the other groups might have resulted in the difference in serum IgG.

Currently no definite treatment for KC has proved effective. Quitting ketamine is the mainstay treatment of KC. Previous studies of eosinophilic cystitis suggested that steroid treatment might be helpful.²⁴ However, patients with KC who continue ketamine abuse usually have severe bladder symptoms and the bladder might be severely damaged. If the patient does not quit ketamine, steroid therapy might not be effective because the inflammatory process persists. Nevertheless, in patients with KC in the early stage steroid therapy combined with cessation of ketamine use might be beneficial.

The current series is a preliminary study of the relationship between serum Ig and clinical symptoms in patients with KC. The main limitations of this study are the small number of cases and the lack of direct laboratory evidence. These data might be heavily weighted by a few extreme values and gender should have been balanced in patients with KC and controls. Some negative findings may also be secondary to the small number of patients. However, in 6 patients in whom IgE

was measured during followup after initial intervention IgE was decreased after quitting ketamine and increased after ketamine reuse. These data strongly support the relationship between serum IgE levels and bladder conditions. Further immunohistochemical studies of IgE local deposition in bladder specimens, an in vitro stimulation test or a patch test in a large KC cohort might be helpful to elucidate whether KC is truly a hypersensitivity disease related to ketamine. The number of eosinophils should also be quantified to obtain a more objective result. Since only 1 pathologist blinded to clinical results reviewed all bladder specimens, there could have been bias in counting eosinophils but the variability between clinical results and pathological findings can be reduced to a minimum. Serum or bladder suburothelial eosinophil granule proteins should also be investigated.

CONCLUSIONS

Increased serum IgE, and mast cell and eosinophil infiltration in the bladder suburothelium were found in patients with KC. Serum IgE, eosinophil infiltration severity and recent ketamine abuse were significantly associated with bladder pain symptoms and a smaller MBC.

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