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COMPREHENSIVE REVIEW OF HISTOPATHOLOGICAL FINDINGS OF KETAMINE RELATED CYSTITIS AND CORRELATION WITH CLINICAL PARAMETERS

Hypothesis / aims of study
Ketamine related cystitis (KC) is an emerging clinical syndrome characterized by severe bladder pain and small bladder capacity in the patients with history of ketamine abuse, but the actual pathophysiology is still unclear. Most previous case reports had revealed inflammation cells infiltration with urothelium denudation in the KC bladders. However, a comprehensive study of histopathology findings of KC bladders is still lacking. Current study is designed to review histopathology findings of the KC bladder and its correlation with clinical symptoms.

Study design, materials and methods
From 2011 to 2015, twenty-six KC patients who were admitted to our hospital were recruited. All patients had intractable urinary tract symptoms which were failure to conservative treatment and were scheduled for supratrigone partial cystectomy with augmentation enterocystoplasty. The clinical symptoms of these patients including drug abuse history and visual analogue scale (VAS) pain score were record. All patients had received urodynamic study and the cystometric bladder capacity (CBC) was recorded. Cystoscopic hydrodistention under general anaesthesia were also performed in these patients, and the maximal bladder capacity (MBC) were also recorded. The bladder speciment taken from partial cystectomy were sent to our pathology department for hematoxylin and eosin stain. A single pathologist blinded to clinical results reviewed bladder histology. The specimen were classifed to 4 area, including mucosa, submucosa, muscle and subserosa layer. A 4-point scale (0-none, 1-mild, 2-moderate and 3-severe) was used to grade submucosa neutrophil, eosinophil, lymphocyte, plasma cells infiltration and nerve hyperplasia. The muscle and subserosa layer were also examined for inflammatory cell infiltration, fibrosis and nerve hyperplasia. The ureter specimens taken from ureteral reimplantation were also sent to histopathology review. The clinical symptoms and objective parameters were also correlated with the histopathology finding.

Results
The mean age of our patients was 29.3±4.6 years old. The mean duration of ketamine abuse was 51.1±32.5 months, and the mean VAS score was 7.8±1.9. The mean CBC and MBC were 56.9±26.9 mL and 162.0±134.1 mL, respectively. Eleven patients (42.3%) had quit ketamine more than 3 month before the surgery, and 20 patients (76.9%) were satisfied with the surgery outcome. A total of 26 bladder specimens and 4 ureter specimens were reviewed. Mucosa denudation was noted in most bladder specimens, and only 3 bladders (11.5%) had intact urothelium. The submucosa, muscle, suserosa inflammatory cell infiltration, and nerve hyperplasia grading results were list in the Table 1. Inflammatory cells infiltration and nerve hyperplasia were involved in all layers of bladder. Fibrinoid necrosis in submucosa was also found in 4 patients (15.4%). The history of ketamine abuse, VAS, CBC and MBC between all kinds of histopathology finding grades did not have significant difference (all $p>0.05$). Cessation of ketamine for 3 month also was not associated with inflammation or nerve hyperplasia severity. Ureteral inflammation, nerve hyperplasia and fibrosis were also noted in all layers (Table 2).

Interpretation of results
The histopathology characteristics of KC bladder included urotehlium denudation, myeloid (neutrophil and eosinophil) and lymphoid progenitor cells (lymphocyte and plasma cell) infiltration in all layers. Nerve hyperplasia and fibrosis were also noted in all layers. The ureter specimen also revealed all layers inflammation, nerve hyperplasia and fibrosis. Long term ketamine abuse could induce a pancystitis with significant fibrosis, and further resulted a contracted bladder. The nerve hyperplasia might cause the severe bladder pain in the KC patients. The histopathology changes, include inflammation and nerve hyperplasia, could not recover even after quit ketamine for 3 months. Our histopathology finding also suggested ketamine could induce inflammation in the ureter. However, the histopathology findings could not be significantly correlated with the clinical symptoms.

Concluding message
Long term ketamine abuse could induce all layers inflammation, nerve hyperplasia and fibrosis in the bladders and ureters. Cessation ketamine for 3 months were not enough for inflammation and nerve hyperplasia recovery in the KC bladder.

Table 1. Histopathology grading results in different KC bladder layers

	none	Mild	Moderate	Severe
Submucosa				
Neutrophil	0 (0%)	14 (53.8%)	10 (38.5%)	2 (7.7%)
Eosinophil	2 (7.7%)	9 (34.6%)	12 (46.2%)	3 (11.5%)
Lymphocyte	0 (0%)	5 (19.2%)	13 (50%)	8 (30.8%)
Plasma cell	0 (0%)	20 (76.9%)	5 (19.2%)	1 (3.8%)
Nerve hyperplasia	0 (0%)	10 (38.5%)	12 (46.2%)	4 (15.4%)
Muscle layer				
Inflammatory cell	0 (0%)	17 (65.4%)	9 (34.6%)	0 (0%)
Fibrosis	15 (57.7%)	7 (26.9%)	4 (15.4%)	0 (0%)
Nerve hyperplsia	10 (38.5%)	8 (30.8%)	8 (30.8%)	0 (0%)
Subserosa layer				
Inflammatory cell	3 (11.5%)	20 (76.9%)	3 (11.5%)	0 (0%)
Fibrosis	14 (53.8%)	11 (42.3%)	1 (3.8%)	0 (0%)
Nerve hyperplsia	13 (50%)	9 (34.6%)	3 (11.5%)	1 (3.8%)

Table 2. Histopathology grading results in KC ureters

	none	mild	Moderate	Severe
submucosa				
neutrophil	0 (0%)	2 (50%)	2 (50%)	0 (0%)
eosinophil	1 (25%)	1 (25%)	2 (50%)	0 (0%)
Lymphocyte	0 (0%)	1 (25%)	3 (75%)	0 (0%)
Plasma cell	0 (0%)	3 (75%)	1 (25%)	0 (0%)
Nerve hyperplasia	2 (50%)	2 (50%)	0 (0%)	0 (0%)
Muscle layer				
Inflammatory cell	0 (0%)	2 (50%)	2 (50%)	0 (0%)
Fibrosis	0 (0%)	3 (75%)	1 (25%)	0 (0%)
Nerve hyperplsia	1 (0%)	3 (75%)	0 (0%)	0 (0%)
Subserosa layer				
Inflammatory cell	0 (0%)	3 (75%)	1 (25%)	0 (0%)
Fibrosis	1 (25%)	3 (75%)	0 (0%)	0 (0%)
Nerve hyperplsia	2 (50%)	2 (50%)	0 (0%)	0 (0%)

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