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MICROVASCULAR INJURY IN KETAMINE-INDUCED BLADDER DYSFUNCTION

Hypothesis / aims of study

To investigate the possible contributing mechanism of ketamine-induced cystitis (KC), the exact pathogenesis of which remains unclear.

Study design, materials and methods

A total of 36 KC patients with exposure to ketamine for more than 6 months and 9 control subjects were prospectively recruited. All participants undertook questionnaires, such as the O'Leary-Sant interstitial cystitis symptom index (ICSI), and the interstitial cystitis problem index (ICPI). All KC patients received the urodynamic study and radiological exams. Bladder tissues were obtained from cystoscopic biopsies in the control group, but otherwise after hydrodistention in KC groups. Double immunofluorescence staining of N-methyl-D-aspartate receptor subunit 1 (NMDAR1) and endothelial marker, cluster of differentiation 31 (CD31), was carried out for the existence of NMDAR1on the endothelium. Electron microscopy (EM) was applied to assess microvascular change in the urinary bladder and to measure the thickening of the basement membrane. Proximity ligation assay (PLA) was used to quantify the co-localization of endothelial CD31 receptor and mesenchymal marker, fibroblast specific protein 1 (FSP-1). The Duolink ImageTool software (Olink Bioscience) was used for image analysis.The Mann-Whitney U test and Spearman's correlation coefficient were used for statistical analysis.

Results

The KC group showed a significantly higher mean ICSI score, 14.38 (±4.16) and ICPI score, 12.67 (±3.54) than the control group, mean ICSI, 0 and mean ICPI, 0 respectively (both $p < 0.001$). KC patients had decreasing cystometric bladder capacity (CBC) with mean volume 65.38 (± 48.67) ml. NMDAR1 was expressed on endothelial cells in both groups under immunofluorescence stain. Moreover, KC patients had significant basement membrane duplication of microvessels in the mucosa of the urinary bladder under EM. Co-expression of the endothelial marker CD31 and mesenchymal marker FSP1 was significantly stained and calculated under PLA.

Interpretation of results

Figure 1 showed basement duplication with significantly layered thickening in the microvessels of ketamine cystitis. Figure 2 showed co-expression of CD31 and FSP1 markers under PLA. In these two tables, most patients have severe symptoms in ICSI and ICPI after ketamine exposure for more than one year.

Concluding message

Microvascular injury and mesenchymal phenotypic alteration of endothelial cells potentially affect KC induced bladder dysfunction.

Figure 1.

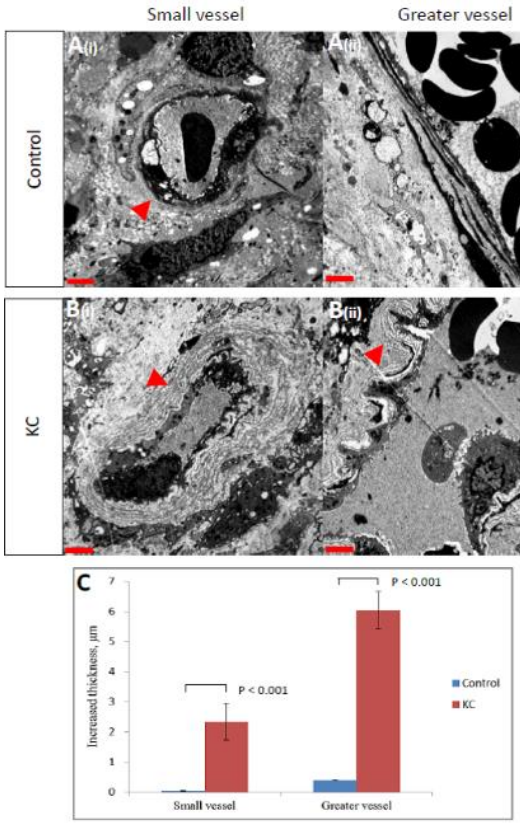

Figure 2.

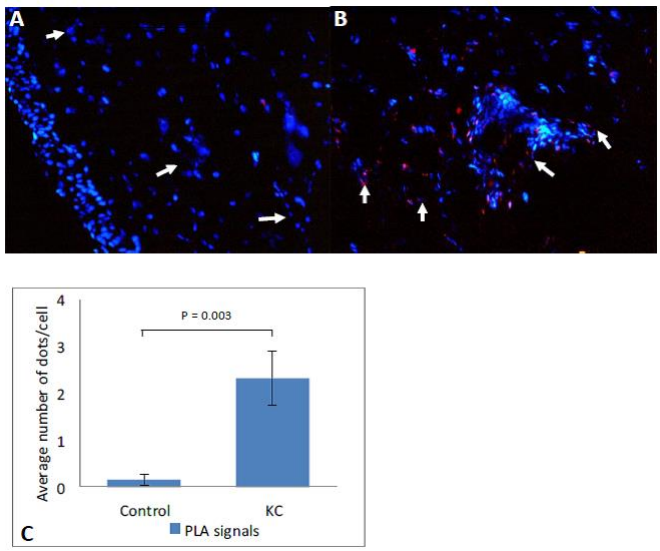

Table 1 Demographic description of KC patient groups.

	KC
Number	*N* = 36
Gender (M:F)	16:20
Mean age (years)	26.89 (±5.05)
Ketamine consumption	
Mean daily dosage (gram)	4.75 (± 1.14)
Mean cumulative duration of exposure to ketamine (years)	3.56 (± 1.83)
Mean interval from initial consumption to LUTS (years)	1.60 (± 1.23)
Bladder capacity in hydrodistention	**Mean (± S.D.)**
Mean MBC (mL)	218.08 (±119.00)
Cystoscopic finding after hydrodistention	***N* (%)**
Mean overall glomerulation grade (± S.D.)	3.22 (±0.99)
Normal appearance	1 (2.8%)
Hypervascularity (grade 1)	1 (2.8%)
Diffuse glomerulation, scattered submucosal ecchymosis (grade 2)	5 (13.9%)
Waterfall bleeding with diffuse submucosal ecchymosis (grade 3)	11 (30.6%)
Cracks or fissures into muscle layer (grade 4)	18 (50%)

Table 2 Demographic and cystoscopic findings in the control and KC patient groups.

	Control Group N = 9	**KC group N = 36**	***p***
Gender (M:F)	4:3	16:20	< 0.0001
Mean age (±SD)	48.43 (±12.21)	26.89 (±5.05)	0.0168
Hydronephrosis	0% (0/9)	22.22% (8/36)	0.179
Vseico-ureteral reflux	0% (0/9)	16.67% (6/36)	0.323
Median ICSI (Minimal, Maximal)	0 (0,0)	14.50 (5,20)	< 0.0001
Median ICPI (Minimal, Maximal)	0 (0,0)	13.00 (2,20)	< 0.0001

References

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3. Jiang X, Sung YK, Tian W, Qian J, Semenza GL, and Nicolls MR. Graft microvascular disease in solid organ transplantation. J Mol Med. 2014;92(8):797-810.

Disclosures

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