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Effective treatment of ketamine-associated cystitis with botulinum toxin type a injection combined with bladder hydrodistention

Jianfeng Zeng[1,2], Haibiao Lai[2], Dongxiang Zheng[2], Liang Zhong[2], Zhifeng Huang[2], Shanyun Wang[3], Weiwei Zou[4] and Lianbo Wei[1,5]

Abstract

Objective: Ketamine-associated cystitis (KAC) has been described in a few case reports, but its treatment in a relatively large number of patients has not been documented. This study aimed to describe our experience of treatment of 36 patients with KAC.

Methods: Thirty-six patients (30 males and 6 females, aged 19–38 years) with KAC, who had previously taken a muscarinic receptor blocker and/or antibiotics, but without symptomatic relief, were treated with botulinum toxin A injection combined with bladder hydrodistention. Urodynamic testing, and the O'Leary–Sant interstitial cystitis symptom index (ICSI) and problem index (ICPI) were used to evaluate baseline values and improvement before and after the treatment.

Results: One month post-treatment, all patients achieved marked relief of symptoms. The nocturia time was markedly reduced, while bladder capacity, the interval between micturition, the void volume, and the maximum flow rate were remarkably increased at 1 month. Additionally, the ICSI and ICPI were significantly improved.

Conclusion: Botulinum toxin A injection along with bladder hydrodistention is effective for managing KAC.

[1]College of Traditional Chinese Medicine, Southern Medical University, Guangzhou, China
[2]Department of Urology Surgery, Hospital of Traditional Chinese Medicine of Zhongshan, Zhongshan, China
[3]Department of Obstetrics and Gynecology, Hospital of Traditional Chinese Medicine of Zhongshan, Zhongshan, China
[4]Department of Anesthesiology, Zhongshan Torch Development Zone Hospital, Zhongshan, China
[5]Center of Integrated Chinese and Western Medicine for Kidney Diseases, Zhujiang Hospital, Southern Medical University, Guangzhou, China

Corresponding author:
Lianbo Wei, Center of Integrated Chinese and Western Medicine for Kidney Diseases, Zhujiang Hospital, Southern Medical University. 253 Middle Industrial Road, Guangzhou 510280, China.
Email: drweilianbo@sina.com

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Introduction

Ketamine, an antagonist of N-methyl-D-aspartate receptor, is mainly used in the induction and maintenance of anaesthesia, especially in paediatric anesthaesia.[1,2] Ketamine is also applied for management of pain.[3–5] Ketamine can affect various organ systems, such as the cardiovascular, respiratory, and central nervous systems.[6,7] This drug causes side effects, which include arrhythmia, hypertension, apnoea, airway obstruction, and respiratory depression.[6] Since the 1980s, ketamine has become a commonly used recreational drug, especially among young people.[8] A variety of symptoms can be present in ketamine abusers, such as impaired consciousness, dizziness, abdominal pain, and lower urinary tract symptoms. Additionally, deaths that resulted from ketamine abuse have been reported.[8–10]

In 2007, ketamine-associated cystitis (KAC) was first described by Shahani et al.[11] They treated nine patients, and all of them had a history of ketamine abuse with severe dysuria, increased frequency and urgency of urination, and gross haematuria. Thickening of the bladder wall, low bladder capacity, and negative urine bacterial cultures were found in all of the patients, as well as cystoscopy-confirmed cystitis. Since this time, a few more case reports on KAC have emerged.[12–15] The use of ketamine as a recreational drug has markedly increased in China in the recent decade,[16] and an increasing number of patients with KAC have visited our centre. Because KAC is a new disorder, treatment of KAC in a relatively large number of patients has not been reported. We present our experience of treatment of 36 patients with KAC using botulinum toxin type A injection along with bladder hydrodistention.

Patients and methods

Patients

For this prospective study, a total of 36 patients (30 males and 6 females, aged 19–38 years) with KAC were recruited at our centre from 2010 to 2014. All of the patients had a history of ketamine abuse ranging from 1 to 5 years. Prior to admission at our centre, they had been treated in outpatient clinics with a muscarinic receptor blocker and/or antibiotics, but without symptomatic relief. The research protocol was approved by the Medical Research Committee, the Affiliated Zhongshan Hospital of Guangzhou University of Chinese Medicine (approval number: ZSZY-LLK-030). Informed written consent was obtained from all of the patients.

Laboratory tests and other examinations

Blood and urine biochemical tests, and urine bacterial culture were performed in our diagnostic laboratory. Ultrasonography and urodynamic testing were carried out to examine bladder structure and function.

Treatment and outcome assessment

A cystoscope was advanced into the bladder under subarachnoid and epidural anaesthesia. A volume of 20 mL of botulinum toxin type A (200 IU in 20 mL saline) was injected into the bladder wall through a cystoscopic injection needle (40 points in the wall were selected and each point received 0.5 mL botulinum toxin type A). The bladder was then distended by filling it with saline under

a pressure of 80 cm, which was maintained for 5 min while the bladder capacity was maintained at 150–200 mL. The saline was then drained, the cystoscope was withdrawn, and a urinary catheter was placed for 3 days. Those with a positive urine bacterial culture were administered cefuroxime (1500 mg/daily) for 7 days.

The O'Leary–Sant interstitial cystitis symptom index (ICSI) and problem index (ICPI) were used to evaluate baseline values and improvement in patients. Urodynamic testing results were compared before and after treatment.

Statistical analysis

All data are expressed as mean ± standard deviation. Comparison of data before and after treatment was performed using the paired Student's t test. $P < 0.05$ was considered statistically significant.

Results

The demographics and clinical characteristics of patients at the time of admission are shown in Table 1. The disease duration ranged from 6–24 months. All of the patients ceased ketamine during the entire study period. At admission, an ultrasonographic examination showed that the major pathological changes included an abnormal bladder shape, low bladder capacity, and bladder wall thickening. Cystoscopy showed mild hyperaemia or erythematous patches in the bladder. Urodynamic testing showed overactivity of detrusor smooth muscle and reduced bladder adaptability.

Table 1. Demographics and clinical characteristics of all patients at admission.

	Patients
N (male/female)	36 (30/6)
Mean age, y (range)	26.0 ± 5.0 (19–38)
Elevation in ALT and AST levels	5
Urine bacterial culture	2 patients were positive for *E. coli* (sensitive to cephalosporin)
Haematuria	3
Suprapubic pain	11

ALT: alanine aminotransferase;
AST: aspartate aminotransferase.

Positive urine bacterial culture in two patients turned sterile after treatment with cefuroxime. Elevated blood alanine aminotransferase and aspartate aminotransferase levels in four of five patients decreased to within the normal range after hepatoprotective treatment. Haematuria in all three patients and suprapubic pain in eight of 11 patients disappeared 1 month post-botulinum toxin A injection and bladder hydrodistention. Three patients still had suprapubic pain, but it was greatly reduced. Other major symptoms, (e.g., increased frequency and urgency of urination, and urinary incontinence) were markedly relieved as reflected by significant improvement in baseline parameters, and the O'Leary–Sant interstitial cystitis symptom index and problem index (Table 2).

Discussion

Ketamine abuse is more often seen in young than in older people, which is consistent with the fact that we treated young people (mean age of 26 years). The mechanism by which ketamine induces cystitis is unclear. High levels of ketamine metabolites (e.g., norketamine and hydroxynorketamine) are detected in urine from individuals with ketamine abuse,[17] suggesting that these active metabolites might be responsible for irritation and inflammation of the bladder. In this study, we were unable to measure urine ketamine metabolites because of a lack of appropriate instruments.

Experience in the treatment of KAC is sparse. Shahani showed that cessation of

Table 2. Changes in parameters in all of the patients after treatment.

Parameters	Baseline	1 month post-treatment	*P* value
Nocturia (times)	9.9 ± 4.6	5.9 ± 2.1	<0.001
Interval between micturition (min)	20.0 ± 10.0	85.0 ± 29.0	<0.001
Void volume (mL)	50.6 ± 12.6	120.0 ± 30.7	<0.001
Postvoid residual urine volume (mL)	6.9 ± 3.3	7.0 ± 2.5	0.88
Maximum flow rate (mL/s)	5.4 ± 1.9	10.2 ± 3.3	<0.001
Bladder capacity (mL)	53.0 ± 20.0	130.2 ± 41.5	<0.001
ICSI	14.9 ± 2.7	6.7 ± 2.1	<0.001
ICPI	13.8 ± 3.0	6.1 ± 2.0	<0.001

ICSI: O'Leary–Sant interstitial cystitis symptom index; ICPI: O'Leary–Sant interstitial cystitis problem index.

ketamine with the addition of pentosan polysulfate appeared to provide some symptomatic relief.[11] Cessation of ketamine plus antibiotic treatment leading to resolved lower urinary tract symptoms has also been reported in a case of KAC.[14] In contrast, in a case report, Chiew et al.[13] showed that treatment with pentosan polysulfate, antihistamine, and corticosteroid did not result in any clinical response. This discrepancy between reports probably reflects the fact that KAC responds differentially to ketamine cessation and pharmacological therapy at different stages. In the early stage, but not the later stage of disease, ketamine cessation together with other medications may resolve lower urinary tract symptoms.[13] In our series, the disease duration ranged from 6–24 months, and all patients had taken a muscarinic receptor blocker and/or antibiotics, but there was no symptomatic relief. Therefore, injection of botulinum toxin type A and bladder hydrodistention were applied to treat the patients. Botulinum toxin type A has been used in a dose range of 100–250 IU for treatment of refractory interstitial cystitis.[18–20] A dose of 100 IU botulinum toxin type A is used in most cases. However, Manning et al.[18] reported that 200 IU abobotulinum A did not lead to improvement in some patients, and they then increased the dose to 500 IU (equivalent to 200–250 IU botulinum toxin type A). Therefore, because of possible inefficacy at a dose of 100 IU, we selected a dose of 200 IU for KAC treatment. This dose resulted in significant relief of symptoms, and marked improvement in baseline parameters, and ICSI and ICPI scores.

Botulinum toxin type A inhibits vesicular release of excitatory neurotransmitters and neuropeptides, such as acetylcholine, norepinephrine, and adenosine triphosphate, thus reducing detrusor smooth muscle overactivity.[21] Additionally, botulinum toxin type A has anti-nociceptive effects on bladder hypersensitivity.[22] Despite these findings, the effectiveness of botulinum toxin type A in the treatment of refractory interstitial cystitis remains controversial.[18–20] In a multicentre, prospective, randomised, double-blind study, Manning et al.[18] reported that treatment with a new botulinum toxin type A formulation, abobotulinum A, did not lead to overall improvement in total O'Leary–Sant scores. Similarly, Lee et al.[19] showed that botulinum toxin A injections did not benefit patients with ulcer-type interstitial cystitis. In contrast, more recently, Akiyama et al.[20] demonstrated that botulinum toxin A injections were effective in the treatment of refractory interstitial cystitis. However, they did not characterize interstitial cystitis. The reason for this disparity in outcomes between studies is probably that different types of

interstitial cystitis respond differentially to botulinum toxin A.

Hydrodistention, performed alone or combined with other therapeutic strategies, is effective in the treatment of interstitial cystitis.[23–26] To date, there is no standard technical protocol for hydrodistention. The American Urological Association suggests that when hydrodistention is carried out for therapeutic purposes, it must be performed at a low pressure (60–80 cm H_2O) and for less than 10 min.[27] This guideline was followed in this study and hydrodistention was performed at a pressure of 80 cm H_2O for 5 min. Recently, Kuo and Chancellor[25] used botulinum toxin type A injection followed by hydrodistention, similar to our strategy, for treatment of patients with refractory interstitial cystitis. They showed that this combination method produced significantly better clinical results than hydrodistention alone.[25] Wu et al.[28] recently suggested different therapeutic strategies for patients with KAC at different clinical stages. They classified patients into three stages (I–III) according to the severity of the disease, the dose, and the duration of ketamine abuse. While pharmacotherapy and bladder hydrodistention were suitable for patients at stages I–II, surgical intervention was proposed for patients at stage III who had multiorgan dysfunction, the longest history, and the highest dose of ketamine abuse. The authors performed surgical intervention in six patients at stage III and improvement was observed in all treated subjects. However, surgical intervention as an effective therapeutic option for advanced KAC still needs to be validated in larger series.

Conclusion

Thirty-six patients with KAC refractory to conservative pharmacotherapy were effectively treated with botulinum toxin A injection along with bladder hydrodistention. These findings are important because experience of treatment for KAC in a relatively large number of patients is still lacking. Because of loss to follow-up, we were unable to provide long-term follow-up results, which is a major limitation of the study. Therefore, long-term follow -up is warranted in future studies. Another limitation of our study is that this was single-centre experience.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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References

1. Howes MC. Ketamine for paediatric sedation/analgesia in the emergency department. *Emerg Med J* 2004; 21: 275–280.
2. Bleiberg AH, Salvaggio CA, Roy LC, et al. Low-dose ketamine: efficacy in pediatric sedation. *Pediatr Emerg Care* 2007; 23: 158–162.
3. Ahern TL, Herring AA, Stone MB, et al. Effective analgesia with low-dose ketamine and reduced dose hydromorphone in ED patients with severe pain. *Am J Emerg Med* 2013; 31: 847–851.
4. Huge V, Lauchart M, Magerl W, et al. Effects of low-dose intranasal (S)-ketamine in patients with neuropathic pain. *Eur J Pain* 2010; 14: 387–394.
5. Safavi M, Honarmand A and Nematollahy Z. Pre-incisional analgesia with intravenous or subcutaneous infiltration of ketamine reduces postoperative pain in patients after open cholecystectomy: A randomized, doubleblind, placebo-controlled study. *Pain Med* 2011; 12: 1418–1426.
6. Strayer RJ and Nelson LS. Adverse events associated with ketamine for procedural sedation in adults. *Am J Emerg Med* 2008; 26: 985–1028.

7. Dong C and Anand KJ. Developmental neurotoxicity of ketamine in pediatric clinical use. *Toxicol Lett* 2013; 220: 53–60.
8. Morgan CJ, Curran HV and Independent Scientific Committee on Drugs. Ketamine use: a review. *Addiction* 2012; 107: 27–38.
9. Chu PS, Ma WK, Wong SC, et al. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? *BJU Int* 2008; 102: 1616–1622.
10. Schifano F, Corkery J, Oyefeso A, et al. Trapped in the ''K-hole'': overview of deaths associated with ketamine misuse in the UK (1993-2006). *J Clin Psychopharmacol* 2008; 28: 114–116.
11. Shahani R, Streutker C, Dickson B, et al. Ketamine-associated ulcerative cystitis: a new clinical entity. *Urology* 2007; 69: 810–812.
12. Colebunders B and Van Erps P. Cystitis due to the use of ketamine as a recreational drug: a case report. *J Med Case Rep* 2008; 2: 219.
13. Chiew YW and Yang CS. Disabling frequent urination in a young adult. Ketamine-associated ulcerative cystitis. *Kidney Int* 2009; 76: 123–124.
14. Ho CC, Pezhman H, Praveen S, et al. Ketamine-associated ulcerative cystitis: a case report and literature review. *Malays J Med Sci* 2010; 17: 61–65.
15. Nomiya A, Nishimatsu H and Homma Y. Interstitial cystitis symptoms associated with ketamine abuse: the first Japanese case. *Int J Urol* 2011; 18: 735.
16. Jia Z, Liu Z, Chu P, et al. Tracking the evolution of drug abuse in China, 2003-10: a retrospective, self-controlled study. *Addiction* 2015; 110(Suppl. 1): 4–10.
17. Moore KA, Sklerov J, Levine B, et al. Urine concentrations of ketamine and norketamine following illegal consumption. *J Anal Toxicol* 2001; 25: 583–588.
18. Manning J, Dwyer P, Rosamilia A, et al. A multicentre, prospective, randomised, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. *Int Urogynecol J* 2014; 25: 593–599.
19. Lee CL and Kuo HC. Intravesical botulinum toxin a injections do not benefit patients with ulcer type interstitial cystitis. *Pain Physician* 2013; 16: 109–116.
20. Akiyama Y, Nomiya A, Niimi A, et al. Botulinum toxin type a injection for refractory interstitial cystitis: a randomized comparative study and predictors of treatment response. *Int J Urol* 2015; 22: 835–841.
21. Apostolidis A, Dasgupta P and Fowler CJ. Proposed mechanism for the efficacy of injected botulinum toxin in the treatment of human detrusor overactivity. *Eur Urol* 2006; 49: 644–650.
22. Smith CP, Radziszewski P, Borkowski A, et al. Botulinum toxin a has antinociceptive effects in treating interstitial cystitis. *Urology* 2004; 64: 871–875.
23. Riedl CR, Knoll M, Plas E, et al. Electromotive drug administration and hydrodistention for the treatment of interstitial cystitis. *J Endourol* 1998; 12: 269–272.
24. Glemain P, Rivière C, Lenormand L, et al. Prolonged hydrodistention of the bladder for symptomatic treatment of interstitial cystitis: efficacy at 6 months and 1 year. *Eur Urol* 2002; 41: 79–84.
25. Kuo HC and Chancellor MB. Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. *BJU Int* 2009; 104: 657–661.
26. Ham BK, Kim JH, Oh MM, et al. Effects of combination treatment of intravesical resiniferatoxin instillation and hydrodistention in patients with refractory painful bladder syndrome/interstitial cystitis: a pilot study. *Int Neurourol J* 2012; 16: 41–46.
27. Hanno PM, Burks DA, Clemens JQ, et al. AUA guideline for the diagnosis and treatment of interstitial cystitis/bladder pain syndrome. *J Urol* 2011; 185: 2162–2170.
28. Wu P, Wang Q, Huang Z, et al. Clinical staging of ketamine-associated urinary dysfunction: a strategy for assessment and treatment. *World J Urol* 2016; 34: 1329–1336.