A murderer of young bladders: Ketamine-associated cystitis

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A B S T R A C T

The use of ketamine as a recreational drug, particularly among teenagers, has increased dramatically in the past few years in Taiwan. Its effects on the central nervous and cardiovascular systems are well characterized, but an increasing amount of evidence demonstrates its association with urinary tract pathologies. Chronic ketamine use has been associated with severe ulcerative cystitis. Symptoms and signs of long-term ketamine abuse include: hematuria; increased voiding frequency; urgency; bladder pain; dysuria; nocturia; decreased bladder capacity; urothelial ulceration, and eosinophil infiltration. Vesicoureteral reflux and renal function impairment may also occur in heavy ketamine users. How ketamine use produces these symptoms is not clear. Dysregulation of purinergic neurotransmission has recently been found to play a role in the detrusor overactivity in ketamine-induced bladder dysfunction. The goal of treatment is to prevent deterioration of the renal function and indeed offer the possibility of symptom resolution. Currently, ketamine cessation is the only effective treatment modality, but the effect is likely to be dependent on the severity and duration of the abuse. Anticholinergic agents fail to relieve the symptoms induced by chronic ketamine use. Intravesical hyaluronan solution instillation may help improve the symptoms, but more clinical studies are required to provide evidence of the effectiveness. A multidisciplinary treatment team of doctors, psychiatrists, nurses, therapists, and clinicians will facilitate best practice management of patients with ketamine-associated cystitis.

1. Introduction

Ketamine is a phencyclidine derivative that was first used in humans in 1965, and has been clinically used as a quick-acting anesthetic drug since the 1970s.1 Its receptor binding has not been fully elucidated but includes an antagonist action at N-methyl-D-aspartate receptors throughout the central and peripheral nervous system. Ketamine has recently become more widely used as a recreational drug, especially in night clubs and dance parties.2 Many young people start using ketamine as teenagers.3 Ketamine has been found to cause a variety of addictive effects, including altered sensations, out of body experiences, and a euphoric rush, in addition to several negative effects, including increased heart and respiratory rates, nausea and vomiting, convulsions, temporary paralysis, and hallucinations. Unique to ketamine, recreational users describe a near-death experience, including buzzing, ringing, and whistling sounds, a sense of travel through a dark tunnel into a light at high speed, and intense visions.4,5 Despite the negative effects, very few deaths have been associated with ketamine overdoses.6 Recently, an increasing amount of evidence has demonstrated ketamine’s association with chronic ulcerative cystitis, which causes severe lower urinary tract symptoms (LUTS), such as increased voiding frequency, urgency, dysuria, and nocturia.7,8 How ketamine use produces these symptoms is not known; others have postulated that accumulation of ketamine and/or its metabolites may induce an inflammatory or autoimmune response within the bladder wall.9 Here we review the recent literature regarding the urological impact of ketamine abuse and its treatment.

2. Epidemiology

The precise prevalence of recreational, nonmedical ketamine use is unknown. A recent government report in Taiwan has indicated that the percentage of ketamine increased dramatically in the past few years, making it one of the most popular drugs of investigation findings. The age of young people tested positive for ketamine was less than a median of 30 years, indicating that the groups abusing ketamine are getting younger. Moreover, the volume of seizures of street ketamine in Taiwan has increased from...
The pathogenesis of bladder dysfunction under this condition is still not clear. It has been proposed that it may result from the two active metabolites of ketamine: norketamine and hydroxynorketamine. Recent studies have shown that ketamine and its active metabolites can be measured in high quantities in the urine of patients using ketamine. It is conceivable that ketamine and its active metabolites may accumulate in the urine and induce significant bladder irritation. Chu et al postulated the following pathophysiological mechanisms that might account for the urinary tract damage: (1) the high concentration of ketamine and its metabolites in the urine might cause direct toxic effects on the bladder interstitial cells, causing a significant chronic submucosal inflammatory response; (2) ketamine and its metabolites might induce microvascular changes in the bladder and possibly the kidney, causing endothelial cell injury of microvessels and leading either to compromised intrinsic microcirculation, or decreased microvascular density in the sub-endothelium; (3) an autoimmune reaction to the bladder urothelium and submucosa triggered by the presence of circulating ketamine or urinary ketamine and its metabolites; and (4) bacteriuria as the possible cause for the cystitis and papillary necrosis is unlikely in these patients, compared with other possible causes as described above.

Recent pathological research on the urinary bladder of ketamine addiction employing mice reveals mononuclear infiltration, similar to that of the clinical situation of interstitial cystitis/painful bladder syndrome (IC/PBS; Table 1). There was also a possible decrease in the cholinergic neurons in the urinary bladder of the ketamine treated animals. A mouse model of ketamine abuse was developed recently and showed that dysregulation of purinergic neurotransmission may be the cause of detrusor overactivity in ketamine-induced bladder dysfunction. Chuang and colleagues state that ketamine also initiated the upregulation of COX-2 and eNOS and eNOS expression, which may play an important role in contributing to ketamine-induced alterations in micturition patterns and ulcerative cystitis. Bladder tissue from KC and IC/PBS patients was found to have similar characteristics of defective functional protein, increased suburothelial inflammation, and increased urothelial cell apoptosis, although decreased expression of E-cadherin, a Ca²⁺-dependent, transmembrane cell adhesion molecule, and increase of apoptosis were more severe in KC bladders than IC/PBS.

4. Clinical presentation

A recent study has demonstrated that using ketamine for at least a 2-year habit of three or more times a week is associated with lower urinary tract dysfunction and that these symptoms may persist for up to 1 year after the cessation of drug use. The symptoms of KC include a variety of LUTS mainly irritative in nature. Typically, patients complain of nocturia, urgency, extreme frequency, bladder pain, and intractable dysuria. Gross hematuria is also a frequent symptom in those suffering from ulcerative cystitis. Tsai et al reported that symptoms appeared after 1 month of starting the usage and became severe by the end of 1 year. Flank pain may occur due to hydronephrosis secondary to ureteral stricture or vesico-ureteric reflux (VUR).

5. Investigation

Symptom questionnaires such as O’Leary’s IC symptom scales, American Urological Association’s symptom score for benign prostatic hyperplasia and overactive bladder symptom scores, may help to evaluate the severity of the symptomatology and monitor disease progression or regression with or without treatment, although they have not been validated as diagnostic criteria. Normally, urinalysis and urine cultures show nonbacterial pyuria on an initial assessment of the mid-stream urine sample. Cystoscopy reveals various degrees of epithelial inflammation and neovascularization of the bladder. Severe cases may present petechial hemorrhages and ulcers of the bladder mucosa, as classically described in patients with IC.

Urodynamically, either detrusor overactivity or decreased bladder compliance with, or VUR was detected to some degree in those patients with KC (Table 1). It has been postulated that VUR is a secondary event to the severely contracted bladder with high detrusor pressure. The functional bladder capacity is commonly < 150 mL. Chen et al reported that patients with KC have worse symptom scores, poor quality of life, and significant decrease of urodynamic parameters compared to those with IC/PBS.

Renal ultrasonography in half of the patients showed either unilateral or bilateral hydropnephrosis on the initial assessment; papillary necrosis suggestive of transmural necrosis has also been reported. It has been demonstrated that retrograde pyelography illuminated bilateral hydropnephrosis and “walking-stick ureters”, characterizing segmental beading from ureteral strictures and straightening of both ureters in a heavy ketamine abuser. Pathological changes of bladder demonstrated denuded and focal reactive urothelium. The lamina propria showed granulation tissue and congested vessels, infiltrated predominantly by lymphocytes, mast cells and a variable number of eosinophils.

### Table 1

<table>
<thead>
<tr>
<th>Symptoms or signs</th>
<th>Ketamine-associated cystitis</th>
<th>Interstitial cystitis/painful bladder syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogen</td>
<td>Ketamine</td>
<td>Unknown</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>Unknown</td>
<td>Neuroimmunoenocrine disorder</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequency</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Urgency</td>
<td>Very common</td>
<td>Not common</td>
</tr>
<tr>
<td>Nocturia</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Suprapubic pain</td>
<td>Very common</td>
<td>Very common</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td>Signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyuria</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Epithelial inflammation</td>
<td>Very common</td>
<td>Very common</td>
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<tr>
<td>and neovascularization of the</td>
<td></td>
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<tr>
<td>bladder</td>
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<tr>
<td>Complications</td>
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<tr>
<td>Ureteral stenosis, VUR reflux,</td>
<td>Common after long term</td>
<td>Occasional</td>
</tr>
<tr>
<td>and renal function impairment</td>
<td>or high dose ketamine use</td>
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</tbody>
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916 kg in 2009 to 1187 kg in 2010. In Australia, lifetime use of ketamine was reported by 1% of Australians aged 14 years or older, with 0.3% reporting recent use. Prevalence of ketamine use was highest among those aged 20–29 years. Only few people used ketamine in their 40s. A recent study assessing the prevalence of urinary symptoms in a large cohort of non–treatment-seeking ketamine users revealed that 26.6% of recent ketamine users experienced urinary symptoms. Urinary symptoms were significantly related to both dose of ketamine used and frequency of ketamine use. Currently, no gender bias has been found in ketamine-associated cystitis (KC), although some series have reported a slight male predominance in ketamine abuse.
6. Treatment

The goal of treatment is to prevent deterioration of the renal function and indeed offer the possibility of symptom resolution. Currently, ketamine cessation is the only effective treatment modality; however, the effect is likely to be dependent on the severity and duration of the abuse. The bladder function of patients with near-normal cystometric bladder capacities has been shown to return to normal after stopping or reducing ketamine abuse. Patient compliance has previously been shown to be poor in patients suffering addiction and failure to abstain may lead to disease progression. Various treatment regimens have been used to treat the patients such as antibiotics, oral nonsteroidal anti-inflammatory drugs, steroids, anticholinergic therapy, and hydrodistention of the bladder; however, all have failed to provide significant and lasting improvement. It is still not clear whether full symptomatic resolution will not be achieved in more advanced cases with severely reduced bladder capacity and compliance and consequent hydronephrosis. Because the clinical features of ketamine-associated cystitis are very similar to IC, the possible etiology of impaired epithelial impermeability leading to leakage of the glycosaminoglycan layer has led to the use of oral pentosan polysulphate (Elmiron) and intravesical instillation of hyaluronic acid (Cystistat) in the treatment of IC. Elmiron, a low molecular weight heparin-like compound, has been tried to rebuild the glycosaminoglycan layer of the damaged urothelium and a few patients experienced symptom relief after treatment. Tsai et al. have reported that all patients who had hyaluronic acid instillation had symptomatic relief, especially in relieving the bladder pain, frequency, and hematuria, but long-term follow-up is needed. It is unclear whether it is purely attributable to the abstinence, therapy, or both. These two options may provide a sense of direction, but longer follow-up is needed.

As with interstitial cystitis or a neurogenically induced spasmic bladder, augmentation enterocystoplasty or cystectomy with conduit diversion should be considered if conservative treatment fails to relieve the symptoms and preserve renal function. However, if the patient continues to abuse ketamine, they should be warned that fibrotic change of the urinary reservoir may occur.

7. Conclusions

Chronic ketamine use has been associated with severe ulcerative cystitis, which may lead to bladder contracture and dysfunction. After long-term ketamine use, patients may suffer from LUTS, including hematuria, increased voiding frequency, urgency, dysuria, and nocturia. Cystoscopy and urodynamic study may reveal urothelial ulceration and reduced bladder capacity and compliance. Histology of the ketamine bladder showed infiltrations of granulocytes (predominantly eosinophils) and mast cells within the bladder tissue. The etiology of ketamine-associated cystitis is still not clear. The goal of treatment is to prevent deterioration of the renal function and indeed offer the possibility of symptom resolution. Currently, ketamine cessation is the only effective treatment modality, but the effect is likely to be dependent on the severity and duration of the abuse. A multidisciplinary approach promoting harm reduction, cessation, and early referral is needed to manage individuals with KC to avoid progression to severe and irreversible urological pathologies.

Conflicts of interest statement

The authors declare that they have no financial or non-financial conflicts of interest related to the subject matter or materials discussed in the manuscript.
References


