General

Ketamine-Induced Cystitis: A Comprehensive Review of the Urologic Effects of This Psychoactive Drug

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Ketamine is a common medical anesthetic and analgesic but is becoming more widely used as a recreational drug. Significant side effects on the urinary tract are associated with frequent recreational ketamine use most notably ketamine-induced cystitis (KIC). Regular ketamine consumption has been shown to increase the risk of cystitis symptoms by 3- to 4-fold, and cessation of ketamine use is usually associated with improvement of symptoms. Common KIC-related problems are urinary pain and discomfort, bladder epithelial barrier damage, reduced bladder storage and increased pressure, ureter stenosis, and kidney failure, all of which significantly impact patients' quality of life. Furthermore, it becomes a vicious cycle when KIC patients attempt to manage their urinary pain with increased ketamine use. The precise pathophysiology of KIC is still unknown but several theories exist, most of which highlight the inflammatory signaling pathways leading to bladder epithelium damage due to presence of ketamine in the urine. Empirical treatment options for KIC are available and consist of ketamine cessation, noninvasive therapies, and surgery, and should be decided upon based on the time course and severity of the disease. Of note, cessation of use is strongly recommended for all KIC patients, and should be supplemented with motivational interviews and psychological and social support. It is crucial for clinicians to be familiar with KIC diagnosis and treatment, and to be prepared to have informed discussions with ketamine-using patients about the potential health consequences of ketamine.

INTRODUCTION

Ketamine is widely known as both a medical anesthetic and a recreational drug.[1,2] Ketamine's hallmark hallucinatory effects can create an out-of-body-experience that is addictive for those who regularly use this drug. It can alter sense of time, visual and auditory perception, attention, and memory.[2] Interestingly, after its popularization, there was anecdotal evidence to suggest that people who use ketamine recreationally had increased rates of urinary tract symptoms that were not associated with any bacterial infection.[3] Notably, ketamine-associated ulcerative cystitis among those who use ketamine daily was first reported in the literature in 2007, demonstrating symptoms of increased urinary urgency, polyuria, dysuria, and hematuria with associated ulcerative cystitis.[4]

Ketamine-induced cystitis (KIC) has since been further characterized in the literature and is associated with several potential disease mechanisms and symptoms. Ketamine is known to be an N-methyl-D-aspartate (NMDA) receptor antagonist with glutamate blocking capacity. Though the exact pathogenesis of KIC is yet unknown, studies suggest

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that it may stem from inflammatory pathways triggered by ketamine metabolism.[5] Damage to the urinary system associated with KIC include deterioration of the bladder epithelial barrier,[6] hydronephrosis caused by ureteral stenosis and impaired ureteral peristaltic activity,[7] bladder wall fibrosis,[8] or even chronic kidney failure from extended ketamine use.[3]

Due to several pathophysiological mechanisms, there is no single treatment for KIC. Early diagnosis of KIC and immediate cessation of ketamine usage has been shown to improve adverse urinary tract symptoms and prevent bladder or renal function damage.[9] Symptomatic treatments include nonsteroidal anti-inflammatory drugs (NSAIDs) and anticholinergics for pain,[3] urothelium protective agents such as intravesical sodium hyaluronate or chondroitin sulfate,[10,11] and botulinum toxin-A to improve polyuria, nocturia, and dysuria while increasing bladder capacity.[12] In cases of severe pain due to hydronephrosis or reduction in bladder size and compliance, surgical intervention can be used to increase bladder capacity, reduce pressure, and decrease pain.[13]

This paper will provide a review of the most recent literature on KIC, highlighting the epidemiology, pathophysiology, clinical presentation, diagnosis, and treatment options for this condition. Awareness of KIC as a differential diagnosis will be beneficial in providing timely and effective treatment for patients presenting with non-bacterial urinary tract symptoms.

KETAMINE OVERVIEW

Ketamine is a dissociative anesthetic that provides analgesia and amnesia and is associated with profound "emergence phenomena" such as delusions, hallucinations, delirium, and confusion. It is a derivative of and replacement for phencyclidine, an anesthetic that is no longer preferred because of its hallucinogenic effects.[1] As a lipid-soluble molecule that crosses the blood-brain barrier, its main mechanism of action is through non-competitive antagonism at NMDA receptors and thereby blocking glutamate, an excitatory neurotransmitter in the brain.[1] Ketamine has a good safety profile as it does not affect respiratory function. Ketamine formulations can be intravenous, oral, intranasal, or sublingual. However, parenteral administration is preferred in medical use due to high bioavailability and a short half-life. Ketamine is used medically for surgical pain management, treatment for neuropathic pain, acute pain relief, and other pain management.[14] An emerging area for ketamine use involves the nasal spray form, which is being explored as an option for treatment-resistant depression and addiction.

Although ketamine originated as an anesthetic in 1964, it has since been widely used as a recreational drug because of its psychological effects. Ketamine induces dissociative effects that vary depending on dose. Low doses induce distortion of time and space, while high doses can lead to states of altered consciousness.[14,15] When used recreationally, ketamine is often snorted and/or smoked.[16] Adverse effects associated with acute or chronic ketamine use include ketamine dependence, as well as physical, psychological, and social harm. Ketamine is not under international control, which partially contributes to its increasing availability and accessibility, and subsequently, widespread non-medical use.

EPIDEMIOLOGY

Lower urinary tract symptoms (LUTS) are common side effects of recreational ketamine use. The incidence of LUTS among people who use ketamine is 6.2 times higher than in the non-drug-using population and 2.8 times higher in comparison to the non-ketamine drug using population.[17] Ketamine-induced urinary symptoms occur in over 25% of patients who use ketamine recreationally and are positively correlated with dose and frequency of ketamine use.[9] Common symptoms include problems with urine storage and voidance.[17,18] Around 20% of frequent ketamine users report cystitis-like symptoms, compared to 6.7% among infrequent users.[9] Cessation of ketamine is reported to improve LUTS among most recreational ketamine users, although symptoms may occasionally persist or worsen after cessation.[9,16] Ketamine-associated ulcerative cystitis is a clinical entity that can have lasting consequences.[4,19] With the increasing availability and recreational use of ketamine, ketamine-induced cystitis is likely to become a prevalent diagnosis among the ketamine-using population.

PATHOPHYSIOLOGY OF KETAMINE INDUCED CYSTITIS

There is no well-defined pathogenesis for ketamine induced cystitis (KIC), but several possible mechanisms are suspected. KIC involves chronic inflammation of the bladder with increased urinary frequency, dysuria, inflammation, and suprapubic pain.[20-22] Some common pathological findings are contraction of the bladder and increased thickness of the bladder wall. The urothelium presents as denuded and contains eosinophils and mast cells due to inflammatory response. The severity of the symptoms is positively correlated with the dose of ketamine. One study showed that among the patient group with severe lower urinary tract symptoms (LUTS), 88.9% of these patients had thickened bladder lining and 44.4% had hydronephrosis, which are significantly higher compared to the mild LUTS group.[23] Another study highlighted an increase in serum IgE among KIC patients compared to the control group with KIC patients displaying increased bladder pain and decreased bladder storage.[24]

A few studies analyzed rodent models of KIC and the effect of different ketamine doses. One common finding is that higher ketamine dose is associated with more profound negative impact on the bladder epithelial barrier.[25,26] This conclusion is further supported by experiments suggesting that bladder fibrosis due to apoptosis is evident in KIC subjects and that ketamine appeared to increase urinary frequency.[27,28] In contrast, a different study on KIC in rats found that the bladder urothelium was not negatively im-

pacted despite implications of increased urinary frequency and bladder contraction, leaving more room for research on the pathogenesis of KIC overall.[29]

Despite the current lack of clarity on the exact pathogenesis of KIC, several signaling pathways are suspected to be involved. Ketamine can act to stimulate adenosine triphosphate, antiproliferative factor, and oxidative stress, yielding abnormalities in the bladder urothelium. Changes to the lamina propria are correlated with cyclooxygenase-2 (COX-2), IgE, and nitric oxide synthase (NOS). The N-methyl-D-aspartate receptor (NMDAR) along with angiogenic factors can contribute to microvascular injury in relation to ketamine use. Pathological changes to the bladder smooth muscle are partially caused by protein kinase B, purinergic signaling, and muscarinic receptor signaling. Neurotrophic factors also impact pathological changes to the bladder.[21] One KIC study showed a significant increase in COX-2 expression and upregulation in iNOS and eNOS (two isoforms of NOS), which play a key potential role in KIC.[30] One study proposed fibrosis of the bladder may occur as a result of metadherin regulating epithelial-mesenchymal transition at the P38 MAPK pathway. Additionally, ketamine leads to activation of the mTOR pathway resulting in fibroblast-specific expression (FSP-1) and subsequent ketamine-induced uropathy.[31,32]

One study was conducted assessing 36 KIC patients and 9 controls for a mechanism involved in microvascular injury of the bladder. The subjects completed a questionnaire that had the O'Leary-Sant interstitial cystitis symptom complex (ICSI) along with the interstitial cystitis problem index ICPI.[33] Cystoscopic biopsies were collected from both groups with NMDA receptor subunit 1 (NMDAR1) and the cluster of differentiation 31 (CD31) stained for comparison. Results showed that the ICPI and ICSI were statistically significant in the KIC patients compared to the controls based on the symptom scores.[33] Additionally, the NMDAR1 was seen in both groups while the CD31 in conjunction with the fibroblast-specific protein 1 had significant staining when analyzed with proximity ligation assay. The results support the implication that microvascular injury plays a role in KIC.[33]

Building upon the evolving theories of KIC pathogenesis, one study found that mesenchymal stem cells (MSCs) from human umbilical cord blood (UCB) can reverse KIC in rats by decreasing fibrosis.[34] Additionally, according to Kidger *et al.*'s case study on a KIC patient with a rare urachal cyst at the top of the bladder, the patient's urachal epithelium, which is not in contact with urine, remained healthy, whereas the bladder urothelium contacting urine has become mostly absent. Based in part on these findings, researchers concluded that KIC is likely instigated by urinary factors (i.e. presence of ketamine in the urine) as opposed to systemic factors. They also emphasized the need to discontinue ketamine administration for KIC patients.[35]

CLINICAL PRESENTATION/DIAGNOSIS OF KIC

One of the key findings of suspected KIC in patients is LUTS. It has been demonstrated that KIC severity is dose dependent.[20] Common indicators upon clinical presentation include hematuria, hydronephrosis, suprapubic pain, dysuria, sterile pyuria, nocturia, and increased eosinophils presence.[20,36,37] Diagnostic tools include urinalysis, cystoscopy, and imaging tests such as X-rays. Upon cystoscopy, findings may include urothelial epithelium with glomerulations, neovascularization, erythematous congestion, and ulceration. One study showed that 75% of chronic ketamine users presented with urothelial denudation, edema, and mast cells as evident on bladder biopsy.[20]

In a literature search, researchers amassed 75 papers relating to the ketamine and bladder in their analysis.[5] The key takeaways were that frequent ketamine users noted pelvic pain and trouble with storing urine. Hydronephrosis appears to align with several findings to include ureteral stenosis, contracted bladder, and bladder fibrosis.

With several potential avenues for treating KIC, greater awareness for recreational ketamine use is imperative. In the case of a teen patient who had ketamine-induced cholangiopathy and ulcerative cystitis, expanding research and training on the subject can better assist the patient-provider relationship towards more effective treatment.[38] It is important to diagnose KIC in the early stages in the hope of decreasing the long-term impact continued ketamine use can yield. This is especially important if improperly diagnosed, further implicating the need to increase KIC awareness as its own diagnosis.[38,39] A study was conducted analyzing the results of KIC in a 26-year-old male who upon obtaining a more comprehensive medical history disclosed he had used 50 mg of ketamine daily as a teen between 15 and 17 years of age. Despite ceasing ketamine use 9 years prior, the patient presented with: dysuria, incontinence, nocturia, suprapubic pain, and hematuria. This study highlighted the importance of improved follow-up for KIC patients after ketamine cessation, which will help clinicians better understand and manage ketamine-related clinical presentations.[40] Additionally, obtaining a clear and complete medical history is recommended for patients with LUTS so as to reveal and discontinue ketamine use if applicable.[41] In contrast to the previous patient's outcome, another study reported that a 25-year-old patient with a long history of ketamine use presented with polyuria, alguria, and dysuria, received botulinum toxin-A but did not cease ketamine use, and subsequently needed an ileum neobladder and prostate-saving cystectomia.[42] It is important to increase awareness of ketamine's negative impact among the younger population (i.e. approximately between age 16 and 35).[43,44] Utilizing appropriate diagnostics can help clinicians better address KIC in patients, especially those with hydronephrosis as it can be analyzed well via ultrasound. This can serve as a first line of defense for emergency physicians before referral to a specialist along with the cessation of ketamine.[45,46]

There are animal and human studies investigating molecular-level pathological presentations of KIC. In several animal studies on the impact of ketamine on the urothelium, it was observed that the rats that were administered ketamine presented with increased bladder activity, apoptosis, and oxidative stress related to mitochondria and endoplas-

mic reticulum pathways. The cadherin and tight junctions appeared to not function properly, further implying increased bladder activity.[6,47] These physiological changes to the rat urothelium could help us better understand KIC.[6,47] In an immunochemistry analysis of 10 KIC patients' bladder biopsies, 9 of the 10 expressed increased p53 immunoreactivity and 7 had medium to high amounts of Ki67 reactivity while cytokeratin 20 appeared to be negative.[48] These findings are of interest as urothelial adjustments in KIC patients may show a carcinoma-like presentation considering the p53 and Ki67 values, but the malignancy risk profile of ketamine has not been well-defined.[48]

TREATMENT OPTIONS

Timely treatment of KIC is crucial for managing LUTS, reducing pain, and preventing upper urinary tract involvement. Treatment is categorized into ketamine cessation, noninvasive interventions, and surgery. Cessation is strongly recommended for all KIC patients. In most cases of early KIC, simply discontinuing ketamine use is sufficient and allows the lower urinary tract to recover to baseline.[3,4] After ketamine cessation, pharmacological and other noninvasive therapies are commonly used, and surgical options are available for severe cases of KIC that have failed conservative management. These treatment options are discussed below.

Discontinuation of ketamine is safe and usually does not lead to physical symptoms, although patients may experience cravings and psychological dependence. Some occasional withdrawal symptoms include mood swings, sweating, and heart palpitations.[49] Tapering the ketamine dose over several days is one way to ameliorate psychological withdrawal symptoms and can be considered if a patient's cystitis is mild and the clinician has weighed the risks and benefits. Despite the lack of evidence for physical dependence on ketamine, it is important to provide patients with psychological and social support after ketamine cessation, which has been shown to improve success rate in quitting.[40]

Using ketamine cessation as the sole treatment is more likely to be effective in the earlier stage of KIC. The limitations to this method are that quitting can be challenging, relapses are common, and some patients resort to heavier ketamine use to manage their emerging urinary pain due to ketamine's role as an analgesic.[50] These limitations lead to delayed medical attention, which correlates with chronic or more advanced stages of bladder damage and the need for more active interventions against KIC.

Pharmacological treatments for KIC include NSAIDs (diclofenac and etoricoxib), anticholinergics (solifenacin), and pentosan polysulfate.[3] These medications are shown to be much more effective if combined with ketamine cessation. For KIC cases that failed pharmacological interventions, hyaluronic acid (HA) solution is a treatment option when administered into the bladder cavity. According to Meng *et al.*, HA is effective likely because it helps restore the damaged GAG components of the urothelial lining, reinforcing the urine barrier. It is important to note that this HA study only included patients who had already discontinued ketamine use, as shown by urine screen.[51] Besides HA, there are studies demonstrating the effectiveness of botulinum toxin-A injection combined with bladder hydrodistension as a treatment option for KIC patients who failed medication treatments.[12] Botox injection may be slightly more invasive than HA instillation, but could be effective if HA does not completely resolve the urinary symptoms. Furthermore, emerging therapies such as chondroitin sulfate and intravesicular instillation of plate-rich plasma are being explored through a case report and animal model, respectively.[11,52]

Patients presenting with late stage KIC are less likely to benefit from pharmacological or noninvasive treatments alone, and often require surgical interventions to restore urinary function. One of these surgical procedures is ureteral implantation, which is a viable option in the case of damaged or stenosed ureters. Another type of surgery is augmentation enterocystoplasty (AE), which involves an initial partial cystectomy to remove damaged parts of the bladder, followed by a bladder reconstruction surgery using enteric structures. Benefits of AE include restoring bladder storage capacity and reducing bladder pressure and pain. Risks of AE include but are not limited to ischemia, ureter strictures, sepsis, ureteral-ileal leak, bowel obstruction, and leaks at the bowel anastomosis. Due to the significant risk profile of these surgical interventions, it is highly advised that KIC patients receive medical attention and treatments early.

CONCLUSION

KIC will continue to be an issue given the availability and recreational use of ketamine.[1,2] Prolonged ketamine use not only affects the lower urinary tract to cause increased urinary urgency, polyuria, dysuria, and hematuria,[4] but also extends to the upper urinary tract to cause bladder wall fibrosis, vesicoureteral reflux, and hydronephrosis.[6-8] While multiple pathophysiological mechanisms exist for KIC,[5-7] there are several treatment options that can provide symptomatic relief in varying degrees. Effective treatment plans for KIC usually include ketamine cessation as a strategy to prevent worsening of LUTS and upper urinary tract deterioration.[10] A combination of treatment options, including urothelium protective agents or even botulinum toxin-A, could be helpful in alleviating pain, easing urinary difficulties, and improving quality of life.[10-12]

Efforts to further elucidate the mechanism of KIC should be explored, with varied treatment options targeting each pathophysiologic pathway. In addition, a standardized treatment method based on condition progression and severity should be developed to prevent any patients from progressing to chronic kidney damage necessitating dialysis. Meanwhile, KIC should be kept as a differential diagnosis when patients present with ulcerative cystitis.

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