Ketamine-Induced Uropathy: A New Clinical Entity Causing Lower Urinary Tract Symptoms

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Objectives: Ketamine abuse can damage the urinary tract and cause lower urinary tract symptoms (LUTS). This report presents our observations and management on urinary tract damage caused by ketamine abuse.

Methods: From November 2006 to February 2009, 20 patients visited Taipei Veterans General Hospital due to ketamine-related lower urinary tract symptoms. We analyzed the clinical presentations, daily ketamine dose, interval between ketamine usage to develop LUTS, urodynamic studies, radiological image findings, cystoscopic and ureterorenoscopic findings, histological findings, urinary ketamine levels and treatment responses.

Results: Of these 20 patients, all had moderate to severe LUTS, including frequency, urgency, dysuria and hematuria. The mean daily consumption of ketamine was 3.2 ± 2.0 g. The mean interval from consumption to the development of LUTS was 12.7 months (range, 2–36 months). Eight patients underwent video urodynamic studies, with a mean cystometric capacity of 70.8 mL. Eight patients had hydronephrosis and six of them underwent ureterorenoscopy. All patients underwent cystoscopy with hydrodistention. Mean bladder capacity under anesthesia was 289.9 mL, and 14 (70%) patients showed significant symptomatic improvement after hydrodistention. Ten patients quit ketamine and nine (90%) experienced symptomatic relief. The response rates of symptomatic improvement to each treatment were 75% (12/16) for oral pentosan polysulfate sodium with prednisolone, 40% (2/5) intravesical instillation of xylocaine and heparin, and 0% (0/2) for intravesical instillation of hyaluronic acid.

Conclusions: Ketamine abuse causes damage to the upper and lower urinary tracts. While ketamine abuse is an illicit drug problem, it is also associated with serious urological damage.

Key words cystitis, drug abuse, hydrodistention, hydronephrosis, ketamine

1. INTRODUCTION

Ketamine hydrochloride, a derivative of phencyclidine hydrochloride, was introduced as a short acting dissociative anesthetic in the 1960s and frequently used in infants and toddlers for elective surgery.1,2 Also known as “K,” “special K,” or “K powder,” ketamine is metabolized by cytochrome P450 (CYP3A4, CYP2B6 and CYP2CP) to nor-ketamine, which has 20–30% of the activity of ketamine, and is eventually hydroxylated to hydroxynor-ketamine and excreted in the urine after conjugated with glucuronate. It is a noncompetitive N-methyl-D-aspartic acid receptor antagonist and provides rapid dissociative anesthesia followed by rapid recovery.2,3

Because of the dissociative effect of ketamine, which described by users as a dramatic feeling of dissociation from one’s self, a sense of “floating from one’s body,” and a near death experience, it is becoming widely used as a recreational drug among teenagers and young adults, especially in nightclubs and rave parties, to supposedly enhance their enjoyment.1,3 The prevailing thought among these youngsters is that ketamine is not as harmful or addictive as other drugs such as heroin. Ahai et al. reported 47% of urine samples were positive for ketamine among rave party participants in Taiwan in 2001.4 Chen et al. reported ketamine as the second most used illegal drug among teenagers in Taiwan.5 Cardiovascular and respiratory toxicities such as hypertension, tachycardia, palpitations and respiratory depression occur with ketamine abuse. Subjects can also develop confusion, negativism, hostility and delirium, along with a wide variety of drug dependence.1 Furthermore, ketamine abusers can also develop lower urinary tract symptoms (LUTS) such as dysuria, frequency, urgency and hematuria.3,6

While the attention of the medical community is aroused about ketamine-induced LUTS, the mechanisms of damage to the urinary tract remain unclear. We report our

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experience with the management of 20 patients with ketamine-induced LUTS.

2. METHODS

From November 2006 to February 2009, 20 patients who abused ketamine visited our institution with complaints of LUTS, including urinary frequency, dysuria, urgency, pain on bladder distention and hematuria. We retrospectively collected their clinical and pathological data and analyzed average daily ketamine dose, interval between ketamine usage and development of LUTS, and urinary ketamine and nor-ketamine levels. We used the O’Leary-Sant Interstitial Cystitis Symptom Index (ICSI) score and mean Interstitial Cystitis Problem Index (ICPI) score questionnaires to evaluate the severity of symptoms in 17 patients. Selected patients had urodynamic studies. All of the patients underwent at least one of the following imaging modalities, including intravenous pyelography, ultrasound, or computed tomography to evaluate their upper urinary tracts. Ureterorenoscopy (URS) was performed if hydronephrosis was noted. All patients underwent hydrodistention under generalized anesthesia after obtaining their permission, and cystoscopic biopsies were taken for evaluation. The outcomes of treatment were also recorded.

3. RESULTS

Among the 20 patients, 13 (65%) were men and 7 (35%) were women. Their mean age was 25.8 years (range, 19–26 years). The mean daily dosage of ketamine was 3.2 ± 2.0 g (range, 1–7.5 g). The mean interval from ketamine consumption to the development of LUTS was 12.7 ± 8.5 months (range, 2–36 months). We checked the liver function of all patients and 10 (50%) of them had abnormal liver function tests and one (5%) had jaundice. Seventeen patients completed ICSI and ICPI questionnaires for the evaluation of symptom severity and its influence on quality of life. The mean ICSI score was 16.8 ± 2.8 (range, 10–20 points, total score 20) and the mean ICPI score was 14.0 ± 2.5 (range, 7–16 points, total score 16). The demographic data and key clinical findings were listed in the Table 1. We collected urine samples from 18 patients. All of the urine samples were positive for ketamine or nor-ketamine. The mean urinary ketamine and nor-ketamine levels were 6694.5 ng/mL (range, 109–25 450 ng/mL) and 6418.6 ng/mL (range, undetectable to 48 193 ng/mL), respectively. In the evaluation of urodynamic studies, 10 patients underwent conventional cystometry and the mean cystometry capacity was 70.8 ± 53.4 mL (range, 11–163 mL). Of the eight patients who underwent video urodynamic study, six had hypersensitive bladders, two had vesicoureteral reflux and one had urethral diverticula. Their mean voiding detrusor pressure at maximal urine flow was 32.8 cm H2O (range, 2–56 cmH2O). On radiological examinations, five patients had bilateral hydronephrosis and three had unilateral hydronephrosis. Among them, six patients with hydronephrosis underwent URS. Five patients had non-obstructive hydronephrosis, while in one patient a left ureteral stone was incidentally found. Biopsies of the ureteral wall were obtained during URS in two patients: the pathological findings were chronic inflammation with reactive changes of the urothelium and formation of granulation tissue with inflammatory exudates (Fig. 1).

Double-J stenting was performed in four patients including the patient with ureteral stone after URS lithotripsy. All patients benefited from this procedure and follow-up imaging studies revealed no hydronephrosis

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ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index.
Ketamine-Induced Uropathy

Fig. 1 High-power (100×) hematoxylin–eosin stain shows ureteral tissue. An inflammatory exudate is present. The urothelium shows reactive changes.

in patients with double-J stents in their ureters. One patient continued to abuse ketamine after removal of the stent. Severe bilateral hydronephrosis with acute right pyelonephritis developed and a right percutaneous nephrostomy was performed (Fig. 2).

Before hydrodistention, the cystoscopic finding showed diffuse neovascularization, glomerulation and multiple erythematous patches in 19 patients (95%); among them, two patients demonstrated diffused submucosal ecchymosis. Only one patient (5%) with pale mucosa before hydrodistention was noted. Hydrodistention for 3 min with 80-cmH2O intravesical pressure was done. After hydrodistention, diffuse oozing, mucosal breakage, and muscle breakage were noted in 15 patients (75%). We observed three patients (15%) with diffuse oozing and two patients (10%) with diffuse submucosal ecchymosis (Fig. 3).

All patients had cystoscopic biopsies, which showed acute or chronic inflammation with denudation of the urothelium (Fig. 4). The mean bladder volume under general anesthesia was 289.9 ± 149.0 mL (range, 65–680 mL). Fourteen patients reported significant symptomatic improvement after hydrodistension. Because the symptoms of these patients mimic interstitial cystitis (IC), additional therapies originally applied for IC were given for patients who did not benefit from hydrodistention or whose residual or recurrent symptoms remained bothersome. Among these patients, we initially prescribed oral pentosan polysulfate sodium (Elmiron; Ortho-McNeil-Janssen Pharmaceuticals, Raritan, NJ, USA) with prednisolone for 16 patients, of whom 12 reported improvement. Intravesical instillation of xylocaine and heparin was given to five patients with refractory severe bladder pain, with symptomatic improvement in two of them. Two patients who did not benefit from the therapies mentioned above received intravesical instillation of hyaluronic acid, but neither of them had any response to the therapy.

Fig. 2 A 28-year-old woman who abused ketamine had bilateral hydronephrosis with right acute pyelonephritis S/P right percutaneous nephrostomy.

Fig. 3 Cystoscopic finding during hydrodistention. (a) Severe neovascularization noted before hydrodistention. (b) Muscle breakage and diffuse oozing was noted after hydrodistention.

Fig. 4 High-power (100×) hematoxylin–eosin stain shows urinary bladder tissue with chronic inflammatory cell infiltration. The urothelium is partially denuded (arrow).
Ten (50%) patients successfully abstained from further ketamine use; the remaining 10 patients (50%) failed to quit ketamine abuse. Among those who successfully stopped ketamine abuse, nine (90%) demonstrated obvious symptomatic relief. Among those patients who failed to quit abusing ketamine, only one reported improvement, despite several types of the treatment. The symptoms recurred in intermittent users, as long as they were exposed to ketamine again.

4. DISCUSSION

Ketamine is a drug used in human and veterinary medicine developed by Parke-Davis in 1962. Its hydrochloride salt is sold as Ketanest, Ketaset and Ketalar. It is a N-methyl-D-aspartic receptor antagonist and also binds to opioid μ receptors and sigma receptors. It was initially developed as a dissociative anesthetic for the induction of general anesthesia. A wide range of effects in humans were noted, including analgesia, anesthesia, hallucinations, elevated blood pressure and bronchodilation. Recreational use of ketamine was first documented on the west coast of the United States in the early 1970s. Incidence of recreational use of ketamine has increased since the mid-1980s. In Taiwan, the two most commonly used illegal drugs by adolescents are ecstasy and ketamine. Ketamine seems more popular within adolescent drug culture, particularly among middle school students, which might be attributed to lenient regulation of ketamine in Taiwan. The most appealing effects of ketamine for users were “melting into the surrounding,” “visual hallucinations,” “out-of-body experiences” and “giggliness.” Unappealing effects were “memory loss” and “decreased sociability.” K-cramps, or severe gastric cramping, are reported by 30% of frequent users. LUTS, such as painful hematuria, dysuria, urgency and postmicturition pain are reported by 20–30% of frequent ketamine users, which was also reported by our patients.

Although the etiology of LUTS and cystitis was unclear, we found varying degrees of inflammation, and neovascularization with petechial hemorrhage during cystoscopy. The biopsies showed inflammatory cell infiltration with detached urothelial cells. Ogawa et al. reported the inhibitory effect of ketamine on endothelium-dependent relaxation in canine pulmonary arteries, by attenuation of the endothelium-derived hyperpolarizing factor. Chen et al. further performed an in vitro study with human umbilical vein endothelial cells showing a time-dependent and dose-dependent effect of ketamine, at clinically relevant concentrations (>100 μM, or 237.7 ng/mL), which reduced NO synthesis via both down-regulating endothelial NO synthase expression and reducing intracellular calcium levels. Higher ketamine concentrations (1000 μM or 2377.3 ng/mL) also contributed to apoptosis and DNA fragmentation of endothelial cells. Similar findings also occurred in the human hepatoma HepG2 cells experimental model. The exposure of HepG2 cells to S- (+)-ketamine increased the release of lactate dehydrogenase and γ-glutamyl transpeptidase, causing elevation of liver function tests, with decreased cell viability and time-dependent shrinkage of HepG2 cells. Bax (a proapoptotic protein) translocation from the cytoplasm to the mitochondria triggered depolarization of the mitochondrial membrane potential, which enhanced the release of apoptotic factors such as cytosolic cytochrome c, and activated caspases-9, -3 and -6, ultimately led to DNA fragmentation and cell programmed apoptosis. The Bax protein amount, cytosolic cytochrome c levels, and activities of caspases-9, - 3 and -6 were augmented after S- (+)-ketamine administration. S- (+)-ketamine demonstrated induction of apoptotic insults to HepG2 cells, via a Bax-mitochondria-caspase protease pathway. These studies suggested that ketamine, in clinically relevant concentrations, decreased endothelium-mediated vaso-relaxation, and induced endothelial apoptosis in a time-dependent and dose-dependent way. Therefore, we postulated that the damage to the lower urinary tract was related to the long-term accumulation of ketamine or the urinary metabolite of ketamine (such as nor-ketamine or hydroxy-norketamine) in the urinary bladder, which caused the apoptosis and detachment of the urothelium observed in the microscopic findings. The alteration of the microvasculature due to decreased vaso-relaxation was also followed by ischemic change to the mucosa and submucosa, and the development of neovascularization, and also influenced the regeneration of the urothelial cells. This vicious cycle further decreased the defensive mechanism of bladder mucosa and caused the penetration of toxic agents and electrolytes to the deeper parts of the bladder wall, which caused the urinary bladder pain.

Eight (40%) patients had hydrourephrosis, and of them five (62.5%) had non-obstructive hydrourephrosis. Similar findings were reported by Chu et al. (30/59, 51%). Interestingly, five of the eight patients with hydrourephrosis did not have vesicoureteral reflux on their voiding cystourethrogram study. Among the five patients with hydrourephrosis, three underwent D-J stenting, and all of them experienced reduced hydrourephrosis. If hydrourephrosis was caused by high intravesical pressure, patients would not benefit from D-J stenting. Therefore, we postulated that ketamine, or a metabolite of ketamine, could also cause direct damage to the upper urinary tract. It is thought that peristalsis of the ureter is initiated by a pacemaker signal, which is generated by the atypical smooth muscle cells located in the proximal region of the renal pelvis, triggering action potential discharge and resulting in an influx of Ca2+ and muscle contraction of the neighboring typical smooth muscle bundles of the upper urinary tract. Ketamine inhibits Ca2+ influx via both voltage-gated Ca2+ influx and norepinephrine induced Ca2+ influx in the mesenteric arteries of rats. Thus, we supposed that the high concentration of urine ketamine might also reduce the Ca2+ influx of atypical or typical smooth muscle cells in the renal pelvis or ureter wall, impairing the peristalsis function of the renal pelvis or ureter, with corresponding development of non-obstructive hydrourephrosis. D-J stenting could facilitate urinary passage to reduce the degree of hydrourephrosis. Because we believe that the damage caused by ketamine...
to the urinary tract was not only to the lower urinary tract, but also to the upper urinary tract, we proposed a new syndrome named “ketamine-induced uropathy” to describe the damage by ketamine to the whole urinary tract. Further investigation and research is still required to clarify the specific mechanism causing the ketamine-induced uropathy.

Since ketamine-induced uropathy is a new clinical entity, consensus on the diagnostic and treatment algorithm is still lacking. Nevertheless, we believe that diagnosis of ketamine-induced uropathy can be confidently made by the history of long-term ketamine abuse and the causal relation between ketamine abuse and LUTS. Functional condition of the lower urinary tract can be assessed by the voiding diary and pressure-flow urodynamic study. For patients with severe bladder pain, like two of our patients, urodynamic study is intolerable and bladder diary may give valuable information. For the upper urinary tract, renal ultrasound is a good screen examination. If hydronephrosis is noted, computerized tomography scan and videourodynamic study with voiding cistourethrogram are useful to identify ureteral obstruction or vesico-ureteral reflux.

Ketamine cessation before irreversible damage to the lower urinary tract was the key in controlling symptoms and inflammation of the lower urinary tract caused by ketamine. The recurrence or worsening of LUTS symptoms and inflammation of the lower urinary tract caused by ketamine use. Because of the symptomatic similarity between ketamine related cystitis and IC, the treatment modalities for IC were used as the basis for managing ketamine related cystitis. Our experience in using oral pentosan polysulfate sodium, along with prednisolone, resulted in a 75% (12/16) response rate. Direct intravesical instillation of heparin, along with xylocaine, resulted in a 40% (2/5) response rate. However, patients receiving intravesical hyaluronic acid instillation reported no improvement (n = 2). This lack of improvement was different from that reported by Tsai et al. This difference suggested that there could also be other differences between ketamine related cystitis and IC, indicating that further experience in the use of intravesical agents is needed. Some authors advocated hyperbaric oxygen (HBO) therapy to treat IC and had good clinical effects. It seems rational for patients with ketamine-related cystitis to undergo HBO therapy because the possible mechanism of ischemia damage appeared to be similar to that of IC. However, further clinical studies are needed to assess the value of HBO therapy for ketamine-induced uropathy. Hydrodistention was effective to partly relieve symptoms in our patients. Among our patients who underwent hydrodistension, 14 out of 20 patients (70%) experienced symptomatic relief. The therapeutic mechanism of hydrodistention for relief of ketamine-related cystitis remains unclear.

5. CONCLUSIONS

The prevalence of recreational use of ketamine has increased in recent years. While ketamine abuse is an illicit drug problem, it also induces upper and lower urinary tract damage. While the mechanism by which ketamine causes both upper and lower urinary tract damage is unclear, cessation of ketamine use before irreversible damage seems to be the most important factor for the control of symptoms. This case series reminds urologists to be aware of ketamine abuse as one of the differential diagnoses in young patients with LUTS.

Disclosure

The content has not been published or submitted for publication elsewhere except as a brief abstract in the proceedings of a scientific meeting or symposium. All authors have contributed significantly, and that all authors are in agreement with the content of the manuscript. The protocol for the research project has been approved by Institutional Review Board Approval. The subjects gave informed consent and patient anonymity was preserved. We declare any financial support or relationships that may pose conflict of interest.

REFERENCES


