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Review Article

Pathophysiology, clinical presentation, and management of ketamine-induced cystitis

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Abstract

Ketamine is illegally used as a recreational drug in many Asian countries. Long-term ketamine abusers often develop irritable bladder symptoms that gradually develop into more severe urinary frequency and urgency and eventually into a painful ulcerated bladder. These patients typically have reduced functional bladder capacity, increased bladder sensation, detrusor overactivity, severe urgency, urinary incontinence, and bladder contracture. Ketamine metabolites can cause severe inflammation of the urothelium, urothelial barrier deficits, vascular endothelial fibrinoid changes, increased oxidative stress, and bladder wall fibrosis. A decrease in bladder compliance, urinary tract infection, severe bladder pain with a full bladder, and painful micturition are also common symptoms. Finally, with continued abuse of ketamine, hydronephrosis, ureteral stricture, vesicoureteral reflux, and renal failure may develop. Cessation of ketamine is the mainstay of treatment. Lower urinary tract symptoms usually relapse if patients reuse ketamine after stopping. In cases of severe ketamine cystitis, only augmentation enterocystoplasty can relieve bladder pain and restore normal lower urinary tract function. This article reviews the underlying pathophysiology, clinical characteristics, and management of ketamine cystitis.

Keywords: *Augmentation, contracted bladder, cystitis, ketamine, treatment*

Introduction

Ketamine is a fast-acting anesthetic agent that has been widely used as an anesthetic and analgesic since the 1960s [1]. Ketamine is an N-methyl-D-aspartic acid (NMDA) receptor antagonist. Hepatic microsomal cytochrome P450 enzymes metabolize ketamine to norketamine and dehydronorketamine, which are further biotransformed into glucuronide conjugates and excreted in urine. Ketamine is highly fat soluble and its metabolites can be absorbed through tissue epithelium after a long period of stasis, especially in hollow organs such as gallbladder and urinary bladder. Over the past decade, ketamine has been increasingly illegally used as a recreational drug in many Asian countries. Because ketamine is a short-acting drug with a wide margin of safety, the youth abuse it without fear of harm, unlike drugs such as heroin. However, long-term ketamine abusers develop irritable bladder symptoms that gradually progress to more severe urinary frequency and urgency symptoms and finally to a painful ulcerated bladder [2].

Ketamine abuse and cystitis

Ketamine has been increasing abused as a recreational drug because it can rapidly achieve the dissociation effect; therefore, it is widely used among young generation groups and has become common in nightclubs [3]. Ketamine users tend to be younger, with a peak age of 16–35 years [3]. The rate of use is increasing yearly, from 0.3% in 2006 to 0.4% in 2007 among users aged 16–59 years and subsequently doubled *to* 0.9% as reported in late 2019 [4]. Because ketamine use is not considered illegal in some countries, the true incidence of ketamine-induced cystitis in the population of abusers is difficult to estimate. Based on a Hong Kong study, the incidence of lower urinary tract symptoms (LUTS) in ketamine abusers is around 30% [3]. However, the rate of urological treatment required for ketamine abusers with severe bladder symptoms or lower urinary tract dysfunction (LUTD) is lower than that for ketamine abusers with LUTS. In clinical practice, most patients experience symptom improvement after stopping ketamine use and receiving urological treatment similar to treatment for interstitial cystitis/bladder pain syndrome (IC/BPS) [5]. However, in patients who continue

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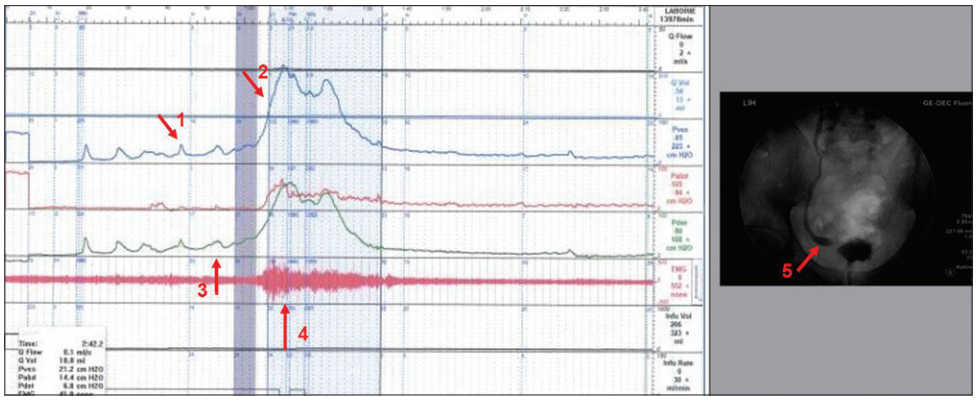

Figure 1: Videourodynamic study of a patient with ketamine cystitis. Detrusor overactivity (arrow 1), decreased bladder compliance (arrow 2), high and rapidly increasing detrusor pressure (arrow 3), dyssynergic external sphincter (arrow 4), and grade 3 left vesicoureteral reflux (arrow 5) are noted

using ketamine or have a long duration of ketamine abuse, severe bladder pain and urinary symptoms may not resolve. Intravesical instillation of hyaluronic acid may have short-term benefits [6], whereas long-term efficacy has been reported with combined intravesical botulinum toxin A (Botox) injection and hyaluronic acid instillation [7]; however, patients with severe ketamine cystitis may not respond to conventional anti-inflammatory therapy, intravesical hyaluronic acid instillation, or combined intravesical Botox injection and hyaluronic acid instillation [3]. Most of these patients have an impaired quality of life and may experience upper urinary tract complications, including ureteral obstruction, vesicoureteral reflux (VUR), hydronephrosis, and chronic renal insufficiency [8].

The interval from beginning ketamine use to the onset of LUTS or LUTD varies from a few weeks to years, and repeated ketamine use leads to an escalation in the stimulant effects of the drug [9]. Bladder pain and bothersome symptoms have been positively correlated with the duration of ketamine abuse [10]. Not all ketamine abusers develop LUTS; therefore, most abusers believe that a smaller dose of ketamine will not induce cystitis. However, it remains unclear whether regular or more frequent ketamine abuse influences the severity of LUTD. Nevertheless, once ketamine abusers develop LUTS, the severity of LUTD can increase with time and result in ketamine-associated hydronephrosis. Upper urinary tract damage first manifests with mild lower ureteral dilatation and stasis, followed by upper ureteral dilatation and hydronephrosis, and finally results in chronic renal insufficiency or end-stage renal failure [11].

Clinical characteristics and symptoms

After long-term ketamine abuse, patients usually have reduced functional bladder capacity, increased bladder sensation, detrusor overactivity, severe urgency, urinary incontinence (UUI), and bladder contracture [4,8]. The common urodynamic findings of ketamine cystitis include reduced maximal bladder capacity, especially in individuals taking a high dose of ketamine for a long duration. However, no significant difference in the incidence of developing ketamine cystitis was observed between patients taking high- or low-dose ketamine or between those with short- or long-duration abuse [12]. A videourodynamic study revealed detrusor overactivity with a very rapid increase in detrusor pressure because of uninhibited detrusor contraction. This condition causes urgency and UUI and is associated with severe bladder and micturition pain [Figure 1].

Decreased bladder compliance, subsequent urinary tract infection, severe pain with a full bladder, and micturition pain often occur if treatment is not initiated. Finally, hydronephrosis, ureteral stricture, VUR, and renal failure may develop in patients who continue long-term abuse of ketamine [13]. Because LUTS causes severe discomfort, including bladder pain, micturition pain, hematuria, and urinary incontinence, most patients cannot successfully perform at work. They may continue to use ketamine to suppress the symptoms and may wear a diaper at work to manage UUI [3]. After long-term ketamine abuse, patients usually experience general malaise and become emaciated. Some individuals may develop symptoms of azotemia because of impaired renal function caused by obstructive uropathy. Intravenous urography findings are characterized by contrast media stasis in the whole ureter, lower ureteral stricture, dilatation, bilateral hydronephrosis, thick bladder wall, and a contracted bladder [Figure 2].

Computerized tomography (CT) of the ketamine cystitis bladder shows focal or diffuse thickening of the bladder wall and marked perivesical lymphatic infiltration [Figure 3]. The bladder CT image reflects severely inflammatory changes with a similar morphology to that seen in ulcer-type IC/BPS. However, perivesical infiltration is more prominent in bladders with ketamine cystitis.

Pathology findings

The pathological features of ketamine cystitis include pancystitis with infiltration of mast cells, eosinophils, lymphocytes, and plasma cells in the bladder wall. These types of infiltration result in a contracted bladder and peritoneal adhesions [14]. A thickened bladder wall is also noted in chronic ketamine cystitis. The microscopic view shows a thin-denuded epithelium with neutrophil, mast cell, lymphocyte, eosinophil, and plasma cell infiltration of the bladder mucosa. Mucosal nerve hyperplasia is also

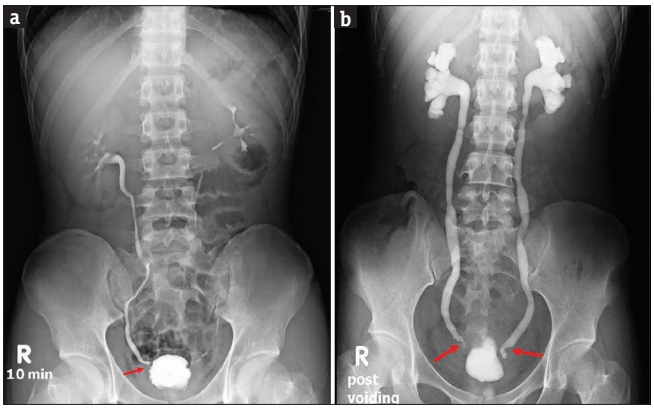

Figure 2: Typical intravenous urography findings in a patient with (a) mild ketamine cystitis with contracted bladder and ureteral stricture (arrow), and (b) severe ketamine cystitis and bilateral obstructive uropathy (arrows)

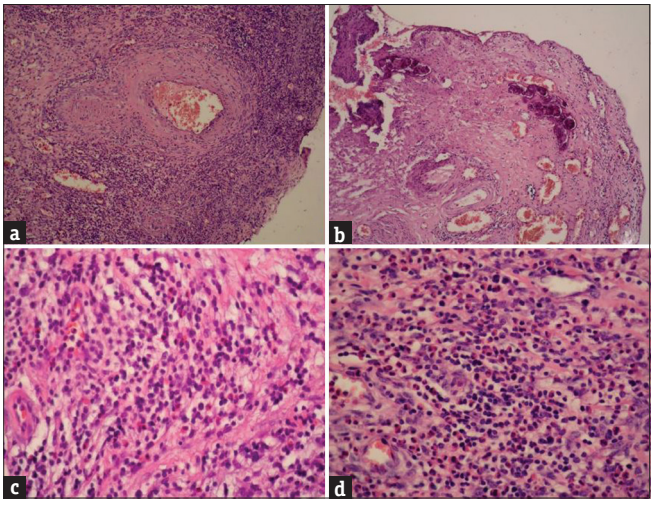

Figure 4: Pathological findings of ketamine cystitis: (a) fibrinoid necrosis of arterioles, (b) focal calcification, (c) eosinophil-predominant inflammation, (d) fibrinoid necrosis of arterioles [14]

seen. A mononuclear inflammatory cell infiltrate in the submucosal tissue, inflammatory cell infiltration and nerve hyperplasia in the muscle layer, and inflammatory cell infiltration in the serosal layer are also present [Figure 4]. An immunohistochemistry study showed an association of increased cyclooxygenase-2 staining, inducible nitric oxide synthase staining, and phospho-S6-positive cells with the degree of inflammation in the bladder tissue of ketamine cystitis [15].

In patients with ureteral stricture and hydronephrosis, urothelial inflammation and dysfunction are evident in the lower ureteral wall. Bladder and ureteral wall biopsies show severe inflammation and fibrosis of the bladder suburothelium and ureteral wall, leading to a severely contracted bladder and ureteral stricture [Figure 5]. In patients who receive bladder augmentation and ureteral reimplantation, it is difficult to determine which part of the affected ureter should be resected and reimplanted. If the affected ureteral part is reserved for reimplantation, a stricture may develop at the ureteral-vesical anastomosis over long-term follow-up.

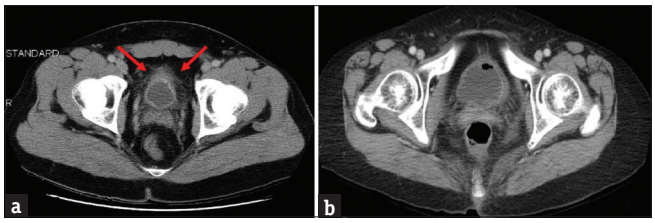

Figure 3: Bladder computerized tomography of ketamine cystitis (KC, a) and Hunner's ulcer interstitial cystitis (HIC, b) reveals more perivesical infiltration (arrows) in KC than in HIC

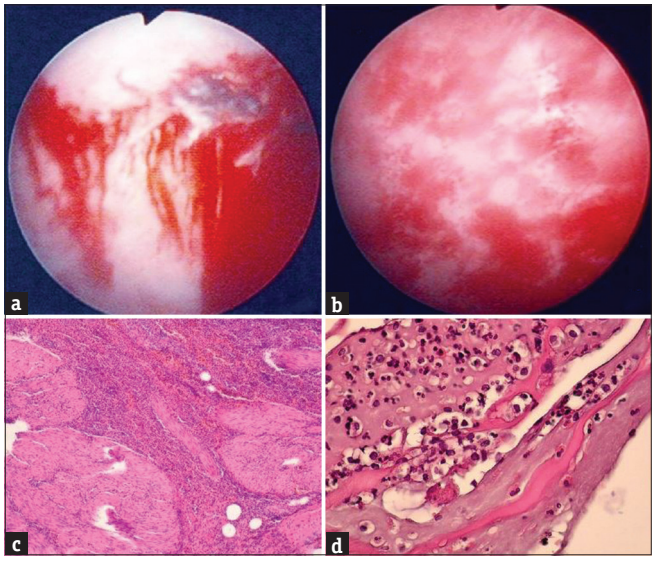

Figure 5: (a) Severe mucosal denudation and (b) diffused hemorrhage from a patient with ketamine cystitis during cystoscopy and after hydrodistention. Histopathology findings revealed (c) severe inflammation and fibrosis of the suburothelium of the bladder and (d) the ureter wall [14]

Pathophysiology

The main pathophysiology of ketamine-related uropathy includes a contracted bladder, ureteral stricture, and hydronephrosis. The VUR causes chronic contraction of the ureteral mucosa with the ketamine metabolites, which also stimulate the bladder [16]. Because tissue damage is related to the duration of exposure and contact with ketamine metabolites, the bladder wall is usually the first organ to present with LUTS, followed by the lower third of the ureter and renal pelvis. In chronic ketamine abuse, the ureter may look like a “walking stick” [17]. A study of ketamine-treated rats revealed noncholinergic contractions and an enhanced P2X1 receptor expression in ketamine-induced cystopathy. The dysregulation of purinergic neurotransmission may underlie the detrusor overactivity in this animal model [18]. A denuded epithelium, chronic inflammation, ulcerative cystitis, and erythematous necrotic cystitis are frequently found in ketamine cystitis bladders [19]. Another study reported that ketamine enhanced the generation of oxidative stress mediated by mitochondria- and endothelial reticulum-dependent pathways. This stress contributed to bladder apoptosis and urothelial lining defects [20]. All these abnormalities result in increased urothelial permeability, hypersensitivity of the bladder afferent purinergic nerves, and overactivity of the detrusor muscle in

ketamine cystitis. The symptoms of ketamine-related uropathy include severe UUI and bladder pain.

Although the clinical presentations of ketamine cystitis are similar to those of IC/BPS, an immunohistochemistry study revealed greater cell apoptosis, mast cell activation, impaired expression of E-cadherin, and suburothelial inflammation in patients with ketamine-related cystitis [21]. Ketamine cystitis and IC/BPS tissues all showed defective junctional proteins, increased suburothelial inflammation, and increased urothelial cell apoptosis. These histopathological findings are associated with the clinical symptoms of ketamine cystitis and IC/BPS [21]. However, histopathological findings of severe ketamine cystitis with lower ureteral obstruction were not found in IC/BPS.

Some patients with serious bladder lesions have defective bladder surface epithelium, with only smooth muscle, collagen, and adipose tissue in the denuded bladder wall. The pathogenesis of ketamine cystitis has been linked with immune response, manifested with increased serum levels of immunoglobulin E (IgE), interleukin-6, and interferon-γ, suggesting the presence of an immunomodulatory imbalance in patients with ketamine cystitis [22]. Markedly increased serum IgE levels have also been noted in patients with active ketamine cystitis, which had higher serum IgE levels than patients with IC/BPS or acute bacterial cystitis or than controls [23]. Serum IgE levels and the severity of eosinophil infiltration of the bladder wall are associated with bladder pain severity and limited maximal bladder capacity [24]. In clinical practice, serum IgE levels gradually decrease in patients whose bladder condition has resolved after conservative or aggressive treatment. However, in patients who returned to ketamine abuse, bladder pain recurred, and serum IgE levels subsequently increased in association with exacerbated LUTS.

Histopathology also shows that diffuse microvascular injury is involved in the pathogenesis of ketamine cystitis [14,25]. The possible mechanism of this microvascular damage is endothelial cell injury by ketamine activation of NMDA receptors. The subsequent pathophysiology includes the thickening of the endothelial basement membrane, chronic inflammation, interstitial fibrosis, and a decrease in the density of microvessels [25]. Histopathological findings in the ketamine cystitis bladder show ulcerative cystitis with fibrinoid necrosis within small- and medium-sized arterioles [26] [Figure 6]. These microvascular injuries may involve antigen–antibody immune complexes in the arterial walls, inflammation, and autoimmune-mediated vascular congestion [4].

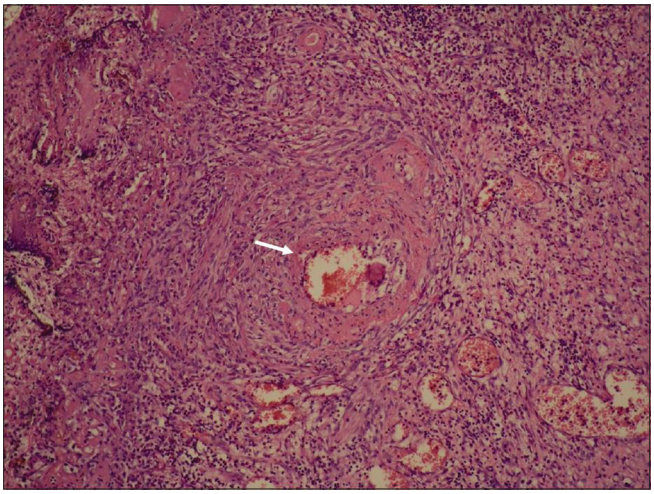

Figure 6: Histopathological finding of ketamine cystitis shows thickening of the endothelial basement membrane (arrow), chronic inflammation, interstitial fibrosis, and fibrinoid necrosis within small- and medium-sized arterioles [26]

Ketamine cystitis-affected bladders are both hypersensitive and overactive. Patients usually cannot hold an adequate bladder volume, resulting in severe frequency, bladder pain, urgency, and UUI. The clinical features of ketamine cystitis are more severe than those of overactive bladder and IC/BPS. However, the exact histopathological mechanism underlying severe bladder dysfunction and chronic bladder pain remains unknown. A direct toxic effect of ketamine metabolites on the bladder and ureteral urothelium has been suggested [5,21]. A study of urothelial dysfunction and sensory receptor expression revealed that bladder mucosa in the setting of ketamine cystitis had significantly less expression of zonula occludens-1 and E-cadherin. In addition, the results demonstrated a higher expression of apoptosis (measured by terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling assay) and an increase in tryptase activity, indicating inflammation [21]. Interestingly, the expression of muscarinic M3 receptor and ß3-adrenoceptors in the ketamine cystitis bladder specimens was significantly greater than that in the controls [27]. These elevated sensory protein expressions may be associated with the clinical presentation of ketamine cystitis.

Because the main symptoms of ketamine cystitis are bladder oversensitivity and pain, neural dysregulation may play a role in their pathogenesis. Fine neurofilament protein and p75 low-affinity nerve growth factor receptors are prominent in the lamina propria of the ketamine cystitis bladder [28]. Our previous histopathology study also found nerve hyperplasia and increased collagen deposition in the bladder wall of ketamine cystitis [23,29]. Nerve hyperplasia and fibrosis are histological characteristics of these bladders, and we found that the expression of neurotrophins was significantly correlated with bladder capacity and pain according to the differing clinical severity of ketamine cystitis [30]. These findings indicate that the upregulation of neurotrophins, transforming growth factor-β, and activation of cell proliferation kinases play an important role in nerve hyperplasia and fibrosis mechanisms in these bladders. This pathophysiology may explain why ketamine cystitis results in a contracted – but strongly contractile – bladder. Recent studies have also revealed that increased apoptosis in ketamine cystitis may be mediated by actin-binding proteins and a Ca^{2+}-activated protease, which correlated with the clinical characteristics of ketamine cystitis bladders, such as erosive bladder mucosa and severe bleeding after hydrodistention. The detrusor overactivity and increased slope of detrusor pressure in ketamine cystitis bladders may be induced by increases in contractile and cytoskeleton proteins [31]. In addition, a recent study revealed that hypersensitivity, small bladder capacity,

and stronger bladder contractility in patients with ketamine cystitis are associated with elevated transient receptor potential vanilloid 1 (TRPV1) in the urothelial cell layer and elevated TRPV4-positive cells in the basal cell layer and lamina propria [32].

Conservative treatment

The cessation of ketamine use is the mainstay of LUTS control and resolution of the deformed or dysfunctional lower urinary tract. Intravesical instillation of hyaluronic acid or other barrier glycoproteins may help mild ketamine cystitis in patients who discontinue ketamine use. Anti-inflammatory agents, antibiotics for urinary tract infection, and antimuscarinics are usually ineffective for the long-term symptomatic relief of ketamine cystitis [3,5]. Most patients experience clinical improvement after stopping ketamine and receiving urological treatment similar to that for IC/BPS [5]. However, LUTS might develop in patients who continue to abuse ketamine or those who have a duration of abuse longer than 2 years [10], and the pain may not respond to empirical oral or intravesical treatments [4].

Cystoscopic hydrodistention

Cystoscopic hydrodistention alone can benefit patients with IC/BPS, whereas the effect of the procedure on ketamine cystitis has not yet been determined. Patients with ketamine cystitis who do not respond to conservative treatment and cannot undergo the augmentation procedure may be treated with repeated cystoscopic hydrodistention to obtain short-term symptomatic improvement. However, improvements in bladder capacity and urodynamic outcomes are inferior to those achieved with bladder augmentation [22]. Of note, in a small cohort study, the therapeutic effect of cystoscopic hydrodistention followed by eight administrations of intravesical hyaluronic acid instillation was inferior to that of intravesical Botox 200 U injection followed by the same hyaluronic acid regimen [7].

Hyaluronic acid instillation

An animal model of ketamine cystitis revealed that hyaluronic acid instillation reduced bladder hyperactivity, lessened bladder mucosal damage, and decreased interstitial fibrosis. The instillation also improved mucosal regeneration, suggesting that hyaluronic acid may modulate inflammatory responses, enhance mucosal regeneration, and repair urothelial integrity defects in ketamine cystitis [33].

Botulinum toxin injection

Intradetrusor Botox injection followed by intravesical hyaluronic acid instillation appears to be an effective long-term option for ketamine cystitis compared with cystoscopic hydrodistention alone [34]. One study showed that intravesical Botox injection is useful in inflammatory bladder diseases, such as chemical, radiation, and ketamine cystitis [35]. Combined with bladder hydrodistention, Botox has been shown to be effective in relieving bladder pain, increasing bladder capacity, and decreasing voiding frequency in patients with ketamine-associated cystitis [36]. Intravesical administration of liposome-encapsulated Botox (Lipotoxin) has also been found to promote the healing of damaged urothelium from liposomes and shown a reduction of urinary symptoms in rats with ketamine-induced cystitis [36]. Evidence supports that intravenous Botox injections are therapeutically effective in ketamine cystitis.

Platelet-rich plasma injection

Platelet-rich plasma (PRP) modulates urothelial regeneration in rats with cyclophosphamide-induced cystitis [37]. Repeat PRP injections have also been shown to improve bladder symptoms, increase urothelial barrier function protein, and increase cell proliferation protein expression in IC/BPS bladders [38]. Recently, PRP treatment in rat ketamine cystitis models has shown that PRP can reduce oxidative stress and enhance anti-inflammation [39]. Moreover, urothelial proliferation and tight junction protein expression improved after PRP injection. The study suggested that PRP treatment triggered bladder angiogenic remodeling and increased nerve regeneration in ketamine cystitis rats.

Refractory ketamine cystitis

Patients with ketamine cystitis are usually treated initially with oral antimuscarinics for UUI, nonsteroidal anti-inflammatory drugs, and analgesic drugs for severe bladder pain. In patients with mild bladder conditions, temporary symptomatic relief may be achieved with these conservative treatments [3,5]. Cystoscopic hydrodistension and intravesical hyaluronic acid or heparin instillation may only be beneficial in patients with mild bladder inflammation for short-term follow-up [5,6,8]. Patients who do not discontinue ketamine and who have recurrent urinary tract infection, a severely contracted bladder wall, upper urinary tract inflammation, ureteral obstruction, intractable bladder pain, severe frequency and urgency, or VUR may be treated with augmentation enterocystoplasty and continent urinary diversion using an intestinal segment [3,40].

Augmentation enterocystoplasty

In select patients with profound urinary tract destruction, surgical intervention to restore the anatomical and functional lower urinary tract may be the treatment of choice [3]. Augmentation enterocystoplasty has been proven to be safe and effective for a contracted bladder in patients with myelodysplasia, spinal cord injury, and chronic inflammatory bladder diseases [41,42]. Augmentation enterocystoplasty provides good pain control in patients with ketamine cystitis [43]. Although the inflammation and mucosal damage may resolve after ketamine discontinuation, the fibrotic bladder wall damage does not resolve. Therefore, augmentation enterocystoplasty plays an important therapeutic role in increasing the reduced bladder capacity, relief of intractable bladder pain, and early recovery of LUTS in these patients [40].

In augmentation enterocystoplasty, an ileum segment of about 40 cm is used to construct a patch for the bladder. The

supratrigonal bladder is partially resected, and the bladder base and trigone are usually preserved to allow the normal micturition reflex to initiate voiding without abdominal strain. The purpose of this procedure is to preserve the micturition reflex while reducing the source of bladder inflammation and pain. This approach increases the bladder capacity with good compliance and decreases detrusor pressure to prevent kidney injury. Augmentation enterocystoplasty can achieve these goals about 6 months after surgery [44]. In a clinical outcome study of augmentation enterocystoplasty in 26 patients with ketamine cystitis, a significant improvement was shown in cystometric bladder capacity, maximum flow rate, voided volume, and bladder compliance; however, the postvoid residual volume also increased after surgery [45]. All 16 patients who discontinued ketamine use remained free of bladder pain postoperatively. However, 10 patients who restarted ketamine use had recurrent bladder pain and urinary tract infections. The changes in symptoms and urinary tract dysfunction in the patients after augmentation enterocystoplasty are shown in Table 1.

Of importance, morphological and functional urinary tract changes do not disappear after augmentation enterocystoplasty. Patients may still experience difficulty urinating because of a tight bladder neck or urethral sphincter. In such cases, a transurethral incision of the bladder neck or urethral sphincter injection of botulinum toxin A is indicated to enable spontaneous voiding [42]. If the ureteral obstruction does not resolve after ureteral reimplantation to the augmented bladder, ureteral reanastomosis or an ileal interposition procedure may be necessary to reconstruct upper urinary tract patency and preserve renal function. In patients with a lower ureteral stricture and low-grade VUR, reflux may persist after augmentation enterocystoplasty if ureteral reimplantation is not performed concomitantly [Figure 7]. Postoperative complications may necessitate reintervention during follow-up.

Patient characteristics for different therapeutic strategies

The goal of treatment for ketamine cystitis-related bladder pain is to increase bladder capacity with good compliance, decrease the detrusor pressure, prevent kidney injury, and eradicate the abnormal, painful sensations from the diseased bladder. Our recent study demonstrated that augmentation enterocystoplasty successfully reduced bladder pain, improved quality of life, and increased bladder capacity in refractory chronic ketamine cystitis pain [43]. Patients can resume a normal life and return to work after augmentation enterocystoplasty. However, patients who reuse ketamine after the operation may experience LUTS, bladder pain relapse, and recurrent urinary tract infections. Currently, no guidelines are available for clinicians on how to manage patients with ketamine cystitis. Based on clinical experience and patient treatment outcomes, we have proposed criteria for patient selection for conservative treatment or augmentation

Table 1: Changes in symptoms and urinary tract dysfunction in patients after augmentation enterocystoplasty [45]

LUTS/LUTD	Baseline, *n* (%)	Postaugmentation enterocystoplasty, *n* (%)
Hydronephrosis	9 (34.6)	2 (7.7)
Frequency	26 (100)	18 (69.2)
Urgency	26 (100)	10 (38.5)
Difficult urination	0	9 (34.6)
Bladder pain	20 (76.9)	10 (38)
Incontinence	6 (23.1)	2 (7.7)
Large postvoid residual	0	2 (7.7)
Chronic urine retention	0	1 (3.8)
Urinary tract infection	18 (69.2)	10 (38.5)
VUR	10 (38.5)	1 (3.8)
Urodynamic detrusor overactivity	18 (69.2)	2 (7.7)

LUTD: Lower urinary tract dysfunction, LUTS: Lower urinary tract symptoms, VUR: Vesicoureteral reflux

Table 2: Indications for patient selection for conservative treatment and augmentation enterocystoplasty [40]

Conservative treatment	Augmentation enterocystoplasty
MBC >300 mL	MBC <100 mL with or without upper urinary tract damage
Normal upper urinary tract	MBC <300 mL with upper urinary tract damage
Improved bladder symptoms after treatment	Intractable bladder symptoms after treatment
Patient refuses surgery	Urge to change bladder condition
Physician opinion	Small functional bladder capacity persists

MBC: Maximal bladder capacity under cystoscopic hydrodistention

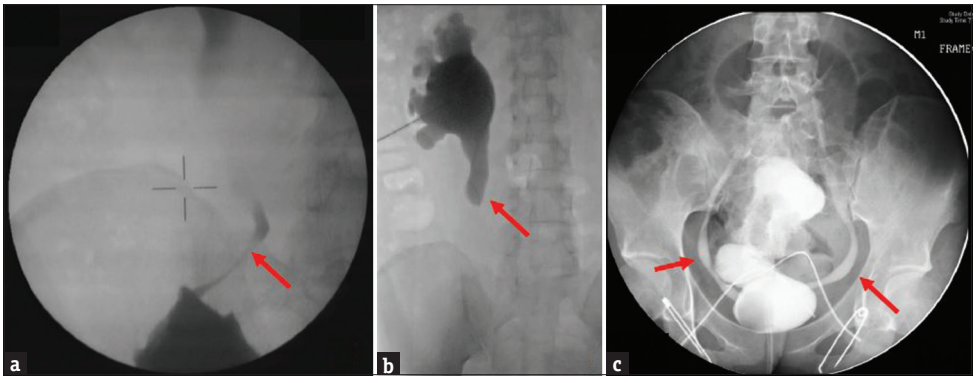

Figure 7: Urinary tract changes after augmentation enterocystoplasty: (a) upper and middle ureteral stricture (arrow) after the operation, (b) severe ureteral stricture (arrow) and hydronephrosis worsen after surgery, (c) persistent bilateral vesicoureteral reflux (arrows) after augmentation enterocystoplasty without concomitant ureteral reimplantation

enterocystoplasty [40]. Patients who underwent augmentation enterocystoplasty had a significantly smaller maximal bladder capacity (under cystoscopic hydrodistention), a thicker bladder wall, and a higher incidence of VUR. These patients usually report a good outcome. In contrast, most patients who received conservative treatment had fair results. Patients with chronic ketamine cystitis who had already developed a contracted bladder with extremely small bladder capacity (<300 mL) and irreversible urinary tract changes may require partial cystectomy and augmentation enterocystoplasty for early restoration of the normal upper urinary tract and functional bladder capacity, reduced bladder pain, and improved quality of life [Table 2].

Most patients had good therapeutic results after augmentation enterocystoplasty, but patients who had conservative treatment did not experience good results. Some patients who received conservative treatment may not have completely quit ketamine, and instead may have only reduced the dose and frequency of ketamine use; therefore, their bladder inflammation did not resolve. In contrast, patients who underwent augmentation enterocystoplasty had a painful surgical experience, which motivated them to permanently discontinue ketamine, and subsequently, they achieved a good resolution of their bladder pain.

Conclusions

Ketamine-related cystitis is an inflammatory bladder disease that progresses slowly to an end-stage bladder condition. Ketamine cessation is the mainstay of treatment. Conservative treatments, such as oral medication, hyaluronic acid instillation, intravesical Botox injection, and intravesical PRP injection, are usually successful if patients completely discontinue ketamine as early as possible. Only augmentation enterocystoplasty can relieve bladder pain and restore normal lower urinary tract function in severe ketamine cystitis cases. If patients restart ketamine use after conservative or surgical treatment, LUTS usually relapses.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

Dr. Hann-Chorng Kuo, the editorial board member at *Tzu Chi Medical Journal*, played no role in the peer review process or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

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