Retrospective Review

Clinical Outcome of Augmentation Enterocystoplasty for Patients with Ketamine-induced Cystitis

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Background: Ketamine abuse has become a global phenomenon in recent years. Ketamine-induced cystitis (KC) is a new clinical syndrome which can result in severely inflamed bladder and intractable bladder pain. Currently there is no guideline for managing patients with KC.

Objectives: To analyze the clinical outcome of patients with KC managed with augmentation enterocystoplasty (AE).

Study Design: Retrospective interventional study.

Setting: A tertiary teaching hospital, Hualien Tzu Chi Hospital.

Methods: We retrospectively collected and analyzed the medical records and video-urodynamic (VUD) test results of 26 patients who underwent AE as treatment for refractory KC during the period 2009 – 2014. All of these patients abused ketamine with nasal snorting, at least 3 grams per dose, twice per week for 6 months. Data from VUD studies performed before AE and 3 – 6 months after surgery that were analyzed in this study included cystometric bladder capacity (CBC), post-void residual (PVR) urine volume, maximum urinary flow rate (Qmax), voided volume, and bladder compliance. A self-report questionnaire was used to assess patient satisfaction with AE.

Results: Patients included 14 women and 12 men aged 20 – 43 years (mean age, 28.5 years) with an average duration of ketamine abuse of 4.7 years (range, 1 – 10 years). All patients had contracted bladder, 9 had hydronephrosis, and 10 had vesicoureteral reflux (VUR). There was significant improvement in CBC (52.7 ± 29.7 v 327 ± 69.4 mL, $P < 0.0001$), Qmax (6.94 ± 4.32 v 13.7 ± 4.96 mL/s, $P < 0.0001$), PVR (8.08 ± 19.2 v 82.6 ± 91.5 mL, $P < 0.0001$), voided volume (44.1 ± 28.3 v 250.7 ± 133.4 mL, $P < 0.0001$), and bladder compliance (11.1 ± 11.9 v 54 ± 43, $P < 0.0001$) after AE. Hydronephrosis resolved in 7 patients after AE and VUR resolved in all patients who underwent AE with ureteral reimplantation. All patients who stopped using ketamine were free of bladder pain postoperatively. However, 10 patients who reused ketamine had recurrent bladder pain and recurrent urinary tract infection.

Limitations: Small number of patients limits scope of study.

Conclusions: AE is effective at treating KC-induced bladder pain and restoring normal lower urinary tract function. However, absolute cessation of ketamine is the key to success in KC treatment.

Key words: Ketamine-induced cystitis, augmentation enterocystoplasty, bladder pain, contracted bladder, inflammation, surgery

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Ketamine, an N-methyl-D-aspartic acid receptor complex antagonist, has been widely used as an anesthetic and analgesic agent since the 1960s, but has also been used as a recreational drug in the USA, Australia, and in Asian and European countries since the 1990s (1-3). In Taiwan, ketamine use as a recreational drug increased markedly from 2008 to 2013, particularly among teenagers and young adults (4-7). Approximately 30% of long-term ketamine abusers experience urinary frequency, urgency, and severe bladder pain, lower urinary tract symptoms that are collectively referred to as ketamine-induced cystitis (KC) (5,8). The prevalence of KC has risen in recent years in Taiwan, Hong Kong, Singapore, Malaysia, and in some European countries (8-10). However, the actual prevalence of KC is difficult to estimate, because of patient's privacy and legal problems.

The pathophysiology of KC is unclear, but is believed to involve many different pathways including a direct toxic effect of ketamine and its metabolites, bladder barrier dysfunction, and several inflammatory reactions (11). Chronic exposure to ketamine and its metabolites has been shown to result in vascular ectasia, submucosal edema, detrusor muscle inflammation, and fibrosis (10,12). Typical findings in patients with KC include sonographic and computed tomographic evidence of contracted bladder with thick bladder wall, ureteral dilatation, ureteral wall thickening, vesicoureteral reflux (VUR), hydronephrosis, urinary tract infection (UTI), and renal function impairment (13,14). Cystoscopic findings in patients with severe KC include erythematous bladder mucosa with or without ulceration, fragile mucosa, mucosal laceration or tearing even after bladder distention, easy bleeding, and glomerular hemorrhage (14,15).

Cessation of ketamine should be the first step in managing KC, followed by conservative treatment with symptomatic medications, intravesical instillation of mucosal protective agents, and intravesical botulinum toxin A injection (9,16-19). Urological treatment is similar to that used for bladder pain syndrome/interstitial cystitis. Most patients who abstain from ketamine show significant clinical improvement after one year (20); however, patients who continue to abuse ketamine and those with longer duration of ketamine abuse tend to develop intractable bladder pain that is refractory to hyaluronic acid instillation, intravesical botulinum toxin A injection, or other conservative treatments (9,21). Some patients with chronic VUR and/or hydronephrosis develop irreversible renal function impairment. Early surgical intervention might be indicated to relieve the symptoms of KC, preserve renal function, and improve quality of life (7).

The treatment goal is to increase bladder capacity and compliance as well as to eradicate the bladder pain. We previously showed that augmentation enterocystoplasty (AE) successfully improves quality of life of these patients by relieving ketamine-related bladder pain and lower urinary tract symptoms and by increasing bladder capacity. However, recurrent UTI and symptom relapse tend to occur in patients who reuse ketamine after AE (7).

The outcomes of conservative treatments for severe KC are often disappointing. Therefore, the clinical outcomes of more aggressive surgical interventions such as AE should be evaluated. This is an update of our previous study which analyzes the clinical outcome of AE in 26 patients who underwent augmentation enterocystoplasty for KC (7).

Methods

Twenty-six patients with chronic KC who underwent AE from 2009 to 2014 were included in this study. All of these patients abused ketamine with nasal snorting for at least 6 months. The frequency of ketamine abuse in these patients was at least twice per week, and the dose was at least 3 grams every time. All patients presented with dysuria, urinary urgency/frequency, and bladder pain. In all patients, KC was refractory to conservative treatments such as non-steroid anti-inflammatory drugs, antimuscarinics, and cystoscopic hydrodistention.

Preoperative evaluations in all patients included history taking, physical examination, urine analysis, urine culture, biochemistry tests (renal function test, liver function tests, and electrolytes), and video urodynamic study (VUDS). Imaging studies included renal ultrasound, excretory urography, and bladder computed tomography (CT) scans. A urodynamic study was used to measure the maximal functional volume. A 3-day voiding diary was used to determine functional bladder capacity (FBC). Upper urinary tract damage was diagnosed in patients with evidence of hydronephrosis with ureteral stricture or VUR on CT scans, excretory urography, or voiding cystography during VUDS. We routinely performed VUDS at baseline and at 3 months and 12 months after the operation. VUDS was performed and the results were interpreted as per International Continence Society (ICS) guidelines (22).

All patients in this study had a cystometric bladder capacity (CBC) of less than 100 mL or low bladder

compliance with or without VUR. We used a modified Hautmann's procedure to create a 40-cm terminal ileal segment for bladder augmentation as reported previously (23). The native contracted bladder was resected as much as possible while taking care to preserve the trigone. The fashioned ileal patch was then anastomosed to the bladder wall. The purpose of trigone preservation was to maintain normal micturition reflex and minimize the source of bladder pain and inflammation. Ureteral reimplantation was indicated in patients with grade 3 – 4 VUR at low intravesical pressure during VUDS or hydronephrosis due to severe ureteral obstruction. Ureteral implantation was not performed in patients with grade 1 or 2 VUR. Cystography was routinely performed 2 weeks after the operation before the urethral catheter was removed to prevent extravasation at the enterovesical anastomosis. After that, patients were allowed to try voiding. Clean intermittent self-catheterization (CISC) was performed if the voiding trial was unsuccessful. In addition, we also suggest patients visit a psychiatric clinic for ketamine cessation after the operation.

Baseline and follow-up data from VUD studies analyzed in this study included CBC, post-void residual (PVR) volume, maximum urinary flow rate (Qmax), voided volume, and bladder compliance. A self-report questionnaire was used to evaluate patient satisfaction with treatment.

Differences between baseline and postoperative data were tested with a paired t-test. A P value < 0.05 was considered to indicate statistical significance. All analyses were performed with the statistical package SPSS (Version 20.0, SPSS Inc, Chicago, IL).

Results

Data on 26 patients were analyzed. The patients included 14 women and 12 men aged 20 – 43 years (mean age, 28.5 years) with an average duration of ketamine abuse of 4.7 years (range, 1 – > 10 years). The follow-up periods ranged from 6 to 62 months (median, 26 months).

All patients had severe frequency and urgency before surgery. Of the 26 patients, 20 (76.9%) had bladder pain, 19 (69.2%) had recurrent UTI, 9 (34.6%) had hydronephrosis, and 5 (19.2%) had VUR. Contracted bladder with small CBC (52.7 ±2 9.7 mL), poor compliance (11.1 ± 11.9), and cystographic evidence of scarring were noted in all patients during VUDS. In addition, all patients had increased bladder sensation and 18 (69.2%) patients had detrusor overactivity.

AE with ureteral reimplantation was performed in 5 patients because of severe VUR. The other patients underwent simple AE. Perioperative complications included postoperative intestinal obstruction in one patient, short-term urine leakage in one patient, and dysuria due to narrowing requiring transurethral incision of the enterovesical anastomosis in 2 patients. There were no cases of urosepsis and no deaths in this series.

Significant increases in bladder capacity (52.7 ± 29.7 v 327 ± 69.4 mL, P < 0.0001), Qmax (6.94 ± 4.32 v 13.7 ± 4.96 mL/s, P < 0.0001), bladder compliance (11.1 ± 11.9 v 54 ± 43, P < 0.0001), voided volume (44.1 ± 28.3 v 250.7 ± 133.4 mL, P < 0.0001), and PVR (8.08 ± 19.2 v 82.6 ± 91.5 mL, P < 0.0001) were noted after AE (Table 1). Hydronephrosis, UUI, VUR, and bladder pain also improved after AE (Table 2). Some patients, however, developed de novo dysuria (n = 9), had large PVR volume (> 150 mL, n = 5), or required CISC (n = 6) after AE. Nonetheless, all patients, with the exception of one with a spinal cord injury, could void spontaneously after surgery. The incidence of UTI decreased significantly but symptomatic UTI still occurred in 10 (38.5%) patients after AE. Persistent or recurrent bladder pain was noted in 10 patients who reused ketamine after AE. In one of those patients, the native bladder was removed because of intractable bladder pain. All patients reported that they were satisfied with the outcome of the surgery.

Discussion

The results of this study show that AE effectively relieves bladder pain and increases bladder capacity in patients with KC. The surgery also protects renal function by reducing the incidence of UTI, hydronephrosis, and VUR. Most patients were able to void spontaneously without catheterization after surgery.

Table 1. *The changes of bladder parameters after augmentation enterocystoplasty.*

	Baseline	Post-AE	*P* value
Bladder capacity (mL)	52.7 ± 29.7	327.0 ± 69.4	< 0.0001
Voided volume (mL)	44.1 ± 28.3	250.7 ± 133.4	< 0.0001
Qmax (mL/s)	6.94 ± 4.32	13.7 ± 4.96	< 0.0001
PVR (mL)	8.08 ± 19.2	82.6 ± 91.5	< 0.0001
Compliance (mL/cmH_2O)	11.1 ± 11.9	54.0 ± 43.0	< 0.0001

AE: augmentation enterocystoplasty, PVR: post-void residual volume, Qmax: maximum flow rate

Table 2. *The changes of symptoms and urinary tract dysfunction in 26 patients after augmentation enterocystoplasty.*

	Baseline		Post-AE	
Hydronephrosis	9	34.6%	2	7.7%
Frequency	26	100%	18	69.2%
Urgency	26	100%	10	38.5%
Dysuria	0	0%	9	34.6%
Bladder pain	20	76.9%	10*	38%
Incontinence	6	23.1%	2	7.7%
Large PVR	0	0%	2	7.7%
Chronic urine retention	0	0%	1	3.8%
UTI	18	69.2%	10	38.5%
VUR	10	38.5%	1**	3.8%
Urodynamic DO	18	69.2%	2	7.7%

AE: augmentation enterocystoplasty, DO: detrusor overactivity, PVR: post-void residual, UTI: urinary tract infection, VUR: vesicoureteral reflux. * patient reused ketamine, ** no antireflux procedure was performed

The first case series on patients with KC was reported by Shahani et al in 2007 (5). Since then investigators from various countries including Taiwan, Hong Kong, Singapore, Malaysia, and England have also reported their clinical observations in this special disease entity (6,8-10). Previous studies have shown that KC tends to occur in patients aged 16 to 35 years (5,6). The mean age in this study was 28.5 years. Several studies showed ketamine's rapid antidepressant effects and its safety in patients with treatment-resistant depression (24,25). The incidence of KC is expected to increase rapidly in the next decades, especially in the younger generation. Thus, the management of this rising disease is very important.

The correlation of ketamine abuse dose and severity of lower urinary tract symptoms is still unclear. The difference in the severity of the symptoms based upon the method of abuse is unknown. No lower urinary tract symptoms (LUTS) as side effects were reported among adult patients with chronic pain, who took a daily dose of 30 – 1000 mg ketamine orally in a systemic review (26). In contrast, a pediatric case report of a 16-year-old girl, who was treated with ketamine orally at 8 mg/kg body weight for neuropathic pain, developed cystitis symptoms (27). An online survey of ketamine abusers in the UK found high-dose and frequent users had higher prevalence rates of LUTS (10). A large cohort of 318 ketamine abusers reported that a higher dosage of ketamine use per week was associated with higher pelvic pain (28). In current series, although the actual ketamine abuse dose is unclear, most patients had a good response even with a high dose of ketamine abuse at baseline.

Cessation of ketamine is always the first and key step in the management of KC. However, long-term cessation of ketamine is difficult for frequent users. Ketamine dependence was reported previously; it is more like a psychological dependence than a physical dependence. For example, the abuser will think about ketamine and have cravings but without severe withdrawal symptoms like nausea or vomiting after stopping use of the drug (29-32). Although no specific ketamine withdrawal syndrome has been reported (16), a recent study found that abstinence from ketamine may cause some non-specific symptoms such as anxiety, poor appetite, drowsiness, and fatigue (33). For patients without irreversible pathological changes, such as thickened bladder walls or severe hydronephrosis, conservative treatment including symptomatic medication, intravesical hyaluronic acid instillation, and intravesical botulinum toxin A injection may be helpful. Unfortunately, many patients will reuse ketamine when bladder symptoms improve after conservative treatment. Continued use of ketamine will lead to severe bladder inflammation and contracted bladder, symptoms that are difficult to completely eradicate with conservative treatment.

Winstock et al (34) reported that KC symptoms resolved after cessation of ketamine use in 51% of patients, did not worsen after resumption of use in 43%, and actually deteriorated after cessation in 3.8% of patients. In our previous study, we found that bladder capacity and hydronephrosis usually do not recover after stopping ketamine (7). Renal function can be preserved with endoscopic ureteral stenting or nephrostomy tube drainage before irreversible damage develops (35). AE and continent diversion using an intestinal segment are considered suitable for these patients as those procedures reduce bladder pain, improve quality of life, and prevent deterioration of renal function (7).

The fibrotic bladder wall in patients with KC is irreversible, requiring excision of the damaged bladder via supratrigonal partial cystectomy. An advantage of removing the bladder wall is that it removes the source of bladder pain. The bladder base and trigone section are preserved during AE in order to maintain normal micturition reflex, which allows for micturition without the need for abdominal straining. However, many patients

with KC who undergo AE experience the urge earlier than patients with neurogenic bladder who receive AE because patients with KC still have increased bladder sensation due to the intact trigone. In this series, none of the patients had difficulty voiding spontaneously after AE with the exception of one patient with a spinal cord injury. In addition, bladder capacity increased and PVR volume was acceptably small after AE, indicating that this surgical technique is feasible (7).

Patients who undergo AE often experience a dramatic reduction in bladder pain. However, frequency, urgency, and small FBC often remain during the first 3 months after surgery (7). In our experience, bladder capacity can be expected to increase and intravesical pressure normally decreases about 6 months after AE (36). The symptoms of urinary frequency and urgency tend to improve over time. However, in patients who continue to use ketamine after AE, bladder pain tends to persist and symptoms often relapse. Nevertheless, FBC after AE in patients who resume using ketamine is still larger than that before AE. In 2 previous case series on AE, continued ketamine abuse was shown to cause symptom relapse, disease progression to the ureteral stricture and renal failure (8,35). In this case series, there were only a few perioperative complications, indicating that AE is a safe procedure for KC.

The limitation of this study is the small case number. In addition, the self-report of ketamine cessation in these patients may be not reliable, which might affect the outcome assessments of this study. This study revealed that AE is effective in relieving bladder pain and increasing bladder capacity in patients with KC refractory to conservative treatment. Further studies with larger case numbers and longer follow-up duration will be necessary to determine the long-term efficacy and safety of AE for KC.

Conclusions

This case series demonstrated that AE is an effective surgical procedure for treating KC-induced bladder pain and restoring normal lower urinary tract function. Absolute cessation of ketamine use is strongly recommended after AE.

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