Systematic review and meta-analysis of ketamine-associated uropathy

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A B S T R A C T

Introduction: This systematic review and meta-analysis focused on the literature regarding ketamine-associated uropathy to summarise its clinical manifestations, the results of urological assessments, and current management.

Methods: A literature search was conducted using keywords and MeSH terms related to ketamine abuse, urinary tracts, and urological examinations. Databases including Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials were searched up to 26 June 2020.

Results: In total, 1365 articles were retrieved; 45 articles (4921 patients) were included in the analysis of patient demographics, clinical manifestations, examination results, and treatments. Frequency was the most common manifestation (pooled prevalence 77.1%, 95% confidence interval [CI]=56.9%-92.2%), followed by urgency (69.9%, 95% CI=48.8%-87.3%) and suprapubic pain (60.4%, 95% CI=35.3%-82.9%). Upper urinary tract involvement was less common; the pooled prevalence of hydronephrosis was 30.2% (95% CI=22.0%-39.2%). Further workup revealed a pooled functional bladder capacity of 95.23 mL (95% CI=63.57-126.88 mL), pooled voided volume of 113.31 mL (95% CI=59.44-167.19 mL), and pooled maximum urine flow rate of 8.69 mL/s (95% CI=5.54-11.83 mL/s). Cystoscopic examinations and bladder biopsy revealed frequent urothelial denudation, inflammatory changes, and inflammatory cell infiltration. Treatments included oral medications for symptomatic relief, intravesical therapy, and surgery (eg, hydrodistension and bladder reconstruction), but ketamine abstinence was necessary for improvement.

Conclusion: Ketamine-associated uropathy frequently involves frequency, urgency, and suprapubic pain; upper urinary tract involvement is less common. Affected patients showed reductions in bladder capacity and urine flow rate. Endoscopic and histological analyses often revealed cystitis. Despite variations in treatment, ketamine abstinence is important for all patients with ketamine-associated uropathy.

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Introduction

First synthesised in the 1960s as an antagonist of the N-methyl-D-aspartate receptor, ketamine is a short-acting anaesthetic agent which can also serve as an analgesic for chronic pain management.[1] Ketamine was used recreationally beginning in the 1970s and subsequently became popular among young people.[2] In Hong Kong, ketamine was the most commonly abused psychotropic substance from 2009 to 2014; for example, 5280 individuals reportedly abused ketamine in 2009.[3] Data from the Central Registry of Drug Abuse indicate that ketamine abuse persists in Hong Kong, although its rate of abuse has decreased in the past several years. For example, 405 individuals reportedly abused ketamine in 2019, which comprised 7.3% of all drug users in Hong Kong that year.[3]

Ketamine abuse is known to affect the urinary system, and lower urinary tract symptoms (LUTS) are the most common manifestations. In 2007, the clinical feature of ketamine-associated cystitis was proposed by Shahani et al[4] in their report of nine patients with a history of ketamine abuse who had LUTS; those patients also presented with bladder wall thickening, reduced bladder capacity, and cystoscopic findings indicative of cystitis. In 2008,

Chu et al[5] described 59 patients with a history of ketamine abuse who had LUTS. Their findings indicated that although ketamine abuse consistently affected the lower urinary tract, it also affected the upper urinary tract in some patients, as indicated by the presence of hydronephrosis, renal papillary necrosis, and an elevated level of creatinine. Because ketamine-associated uropathy (KAU) is a relatively new clinical entity, and its incidence is influenced by the time- and location-dependent popularity of ketamine, relevant literature remains limited. Thus, it is challenging to optimise management for young patients who present with uropathy and a history of ketamine abuse.

Here, we performed a systematic review and meta-analysis of KAU to summarise its key clinical manifestations, the results of urological assessments, and current management approaches. This review is expected to provide insights concerning the optimal management of KAU.

Methods

This systematic review and meta-analysis of published literature regarding KAU was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement.[6]

Literature search

A literature search was conducted using combinations of keywords and Medical Subject Headings (MeSH) terms related to 'ketamine use', 'ketamine addict', 'urinary tracts', 'urinary organs', and 'urological examinations'. Databases included in the search were Embase, MEDLINE, and the Cochrane Central Register of Controlled Trials. The search was limited to human studies published in English up to 26 June 2020, excluding conference abstracts. The reference lists of the included articles were searched to identify additional relevant literature. The search strategy is shown in the online supplementary Appendix 1.

Screening process and selection criteria

All articles retrieved from the literature search were independently screened by at least two independent reviewers. Case series, case-cohort studies, non-randomised studies, and randomised controlled trials related to ketamine abuse and uropathy were included. Articles were excluded if they met any of the following criteria: they were editorials, commentaries, reviews, or case reports; they described non-human studies; the full text was not available in English; no full text was available; and/or they described the use of ketamine for anaesthesia. Disagreements during the screening process were resolved by a third senior reviewer.

與吸食氯胺酮有關的尿路病變的系統性文獻回顧及統合分析

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引言：對與吸食氯胺酮有關的尿路病變相關的文獻進行系統性文獻回顧及綜合分析，以總結其臨床表現、泌尿評估結果及現時的治療方法。

方法：本研究使用與濫用氯胺酮、泌尿道及泌尿外科檢查相關的關鍵詞及MeSH主題詞，在Embase、MEDLINE及考科藍對照試驗中心註冊庫中檢索涵蓋至2020年6月的文獻。

結果：共搜尋了1365篇文章，並分析了其中45篇（涉及4921名病人），分析內容包括病人的人口學統計資料、臨床表現、診斷結果及治療。尿瀕是最常見的表現（合併現患率77.1%，95%置信區間=56.9%-92.2%），其次是壓迫性尿急（69.9%，95%置信區間=48.8%-87.3%）及上恥骨痛（60.4%，95%置信區間=35.3%-82.9%）。牽涉上泌尿道的臨床表現則較為少有；腎積水的合併現患率為30.2%（95%置信區間=22.0%-39.2%）。進一步檢查發現合併功能性膀胱容量為95.23 mL（95%置信區間=63.57-126.88 mL），合併排尿量為113.31 mL（95%置信區間=59.44-167.19 mL），以及合併最大尿流速為8.69 mL/s（95%置信區間=5.54-11.83 mL/s）。膀胱鏡檢查及膀胱活組織檢查顯示尿道上皮剝落、炎性變化及炎性細胞浸潤經常出現。與吸食氯胺酮有關的尿路病變的治療方法包括緩解症狀的口服藥物、膀胱內藥物灌注及手術（例如膀胱水擴張及膀胱重建），但病人仍須戒掉氯胺酮，方能改善情況。

結論：與吸食氯胺酮有關的尿路病變通常牽涉尿瀕、壓迫性尿急及上恥骨痛；牽涉上泌尿道的臨床表現則較為少有。受影響的病人會出現膀胱容量及尿流速下降的問題。內窺鏡及組織學分析通常得出的結果是膀胱炎。雖然相關病變有多種療法，但對於所有患上該病變的病人而言，戒掉氯胺酮十分重要。

Data extraction

The following data were extracted from eligible studies using a standardised form: patient demographics, clinical features, examination results (eg, urodynamics, radiological workup, and endoscopic workup), and the treatment administered. Patient demographics included age, sex, and cumulative exposure to ketamine. Clinical features included presenting symptoms and the results of urinalysis and renal function tests. Urodynamic results included the voided volume, maximum urine flow rate (Qmax), and detrusor overactivity. Radiological features included hydronephrosis, ureteral stricture, and descriptive findings (eg, bladder wall thickening). Endoscopic workup included cystoscopic findings and bladder biopsy results. Questionnaire scores were also recorded. Finally, treatments and the corresponding responses were recorded.

Data analysis and statistical analysis

Quantitative and qualitative assessments were conducted in this systematic review and meta-analysis. Quantitative assessments included

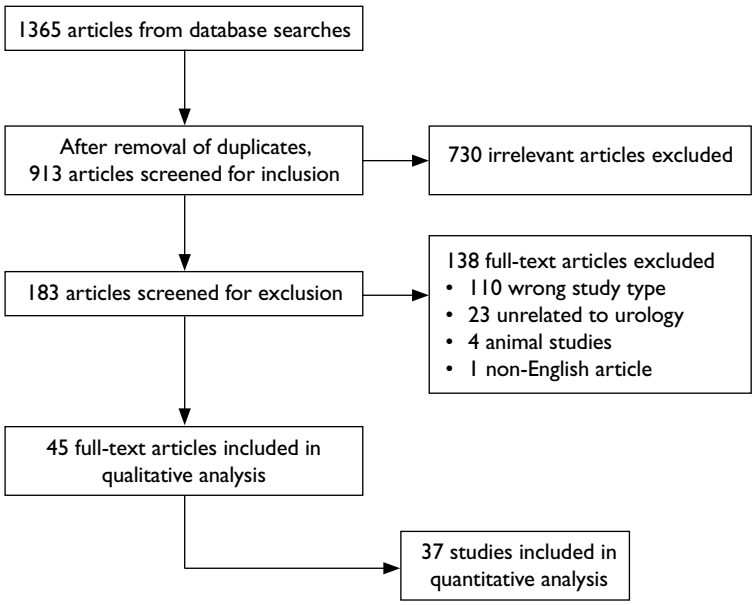

FIG. PRISMA flow diagram of literature search

TABLE 1. Clinical manifestations of ketamine-associated uropathy

	Pooled prevalence	95% Confidence interval
Frequency	77.1%	56.9%-92.2%
Urgency	69.9%	48.8%-87.3%
Detrusor overactivity*	63.9%	45.6%-80.3%
Suprapubic pain	60.4%	35.3%-82.9%
Nocturia	58.0%	38.5%-76.2%
Dysuria	49.8%	28.5%-71.1%
Haematuria	46.3%	22.6%-71.0%
Incontinence	43.9%	21.0%-68.2%
Hydronephrosis	30.2%	22.0%-39.2%
Vesicoureteral reflux	22.0%	12.4%-33.5%
Ureteral stricture	19.4%	7.3%-35.5%
Impaired renal function	8.3%	4.8%-12.6%

* Frequency and urgency are common symptoms of detrusor overactivity

prevalences of urological symptoms, scores of questionnaires that reflected urological symptoms, and results of urodynamics workups. Pooled data were analysed by OpenMeta[Analyst] when results were available for more than two studies with >100 patients. The studies included in each pooled analysis were individually reviewed to ensure that there was no patient overlap among the studies. Random effects models and double arcsine transformation were used to pool the results. Cochran's Q test was used to identify heterogeneity, and P<0.10 was considered indicative of significant heterogeneity. I^2 statistics were used to measure variations across studies, and I^2>50% was considered indicative of significant heterogeneity. Qualitative assessments included narrative descriptions of cystoscopic findings, bladder biopsy results, and treatments administered.

Results

In total, 1365 articles were identified by database searches, whereas no articles were identified by manual searches. After the removal of duplicates, 913 articles remained; 730 articles were removed during the initial screening, and 138 articles were removed during full-text screening. Forty-five articles were included in the qualitative analysis, and 37 articles were included in the quantitative analysis. The PRISMA flow diagram is shown in the Figure.

Demographics

Our analysis included 4890 patients (3518 men and 1372 women) with a mean age of 25.46 ± 6.03 years and mean ketamine exposure duration of 54.99 ± 43.54 months.

Clinical manifestations

Our meta-analysis concerning clinical manifestations of KAU included 37 studies with 4314 patients. All reported manifestations are summarised in Table 1 and online supplementary Appendix 2. Frequency was the most common manifestation (pooled prevalence 77.1%, 95% confidence interval [CI]=56.9%-92.2%), followed by urgency (69.9%, 95% CI=48.8%-87.3%), bladder or suprapubic pain (60.4%, 95% CI=35.3%-82.9%), and nocturia (58.0%, 95% CI=38.5%-76.2%). Additionally, substantial numbers of patients presented with dysuria, haematuria, and/or incontinence. Upper urinary tract involvement was less common. The pooled prevalence of hydronephrosis was 30.2% (95% CI=22.0%-39.2%), whereas approximately 20% of patients presented with ureteral strictures and 10% of patients presented with impaired renal function.

Symptom scores

Various questionnaires and scoring systems were used among studies to assess the severities of patient symptoms. The International Prostate Symptom Score (IPSS), Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), Pelvic Pain and Urgency/Frequency (PUF) total score, and Visual Analogue Scale (VAS) were most commonly used. Our meta-analysis of symptom scores included 13 studies (2135 patients); the results are summarised

in Table 2 and online supplementary Appendix 3. Five studies with 1366 patients were focused on IPSS; the pooled score was 11.61 (95% CI=6.37-16.84). Five studies (1263 patients) were focused on ICSI and ICPI; the pooled ICSI score was 11.11 (95% CI=4.12-18.09) and the pooled ICPI score was 10.24 (95% CI=3.84-16.64). The pooled PUF score was 21.66 (95% CI=20.12-23.20), and the pooled VAS score was 6.46 (95% CI=4.62-8.30).

TABLE 2. Urological findings in patients with ketamine-associated uropathy

	Pooled mean score	95% Confidence interval
Symptom scores		
International Prostate Symptom Score (n=1366)	11.61	6.37-16.84
Interstitial Cystitis Symptom Index (n=1263)	11.11	4.12-18.09
Interstitial Cystitis Problem Index (n=1263)	10.24	3.84-16.64
Pelvic Pain and Urgency/Frequency (n=750)	21.66	20.12-23.20
Visual Analogue Scale (n=161)	6.46	4.62-8.30
Bladder assessment		
Functional bladder capacity, mL (n=717)	95.23	63.57-126.88
Cystometric capacity, mL (n=491)	97.37	58.23-136.51
Maximum cystometric capacity, mL (n=140)	202.09	169.06-235.13
Voided volume, mL (n=630)	113.31	59.44-167.19
Maximal urine flow rate/Qmax, mL/s (n=451)	8.69	5.54-11.83

Bladder assessments

Bladder assessments in the reviewed articles included cystoscopy, urodynamic studies, videocystometry, bladder imaging, and bladder biopsy. The results are shown in Table 2 and online supplementary Appendix 4. Fifteen studies (1221 patients) included data regarding bladder capacity, including functional bladder capacity, cystometric capacity, or maximum cystometric capacity. The pooled functional bladder capacity was 95.23 mL (95% CI=63.57-126.88 mL). The pooled and maximum cystometric capacities were 97.37 mL (95% CI=58.23-136.51 mL) and 202.09 mL (95% CI=169.06-235.13 mL), respectively.

Urodynamic studies revealed a pooled mean voided volume of 113.31 mL (95% CI=59.44-167.19 mL) and a pooled mean Qmax of 8.69 mL/s (95% CI=5.54-11.83 mL/s). The pooled prevalence of detrusor overactivity was 63.9% (95% CI=45.6%-80.3%). Videocystometry or bladder imaging (eg, ultrasound or computed tomography) showed vesicoureteral reflux with a pooled prevalence of 22.0% (95% CI=12.4%-33.5%).

In total, 14 studies included cystoscopy results and bladder biopsy findings. Common findings on cystoscopy included epithelial inflammation in the bladder mucosa, erythematous patches, neovascularisation, and ulcerations. Petechial haemorrhage was observed in patients with severe disease. Bladder biopsy results were consistent with the above inflammatory changes. Urothelial denudation and focal reactive changes were evident. The lamina propria exhibited granulation tissue, vascular congestion, and oedema, along with infiltrating inflammatory cells including lymphocytes, eosinophils, and mast cells. Perivesical fibrosis was present in some patients. Chu et al[5] found such inflammatory changes in 71% of their patients.

Treatments

Treatments for KAU considerably varied among studies, and there were no trends consistent among all studies. In total, 19 articles described the treatment of KAU, which included oral, intravesical, and surgical treatments. Yee et al[7] and Wu et al[8] adopted a tiered treatment approach, which began with the least invasive oral treatment and was escalated to the most invasive surgical treatment if other treatments failed. However, ketamine abstinence was regarded as a key aspect of patient management in 11 of the 19 articles. Various treatments with their potential indications and efficacies are summarised in Table 3.[7-18]

Oral treatment

Oral treatment approaches involved non-steroidal anti-inflammatory drugs, opioid or non-opioid analgesics, anticholinergics, pregabalin, steroids, antibiotics, antihistamines, antioxidants, and/or pentosane polysulphate sodium. Yee et al[7] and Wu et al[18] reported that oral treatments led to positive outcomes; most patients showed improvements in symptoms, functional bladder capacity, voided volume, PUF scores, and EuroQol VAS scores. In a case series of nine patients, Shahani et al[4] observed that oral pentosane polysulphate sodium produced symptomatic relief when combined with ketamine abstinence. However, 11 patients in another study exhibited poor responses to treatment involving non-steroidal anti-inflammatory drugs, anticholinergics, and antibiotics.[14]

Intravesical treatment

In total, seven studies reviewed intravesical instillation of hyaluronan solutions (eg, sodium hyaluronate and hyaluronic acid). In six of these studies (34 patients), 30 patients showed improvements in symptoms, including suprapubic pain (2 patients) and bladder capacity (4 patients).[7,13-16,19] In the remaining study (2 patients), intravesical treatment did not lead to symptomatic improvement.[12]

TABLE 3. Indications and efficacies of treatments for ketamine-associated uropathy

Treatment	Indications	Efficacy findings	
Oral medications	1. First-line treatment administered at initial presentation 2. No bladder or ureteral wall changes[8]	Yee et al (n=290)[7]	Medications: NSAIDs, non-opioid analgesics, anticholinergics Results: 234 patients (80.7%) reported improvements in EuroQol VAS score, PUF score, and FBC
		Yee et al (n=62)[7]	Medications: Opioid analgesics, pregabalin Results: 42 patients (67.7%) reported improvements in EuroQol VAS score, PUF score, and FBC
		Wu et al (n=24)[18]	Medications: anticholinergics, antihistamines, steroids, antibiotics, antioxidants Results: improvements in voided volume, micturition interval, nocturnal void frequency, and PUF score
Intravesical instillation (hyaluronan solution)	–	Yee et al (n=8)[7]	5 Patients (62.5%) subsequently able to reduce treatment
		Chen et al (n=2)[16]	2 Patients (100%) reported improved suprapubic pain
		Lai et al (n=6)[15]	4 Patients (66.7%) reported improved bladder capacity
		Li et al (n=7)[13]	5 Patients (71.4%) responded
		Tsai et al (n=6)[14]	Improved urinary tract symptoms
Hydrodistension	1. Presence of fibrosis 2. Bladder changes[8] 3. No ureteral wall changes[8]	Chang et al (n=20)[12]	14 Patients (70%) showed significant symptomatic relief
		Li et al (n=14)[13]	10 Patients (71.4%) responded
		Wu et al (n=47)[8]	Improvements in voided volume, PUF score, frequency, and nocturia
Bladder reconstruction: 1. Augmentation cystoplasty 2. Cystectomy with neobladder or ileal conduit	1. Intractable bladder symptoms after conservative treatment[11] 2. Persistently low FBC[11] 3. Ketamine abstinence (≥6 months)[7] 4. CBC <100 mL[10] 5. Bladder and ureteral wall changes[8]	Jhang et al (n=28)[11]	• Improved CBC (52.7 ± 29.7 vs 327 ± 69.4 mL) • Improved maximum urine flow rate (6.94 ± 4.32 vs 13.7 ± 4.96 mL/s) • Improved voided volume (44.1 ± 28.3 vs 250.7 ± 133.4 mL) • Improved post-void residual (8.08 ± 19.2 vs 82.6 ± 91.5 mL)
		Hung et al (n=8)[9]	• Improved FBC (47.75 ± 10.07 vs 273.13 ± 54.96 mL) • Improved VAS score (6.0 ± 1.2 vs 1.75 ± 0.89)
		Ng et al (n=4)[17]	• Improved MBC (37.5 vs 400-500 cc)
		Wu et al (n=10)[18]	Improvements in voided volume, PUF score, frequency, and nocturia

Abbreviations: CBC = cystometric bladder capacity; FBC = functional bladder capacity; MBC = maximal bladder capacity; NSAIDs = non-steroidal anti-inflammatory drugs; PUF = Pelvic Pain and Urgency/Frequency; VAS = Visual Analogue Scale

Surgical treatment

Surgical treatments for patients with KAU included hydrodistension and bladder reconstruction. In most studies, surgical treatments were performed after patients had not responded to oral treatment. Three studies described the efficacy of hydrodistension, which involves the use of fluid to stretch the bladder in an anaesthetised patient. Wu et al[8] reported that hydrodistension led to improvements in voided volume, PUF score, frequency, and nocturia in 35 of 47 patients (74.5%). Chang et al[12] and Li et al[13] reported that 70.0% (14/20) and 71.4% (10/14) of patients, respectively, exhibited symptomatic relief after hydrodistension. In a few studies, botulinum toxin type A injection was conducted along with hydrodistension. Whereas Zeng et al[20] reported that symptoms were generally improved with such treatment, Sihra et al[21] found that only four of 29 patients experienced subjective symptomatic relief.

Another surgical approach comprises bladder reconstruction, which can be achieved by augmentation cystoplasty or by cystectomy and subsequent construction of a neobladder or an ileal conduit.[21] Augmentation cystoplasty increases the bladder capacity by anastomosing a segment of elastic gastrointestinal tract to the diseased fibrotic bladder wall. In the cystectomy method, retention of the bladder neck is combined with the construction of a neobladder to store urine or an ileal conduit to divert urine. Among five studies concerning these reconstruction methods, all demonstrated efficacy in the treatment of advanced ketamine cystitis (KC; a key feature of KAU).[9-11,17,22] Lee et al[10] reported that 26 of 26 patients showed postoperative improvements in bladder capacity, voided volume, and residual volume; similarly, Hung et al[9] reported that all eight patients showed postoperative improvements in bladder capacity, renal function, and pain perception. Furthermore, concomitant ureteral reimplantation can be performed in patients with vesicoureteral reflux severity of grade ≥3.[10] Importantly, surgical treatments were only effective when patients avoided further ketamine abuse.[10,11,17,22]

Discussion

Clinical presentation of ketamine-associated uropathy

Ketamine-associated uropathy is a clinical entity that has emerged with the increasing popularity of

ketamine as an illicit drug among young people. In 37 studies with >4000 patients, the most common manifestations—observed in approximately 60% of patients diagnosed with KAU—were frequency, nocturia, urgency, and bladder pain. Other common urinary symptoms, with prevalences of 40% to 50%, included dysuria, haematuria, and incontinence. Upper urinary tract involvement (eg, hydronephrosis and/or ureteral stricture) was observed in fewer than one-third of patients; renal function was impaired in <10% of patients. Further examinations revealed functional and cystometric bladder capacities of <100 mL, as well as voiding dysfunction. The bladder assessment findings were consistent with the clinical manifestations among affected patients. Symptom severity may be associated with the chronicity and dose of ketamine abuse.[23] In the United Kingdom, a survey of 3806 individuals—51.1% with a long-term history of ketamine abuse and 33.8% with a history of ketamine abuse in the previous 1 year—revealed that the dose and frequency of ketamine abuse were associated with the extent of urinary symptoms.[23] In Taiwan, Tsai et al[14] observed that urinary symptoms began 1 month after the initiation of ketamine abuse and were considerably worse after 1 year of abuse.

Potential pathophysiology of ketamine-associated uropathy

Despite the establishment of an association between ketamine abuse and urinary tract damage, the underlying pathophysiology remains unclear. Multiple hypotheses have been proposed to explain the mechanisms that underlie the onset of urinary tract damage. Chu et al[5] described four potential mechanisms: direct toxin damage to the urinary tract interstitium, microvascular injury to the urinary tract, autoimmune reaction to ketamine exposure in the urothelial epithelium and submucosa, and (less likely) unrecognised bacteriuria. The initial mechanism ultimately induces chronic inflammatory changes in the bladder, which lead to fibrosis, poor compliance, and contracture. The extent of bladder fibrosis may serve as an indicator of disease severity.[24] The occurrence of fibrotic changes is consistent with the common manifestations of frequency, nocturia, and pain associated with reduced bladder capacity; the occurrence of such changes is also consistent with the reduced bladder capacity observed during further urological workup. Wu et al[8] attributed the onset of LUTS and reduced bladder capacity among individuals abusing ketamine to a dysfunctional bladder epithelium and a defective glycosaminoglycan layer. The results of our review indicated that glomerulation, erythematous congestion, neovascularisation, and ulceration were common findings in cystoscopic examination of the urothelial epithelium. Bladder biopsy examinations revealed that urothelial denudation was common; infiltrating eosinophils and mast cells were observed in the lamina propria. Accordingly, KAU may involve hypersensitivity or an allergic reaction; this hypothesis is supported by the work of Jhang et al,[25] who found that the level of serum immunoglobulin E was higher in patients with KAU than in the control group. Although the exact pathophysiological mechanism remains unclear, the urothelial changes induced by ketamine and its metabolites suggest the onset of an inflammatory process that results in cystitis.[8]

Clinical diagnosis of ketamine-associated uropathy

Ketamine cystitis, a key feature of KAU, is closely associated with LUTS. Notably, KC is similar to interstitial cystitis (IC) in terms of clinical and histological findings. Despite these similarities, it is not difficult to distinguish KC and IC. The presence of cystitis in a patient with a history of ketamine abuse is strongly suggestive of KC. However, it is challenging to determine whether a patient is engaged in ketamine abuse because many patients do not voluntarily provide such information. The onset of cystitis in a patient aged ≤30 years is a potential clue because IC / bladder pain syndrome usually occurs in patients aged ≥40 years. Because of differences in pathophysiology, Yek et al[26] suggested that the course of disease progression differed between KC and IC. For example, KC causes bladder contraction that leads to progressive obstructive uropathy and the onset of hydronephrosis / hydroureter. This process explains the potential for upper urinary tract involvement in patients with KAU. In contrast, IC is a chronic bladder condition; its severity generally is not equivalent to the severity of KC.[24] In a comparison of clinical characteristics between 16 patients with IC and 13 patients with KC, Wu et al[18] found that patients with KC had more severe bladder dysfunction, along with reduced bladder capacity, greater bladder wall thickness, and increased bladder mass volume. Patients with KC also reported greater subjective discomfort (ie, a lower VAS score), compared with patients who had IC.

The similarities between KC and IC should be considered during the workup of suspected KAU. The main consideration involves the use of questionnaires in assessing symptoms and disease severity. Among the articles included in this review, the IPSS, ICSI, ICPI, and PUF were commonly used to assess IC; they generally helped to identify patients who required further examination.[27] Clemons et al[28] suggested that the ICSI and ICPI were suitable for the assessment of LUTS in patients with IC, but these questionnaires may not be appropriate for use during initial diagnosis. Accordingly, Clemons et al[28] proposed that 7 of 15 and 5 of 14 should

be regarded as the respective scores for the ICSI and ICPI. In our review, the pooled ICSI and ICPI scores were 11.11 and 10.24, respectively. In 2012, the PUF score was validated by Ng et al[29] for the assessment of LUTS associated with the use of street ketamine—the score was correlated with disease severity, as indicated by patient symptoms and the results of other examinations. In that study, Ng et al[29] proposed using a PUF score of 17 as a threshold to indicate serious urological consequences. In our review, the pooled PUF score was 21.66. The use of questionnaires during the workup of suspected KAU is a subjective assessment of patient symptoms that may provide insights concerning disease severity and quality of life. Although there is no consensus or standardised questionnaire specific to KAU, these non-invasive questionnaires are useful for initial patient assessment and can help guide subsequent management.

In addition to the use of subjective questionnaires, the workup of suspected KAU commonly consists of radiological, urodynamic, and endoscopic assessments. Despite the absence of standard diagnostic criteria, suspicion of KAU may be based on the presence of urinary tract symptoms combined with a history of ketamine abuse. Multiple aspects should be considered during the workup of suspected KAU. The main goal is the exclusion of other causes that explain the symptoms, including urinary tract infections and urolithiasis. Therefore, standard initial examinations comprise urinalysis, urine culture, and X-ray imaging. Anatomical involvement can be assessed by computed tomography urography to identify upper urinary tract involvement (eg, ureteral stricture, vesicoureteral reflux, and hydronephrosis) and confirm lower urinary tract involvement (eg, diffuse bladder wall thickening, mucosal enhancement, and inflammatory changes in perivesical tissue).[30] Urinary system functionality can be evaluated by urodynamics studies that investigate voided volume, Qmax, detrusor compliance, and detrusor overactivity. Cystoscopy and biopsy enable detailed bladder assessments that clarify cystitis severity and should be considered during a later stage of workup if indicated. However, caution is needed when considering the use of cystoscopy. Routine cystoscopy is not recommended[17] because it may discourage young patients from undergoing further medical examinations, with long-term impacts on their health.

Management of ketamine-associated uropathy

Although there is no specific regimen or algorithm for the treatment of KAU, ketamine abstinence is consistently effective, regardless of KAU severity. The effects of ketamine abstinence on alleviating and controlling symptoms of KAU are well known.[31,32] In a study of 66 individuals with a history of ketamine abuse, Mak et al[33] observed significantly improved maximal voided volume after ≥1 year of abstinence (387 mL), compared with patients who had <3 months of abstinence (243 mL). Yee et al[24] found that hydronephrosis spontaneously resolved in patients who abstained from ketamine abuse. At initial presentation, medications such as analgesics, anti-inflammatory drugs, and antihistamines were commonly used for symptomatic control.[26] Further management options involve intravesical instillation of pentosan polysulphate and hyaluronic acid to protect the bladder lining and repair the damaged glycosaminoglycan layer in the urothelium.[19] There is considerable variation in patient responses to the above oral and intravesical treatments. Surgery is indicated when conservative treatments fail. Bladder reconstruction surgery generally leads to improvements in symptoms and bladder functionality,[32] but it carries more risks than other treatment options. The available treatment options comprise a spectrum of effectiveness and invasiveness. The most invasive bladder reconstruction surgery is associated with greater effectiveness. Yee et al[7] proposed a standardised treatment protocol that comprised the following four-tier approach, where patients receive increasingly invasive treatment if less invasive treatments are ineffective: (1) anti-inflammatory or anticholinergic drugs, (2) opioid or pregabalin, (3) intravesical hyaluronic acid, and (4) hydrodistension and bladder reconstruction surgery (including augmentation cystoplasty and cystectomy with an ileal conduit or neobladder). Wu et al[8] adopted a similar tiered approach that involved assigning patients to three clinical staging groups according to their radiological and urodynamic findings. Stage I patients received lifestyle modification guidance and appropriate medications, stage II patients underwent hydrodistension, and stage III patients underwent bladder reconstruction surgery if other treatments were ineffective for 3 months. This tiered approach favourably balances the invasiveness and effectiveness among the available treatment modalities.

Limitations

There were some limitations in this systematic review and meta-analysis. First, all included studies were retrospective; there is a need for prospective studies of patients with KAU. Second, there was heterogeneity among the included studies, primarily because of variations in workup and treatment; standardisation would be beneficial for future management of patients with KAU. Third, treatment efficacy could not be fully assessed because baseline characteristics were not described in a consistent

manner in the included studies. Fourth, because the incidence of KAU depends on the locality-dependent popularity of ketamine, most studies were from Asian countries/regions (eg, Taiwan and Hong Kong). Nevertheless, this comprehensive review provides an important summary concerning the limited available information about KAU.

Conclusion

Patients with KAU most commonly present with frequency, urgency, suprapubic pain, and nocturia; the upper urinary tract is occasionally involved. The occurrence of urinary symptoms in young patients with a history of ketamine abuse should lead to suspicion of KAU. Validated symptom scores are useful in patient-based subjective assessment of symptom severity and treatment progress, whereas radiological and urodynamic examinations objectively define the extent of urinary tract involvement and the functional impairment that results from KAU. In terms of management, ketamine abstinence is essential and a tiered treatment approach is preferred, beginning with the least invasive medications and progressing to surgery if conservative treatments are ineffective.

Author contributions

Concept or design: EOT Chan, VWS Chan, MCS Wong, JYC Teoh.
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Analysis or interpretation of data: EOT Chan, VWS Chan, JYC Teoh.
Drafting of the manuscript: EOT Chan.
Critical revision of the manuscript for important intellectual content: MCS Wong, CH Yee, CF Ng, JYC Teoh.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

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References

1. Noppers I, Niesters M, Aarts L, Smith T, Sarton E, Dahan A. Ketamine for the treatment of chronic non-cancer pain. Expert Opin Pharmacother 2010;11:2417-29.
2. Morgan CJ, Curran HV, Independent Scientific Committee on Drugs. Ketamine use: a review. Addiction 2012;107:27-38.
3. Narcotics Division, Security Bureau, Hong Kong SAR Government. Central Registry of Drug Abuse Sixty-ninth Report. 2019. Available from: https://www.nd.gov.hk/en/crda_69th_report.html. Accessed 11 Nov 2020.
4. Shahani R, Streutker C, Dickson B, Stewart RJ. Ketamine-associated ulcerative cystitis: a new clinical entity. Urology 2007;69:810-2.
5. Chu PS, Ma WK, Wong SC, et al. The destruction of the lower urinary tract by ketamine abuse: a new syndrome? BJU Int 2008;102:1616-22.
6. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336-41.
7. Yee CH, Lai PT, Lee WM, Tam YH, Ng CF. Clinical outcome of a prospective case series of patients with ketamine cystitis who underwent standardized treatment protocol. Urology 2015;86:236-43.
8. Wu P, Wang Q, Huang Z, Wang J, Wu Q, Lin T. Clinical staging of ketamine-associated urinary dysfunction: a strategy for assessment and treatment. World J Urol 2016;34:1329-36.
9. Hung CH, Hsieh SW, Chen SK, Lin CM. Augmentation enterocystoplasty for patients with ketamine-induced cystitis: an 8-year experience and a review of series. Urol Sci 2019;30:232-7.
10. Lee YK, Jhang JF, Kuo HC. Clinical outcome of augmentation enterocystoplasty for patients with ketamine-induced cystitis. Pain Physician 2017;20:E431-6.
11. Jhang JF, Birder LA, Chancellor MB, Kuo HC. Patient characteristics for different therapeutic strategies in the management ketamine cystitis. Neurourol Urodyn 2017;36:687-91.
12. Chang T, Lin CC, Lin AT, Fan YH, Chen KK. Ketamine-induced uropathy: a new clinical entity causing lower urinary tract symptoms. Low Urin Tract Symptoms 2012;4:19-24.
13. Li CC, Wu ST, Cha TL, Sun GH, Yu DS, Meng E. A survey for ketamine abuse and its relation to the lower urinary tract symptoms in Taiwan. Sci Rep 2019;9:7240.
14. Tsai TH, Cha TL, Lin CM, et al. Ketamine-associated bladder dysfunction. Int J Urol 2009;16:826-9.
15. Lai Y, Wu S, Ni L, et al. Ketamine-associated urinary tract dysfunction: an underrecognized clinical entity. Urol Int 2012;89:93-6.
16. Chen CH, Lee MH, Chen YC, Lin MF. Ketamine-snorting associated cystitis. J Formos Med Assoc 2011;110:787-91.
17. Ng CF, Chiu PK, Li ML, et al. Clinical outcomes of augmentation cystoplasty in patients suffering from ketamine-related bladder contractures. Int Urol Nephrol 2013;45:1245-51.
18. Wu SY, Jhang JF, Jiang YH, Kuo HC. Increased bladder wall thickness is associated with severe symptoms and reduced bladder capacity in patients with bladder pain syndrome. Urol Sci 2016;27:263-8.
19. Meng E, Tsao CW, Tang SH, et al. Intravesical hyaluronic acid treatment for ketamine-associated cystitis: preliminary results. Urol Sci 2015;26:176-9.

20. Zeng J, Lai H, Zheng D, et al. Effective treatment of ketamine-associated cystitis with botulinum toxin type a injection combined with bladder hydrodistention. J Int Med Res 2017;45:792-7.
21. Sihra N, Ockrim J, Wood D. The effects of recreational ketamine cystitis on urinary tract reconstruction—a surgical challenge. BJU Int 2018;121:458-65.
22. Chu PS, Kwok SC, Lam KM, et al. 'Street ketamine'–associated bladder dysfunction: a report of ten cases. Hong Kong Med J 2007;13:311-3.
23. Winstock AR, Mitcheson L, Gillatt DA, Cottrell AM. The prevalence and natural history of urinary symptoms among recreational ketamine users. BJU Int 2012;110:1762-6.
24. Yee CH, Teoh JY, Lai PT, et al. The risk of upper urinary tract involvement in patients with ketamine-associated uropathy. Int Neurourol J 2017;21:128-32.
25. Jhang JF, Hsu YH, Jiang YH, Kuo HC. Elevated serum IgE may be associated with development of ketamine cystitis. J Urol 2014;192:1249-56.
26. Yek J, Sundaram P, Aydin H, Kuo T, Ng LG. The clinical presentation and diagnosis of ketamine-associated urinary tract dysfunction in Singapore. Singapore Med J 2015;56:660-4.
27. Kushner L, Moldwin RM. Efficiency of questionnaires used to screen for interstitial cystitis. J Urol 2006;176:587-92.
28. Clemons JL, Arya LA, Myers DL. Diagnosing interstitial cystitis in women with chronic pelvic pain. Obstet Gynecol 2002;100:337-41.
29. Ng CM, Ma WK, To KC, Yiu MK. The Chinese version of the pelvic pain and urgency/frequency symptom scale: a useful assessment tool for street-ketamine abusers with lower urinary tract symptoms. Hong Kong Med J 2012;18:123-30.
30. Mason K, Cottrell AM, Corrigan AG, Gillatt DA, Mitchelmore AE. Ketamine-associated lower urinary tract destruction: a new radiological challenge. Clin Radiol 2010;65:795-800.
31. Wood D, Cottrell A, Baker SC, et al. Recreational ketamine: from pleasure to pain. BJU Int 2011;107:1881-4.
32. Chung SD, Wang CC, Kuo HC. Augmentation enterocystoplasty is effective in relieving refractory ketamine-related bladder pain. Neurourol Urodyn 2014;33:1207-11.
33. Mak SK, Chan MT, Bower WF, et al. Lower urinary tract changes in young adults using ketamine. J Urol 2011;186:610-4.