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Abstract

Introduction – Ketamine consumption in on the increase as a recreationally abuses substance. It is reported to cause lower urinary tract symptoms and published accounts of its deleterious effects are increasing. We reviewed the available literature regarding the urological impact of Ketamine abuse and its management.

Methods – twenty two publications were found in total after a search of all databases including Pubmed, Medline and Google Scholar using the words “ketamine”, “bladder” and “cystitis” with no limits imposed.

Results – There are approximately 110 cases reported in the literature in the form of case series, case reports and letters. The effect of ketamine abuse on the bladder is universally similar however there is no uniform method adopted in reporting the symptoms, diagnosis and management. Very little is known regarding the pathogenesis of its effects on the urinary tract.

Discussion – Patients with severe irritative lower urinary tract symptoms, a positive history of ketamine abuse and the absence of any other aetiology should be considered to have ketamine induced vesicopathy, (KIV). Effort must be made to elicit the history of drug abuse in those with no found cause of lower urinary tract symptoms especially in the young. Presently ketamine cessation is only effective treatment modality to prevent deterioration of the renal function and indeed offer the possibility of symptom resolution. Management akin to that formulated for IC patients would appear to offer the greatest opportunity for effective treatment

Introduction -

Ketamine is a dissociative anaesthetic agent commonly utilised as a horse tranquiliser and is often prescribed for chronic pain conditions. Its main function is that of an N-methyl D-aspartate (NMDA) receptor antagonist. The ability of Ketamine to remove the subject from his or her surroundings with no response to pain and its highly addictive nature has led to a massive increase in its social consumption.

Also known as K, Super K, vitamin K and special K, Ketamine may be consumed via inhalation, smoking or intravenous injection.

As consumption of ketamine has increased, so too have the number of published accounts of its deleterious effects both urological and otherwise. Recent reports suggest that approximately 20%-30% of ketamine abusers suffer from lower urinary tract symptoms [1, 2]. We reviewed the available literature regarding the urological impact of Ketamine abuse and its management

Materials and Methods -

All databases including Pubmed, Medline and Google Scholar were searched using the key words “ketamine”, “bladder” and “cystitis”, no limits were imposed. 22 publications were found (Table 1) comprising three case series, four case reports, one review and numerous letters. Of these, five reports are regarded as extension of case series. As a result twenty reports involving 111 patients were taken into consideration.

Epidemiology

Ketamine abuse is on the increase with a recent British Crime Survey [3] reporting an increase from 0.30% in 2006 to 0.40% in 2007 amongst 16 to 59 years old. The life time use of ketamine in was found to be 1% in those aged 14 and above with a many reporting increased usage in recent years [4]. In general, affected patients tend to be young, with a peak age range of 16-35 years [2, 5]. Whilst some series have reported a slight male predominance, this is insignificant and not universally witnessed. At the present time it would seem that ketamine induced vesicopathy does not exhibit any gender bias. [2]

Presentation -

The time of onset of lower urinary tract symptoms (LUTS) following ketamine abuse varies from a few days to a few years following the onset of abusive use with the severity being, in part, determined by the chronicity of the abuse with up to 100% of those using more than 5gm/day reporting urinary symptoms [6]. It is unclear whether the severity of abuse with respect to regular ingested dosage also influences the time to onset and the severity of

LUTS but it is likely that this will eventually prove to be the case just as it is within the context of intermittent ketamine use [7]. In fact Tsai TH et al have documented that although symptoms have appeared after a month of starting the usage they became severe by the end of one year [8].

The symptoms of ketamine induced vesicopathy include a range of LUTS mainly irritative in nature. Typically the patients will complain of intense urgency, extreme frequency, and intractable dysuria while gross haematuria is also a frequent symptom in those suffering from ulcerative cystitis. Only one series used a validated Pelvic pain and Urgency/Frequency (PUF) scoring in 24/59 patients with a PUF score > 15 being regarded as significant [2]. PUF scoring uses symptom and bother scoring to grade the symptoms. It has been validated with potassium sensitivity test (PST) and high scores have been found to correlate with symptoms. The PUF score has previously proved useful in detecting interstitial cystitis. 91% of those scoring > 20 are more likely to have a positive PST, whilst scores of 10-14, and 15-19, have a 74% and 76% likelihood of a positive test respectively; [9, 10].

Patients with ketamine induced vesicopathy often exhibit urge incontinence and decreased bladder compliance with all of them demonstrating detrusor overactivity with low volumes [2, 8]. This is in contrast to IC where urge incontinence is not common [11]. Symptom scoring can be useful in research purposes when trialling a new drug or monitoring the progress of the patient while undergoing treatment.

Investigations -

Renal function estimation is required both at the time of initial assessment and during management, particularly when management is conservative and focussed around ketamine withdrawal.

Sterile urine is the norm although an occasional contaminated growth may be encountered [2] and occasionally sterile pyuria may be present [8, 12, 13, 14]

A voiding diary including fluid intake, voided volumes and frequency is mandatory in the assessment of such patients with the typical picture being one of increased frequency and small voided volumes usually in the region of 200mls or less, [2, 8].

Urodynamic studies have been utilised, in particular to assess bladder capacity with most values being less than 150mls and very few being greater than 300mls [2, 8]. It has been postulated that in established KIV cases, vesico-ureteric reflux (VUR) occurs due to a small bladder capacity combined with high bladder pressures

(detrusor overactivity) [2] whilst early VUR cases in general commonly exhibit large bladder capacity with detrusor overactivity being rare [15].

Upper renal tract imaging in the form of simple ultrasonography will showed bilateral hydronephrosis in 50% of patients (35/73), Papillary necrosis suggestive of transmural necrosis has also been reported [2]. In addition ultrasonography also allows assessment of bladder wall thickness. Bilateral hydronephrosis is seen in those patients with transmural inflammation at the VUJ [2, 8, 14, 16, 17, 18].

Whilst IVU will demonstrate both dilated upper tracts and a contracted bladder [2, 19, 20, 21], this will also be visible on CT Urography which is certain to become the imaging modality of choice when faced with possible ketamine induced vesicopathy. Recent evidence in mice has shown that ketamine addiction leads to mono nuclear inflammatory infiltration in the renal papilla suggesting a possible pathogenesis of papillary necrosis [22].

Rigid cystoscopy should be considered essential in the initial assessment, not least of all to exclude any other cause of haematuria and severe LUTS eg: Carcinoma in situ. Cystoscopy also allows detection of ulceration if present and is unlikely to be tolerated whilst awake due to intense urgency and bladder pain, both of which are hallmark symptoms of ketamine induced vesicopathy. Cystoscopic findings are consistent with ulcerative cystitis with severe inflammation and epithelial denudation. (Table 2)

Many features of ketamine induced vesicopathy are common to those of interstitial cystitis (IC) as determined by the NIDDK criteria. Bladder biopsies typically show ulceration, inflammatory cell infiltrate and a varying degree of fibrosis. Some have likened the appearances to those of interstitial cystitis based on the presence of vacuoles at the periphery of the biposied muscle (querciphylloid feature) [1]. The cystoscopic picture and the presence of an eosinophilic infiltrate may suggest eosinophilic cystitis, but the absence of documented peripheral eosinophilia and eosinophilic sediment excludes this diagnosis. Whether ketamine induced vesicopathy represents a new type of eosinophilic cystitis is unclear at the present time.

Management -

At the present time, there is no single definitive management pathway to suit every patient and the key issues in patient management are those of individualised care plans and emphasis on compliance which has previously been shown to be poor in patients suffering addiction. Compliance is often poor and failure to abstain may lead to disease progression [2, 12, 16, 23].

Various treatment regimens have been employed ranging from antibiotics, oral NSIADS, steroids, anticholinergic therapy [2] and cystodistension [8]. All have failed to provide significant and lasting improvement but again, experience is lacking and the only universally held belief is that ketamine withdrawal often results in some degree of symptom resolution. It is unclear whether this is the case in all scenarios and it is likely that full symptomatic resolution will not be achieved in more advanced cases with severely reduced bladder capacity and compliance and resultant hydronephrosis. Nevertheless, it is worth persevering with withdrawal before undertaking invasive management provided renal function is both stable and regularly monitored. Renal function deterioration mandates more aggressive therapy, which may initially involve insertion of nephrostomies.

The theory of impaired epithelial impermeability leading to leakage of glycosaminoglycans has led to the use of intravesical instillation of Hyaluranic acid (Cystitstat) and oral Pentosan polysulphate (Elmiron) in the treatment of IC. Applying the same corollary, two case series have used the above substances in the treatment of ketamine induced vesicopathy. Shahani R et al [24] has found varying degrees of symptomatic relief in all patients with the use of Pentosan sulphate and cessation of ketamine. It is unclear whether it is purely due to the abstinence, therapy or both. All patients who had hyaluronic acid instillation had symptomatic relief but long time follow up is needed [8]. These two options may provide a sense of direction but longer follow up is needed.

Ultimately urinary diversion may be required which usually leads to symptom resolution akin to that experienced by the advanced IC patient undergoing the same procedure. Whether the bladder must be removed synchronously is unclear. From a symptomatic view, it would appear un-necessary but with further experience, phantom bladder pain may be experienced and the long term potential risks in terms of pyocystis and malignancy in a remaining defunct bladder are unclear [25, 26]. There are two reported cases of augmentation cystoplasty in the literature but in both cases ketamine abuse continued leading to continued symptoms and disease progression to ureteric stricturing and renal failure. [2, 16]

Conclusion -

Patients with severe irritative lower urinary tract symptoms, a positive history of ketamine abuse and the absence of any other aetiology should be considered to have ketamine induced vesicopathy, (KIV). Investigations will provide information about the effect of the drug on the renal tracts and in particular will enable the assessment of potential irreversible renal deterioration. At the present time, ketamine cessation is only effective treatment modality but the effect is likely to be dependent upon the severity and duration of the abuse. Individualised

management akin to that formulated for IC patients would appear to offer the greatest opportunity for treatment success.

It is difficult to prognosticate the exact time at which the symptoms and changes are irreversible. The pathogenesis of ketamine induced vesicopathy is unclear, although may share similarities with IC.

More research is required in order to understand its genesis, consequences and possible management but clinicians should have a high index of suspicion in those with a higher incidence of drug abuse suffering from unexplained lower urinary tract symptoms.

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Table 1

number	Author	Year of publication	Type of publication	Number of patients
1	Chu PS et al	2008	Case series	59
2	Chu PS et al[1]	2007	Case series	10
3	Wai Kit Ma et al[2]	2008	Poster (AUA)	54
4	Cottrell A et al	2009	Poster (EAU)	12
5	Cottrell AM et al[3]	2008	Letter to the Editor	11
6	Cottrell AM et al[4]	2008	Case report	1
7	Cottrell AM et al[5]	2008	Editorial	0
8	Tsai TH et al	2009	Case series	11
9	Shahani R et al	2007	Case series	9
10	Chen KT et al	2008	Letter to the Editor	4
11	Tsai JH et al	2008	Letter to the Editor	3
12	Storr TM and Quibell R	2009	Article	3
13	Chen YL et al	2009	Letters to the Editor	2
14	Huang YC et al	2008	Case report	1
15	Selby NM et al	2008	Case report	1
16	Gregiore MC et al	2008	Letter to the Editor	1
17	Hoskins R	2008	Case study	1
18	Colebunders B et al	2008	Case report	1
19	Dhillon BS et al	2008	Minerva	1
20	Lee PY et al	2009	Review article	1
21	Chiew YW	2009	Case report	1
22	Shahzad et al	2009	Poster	1

1, 2, 3, 4, 5, are by single authors

Table 2: Cystoscopic findings

Cystoscopy findings
Epithelial inflammation, neovascularisation and petechia
Denuded epithelium with chronic inflammation
Cystitis including hemorrhagic cystitis
Ulcerative cystitis
Erythematous necrotic cystitis
Denuded mucosa, marked inflammation
Marked and diffuse inflammation