

Three-Step Treatment of Ketamine-Induced Interstitial Cystitis- A Case Study in Nigeria

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ABSTRACT

Introduction: Ketamine abuse in Nigeria is rare. This case was managed in a rural area of central Nigeria, and the patient refused to go to a tertiary institution because of past trauma. Therefore, the aim of this case study is to add to the literature our protocol for treating ketamine-induced cystitis, especially for Nigerian physicians. I also ensured that the symptoms associated with the patient's mental health condition were addressed in the best possible and most feasible way, as attained by the facility in the setting where it is situated.

Method: The three-step management of this case included bladder hydrodistention, followed by one-dose administration of haloperidol, which was repeated, and general symptomatic treatment.

Results: patient recovered from severe pelvic. She also recovered from more than 100 voiding episodes per day, frequent syncope to 12 voiding episodes per day, and rare episodes of syncope during a 4-week management protocol. She also improved her mental health as assessed using the NHS well-being self-assessment tool.

Discussion: A two-time low dose of haloperidol, hydrodistention of the bladder, and general symptomatic management, which included simple music therapy on account of the patient's interest, were effective in treating this patient with ketamine-induced cystitis.

Keywords: Interstitial Cystitis; Bladder Pain Syndrome; Bladder Hydrodistention; Ketamin-Induced Psychosis; Ketamine-Induced Uropathy

Introduction

Ketamine-induced cystitis (KIC) is a bladder condition caused by repeated or heavy ketamine use. The main component of treatment are:

1. Ketamine use cessation
2. Symptomologic intervention
3. Addressing complications (Clemens, et al. [1-2]).

Symptomologic intervention may include the use of NSAIDs or neuropathic pain agents for pain management, Anticholinergics to tackle urgency or spasms, and Beta-3 agonists medications to treat an overreactive bladder. (Clemens, et al. [1]). Bladder protection and anti-inflammatory therapy are vital in treating ketamine-induced in-

terstitial cystitis (Chen, et al. [3-4]) and some of the agents commonly used are:

1. Pentosan polysulfate sodium (PPS),
2. Intravesical hyaluronic acid or chondroitin sulphate,
3. Intravesical heparin/lidocaine in some cases, or
4. Corticosteroids (short course) for severe inflammation in selected patients (Abdelrahman, et al. [5-7]).

Complications such as recurrent UTIs, ulcerations, hydronephrosis from ureteral obstruction and reduced bladder capacity may occur; and the management include antibiotics (if bacterial infection is confirmed), hydration, and close monitoring (Zhou, et al. [7]). In severe cases when the disease is advanced or when the bladder be-

comes severely contracted or kidney function is threatened, the trans-urethral fulguration of ulcerated areas, ureteral stenting if obstruction occurs, bladder augmentation (enterocystoplasty) or the rarely done urinary diversion for end-stage bladder destruction are possible added options in the management plan of a patient with ketamine-induced cystitis [Jhang, et al. [6-7]]. Nevertheless, the most important treatment plan of ketamine-induced cystitis remains ketamine-use cessation and unless this is achieved, all other management plans would become futile [Jhang, et al. [6]]. Cessation is difficult, and symptoms often stabilize or improve within weeks to months after cessation [Jhang, et al. [6]]. Therefore, an effective clinical approach is needed to aid in the cessation of ketamine- ketamine-abuse being the root cause of this ailment, and this is where haloperidol comes in [Abdelrahman, et al [5,7]]. This would be further explained in the Discussion section of this paper.

What is known about this case study is that ketamine intoxication is not prevalent in Nigeria and hence, not a common clinical case in that setting. In addition, the definitive diagnosis of interstitial cystitis is clinical; however, if complications are present, bladder hydrodistension is indicated [Clemens, et al. [1]]. What this case study adds to the literature is that a one- or two-time dose of haloperidol, bladder distension with cystoscopy protocol, and simple mental health assessment and management could effectively improve the condition of patients with ketamine-induced cystitis [Kirk, et al. [2-8]]. Nevertheless, a multidisciplinary approach is needed to effectively treat ketamine-induced cystitis from the beginning of management until the follow-up treatment. Therefore, this case study, as reported using the CASE-Statement guideline, is relevant to the Nigerian Health system in terms of adding more knowledge to the health system and triggering the need for more research on the epidemiology of ketamine intoxication in the country, mental health complications and treatment of ketamine intoxication, and the clinical significance of interstitial cystitis in Nigeria.

Patient's Information

A 30-year-old woman presented with dysuria, frequent urination, and nocturia. Symptoms persisted for 2 years and 6 months after she started ketamine self-medication to treat lower abdominal pain, which was prescribed to her by a quack. For one year, she had withdrawal syndrome characterized by generalized body pain and increased sharp pelvic pain associated with burning sensations, which were more severe just before micturating. Dizziness, frequent syncope, severe depression, and agitation were associated with hunger and withdrawal syndromes. No unusual vaginal discharge, itching, or foul odor. She was unsuccessfully treated for similar symptoms in three other health facilities approximately seven months prior to presentation. The patient had no history of diabetes, hypertension, or peptic ulcer disease. No history of surgery, and her Last Menstrual Period was two weeks prior to the time of presentation.

Clinical Findings

She was afebrile, pale (++), anicteric, acyanosed, had no pedal edema, and dehydrated (++) on the first day of admission. Weight: 57 kg; Height: 1.68M and BMI: 20.2Kg/m² on the first day of admission. Normal respiratory, cardiovascular, and musculoskeletal systems were observed. An abdominopelvic ultrasound scan showed normal abdominal and pelvic organs. However, the urinary bladder could not be examined in detail because the patient was unable to achieve a full bladder. At the time of presentation, she voided approximately 17 times during a 44 minutes session. Urine microscopy, culture, and serology revealed no significant bacterial culture. On urinalysis, hematuria was present (++) and the urine was cloudy and reddish with a pH of 6. Full blood count, serum creatinine, serum Urea and Liver function tests yielded normal values, except for serum sodium levels, which were slightly low (128 mmol/L). VDRL was non-reactive, and both hepatitis C antibody and hepatitis B surface antigen tests showed negative results. On ELISA, the patient tested negative for HIV. Contrast-enhanced abdominal CT was not performed because the patient refused referral to a tertiary facility and refused to undergo the test at any of these facilities for personal reasons she could not disclose. Contrast CT was beyond the affordability of private facilities at the time of this case study.

Diagnostic Assessment

Interstitial cystitis or bladder pain syndrome is diagnosed clinically by excluding other symptoms [Clemens, et al. [1]]. Nevertheless, in situations where complications such as urinary incontinence or an overactive bladder, as in this case study, bladder hydrodistention under anesthesia is indicated [Kim [2]]. Cystoscopy with hydrodistention is performed under either regional or general anesthesia to investigate the bladder walls while being stretched by fluid [Chen, et al, [3]]. Cystoscopy with hydrodistention is a surgical procedure; hence, basic blood workup is necessary to ensure that the patient is clinically fit to undergo the procedure [Yu, et al. [4]]. The potential side effects of this procedure include hematuria, urinary tract infection, bladder wall perforation, temporary urinary retention, and worsening of symptoms such as urethral burning and pelvic pain that may last up to 3 weeks [Zhou, et al. [7]]. This procedure is not invasive, and the patient may return home the same day [Clemens, et al. [1,4]].

Study Medication

Typically, small doses of haloperidol, such as a 5 mg intravenous dose, are adequate to treat ketamine-induced delirium [Atlas [9]]. Also, low doses of haloperidol prevent or minimize side effects, including cardiac dysrhythmias, tardative dyskinesia, neuroleptic malignant syndrome, dry mouth, constipation, reduced respiratory rate, sweating, reduced blood pressure, dizziness, weakness, nausea and vomiting, itching, body swelling and headaches [Cole, et al. [10]].

Therapeutic Intervention

After the necessary workup, bladder hydrodistention was performed immediately on the day of admission. A 4-week treatment plan was initiated and executed, which included one-time administration of 5 mg intravenous haloperidol, followed by other management protocols such as bed rest, intravenous fluids, intravenous NSAIDs, oral hematinics, oral nitrofurantoin, psycho-emotional support, and careful observation of the side effects of haloperidol. All other medications were started 24 hours after haloperidol administration to avoid possible drug interactions. The side effects of haloperidol were charted and checked every 2 h until 10 p.m. every day for the first

three days of admission after the dose was administered. Owing to the resulting excruciating pain felt on the insertion of the urethral catheter, it was removed while she was subsequently micturated manually. She loved classical music in the 80s and so a playlist was assembled for her to listen to, as she wished. She did not want any family members or friends around and this was respected. For a good analytic idea of monitoring the progress of her well-being, the 2011 NHS well-being self-assessment tool, as shown in (Table 1), was adopted (Stewart-Brown, et al. [11]). Being an educated woman, she was given adequate orientation and guidance on how she could fill in the assessment form and hand it over to the doctor alone for evaluation.

Table 1: 2011 NHS Wellbeing Self-Assessment Tool.

Score Definitions	Methodology
1: None of the time 2: Rarely 3: Some of the time 4: Often 5: All of the time	For a person to get their wellbeing score, the fourteen statements below will be run through and score allocated according to the individual's most accurate perception of themselves. The scores are from 1 to 5 as highlighted on the left and these scores best describe the individual's feelings and thoughts over the last two weeks.
Statement	Score Box (1-5)
I have been feeling optimistic about the future	
I have been feeling useful	
I have been feeling relaxed	
I have been feeling interested in other people	
I have had energy to spare	
I have been dealing with problems well	
I have been thinking clearly	
I have been feeling good about myself	
I have been feeling close to other people	
I have been feeling confident	
I have been able to make up my own mind about things	
I have been feeling respected	
I have been interested in new things	
I have been feeling cheerful	
Results	
0 - 31 Points	Wellbeing score is very low. Most people have a score between 41 and 59. Those in this category may want to start talking to a professional about how they can address their mental health issues.
32 - 40 Points	Wellbeing score is below average. Most people have a score between 41 and 59, therefore, those in this category may take actions in relation to behavioural changes (social networking/relationships, hobbies, reduce dormancy etc). A professional is still recommended.
41 - 59 Points	Wellbeing score is average. This is the category where most people belong to this category and behavioural adjustments are essential in making them happier and mentally healthier.
60 - 70 Points	Wellbeing score is above average. Those in this category are mentally healthy individuals and should continue doing the things that are keeping them happy and mentally sound.

Timeline

Recovery was slow in the first week, and another single dose of 5 mg haloperidol i/v was administered again in the 2nd week. Recovery became significant after the second and final doses were administered. By the 4th week of admission, she had started allowing family members and friends to visit her. The urinary frequency, Nocturia and Dysuria improved after the 3rd day of treatment and continued to improve thereafter. She manifested side effects of haloperidol on both occasions (muscle rigidity, itching, sweating, dizziness, and weakness), which were aborted with 200 mg of intravenous hydrocortisone and 25 mg of intravenous promethazine during every episode. By the 4th week of inpatient treatment, the average interval between

micturation was about 1.5 hours, and she voided a maximum of four times at night after 10pm. Dysuria also resolved. At this point, intravenous fluids were stopped, and the administration of oral drugs was continued (hematinics); relatives could visit, have a nice time with her, and she could, at this time, walk around the hospital vicinity. Psycho-emotional support provided tremendous results, as analyzed using her well-being self-assessment tool. By the end of the 4th week, all symptoms had disappeared, but urinary frequency sometimes manifested. She experienced a few episodes of syncope and dizziness. Recovery continued to improve until the end of the 4th week when no symptoms manifested, and before the 5th week began, she was discharged. (Table 2) defines the indicators used to monitor progress.

Table 2: The Indicators for Recovery Progression.

Indicators	Measurement	How it was derived
Haloperidol administration	+: administered -: not administered	A one-time administration of i/v 5mg of Haloperidol.
Haloperidol administration		A one-time administration of i/v 5mg of Haloperidol.
Haloperidol side effects	(+++): severe (++): significant	The number of symptoms manifested within 24 hours of i/v 5mg Haloperidol administration, was 6. Therefore 5-6 symptoms were scored (+++). 3-4 were scored (++) , 1-2 were scored (+) and no symptom was scored (-).
Pelvic pain	(+): present (-): Absent	Patient was asked to rate their pain on a scale of 1-10. 8-10 (+++), 4-7 (++) , 1-3 (+) , no pain (-). Weekly values were calculated and divided by 7 to give a daily average score.
Dizziness		From first consultation, patient attested to being dizzy for an average of 8 times every day. Therefore 6-8 times were allocated the score (+++), 2-5 times (++) , 1-2 times (+) and no dizziness (-). Weekly values were calculated and divided by 7 to give a daily average score.
Syncope		From the first clinic consultation, patient attested to having a minimum of 6 episodes of syncope per week. Therefore 5 and 6 (+++), 3 and 4 (++) , 1 and 2 (+) , and no syncope (-). Weekly values were calculated and divided by 7 to give a daily average score.

Follow up, Outcomes and Patient's Perspective

She was discharged and booked for check-ups every two weeks for the next three months. After her second check-up, she was referred to the nearest tertiary institution for multidisciplinary management of her case. She was managed by a team of physicians, urologists, dietitians, nutritionists, nurses, visiting gynecologists, and mental health specialists. The elimination diet strategy was used to draft out her diet plan (Clemens, et al. [1]). Further Wellbeing results showed even more improved progress of her mental health and the time between

her micturation reached 5 hours. However, she never continued her post-admission management after the 14th week post-discharge, and from the 15th week, we never heard from her again, as she never responded to the hospital's calls, which is a typical challenge for the average Nigerian patient. Overall, she was happy with our treatment and was satisfied with the great improvement in the symptoms she suffered, which was, unfortunately, a stumbling block for her to continue treatment in a tertiary health facility. (Table 3) summarizes her recovery progression from before hydrodistention to 2-week post discharge.

Table 3: A Summary of Patient's Recovery Progression.

Indicators	Before cystoscopy	Admission period				After discharge		
		1 st week	2 nd week	3 rd week	4 th week	2 nd week	4 th week	6 th week
Haloperidol administration	–	+	+	–	–	–	–	–
Haloperidol side effects	–	+	+	–	–	–	–	–
Pelvic pain	+++	++	+	+	–	–	+	–
Dizziness	+++	+++	+	+	++	–	+	–
Syncope	+++	+++	++	++	+	+	–	–
Wellbeing score	25	21	19	38	45	61	55	63
Average duration between micturation in minutes and seconds	02:17	15:43	39:03	51:11	88:51	177:30	243:44	294:58
Average number of voiding per day	>100	71	32	20	12	7	5	3

Discussion

Interstitial cystitis, sometimes referred to as Bladder Pain Syndrome (BPS), was present with recurring pelvic pain, pressure, or discomfort in the bladder and pelvic region (Clemens, et al. [1]). The gold standard for diagnosing interstitial cystitis is clinical; however, if complications are present, cystoscopy with hydrodistention is recommended (Chen, et al. [3-4]) interstitial cystitis can be ulcerative or non-ulcerative. Ninety percent of the patients were non-ulcerative and presented with glomerulations in the bladder wall. These are pinpoint hemorrhages but are not peculiar to interstitial cystitis as any inflammatory condition may cause glomerulations as well (Kim [2]). 5 to 10% of interstitial cystitis patients have the ulcerative variant which typically present as Hunner's ulcers or patches- red actively bleeding regions of the bladder wall (Cunningham et al, 2030; Whitmore et al., 2011). Interstitial cystitis impacts the life of the patient socially, specifically in relationships, jobs etc. Management includes behavioral, pharmacological, intravesical, interventional, and surgical strategies (Zaporowska-Stachowiak, et al. [12]). Ketamine is a dissociative anesthetic used to induce and maintain anesthesia (Zanos et al., 2020). It is also an anti-depressant and an agent for pain management (Perlowski, et al. [13]). Due to its hallucinogenic and dissociative effects, it is used as a recreational substance both in liquid form or as a crystalline powder (Castellani, et al. [14]). But its long-term use may lead to liver and urinary toxicity, leading to disorders such as cystitis, hydronephrosis or kidney failure (Perlowski, et al. [13]). Ketamine-induced cystitis manifests as dysuria, urinary urgency, frequent urination and haematuria. Due to the thickened bladder wall, its capacity reduces to as low as 10-15mL as compared to the normal average of 300-400mL (Zaporowska-Stachowiak, et al. [12]) The main treatment is ketamine cessation. But importantly, the induced delirium is prioritized and treated, which is done through haloperidol administration (Anderson, et al. [10,15]). Symptomatic treatment is

also essential, treating pain, inflammation, infection etc and as well, diet therapy (Clemens, et al. [1]). Diet modification to help patients avoid irritants to the damaged wall is essential for long-term recovery (Anderson, et al. [15]).

Rationale for Haloperidol in Ketamine-Induced Cystitis

As already mentioned in the introduction section of this paper, it is paramount to understand the rationale behind the administration of haloperidol in this case of ketamine-induced cystitis, and there are three reasons why this medication is needed. These reasons are:

1. To manage ketamine-related agitation, hallucinations, or psychosis. Patients with heavy or chronic ketamine use may present with: agitation confusion dissociation psychotic symptoms. These states can make medical evaluation difficult, increase the risk of harm, and impede the ability to stop ketamine, which is essential for halting cystitis progression. Therefore, haloperidol is sometimes used acutely to: calm agitation treat psychotic symptoms stabilize behaviour so that supportive treatment for Ketamine-induced cystitis can facilitate the safe cessation of ketamine. This is, hence, a behavioural/psychiatric stabilization, not cystitis treatment (Orhurhu, et al. [16]).
2. To aid ketamine cessation when psychiatric symptoms drive continued use. If cravings or dissociative/psychotic episodes contribute to ongoing ketamine use, haloperidol may be used short-term as part of: withdrawal management, and acute stabilization in detox settings (Zanos, et al. [17-20]). The rationale is to stop ketamine that eventually reduces ongoing bladder damage. Again, haloperidol is helping treat the cause (continued ketamine use), not the bladder condition (Culp, et al. [19]).

- Historical use in emergency settings for severe intoxication. In some Emergency Department protocols, haloperidol is used for: severe ketamine intoxication violent agitation dysphoria or severe confusion. This allows clinicians to prevent self-injury, ensure hydration, catheterization if necessary, and initiate workup for KIC. This is supportive care rather than direct cystitis treatment (Culp, et al. [16,19]).

Therefore, it is paramount to emphasize on what haloperidol does not do and they are:

- It does not reduce bladder inflammation,
- It does not repair the urothelial lining,
- It does not treat urgency, pain, or frequency,
- It does not reverse fibrosis or contracted bladder (Culp, et al. [16,19]).

Therefore, Ketamine-Induced Cystitis management requires cessation + urological treatment (Clemens, et al. [1-2]). And haloperidol is sometimes used around the treatment of ketamine-induced cystitis, but its purpose is psychiatric stabilization to enable ketamine cessation, not direct treatment of the cystitis itself (Culp, et al. [16,19]).

Conclusion

This case report presents the combined use of two low doses of haloperidol, bladder hydrodistention, and general symptomatic management, including music therapy tailored to the patient's preference. These interventions proved effective in treating ketamine-induced cystitis. What is known about this case study is that ketamine-intoxication is not prevalent in Nigeria and hence, not a common clinical case in that setting. Also, the definitive diagnosis for interstitial cystitis is clinical, but if complication is present, bladder hydrodistension is indicated. What this case study adds to the literature is, a one or two-time dose of haloperidol, a bladder distension with cystoscopy protocol and a simple mental health assessment and management could effectively improve the condition of a patient with ketamine-induced cystitis. Nevertheless, a multidisciplinary approach is needed for the effective treatment of Ketamine-induced cystitis from the beginning of management until follow-up treatment. Therefore, this case study is relevant to the Nigerian Health system in terms of adding more knowledge to the health system as well as triggering the need for more research on the epidemiology of ketamine intoxication in the country, the mental health complications and treatment of ketamine intoxication, and the clinical significance of interstitial cystitis in Nigeria.

Informed Consent

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This would be provided.

Institutional Approval

This was not needed for this report to be published because this case was managed in a private facility owned by the Author of this case study. Only patient consent was needed.

Statements and Declarations

Disclosure of Interest: There is no interest or relationship, financial or otherwise that might be perceived as influencing the Author's objectivity in writing this manuscript. No source of conflict of interest such as patent or stock ownership, membership of a company board of directors, membership of an advisory board or committee for a company, consultancy for or receipt of speaker's fees from a company or any other source is affiliated to this study. Therefore, the Author has declared no conflict of interest.

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