Intravesical hyaluronic acid treatment for ketamine-associated cystitis: Preliminary results


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ABSTRACT

Introduction: Long-term ketamine abuse may cause variable lower urinary tract symptoms (LUTS) and severe cystitis. The clinical features of ketamine-associated cystitis (KC) are very similar to bladder pain syndrome/interstitial cystitis (BPS/IC). Intravesical administration of hyaluronic acid (HA) is one of the regimens for treating BPS/IC. In this study, we aim to investigate whether intravesical HA therapy may improve the LUTS of patients with KC.

Materials and methods: Four female patients and one male patient with KC who failed oral medications were enrolled in this study. HA (Cystistat) at a dose of 40 mg in a volume of 50 mL of phosphate-buffered saline was injected into the bladder on a weekly basis for 6 weeks and then monthly for a further 3 months. Response to therapy was evaluated by the visual analog scale (VAS) for pain, International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), and Interstitial Cystitis Problem Index (ICPI). Treatment efficacy was assessed by comparing the pretreatment and posttreatment mean scores of the five questionnaires using the paired t test.

Results: The mean age of the patients was 22 ± 1.5 years. The mean duration of ketamine abuse was 68 ± 16.7 months. After intravesical HA therapy for 4 weeks, statistically significant mean decreases in VAS (from 7 to 4.4, \( p = 0.03 \)), IPSS voiding subscore (from 16.2 to 11.6, \( p = 0.017 \)), and ICSI (from 16.4 to 13.6, \( p = 0.016 \)) questionnaire scores were seen. However, only ICSI constantly reduced after 4 weeks of treatment.

Conclusion: Intravesical HA therapy may have short-term benefits for improving bladder pain and voiding symptoms in patients with KC.

1. Introduction

Ketamine is a phencyclidine derivative which was first used in humans in 1965, and has been clinically used as a quick-acting anesthetic drug since the 1970s. Its receptor binding has not been fully elucidated but includes an antagonist action at N-methyl-D-aspartate receptors throughout the central and peripheral nervous system. Ketamine is recently becoming more widely used as a recreational drug, especially in night clubs and dance parties. Many young people start using ketamine as teenagers. The precise prevalence of recreational, nonmedical ketamine use is unknown. A recent government report in Taiwan has indicated that the percentage of ketamine increased dramatically in the past few years, making it one of the most popular drugs of investigation findings. A recent study assessing the prevalence of urinary symptoms in a large cohort of nontreatment-seeking ketamine users revealed that 26.6% of recent ketamine users experienced urinary symptoms. Urinary symptoms were significantly related to both dose of ketamine used and frequency of ketamine use.

The symptoms of ketamine-associated cystitis (KC) include a variety of lower urinary tract symptoms (LUTS) which are very similar to bladder pain syndrome/interstitial cystitis (BPS/IC). Typically, the patients complain of nocturia, urgency, extreme frequency, bladder pain, and intractable dysuria. Gross hematuria is
also a frequent symptom in those suffering from ulcerative cystitis.5 Tsi et al6 reported that although symptoms appeared after 1 month of starting the usage, they became severe after 1 year.

The pathogenesis of bladder dysfunction under this condition has still not been established. A recent pathological research on the urinary bladder of ketamine addiction employing mice reveals mononuclear infiltration, very similar to that of the clinical situation of BPS/IC. There was also a possible decrease in the cholinergic neurons in the urinary bladder of the ketamine-treated animals.1 A mouse model of ketamine abuse showed that dysregulation of purinergic neurotransmission may be the cause of detrusor overactivity in ketamine-induced bladder dysfunction.9

The goal of treatment is to prevent deterioration of the renal function and indeed offer the possibility of symptom resolution. Currently, ketamine cessation is the only effective treatment modality, but the effect is likely to be dependent on the severity and duration of the abuse.5,6 Patient compliance has previously been shown to be poor in patients suffering addiction and failure to abstain may lead to disease progression.5,10 Various treatment regimens have been used to treat the patients such as antibiotics, oral NSAIDS, steroids, anticholinergic therapy,2 and hydrodistention of the bladder;4 however, all have failed to provide significant and lasting improvement.

Since the clinical features of KC are very similar to BPS/IC, the possible etiology of impaired epithelial impermeability leading to leakage of glycosaminoglycan (GAG) layer has led to the use of intravesical instillation of hyaluronic acid (HA) in the treatment of IC. Tsi et al6 reported that all patients who had HA instillation had symptomatic relief, especially in bladder pain, frequency, and hematuria, however no convincing evidence has been provided in this article. In this study, we aim to investigate the efficacy of intravesical instillation of HA in the treatment of KC.

2. Materials and methods

Patients (≥18 years of age) attending the Tri-Service General Hospital, Taipei, Taiwan for treatment of symptoms of KC were recruited for this open, prospective, unblinded, uncontrolled study. The study was approved by the Institutional Review Board of the Tri-Service General Hospital, Taipei, Taiwan (TSGH- 100-05-188) and all patients gave their written informed consent before participating in the study. Eligible patients had a ≥6-month documented history of KC. The diagnosis of KC was made according to their history and clinical features. Other common causes of LUTS, such as urinary tract infection, urological malignancy, bladder outlet obstruction, neurological disease, or trauma were excluded. Careful history taking of ketamine use, including mean dose usage/d, duration of drug abuse, and the route of use, was performed by one urologist with confidential interviews. Physical examinations and assessment of symptoms were performed in all patients in an outpatient department. Urinary cultures, urinary cytology, and acid-fast stain for urinary tuberculosis were completed in enrolled patients to exclude other possible causes. Before any treatment was initiated, urodynamics investigations were conducted mainly on an outpatient basis. A standard uroflowmetry was performed before pressure flow studies. Postvoiding residual urine was measured by urethral catheterization. The pressure flow studies were performed according to the ICS standardization.7 After the urodynamic studies, cystoscopy under spinal anesthesia with hydrodistention and a biopsy of the bladder wall was performed to confirm the diagnosis. Maximum bladder capacity under spinal anesthesia was measured before hydrodistention, using an infusion height of 80 cm above the symphysis pubis, and the amount when the bladder had been filled and fluid had stopped dribbling from a dripping chamber was recorded.

Patients were excluded from the study if they were pregnant, had received another medical or mechanical treatment for KC (excluding pain treatment) 1 month prior to screening, or if they had a known sensitivity to any component of the HA preparation used for bladder instillation. Over the study period, no other treatments for KC were permitted, besides analgesics. Before each HA instillation, every patient received a urine screening test using a direct enzyme-linked immunosorbent assay kit for ketamine (Firststep Bioresearch, Inc., Tainan, Taiwan) and the patients with a positive result were withdrawn from the study.

Eligible patients received intravesical instillations of HA (Cystistat; Bioniche Life Sciences Inc., Belleville, ON, Canada) at a dose of 40 mg in a volume of 50 ml of phosphate-buffered saline. The intravesical instillation was performed using a catheter, under sterile conditions, after the removal of residual urine. Following the instillation, patients were asked to retain the HA in their bladders for as long as possible, with a minimum retention time of 30 minutes. HA acid was administered to all patients once weekly for 6 weeks (Day 0, Day 7, Day 14, Day 21, Day 28, and Day 35) and then once monthly for 3 months (total of 9 instillations).

Response to therapy was assessed using a questionnaire administered to all patients at baseline and at each hospital visit. The questionnaire assessed O’Leary-Sant Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), International Prostate Symptom Score (IPSS), Overactive Bladder Symptom Score (OABSS), and use of analgesics since the last visit. In addition, the level of pain was assessed at each visit using a visual analog scale (VAS; 10-point scale). To assist in recording the information, all patients were given a diary and asked to record relevant symptoms between visits. This diary then served as an information source during the administration of the questionnaire. The questionnaire also asked the patients to record how long they had retained the HA solution in their bladders after each instillation.

Continuous variables are analyzed with the paired t test. A p value < 0.05 is considered statistically significant.

3. Results

Nine patients were recruited for the study and four of them were withdrawn due to being unable to tolerate the catheterization. Only five patients completed the whole course of treatment (Table 1). The mean age (±standard deviation) of the patients was 22 ± 1.5 years. The mean duration of ketamine abuse was 68 ± 16.7 months.

There was a large variation in the time for which patients were capable of keeping the HA solution in the bladder (Fig. 1). The mean time of keeping HA in the bladder seemed to have a trend of being longer in the first 4 weeks (from 46.4 ± 52.6 minutes to 76.4 ± 65.5 minutes), although there was no significant difference. There was no correlation between the efficacy of HA and the time for which the solution was retained in the bladder.

Table 2 shows change in scores of the five questionnaires in five patients receiving intravesical HA treatment. After intravesical treatment of HA for 4 weeks, statistically significant mean decreases in VAS (from 7.0 ± 2.2 to 4.4 ± 0.6, p = 0.03), IPSS voiding subscore (from 16.2 ± 3.8 to 11.6 ± 4.2, p = 0.017), and ICSI (from 16.4 ± 2.7 to 13.6 ± 2.0; p = 0.016) questionnaire scores were seen. However, only ICSI constantly reduced after 4 weeks of treatment until the 14th week. No significant changes were seen before and after treatment in OABSS questionnaire values. No cases of side effects or complications were observed.
required to determine if there is a long-term ef

temporary to reduce the pain and improve voiding symptoms.

Table 2
Change in scores of questionnaires after hyaluronic acid (HA) treatment (mean ± standard deviation).

<table>
<thead>
<tr>
<th>Time after HA treatment</th>
<th>0 (Baseline)</th>
<th>1 wk</th>
<th>2 wk</th>
<th>3 wk</th>
<th>4 wk</th>
<th>5 wk</th>
<th>6 wk</th>
<th>10 wk</th>
<th>14 wk</th>
<th>18 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS</td>
<td>7.0 ± 2.2</td>
<td>6.4 ± 2.7</td>
<td>5.4 ± 1.9</td>
<td>5.0 ± 2.2</td>
<td>4.4 ± 0.6</td>
<td>4.6 ± 1.9</td>
<td>3.6 ± 1.1</td>
<td>4.4 ± 3.6</td>
<td>3.8 ± 1.8</td>
<td>3.3 ± 2.1</td>
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<tr>
<td>Change from baseline</td>
<td>-0.60 ± 1.8</td>
<td>-1.6 ± 2.5</td>
<td>-2.0 ± 3.2</td>
<td>-2.6 ± 1.8*</td>
<td>-2.4 ± 3.5</td>
<td>-3.4 ± 2.7*</td>
<td>-2.6 ± 4.7</td>
<td>-3.2 ± 3.4</td>
<td>-4.2 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>IPSS</td>
<td>28.8 ± 4.8</td>
<td>26.4 ± 3.1</td>
<td>26.2 ± 3.1</td>
<td>25.2 ± 5.3</td>
<td>22.4 ± 4.3</td>
<td>23.2 ± 4.6</td>
<td>22.8 ± 3.3</td>
<td>23.2 ± 3.1</td>
<td>22.6 ± 6.1</td>
<td>20.0 ± 6.0</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.4 ± 5.8</td>
<td>-2.6 ± 4.4</td>
<td>-3.6 ± 4.9</td>
<td>-6.4 ± 3.2</td>
<td>-5.6 ± 3.8</td>
<td>-6.0 ± 4.5</td>
<td>-5.6 ± 3.1</td>
<td>-6.2 ± 6.8</td>
<td>-7.8 ± 8.2</td>
<td></td>
</tr>
<tr>
<td>IPSS-V</td>
<td>16.2 ± 3.8</td>
<td>13.4 ± 1.8</td>
<td>14.0 ± 4.3</td>
<td>13.6 ± 4.7</td>
<td>11.6 ± 4.2</td>
<td>12.4 ± 4.7</td>
<td>12.0 ± 3.9</td>
<td>12.8 ± 4.4</td>
<td>11.8 ± 5.1</td>
<td>10.3 ± 3.2</td>
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<tr>
<td>Change from baseline</td>
<td>-2.8 ± 3.6</td>
<td>-2.2 ± 3.3</td>
<td>-2.6 ± 3.2</td>
<td>-4.6 ± 2.6*</td>
<td>-3.8 ± 2.9</td>
<td>-4.2 ± 3.0</td>
<td>-3.4 ± 3.2</td>
<td>-4.4 ± 3.4</td>
<td>-4.5 ± 4.5</td>
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<td>IPSS-S</td>
<td>12.0 ± 2.4</td>
<td>11.6 ± 2.3</td>
<td>11.2 ± 1.9</td>
<td>10.8 ± 1.9</td>
<td>10.6 ± 1.7</td>
<td>10.0 ± 2.5</td>
<td>10.0 ± 1.9</td>
<td>8.8 ± 3.0</td>
<td>9.2 ± 3.6</td>
<td>9.7 ± 4.0</td>
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<tr>
<td>Change from baseline</td>
<td>0.40 ± 2.5</td>
<td>-0.40 ± 1.7</td>
<td>-1.0 ± 1.9</td>
<td>-1.8 ± 1.3</td>
<td>-1.8 ± 1.6</td>
<td>-1.8 ± 2.3</td>
<td>-2.2 ± 2.2</td>
<td>-1.8 ± 3.1</td>
<td>-2.0 ± 4.8</td>
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<tr>
<td>OABSS</td>
<td>11.2 ± 2.7</td>
<td>9.4 ± 2.8</td>
<td>10 ± 2.9</td>
<td>8.8 ± 2.5</td>
<td>9.2 ± 1.6</td>
<td>8.6 ± 2.7</td>
<td>8.4 ± 2.5</td>
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<td>7.2 ± 2.9</td>
<td>7.5 ± 2.4</td>
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<tr>
<td>Change from baseline</td>
<td>-1.8 ± 1.8</td>
<td>-0.80 ± 0.8</td>
<td>-2.4 ± 1.9</td>
<td>-2.0 ± 2.7</td>
<td>-2.6 ± 1.5</td>
<td>-2.8 ± 3.6</td>
<td>-3.0 ± 2.9</td>
<td>-4.0 ± 1.0</td>
<td>-3.0 ± 2.4</td>
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<tr>
<td>ICSI</td>
<td>16.4 ± 2.7</td>
<td>14.4 ± 2.1</td>
<td>14.8 ± 3.0</td>
<td>13.4 ± 2.3</td>
<td>13.6 ± 2.0</td>
<td>12.2 ± 2.2</td>
<td>12.6 ± 2.1</td>
<td>12.4 ± 3.4</td>
<td>11.8 ± 2.7</td>
<td>13.5 ± 1.3</td>
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<tr>
<td>Change from baseline</td>
<td>-2.0 ± 1.4</td>
<td>-1.6 ± 1.1</td>
<td>-3.0 ± 1.6*</td>
<td>-2.8 ± 1.5*</td>
<td>-4.2 ± 2.4*</td>
<td>-3.8 ± 2.2*</td>
<td>-4.0 ± 1.4*</td>
<td>-4.6 ± 3.4*</td>
<td>-1.5 ± 3.9*</td>
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<tr>
<td>ICPI</td>
<td>14.2 ± 2.2</td>
<td>12.0 ± 2.6</td>
<td>13.0 ± 3.3</td>
<td>12.6 ± 4.0</td>
<td>11.8 ± 3.8</td>
<td>12.4 ± 3.6</td>
<td>12.4 ± 3.8</td>
<td>12.4 ± 3.5</td>
<td>11.4 ± 2.9</td>
<td>11.7 ± 4.5</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>-2.2 ± 1.9</td>
<td>-1.2 ± 1.6</td>
<td>-1.6 ± 2.5</td>
<td>-2.4 ± 2.9</td>
<td>-1.8 ± 2.2</td>
<td>-1.8 ± 2.7</td>
<td>-1.8 ± 2.5</td>
<td>-2.8 ± 2.4</td>
<td>-2.8 ± 2.5</td>
<td></td>
</tr>
</tbody>
</table>

*p < 0.05.
**p < 0.01.

ICSI – Interstitial Cystitis Problem Index; ICPI – Interstitial Cystitis Symptom Index; IPSS – International Prostate Symptom Score; OABSS – Overactive Bladder Symptom Score; VAS – visual analog scale.

The p value was determined using paired t test. The p value refers to the comparison of scores of questionnaires between baseline and indicated weeks after hyaluronic acid treatment.

Fig. 1. The mean duration of keeping hyaluronic acid in the bladder.

4. Discussion

KC is a new disease entity and its clinical features are very similar to BPS/IC. Intravesical HA instillation has been used to treat BPS/IC with a good symptom response rate. However, the treatment strategy of KC is to be established. In this study, we investigate the therapeutic effect of intravesical HA instillation in patients with KC. The results showed that HA instillation may temporarly reduce the pain and improve voiding symptoms associated with KC after 4 weeks of treatment. Intravesical instillation of HA on a monthly basis may not be as effective as on a weekly basis. However, large, long-term randomized studies are required to determine if there is a long-term efficacy of intravesical hyaluronic therapy in KC.

Long-term ketamine abuse can cause severe cystitis and LUTS. Cystoscopy reveals various degrees of epithelial inflammation and neovascularization of the bladder with KC. The urothelium is particularly fragile and easily denuded, indicating a defective connection to the lamina propria. Severe cases may present petechial hemorrhages and ulcers of the bladder mucosa, as classically described in patients with IC. Abnormal expression of GAG-related proteins—chondroitin sulfate, perlecan, biglycan, decorin, syndecan-1, uropadkin, E-cadherin, keratin 18, and keratin 20, as well as the tight-junction-associated protein ZO-1—seems to be associated with BPS/IC. GAG derivatives are therefore used as substitutes for components of the GAG layer of the urothelial lining, which is severely damaged in BPS/IC. Hyaluronan may reinforce the urine-tissue barrier by integration in the GAG layer on the luminal surface and the base of urothelial cells; it also has unique antiinflammatory mechanisms, like inhibition of leukocyte migration, adherence of immune complexes, and binding to specific receptors (Intercellular Adhesion Molecule 1, ICAM-1; Cluster of Differentiation 44, CD 44) involved in the inflammatory process.

The use of HA instillations in treating BPS/IC is supported by several studies with level 2b evidence, although some researchers questioned its efficacy. Monotherapy with HA (4-weekly 1 mg/mL in saline, followed by 2-monthly instillations) has been reported to produce response rates of 30–85%. In our study, we performed HA treatment after hydrodistention. A randomized controlled trial examined the use of HA after hydrodistention, and the researchers found prolonged symptom improvement with HA treatment and hydrodistention compared with hydrodistention alone in 78% of patients.

Our instillation protocol was once weekly in intravesical instillations of HA for 6 weeks and three more instillations were performed monthly. This protocol was similar to that of other groups. In the literature, several different protocols have been

Table 1
Patient characteristics and urodynamic data.

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age</th>
<th>Dose (g/d)</th>
<th>Duration of ketamine abuse (mo)</th>
<th>FBC (mL)</th>
<th>MBC (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Female</td>
<td>25</td>
<td>1–5</td>
<td>84</td>
<td>41</td>
<td>100</td>
</tr>
<tr>
<td>2</td>
<td>Female</td>
<td>21</td>
<td>1–5</td>
<td>54</td>
<td>14</td>
<td>120</td>
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<tr>
<td>3</td>
<td>Female</td>
<td>21</td>
<td>1–5</td>
<td>72</td>
<td>146</td>
<td>250</td>
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<tr>
<td>4</td>
<td>Female</td>
<td>24</td>
<td>1–5</td>
<td>84</td>
<td>255</td>
<td>500</td>
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<tr>
<td>5</td>
<td>Male</td>
<td>21</td>
<td>6–10</td>
<td>48</td>
<td>75</td>
<td>150</td>
</tr>
</tbody>
</table>

FBC – functional bladder capacity; MBC – maximal bladder capacity under anesthesia.
described for instillation. Many uncontrolled studies used 40 mg
HA dissolved in 40 mL of normal saline solution weekly for 4—6
weeks and then monthly.10,23,24

In the present study, improvements regarding the VAS for pain,
voiding symptoms, and ICSI were statistically significant after 4
weeks of treatment compared with the respective baseline values.
However, there was no significant improvement in the storage
symptoms and ICPI. Only ICSI constantly reduced after 6 weeks
of treatment. The result suggests that intravesical HA instillation may
temporarily relieve voiding symptoms and pain caused by KC.

The relatively poor response of intravesical HA instillation in
treating KC may be due to: (1) KC has been reported as a severe
form of BPS/IC15 and the damage to the urothelium may be more
difficult to repair than in BPS/IC; (2) monotherapy with HA used in
the present study may not be as effective as combination intra-
vesical therapy using both sodium HA and chondroitin sulfate5—7; and
(3) young patients have poor tolerance to intravesical HA
instillation and are not able to keep HA in the bladder for a long
time.

The present findings give hope to KC patients that are suffering
from the diagnosis of a chronic and incurable disease. However, this
study has some limitations which are mainly represented by the
small sample size, the short follow up, and the lack of a placebo
control group. Although a randomized, placebo-controlled study is
necessary to further confirm efficacy of HA instillation for KC pa-
cients, we felt that an randomized controlled trial (RCT) design,
where patients would be randomized to no treatment or placebo,
may be difficult, as these patients were in severe pain and were
desperate for treatment.

5. Conclusion

In spite of the small number of patients included in this study,
there is evidence to indicate that intravesical HA therapy has a
short-term positive impact on the treatment of KC. The therapy
may reduce pain and improve voiding symptoms associated with
KC after 4 weeks of HA instillation. Large, long-term randomized
studies are required to determine if there is a long-term efficacy of
intravesical HA therapy in KC.

Conflicts of interest

The authors declare that they have no financial or non-financial
conflicts of interest related to the subject matter or materials dis-
cussed in the manuscript.

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ketamine-induced cystitis (KC) have more severe lower urinary tract symp-
oms and smaller bladder capacity than patients with interstitial cystitis/ bladder
of intravesical hyaluronic acid and hyaluronic acid-chondroitin sulphate
therapy for patients with bladder pain syndrome/interstitial cystitis. Can Urol
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luronate/chondroitin sulfate therapy for interstitial cystitis/bladder pain syndro-
intravesical hyaluronic acid and chondroitin sulfate on bladder pain syndrome/