Retrospective Clinical Research Report

Journal of INTERNATIONAL MEDICAL RESEARCH

Journal of International Medical Research
48(11) 1–13

DOI: 10.1177/0300060520973100
journals.sagepub.com/home/imr
SAGE

Comparison of intravesical instillation of hyaluronic acid with intradetrusor botulinum toxin A injection or cystoscopic hydrodistention for ketamine-associated cystitis

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Abstract

Objective: This study aimed to compare the therapeutic effect of intravesical instillation hyaluronic acid with intradetrusor botulinum toxin A (BTX-A) injection or cystoscopic hydrodistention for ketamine-associated cystitis.

Methods: Thirty-six patients were evenly randomly divided into the BTX-A group or the hydrodistention group. Patients received 200 U BTX-A detrusor injections in the BTX-A group and cystoscopic hydrodistention in the hydrodistention group. Intravesical instillation of hyaluronic acid was administrated in both groups for eight times. Patients with involuntary detrusor contraction were divided into the persistent involuntary detrusor contraction group and resolved involuntary detrusor contraction group after treatment in 6 months. The predictors of persistent involuntary detrusor contraction were analyzed.

Results: Twelve months after treatment, the daytime frequency, Interstitial Cystitis Symptom Index, maximal capacity, and maximal cystometric capacity in the BTX-A group were significantly better than those in the hydrodistention group. Patients with resolution of involuntary detrusor contraction had a significantly shorter duration of ketamine, lower amount of fibrosis in pathology, and higher maximal capacity than those with persistent involuntary detrusor contraction 6 months after therapy.

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Conclusion: Intravesical instillation of hyaluronic acid with intradetrusor BTX-A injection appears to be a preferable option for long-term effectiveness compared with cystoscopic hydrodistention.

Keywords
Ketamine-associated cystitis, intravesical instillation, hyaluronic acid, botulinum toxin A, cystoscopic hydrodistention, detrusor contraction

Date received: 21 June 2020; accepted: 22 October 2020

Introduction

Ketamine was developed to replace pentachlorophenol in 1963.[1] In most cases, ketamine served as an animal tranquilizer in veterinary medicine, while it was used as an anesthetic in humans.[2] Ketamine is primarily used for induction and maintenance of general anesthesia in humans, usually in combination with a sedative.[3] Because ketamine turned into a recreational drug, ketamine abuse has risen since the late 1980s.[4] The exact prevalence of ketamine abuse is difficult to measure numerically. However, actual ketamine abusers have increased in recent years, and a large part of abusers are "hidden ketamine abusers". A total of 51% of ketamine abusers younger than 21 years have admitted to abusing ketamine at home or at a friend's home.[5] Long-term ketamine abuse causes urinary complications. Endoscopic findings and pathological changes in bladder biopsies in ketamine abusers are similar to those of patients with interstitial cystitis.[4] Patients with chronic ketamine abuse suffer from serious urinary tract damage, including bladder contracture, bilateral hydronephrosis, narrowing of the ureters, and detrusor instability.[6] In recent years, ketamine-associated cystitis has become a serious problem. However, there is no standard therapy for ketamine-associated cystitis at present. In this study, we compared intravesical instillation of hyaluronic acid with intradetrusor injection of botulinum toxin A (BTX-A) and intravesical instillation of hyaluronic acid with cystoscopic hydrodistention in patients with chronic recreational ketamine use.

Methods

Patients

Patients who had a history of chronic recreational ketamine use and suffered from consequent ketamine-related lower urinary tract symptoms (LUTS) were enrolled in this prospective study. Patients in this study provided written informed consent. The study was approved by the Ethics Committee of Zhujiang Hospital, Southern Medical University, Guangzhou, Guangdong Province, China (2014A020 212400). We excluded patients with urethral stricture and other bladder diseases. Treatment modalities, such as anticholinergics or antidepressants, and oral or intravenous therapies, had previously failed in all patients. Susceptibility results based or empirical antibiotics were administered to patients with urinary tract infection until a urine test was normal. Routine blood tests and urine culture, as well as imaging and a computed tomographic scan of the urinary tract, were performed before therapy for baseline evaluation. Patients received a urodynamic examination and frequency-volume (FV) chart and the visual analog

scale (VAS) was used for quantification of pain before therapy. From December 2013 to December 2017, patients who fulfilled all criteria in the study were evenly randomly divided into the BTX-A group and the hydrodistention group. A randomization sequence (1:1 ratio) was performed by the PROC PLAN process using SAS software. Allocation concealment was conducted using sealed opaque envelopes. Patients with involuntary detrusor contraction (IDC) were divided into the persistent IDC group and resolved IDC group after treatment in 6 months. The predictors of persistent IDC were analyzed.

Study plan and treatment

Surgical procedures. All surgeons who performed the operations were licensed urologists trained and experienced with detrusor injections of BTX-A and cystoscopic hydrodistention in more than 50 cases.

Detrusor injections of BTX-A. The detrusor injection procedure was performed under spinal anesthesia. The dosage of BTX-A (Botox®; Allergan) was 200 U and diluted in 20 mL of 0.9% NaCl. Detrusor injections were carried out by a flexible needle through a cystoscope. A volume of 1 mL of 0.9% NaCl with 10 U of BTX-A was used at each injection point in the bladder detrusor without the trigone. The distribution of injection points is shown in Figure 1. Following the detrusor BTX-A injection, a biopsy of the detrusor in the trigone of the bladder was performed by a bipolar resectoscope. A 22 F triple lumen catheter was then retained for overnight. Bladder irrigation was used according to the degree of hematuria.

Cystoscopic hydrodistention. Hydrodistention was carried out under spinal anesthesia. The intravesical pressure was 80 cm H_2O and the bladder was kept full for 5 minutes. After hydrodistention, the maximal bladder capacity was recored.[7] Following hydrodistention, biopsy of the detrusor in the trigone of the bladder was performed by a bipolar resectoscope. The possible bleeding points in the bladder wall were treated with coagulation via the bipolar resectoscope. After BTX-A injections, a 22 F triple lumen catheter was retained for overnight. Bladder irrigation was used according to the degree of hematuria.

Susceptibility results based or empirical antibiotics were administered to all of the patients until 48 hours after the surgical procedure. Two weeks after detrusor injections of BTX-A or cystoscopic hydrodistention, intravesical instillation of 40 mg/

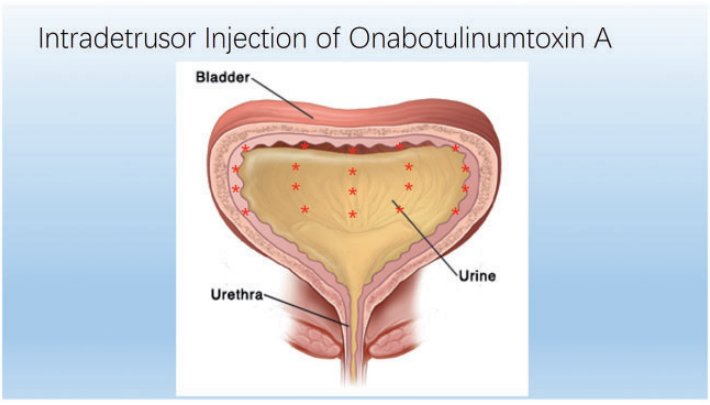

Figure 1. Distribution of the injection points of botulinum toxin A.

50 mL hyaluronic acid (Bioniche Phama, Inverin, Ireland) was administered in both groups. Intravesical instillations were performed using 8 F silicone catheters. Patients were informed to hold their urine for the next 60 minutes. Intravesical instillations were administered weekly and eight doses were provided.[8] Subjective and objective parameters were followed up after 6 and 12 months.

Data analysis

Data are presented as frequencies and percentages, or mean ± standard deviation. Variables were evaluated for statistically significant differences using the chi-square test or independent-sample t-test. A 5% level was used for all statistical testing as a significant difference and all statistical tests were two-sided. The Statistical Package for the Social Sciences, version 18.0 (SPSS, Inc., Chicago, IL, USA) was used for data analysis.

Results

Twenty-four male patients and 12 female patients had a mean age of 23.31 ± 4.14 years and a mean duration of ketamine abuse of 3.14 ± 1.15 years. There were 16 patients in each group. All of the preoperative parameters, including mean age, duration of ketamine abuse, duration of abstinence, main complications, bladder capacity, daytime frequency, nocturia, Interstitial Cystitis Problem Index (ICPI) score, Interstitial Cystitis Symptom Index (ICSI) score, quality of life (QOL) score, overactive bladder symptom score (OABSS), visual analog scale (VAS) score, maximal capacity (MC), compliance, IDC, and maximal cystometric capacity (MCC) were similar between the two groups (Tables 1 and 2). Fifteen patients in the BTX-A group and 16 patients in the hydrodistention group had thickening of the bladder wall and a tower-like shape of the bladder in a computed tomographic scan or cystography. One patient in each group had hydronephrosis. Thickening of the bladder wall, a tower-like shape of the bladder, and hydronephrosis are shown in Figures 2 to 4.

In cystoscopy, bladder capacity was decreased in both groups, accompanied by extensive mucosal hemorrhage, and 8 patients in the BTX-A group and 11 patients in the hydrodistention group had

Table 1. Patients' characteristics.

Parameters	BTX-A group (n = 18)	Hydrodistention group (n = 18)	All (n = 36)	P value (BTX-A group vs hydrodistention group)
Age (years)	23.11 ± 2.91	23.5 ± 5.17	23.31 ± 4.14	0.783
Sex				
Male (n)	10	14	24	0.157
Female (n)	8	4	12	
Duration of ketamine abuse (years)	3.06 ± 0.87	3.22 ± 1.40	3.14 ± 1.15	0.670
Duration of abstinence (weeks)	4.28 ± 2.97	5.00 ± 2.20	4.64 ± 2.60	0.412
Urinary tract infection (n)	14	13	27	0.700
Bladder wall thickening (n)	15	16	31	0.630
Hydronephrosis (n)	1	1	2	1.000
Ureteral stricture (n)	1	1	2	1.000

BTX-A, botulinum toxin A.

Table 2. Changes in subjective and objective parameters between the groups.

Parameter	BTX-A group (n = 18) Preoperative	Hydrodistention group (n = 18) Preoperative	P	BTX-A group (n = 17) 6 months postoperatively	Hydrodistention group (n = 16) 6 months postoperatively	P	BTX-A group (n = 16) 12 months postoperatively	Hydrodistention group (n = 15) 12 months postoperatively	P
ICPI score	12.50 ± 1.47	12.67 ± 1.53	0.741	2.41 ± 1.54	3.75 ± 2.72	0.09	0.94 ± 0.77	1.93 ± 1.03	0.005
ICSI score	17.06 ± 1.83	17.33 ± 1.68	0.638	5.82 ± 2.16	7.25 ± 3.79	0.190	4.56 ± 0.63	5.33 ± 1.11	0.023
QOL score	5.50 ± 0.51	5.67 ± 0.49	0.324	1.59 ± 1.18	1.75 ± 1.48	0.730	1.25 ± 0.77	1.33 ± 0.98	0.739
OABSS	10.89 ± 1.23	11.06 ± 0.80	0.634	2.71 ± 0.99	3.50 ± 1.67	0.104	0.13 ± 0.34	0.33 ± 0.72	0.323
VAS score	7.39 ± 1.72	7.33 ± 1.50	0.918	0.88 ± 1.69	1.00 ± 2.16	0.862	0.25 ± 0.68	0.33 ± 0.62	0.725
FV chart									
DF	12.44 ± 1.82	13.17 ± 1.50	0.204	6.12 ± 1.11	6.81 ± 1.47	0.134	5.56 ± 0.73	6.27 ± 1.03	0.035
Nocturia	14.78 ± 1.26	14.89 ± 1.13	0.783	2.29 ± 0.69	2.56 ± 0.51	0.215	0.13 ± 0.34	0.33 ± 0.72	0.323
MC (mL)	32.26 ± 11.42	30.59 ± 14.51	0.703	259.10 ± 38.23	243.57 ± 45.86	0.298	333.56 ± 42.66	301.16 ± 42.87	0.044
Free flowmetry									
Qmax (mL/s)	6.13 ± 1.84	5.77 ± 1.59	0.528	19.38 ± 1.75	19.11 ± 2.07	0.683	21.08 ± 2.30	20.76 ± 2.21	0.696
PVR (mL)	5.97 ± 4.73	4.85 ± 3.76	0.437	6.48 ± 3.06	5.05 ± 3.19	0.196	5.67 ± 3.94	5.11 ± 2.95	0.658
Urodynamic study									
Compliance	1.75 ± 1.42	1.62 ± 1.70	0.800	22.05 ± 5.06	20.87 ± 5.51	0.525	23.90 ± 6.63	22.17 ± 6.45	0.255
IDC, n (%)	18 (100)	18 (100)	1.000	3 (17.65)	5 (31.25)	0.362	1 (5.88)	2 (13.33)	0.505
MCC (mL)	24.22 ± 10.90	26.89 ± 12.10	0.492	269.41 ± 43.50	257.06 ± 45.36	0.431	344.31 ± 46.77	309.40 ± 43.71	0.041
MDP (cm H_2O)	61.59 ± 5.20	64.14 ± 6.26	0.193	39.27 ± 4.59	42.73 ± 3.39	0.020	39.15 ± 3.86	40.35 ± 5.05	0.459
UI, n (%)	5 (27.78)	6 (33.33)	0.717	0	0	1.000	0	0	1.000

Values are mean ± standard deviation or n (%).

BTX-A, botulinum toxin A; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; QOL, quality of life; OABSS, overactive bladder symptom score; VAS, visual analog scale; FV chart, frequency-volume chart; DF, daytime frequency; MC, maximal capacity; Qmax, maximal flow rate; PVR, postvoid residual urine; IDC, involuntary detrusor contraction; MCC, maximal cystometric capacity; MDP, maximum detrusor pressure; UI, urgency incontinence.

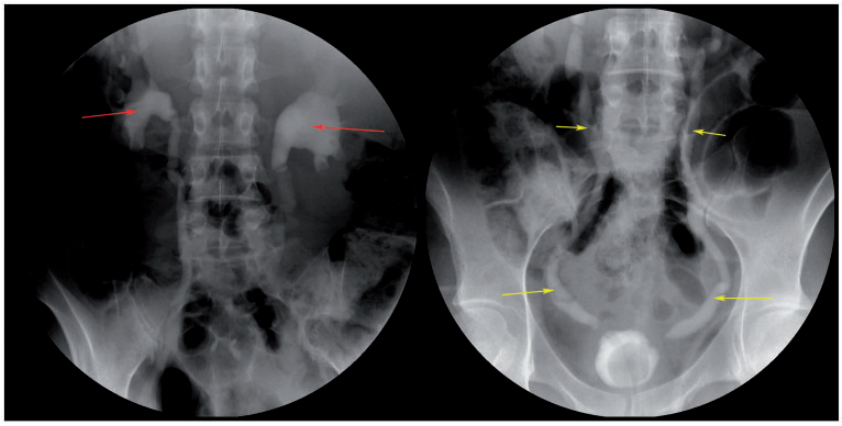

Figure 2. Intravenous pyelography shows bilateral hydronephrosis (red arrows) and bilateral ureteral dilation (yellow arrows).

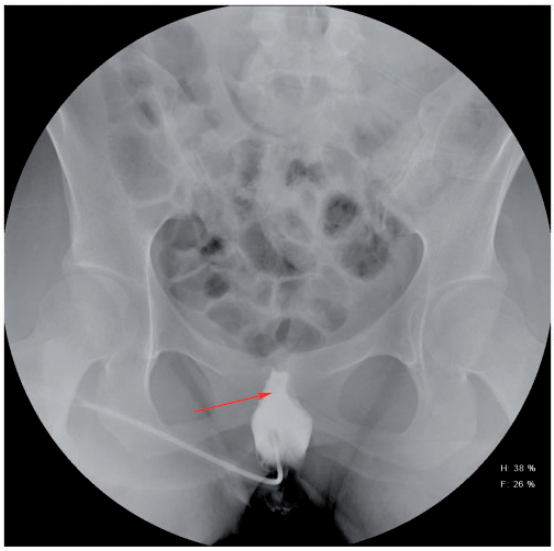

Figure 3. Cystography shows a small capacity of the bladder and tower-like shape of the bladder (red arrow).

lichenification of the trigone. Pathological examinations showed glandular cystitis in seven patients in the BTX-A group and in nine patients in the hydrodistention group. One patient in the BTX-A group and two patients in the hydrodistention group had chronic cystitis. Fibrosis was found in five patients in the BTX-A group and in six patients in the hydrodistention group. The pathological examination results of one patient is shown in Figure 5.

No patients required clean bladder catheterization after treatment in both groups. Two patients had prolonged administration of empirical antibiotics owing to urinary tract infection in the BTX-A group.

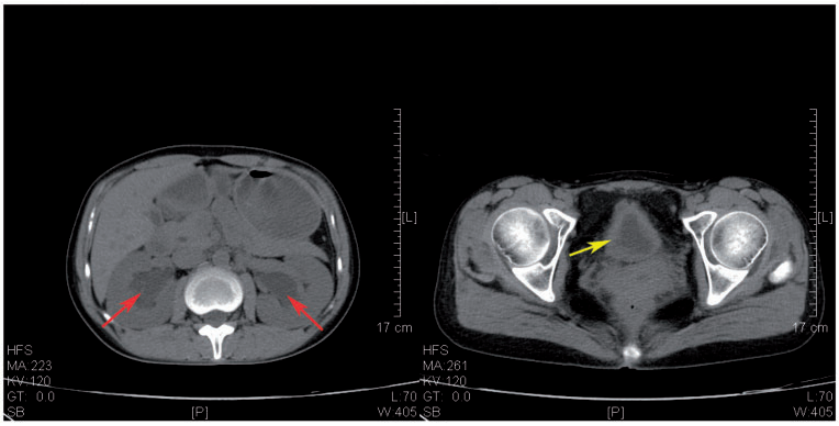

Figure 4. Computed tomographic scans show bilateral hydronephrosis (red arrows) and thickening of the bladder wall (yellow arrow).

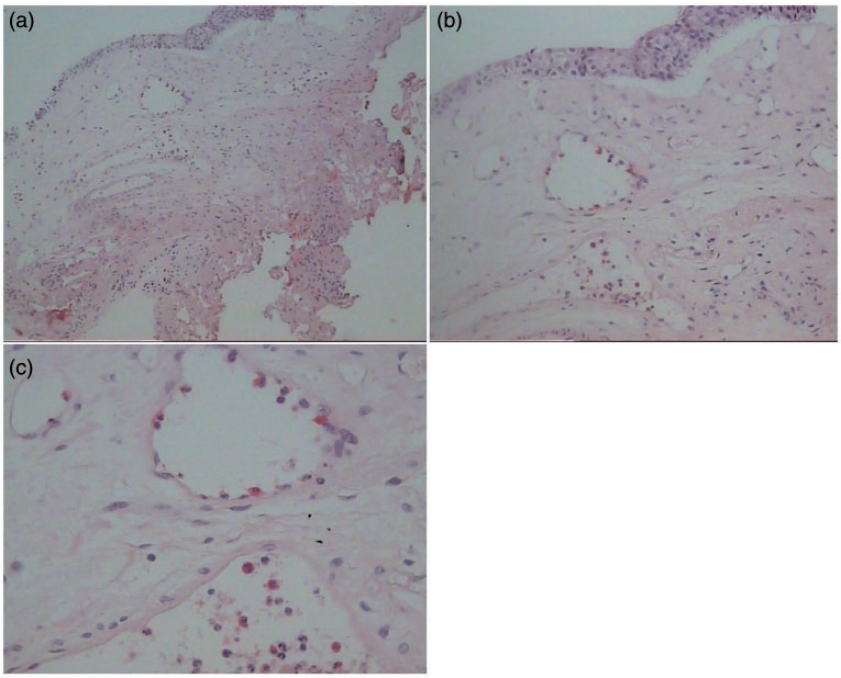

Figure 5. Pathological examination shows fibrosis in the muscular layer of the bladder. Hematoxylin–eosin staining, with 100×, 200×, and 400× in panels a, b, and c, respectively.

Except for one patient in the hydrodistention group who was treated with bladder clot removal due to bleeding of the bladder wall, no serious complications occurred in either of the groups. The patients with hydronephrosis in each group recovered.

The symptoms of patients in both groups were significantly improved at 6 months

after treatment compared with before treatment (all $P < 0.05$, Table 3). Six months after treatment, the mean daytime frequency, nocturia, scores for ICSI, QOL, OABSS, and the VAS, MC, compliance, and MCC were not significantly different between the two groups (Table 2). Twelve months after treatment, the mean daytime frequency, ICSI score, MC, and MCC in the BTX-A group were significantly better than those in the hydrodistention group (all $P < 0.05$). A detailed description of the data is shown in Tables 2 and 3.

We then compared the duration of ketamine abuse, MCC, OABSS, compliance, ICPI score, QOL score, fibrosis in pathology, MC, and maximal flow rate between the resolved IDC group and the persistent IDC group (Table 4). At 6 months after therapy, the duration of ketamine abuse was significantly longer, the amount of fibrosis in pathology was greater, and MC was less in the persistent IDC group than in the resolved IDC group (all $P < 0.05$). Multiple comparisons between patients in the resolved IDC group and those in the persistent IDC group 6 months after therapy showed that fibrosis in pathology might be an independent factor for predicting the persistence of detrusor overactivity. Taken fibrosis in pathology as the horizontal axis, the duration of ketamine abuse, compliance, QOL, and maximal flow rate showed a significant difference between the two groups ($P = 0.039$, $P = 0.033$, $P = 0.045$, $p = 0.046$, respectively).

Discussion

Ketamine abuse is a preventable problem, which could be solved by prohibition of ketamine abuse rather than remedial treatment for ketamine-associated cystitis. However, patients with ketamine-associated cystitis require correct recommended therapies to achieve a better recovery. IDC overactivity in patients with ketamine-associated cystitis is the main symptom, but the pain component should be emphasized in these patients. Moreover, the pathological changes in ketamine-associated cystitis are similar to interstitial cystitis.[9,10] The recommended therapies of interstitial cystitis may be effective for ketamine-associated cystitis. Some studies have reported experimental methods to treat ketamine-associated cystitis, but recommended therapies for ketamine-associated cystitis remain unknown.[11] Therefore, in addition to rehabilitation from ketamine abuse, therapies include intradetrusor BTX-A injection, cystoscopic hydrodistention, bladder instillation of hyaluronic acid, amitriptyline hydrochloride, and muscarinic cholinergic receptor antagonists.[12–16] Although comprehensive therapy is usually required for patients with interstitial cystitis, instillation therapy of hyaluronic acid can also be considered as a single modality. However, the mean bladder capacity of patients with ketamine-associated cystitis in this study was 32.26 mL in the BTX-A group and 30.59 mL in the hydrodistention group, which is much less than the instillation volume proposed for the bladder. Bladder enlargement therapy plays a major role in comprehensive treatment. This is the rationale for choosing 200 units for BTX-A, which is a greater dosage than the routine dosage of 100 units for interstitial cystitis.[17] Cystoscopic hydrodistention has the same aim as BTX-A of enlarging the bladder volume first.

The specific history of ketamine abuse contributes to underlying diagnosis of ketamine-associated cystitis with objective data to follow up. Urodynamic data are optimal. Therefore, assessment of urodynamics was performed in each patient in this study. We found that intradetrusor BTX-A injection and cystoscopic hydrodistention followed by bladder instillation of hyaluronic acid showed satisfactory results in enlarging bladder volume and LUTS for

Table 3. Changes in subjective and objective parameters within the groups.

Parameter	BTX-A group (n = 18) Preoperative	BTX-A group (n = 17) 6 months postoperatively	BTX-A group (n = 16) 12 months postoperatively	P1	P2	Hydrodistention group (n = 18) Preoperative	Hydrodistention group (n = 16) 6 months postoperatively	Hydrodistention group (n = 15) 12 months postoperatively	P1	P2
ICPI score	12.50 ± 1.47	2.41 ± 1.54	0.94 ± 0.77	<0.001	0.002	12.67 ± 1.53	3.75 ± 2.72	1.93 ± 1.03	<0.001	0.022
ICSI score	17.06 ± 1.83	5.82 ± 2.16	4.56 ± 0.63	<0.001	0.033	17.33 ± 1.68	7.25 ± 3.79	5.33 ± 1.11	<0.001	0.069
QOL score	5.50 ± 0.51	1.59 ± 1.18	1.25 ± 0.77	<0.001	0.340	5.67 ± 0.49	1.75 ± 1.48	1.33 ± 0.98	<0.001	0.367
OABSS	10.89 ± 1.23	2.71 ± 0.99	0.13 ± 0.34	<0.001	<0.001	11.06 ± 0.80	3.50 ± 1.67	0.33 ± 0.72	<0.001	<0.001
VAS score	7.39 ± 1.72	0.88 ± 1.69	0.25 ± 0.68	<0.001	0.169	7.33 ± 1.50	1.00 ± 2.16	0.33 ± 0.62	<0.001	0.252
FV chart										
DF	12.44 ± 1.82	6.12 ± 1.11	5.56 ± 0.73	<0.001	0.102	13.17 ± 1.50	6.81 ± 1.47	6.27 ± 1.03	<0.001	0.244
Nocturia	14.78 ± 1.26	2.29 ± 0.69	0.13 ± 0.34	<0.001	<0.001	14.89 ± 1.13	2.56 ± 0.51	0.33 ± 0.72	<0.001	<0.001
MC (mL)	32.26 ± 11.42	259.10 ± 38.23	333.56 ± 42.66	<0.001	<0.001	30.59 ± 14.51	243.57 ± 45.86	301.16 ± 42.87	<0.001	0.001
Free flowmetry										
Qmax (mL/s)	6.13 ± 1.84	19.38 ± 1.75	21.08 ± 2.30	<0.001	0.023	5.77 ± 1.59	19.11 ± 2.07	20.76 ± 2.21	<0.001	0.040
PVR (mL)	5.97 ± 4.73	6.48 ± 3.06	5.67 ± 3.94	0.703	0.510	4.85 ± 3.76	5.05 ± 3.19	5.11 ± 2.95	0.869	0.958
Urodynamic study										
Compliance	1.75 ± 1.42	22.05 ± 5.06	23.90 ± 6.63	<0.001	0.371	1.62 ± 1.70	20.87 ± 5.51	22.17 ± 6.45	<0.001	0.887
IDC, n (%)	18 (100)	3 (17.65)	1 (5.88)	<0.001	0.316	18 (100)	5 (31.25)	2 (13.33)	<0.001	0.233
MCC (mL)	24.22 ± 10.90	269.41 ± 43.50	344.31 ± 46.77	<0.001	<0.001	26.89 ± 12.10	257.06 ± 45.36	309.40 ± 43.71	<0.001	0.003
MDP (cm H_2O)	61.59 ± 5.20	39.27 ± 4.59	39.15 ± 3.86	<0.001	0.933	64.14 ± 6.26	42.73 ± 3.39	40.35 ± 5.05	<0.001	0.133
UI, n (%)	5 (27.78)	0	0	0.019	1.000	6 (33.33)	0	0	<0.011	1.000

Values are mean ± standard deviation or n (%).

P1: preoperative versus 6 months postoperatively; P2: 6 months postoperatively versus 12 months postoperatively.

BTX-A, botulinum toxin A; ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; QOL, quality of life; OABSS, overactive bladder symptom score; VAS, visual analog scale; FV chart, frequency-volume chart; DF, daytime frequency; MC, maximal capacity; Qmax, maximal flow rate; PVR, postvoid residual urine; IDC, involuntary detrusor contraction; MCC, maximal cystometric capacity; MDP, maximum detrusor pressure; UI, urgency incontinence.

Table 4. Clinical characteristics of patients in the resolved IDC group and those in the persistent IDC group 6 months after therapy.

	Persistent IDC group (n = 8)	Resolved IDC group (n = 25)	P
Duration of ketamine abuse	4.50 ± 1.51	2.80 ± 0.65	<0.001
MCC (mL)	22.50 ± 7.65	24.84 ± 11.33	0.591
OABSS	11.25 ± 1.04	10.84 ± 1.07	0.352
Compliance	1.39 ± 0.92	1.60 ± 1.57	0.724
ICPI score	13.50 ± 1.31	12.52 ± 1.39	0.088
QOL score	5.88 ± 0.35	5.56 ± 0.51	0.067
Fibrosis in pathology	100%	12%	0.000
MC (mL)	22.78 ± 10.66	33.73 ± 12.67	0.035
Qmax (mL/s)	5.34 ± 1.95	6.19 ± 1.70	0.241

Values are mean ± standard deviation or %.

IDC, involuntary detrusor contraction; MCC, maximal cystometric capacity; OABSS, overactive bladder symptom score; ICPI, Interstitial Cystitis Problem Index; QOL, quality of life; Qmax, maximal flow rate.

patients with ketamine-related cystitis in 6 and 12 months of follow-up. The ICPI score, OABSS, rate of nocturia, MC, maximal flow rate, and MCC were even more significantly improved in 12 months of follow-up than in 6 months of follow-up in both groups. However, intradetrusor BTX-A injection or cystoscopic hydrodistention cannot satisfactorily explain the long-term effect for ketamine-associated cystitis. For interstitial cystitis, intradetrusor BTX-A injection or cystoscopic hydrodistention usually requires repeated treatments because the fundamental cause of interstitial cystitis cannot be eliminated.[18–21] However, the fundamental cause of ketamine-related cystitis can be thoroughly solved by abstaining from ketamine. The LUTS of preliminary ketamine-associated cystitis may be caused by inducible nitric oxide synthase in the bladder epithelial layer, but not by detrusor fibrosis.[10] As interstitial cystitis becomes aggravated, fibrosis of the detrusor will occur. Therefore, the long-term effect of these two therapies may be caused by recovery of reversible bladder injury.

Variables that were measured at the 6-month follow-up were not significantly different, except for maximum detrusor pressure, compared with those measured preoperatively in the two groups. However, at 12 months of follow-up, the mean daytime frequency, ICSI score, MC, and MCC in the BTX-A group were significantly better than those in the hydrodistention group. These findings indicated that intradetrusor BTX-A injection had a similar effectiveness to that of cystoscopic hydrodistention, but had better long-term effectiveness. A possible explanation for this effectiveness is that cystoscopic hydrodistention and BTX-A injection help to provide sufficient bladder capacity for instillation therapy. A long-term effective treatment in both groups might be instillation therapy of hyaluronic acid. Ou et al. provided evidence to support such a viewpoint.[22] Reasons for providing instillation therapy of hyaluronic acid may be as follows. First, although the effect of intradetrusor BTX-A injection has a limited time, there is sufficient time for a reversible process. Second, the bladder of patients with ketamine-associated cystitis is much more vulnerable than that of interstitial cystitis, and after hydrodistention, the mucosa and the detrusor were torn in our patients.

Some patients suffer from a side effect of cystoscopic hydrodistention, such as pelvic pain and scarring of the bladder, which may worsen storage symptoms.[23,24]. However, despite the significant difference in long-term treatment between the groups, this difference might not translate into clinical relevance. In fact, the patients in both groups were satisfied with their treatment.

In this study, we analyzed the predictive factors for prognosis by comparing variables of patients with resolution of IDC and those with persistent IDC 6 months after therapy. Because of the small sample size, there were only enough data at the 6-month follow-up. We found that the duration of ketamine abuse, amount of fibrosis in pathology, and preoperative MC may be predictive factors for the prognosis of ketamine-associated cystitis. However, the duration of ketamine abuse is not an objective variable. Moreover, the ketamine abuse volume, which is another important predictive factor, is difficult to assess by the duration of abuse because the patients have difficulty in remembering the actual abuse volume. Therefore, the duration of ketamine abuse is not a good predictive factor to be standardized. Preoperative MC is an objective variable, but such a variable is easily affected owing to accompanying bladder pain. When cystometry was performed by filling with normal saline without anesthesia, the true MC of the bladder was underestimated because the patient would ask to stop filling the bladder because of severe pain. A study by Huang et al.[25] showed that urodynamic test results help diagnose ketamine-associated cystitis, but may not be useful in determining the severity of this disease. This may be the reason why the therapeutic effect was good for chronic ketamine-associated cystitis, which is similar to the results by Ou et al.[22] Therefore, we consider that the amount of fibrosis in pathology might be the optimal variable as the predictive factor for prognosis of ketamine-associated cystitis. Multiple comparisons between patients with resolution of IDC and those with persistent IDC 6 months after therapy support our hypothesis. Although repeated bladder detrusor biopsies are impossible, we can estimate the prognosis by the first bladder detrusor biopsy. No fibrosis, mild fibrosis, and serous fibrosis may predict a good, mild, and poor prognosis, respectively, of ketamine-associated cystitis. Therefore, bladder detrusor biopsy is essential for helping to decide on management and for predicting the prognosis. Microinvasive treatments, such as intradetrusor BTX-A injection, cystoscopic hydrodistention, and instillation of hyaluronic acid, were used for patients with no fibrosis and mild fibrosis in the bladder detrusor. If serious fibrosis develops in the bladder detrusor, augmentation of the bladder may be required owing to irreversible damage to the bladder.

Except for one patient in the hydrodistention group who had bladder clot removal performed owing to bladder wall bleeding, no serious complications occurred in either group. Generally, both methods were safe. However, the bladder wall of patients with ketamine-associated cystitis is much more vulnerable than that with interstitial cystitis. Therefore, coagulation should be performed for the point of bleeding in the bladder wall by a bipolar resectoscope after hydrodistention to prevent serious bleeding.

This study has some limitations as follows. First, better staging criteria, including standardized pathological stages, need to be established. Second, management of ketamine-related cystitis varied. Therefore, the best or recommended treatment for different pathological stages needs to be confirmed. In addition to a history of recreational use of ketamine, specific markers for making a definite diagnosis or differentiate diagnosis need to be found.

Therefore, further studies need to be carried out in the future.

In conclusion, intravesical instillation of hyaluronic acid with intradetrusor BTX-A injection or cystoscopic hydrodistention shows good outcomes in enlarging the bladder volume and has a low rate of urinary tract symptoms for patients with ketamine-related cystitis. However, intravesical instillation of hyaluronic acid with intradetrusor BTX-A injection appears to be a preferable option for long-term effectiveness.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This work was supported by the Science and Technology Planning Project of Guangdong Province (Grant Number: 2014A020212400).

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