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Original Article

Amitriptyline plus hydrodistension versus hydrodistension alone for treating interstitial cystitis/bladder pain syndrome

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Abstract

Purpose: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating condition that is difficult to diagnose and treat. The aim of this study was to investigate whether a combination treatment of amitriptyline after bladder hydrodistension is more beneficial for IC/BPS patient.

Methods: Seventy-six patients' dates diagnosed with IC/BPS were collected: the hydrodistension group (34 patients) and the combination group (42 patients), which received amitriptyline (25 mg ~ 50 mg/d) for 3 months following hydrodistension. The efficacy was evaluated at the 3rd and 6th months by using index scores. In addition, adverse events of amitriptyline and hydrodistension were recorded.

Results: There was no difference in two groups at baseline. The ICSI, ICPI, AIS, SAS, OABSS, VAS and FVC scores improve significantly in the combination group than in the hydrodistension group at 3 months after hydrodistension . After 3 months of amitriptyline withdrawal, obvious improvement in the combination group was observed only for the AIS at the 6th month. At the 6th month, the indexes of the two groups still improved significantly compared with those recorded prehydrodistension; however, there was no difference in the improvement of maximum bladder volume in both groups before and after hydrodistension ($P > 0.05$). The adverse events of amitriptyline all were in the tolerable range.

Conclusions: Hydrodistension under general anesthesia effectively relieved IC patients' symptoms for at least 6 months. The three-month usage of amitriptyline alleviated the symptoms and problems more quickly and safely after hydrodistension in patients with IC/BPS.

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a syndrome with frequent urination, acute urination and bladder pain [1]. Because the etiology and pathogenesis of IC/BPS are unknown, the treatment principle is symptomatic treatment and improvement of quality of life [2,3].

Although IC/BPS is a syndrome that requires a multimodal therapy, amitriptyline is recommended as the second-line oral drug for IC/BPS [4]. Possible mechanisms of amitriptyline therapy include providing central and peripheral anticholinergic effects, blocking the active transport system of presynaptic nerve endings, promoting the reabsorption of serotonin and norepinephrine, and acting as a sedative [5]. Studies have shown that long-term and low-dose amitriptyline is a safe, effective and tolerable treatment for IC/BPS [6].

Bladder hydrodistension is a widely used method for the treatment of IC/BPS [7]. Cystoscopy with hydrodistension is helpful for the diagnosis of complicated interstitial cystitis/bladder pain syndrome and short-term, low-pressure water dilation, while cystoscopy under anesthesia is the recommended third-line treatment of AUA guidelines. Cystoscopy with hydrodistension not only diagnoses typical IC lesions in the bladder but also detects other bladder diseases, such as bladder leukoplakia, cystitis glandularis, and bladder tumors [8]. The therapeutic effect of hydrodistension is mainly through increasing bladder volume and prolonging urination interval to alleviate the clinical symptoms of patients and promote the replacement of defective mucosal epithelial cells by new epithelial cells [9,10].

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The clinical manifestations of IC/BPS patients vary greatly, mainly involving lower urinary tract symptoms, pain, sleep disorders, anxiety, and even depression [11]. For these reasons, it is very difficult to diagnose IC/BPS and evaluate its clinical efficacy. At present, the O'Leary Sant Questionnaire (ICSI/ICPI) is widely used in the primary screening and therapeutic evaluation of IC/BPS. The visual analog scale (VAS), overactive bladder syndrome score (OABSS), 2-day frequency-volume chart (FVC), Assens Insomnia Scale (AIS) and self-rating anxiety scale (SAS) are also used to systematically assess the symptoms and problems of IC/BPS for diagnosis or evaluation of therapeutic efficacy. Huang et al confirmed that the O'Leary-Sant ICSI and ICPI should be useful in the quantitative evaluation of therapies for Chinese patients with IC [12-14].

After retrieving the inpatient case system, 76 IC/BPS patients treated with hydrodistension were identified and analyzed. Among these patients, some were treated with amitriptyline orally for 3 months, while the others had no amitriptyline. Each group was evaluated at baseline and at the 3rd and 6th months after hydrodistension using clinical indexes, including the ICPI score, ICSI score, OABSS, VAS, AIS, SAS, 24-hour frequency and maximum bladder volume. Questionnaires and follow-up of urinary flow rate are routinely implemented in our hospital patients who undergo hydrodistension.

Methods

Patients and study design

The study based on the data which were extracted from both inpatient and outpatient electronic medical record systems of our hospital from January 1, 2017 to June 31, 2018. It was designed as a chart review between treatment with amitriptyline/hydrodistension (combination treatment group) and treatment with hydrodistension alone (control group). All patients had a history of pain/discomfort associated with bladder filling, accompanied by other symptoms, such as daytime and/or nighttime micturition frequency without infection or other pathology. They had undergone physical examination, urinary analysis, and cystoscopy with hydrodistension under general anesthesia during hospitalization. The O'Leary Sant Questionnaire scores of patients were all higher than 12. Patients were willing and able to complete the necessary questionnaires. Written informed consent was obtained from each participant.

The inclusion criteria included patients older than 18 years of age, complaints present for at least 6 months, no treatment received for IC during the last 6 months, no history of neurological disease, no history of previous pelvic surgery, no history of pelvic irradiation, no diagnosis of diabetes mellitus, no history of clinical urinary system infection within the last 1 month, and no pelvic organ prolapse. The exclusion criteria were as follows: patients who were younger than 18 years old or who were pregnant or lactating and patients with bladder cancer and stones, bladder outlet obstruction (maximum flow rate<10 mL/s), acute urinary infection, postvoid residual (PVR) >50 mL, neurogenic disorders, or a gynecologic disorder (endometriosis or vaginitis). Patients with contraindications to oral amitriptyline (such as severe heart disease, recent history of myocardial infarction, epilepsy, glaucoma, urinary retention, hyperthyroidism, liver damage, and allergies to tricyclics) and patients with Hunner's ulcer were also excluded before admission.

Cystoscopic hydrodistension under general anesthesia

During the cystoscopy procedure under general anesthesia, saline was instilled into the bladder at a height of 80-100 cm away from the pubic symphysis. The bladder was distended under gravity for 8-10 min, and the volume of bladder infusion was less than 700 ml. The maximum bladder perfusion capacity was recorded. Then, the bladder walls were observed for glomerulations or Hunner's ulcers, and photographs were taken. Biopsies were carried out on suspicious lesions, and routine pathological examinations were performed. The three-chamber catheter was indwelled, and the bladder was continuously irrigated or directly drained. The catheter was removed on the first day after the examination. Positive criteria for IC/BPS were diffuse submucosal punctate hemorrhage, with a range of more than three quadrants; each quadrant exceeded 10. The maximum volume of the water-dilated bladder was more than 200 ml in all patients.

Amitriptyline therapy

The initial dose of amitriptyline was 25 mg/d. The maximum dose was 50 mg/d according to the therapeutic effect. The drug was taken before bedtime. The treatment lasted 3 months after hydrodistension.

Table 1. *Comparisons of demographics and bladder volume between patients in study (treatment combined with amitriptyline) and control groups*

	Hydrodistension group (n=34)	Combination group (n=42)	P-value
Age (years)	50.09±13.08	51.71±9.67	0.535
Mean ± SD			
BMI	23.7±5.15	24.5±6.22	0.521
ICSI	14.03±1.83	13.98±2.18	0.915
ICPI	12.88±2.17	12.55±2.24	0.519
AIS	12.44±4.23	12.45±3.96	0.992
SAS	60.5±1.38	59.10±1.38	0.479
OABSS	8.62±1.44	8.74±1.34	0.708
VAS	4.68±2.32	4.41±2.41	0.623
V (mL)	225.3±91.13	217.9±68.27	0.687
F	17.33±2.50	16.79±3.64	0.464

Outcome assessment and study endpoints

To evaluate the therapeutic efficacy, the O'Leary-Sant score (including ICPI and ICSI), OABSS, VAS, AIS, SAS and FVC were recorded before treatment and 3 and 6 months after hydrodistension to compare the therapeutic efficacy. FVC included 24-hour frequency (F:Times/24 hours) and maximum bladder volume (V: mL).

Statistical analysis

The data were analyzed by SPSS 24.0 software (SPSS Inc., Chicago, IL). We used the mean ± SD to express quantitative data. Student's t-test and Welch's t-test were used to compare the differences between different groups when the variances followed a normal distribution or not. A p-value less than 0.05 was deemed statistically significant.

Results

Comparison of the two groups of patients before treatment

In total, 76 patients were screened. Of these, 42 patients were in the combination group and received amitriptyline (25 mg ~ 50 mg/d) for 3 months following hydrodistension, and 34 patients were in the control group (hydrodistension only). No patient was excluded. The demographic data, including age and BMI, and patients' baseline scores in both groups are shown in Table 1. No significant differences between the two groups were observed (P> 0.05).

Evaluation of therapeutic effects

In both the combination group and hydrodistension group, the values of the ICSI, ICPI, OABSS, VAS, SAS, AIS and FVC were significantly different from the baseline values after 3 months of different processing (Tables 2 and 3), suggesting an improvement in these indexes. In the combination group, after withdrawal of amitriptyline for three months, the improvement in the ICSI, ICPI, OABSS, VAS, SAS, AIS and FVC was still significant when compared with the baseline values ($P < 0.05$). However, compared with the results at the 3rd month, the treatment was less effective according to the ICSI, ICPI, SAS, AIS and FVC. In the control group, the OABSS and FVC increased significantly 6 months after hydrodistension alone. Except for the maximum bladder volume, other scores still showed statistically significant improvement ($P < 0.05$).

Compared with baseline, the maximum voided volume increased significantly at the 3rd and 6th month in the combination group ($P = 0.024 < 0.05$) but only at the 3rd month in the hydrodistension group ($P = 0.226$); these results are shown in Table 4. There was no significant difference between the amitriptyline group and the hydrodistension group ($P > 0.05$).

At the third month, the improvement in the ICSI, ICPI, OABSS, VAS, SAS, AIS and 24-h frequency was significant in the combination group compared with the hydrodistension group ($P < 0.05$). However, only the AIS score was significantly lower in the combination group than in the hydrodistension group at the 6th month ($P < 0.05$).

Table 2. *Comparison of efficacyof the hydrodistensiononly group between different time pots*

	Baseline	3 Months	P-value†	6 Months	P-value†	P-value‡
ICSI	14.03±1.83	6.73±1.53	<0.001	6.76±1.92	<0.001	0.944
ICPI	12.88±2.17	4.79±1.75	<0.001	5.55±1.58	<0.001	0.069
AIS	12.44±4.23	6.94±2.40	<0.001	7.42±2.60	<0.001	0.432
SAS	60.5±1.38	44.79±6.84	<0.001	45.48±6.24	<0.001	0.667
OABSS	8.62±1.44	4.68±1.15	<0.001	5.32±1.15	<0.001	0.023
VAS	4.68±2.32	1.97±1.27	<0.001	2.21±1.41	<0.001	0.463
V (mL)	225.3±91.13	269.26±26.20	0.009	245.63±23.82	0.226	<0.001
F	17.33±2.50	269.26±26.21	<0.001	10.73±1.40	<0.001	0.027

†Comparisons between baseline and post-hydrodistensionfor 3 monthsor6 months using Student's paired t-test.
‡Comparisons of improvement between 3 month and 6 month after hydrodistensiontreatmentalone using Student's paired t-test.

Table 3. *Comparison of efficacyof the hydrodistensiononly group between different time pots*

	Baseline	3 Months	P-value†	6 Months	P-value†	P-value‡
ICSI	13.98±2.18	3.95±2.93	<0.001	6.61±3.99	<0.001	0.026
ICPI	12.55±2.24	3.58±2.55	<0.001	6.35±4.86	<0.001	0.046
AIS	12.45±3.96	3.00±1.70	<0.001	5.22±3.96	<0.001	0.039
SAS	59.10±1.38	32.11±5.87	<0.001	41.39±12.98	<0.001	0.011
OABSS	8.74±1.34	3.42±2.09	<0.001	4.28±2.59	<0.001	0.274
VAS	4.41±2.41	1.63±1.17	0.003	2.28±2.35	<0.001	0.292
V (mL)	217.9±68.27	276.32±31.53	0.001	256.67±27.01	0.024	0.05
F	16.79±3.64	8.74±1.73	<0.001	11.11±3.41	<0.001	0.011

†Comparisons between baseline and post-combination treatment for 3 months or 6 months using Student's paired t-test.
‡Comparisons of improvement between 3 month and 6 month after combination treatment using Student's paired t-test.

Table 4. *Comparison of the treatments-efficacy between study (treatment combined with amitriptyline) and control groups.*

	3 Months			6 Months		
	Hydrodistension group	**Combination group**	**P-value**	**Hydrodistension group**	**Combination group**	**P-value**
ICSI	6.73±1.53	3.95±2.93	<0.001	6.76±1.92	6.61±3.99	0.885
ICPI	4.79±1.75	3.58±2.55	<0.001	5.55±1.58	6.35±4.86	0.513
AIS	6.94±2.40	3.00±1.70	<0.001	7.42±2.60	5.22±3.96	0.021
SAS	44.79±6.84	32.11±5.87	<0.001	45.48±6.24	41.39±12.98	0.221
OABSS	4.68±1.15	3.42±2.09	0.023	5.32±1.15	4.28±2.59	0.118
VAS	1.97±1.27	1.63±1.17	0.004	2.21±1.41	2.28±2.35	0.914
V (mL)	269.26±26.20	276.32±31.53	0.387	245.63±23.82	256.67±27.01	0.14
F	269.26±26.21	8.74±1.73	<0.001	10.73±1.40	11.11±3.41	0.653

Adverse reactions of treatment

Among the 42 patients treated with amitriptyline, 33 (78.57%) suffered from different degrees of drowsiness, 22 (52.38%) suffered from vertigo, 9 (21.42%) suffered from constipation and 7 (16.67%) suffered from dry mouth. The adverse reactions of amitriptyline were well tolerated.

In 76 patients with hydrodistension treated by cystoscopy, 25 (46.05%) had gross hematuria, and the catheter had to be retained for 1-2 days. There was no bladder rupture or necrosis.

Discussion

In the present study, we investigated whether amitriptyline caused any change in the efficacy of hydrodistension treatment in IC/BPS patients. According to the EAU guidelines and systematic reviews, pentosan polysulfate (PPS) is recommended as one of the best oral drugs for the treatment of IC/BPS symptoms, but this drug is not available in China. Lusty et al found that the only therapies that seem to align between this reported effectiveness and published efficacy include amitriptyline (with the strongest alignment), hydroxyzine, PPS, and/or combinations [15]. Therefore, orally administered amitriptyline is still an efficacious medicine for IC/BPS and would be the first treatment offered [16].

National guidelines recommend oral amitriptyline as a second-line treatment option that may provide benefit in a subset of patients. Amitriptyline acts via the blockade of acetylcholine receptors, blockade of histamine H1 receptors, and inhibition of reuptake of released serotonin and norepinephrine [17]. Amitriptyline treatment for IC/BPS in several controlled and noncontrolled trials demonstrated efficacy rates of 50% to 77% at a dose over 50 mg daily [18]. In a study performed by Hertle et al., the response rate to long-term administration of amitriptyline (average 19.0 months) was 64% and when compared with baseline significantly improved the various IC/BPS symptoms [19]. In our previous study, lower-dose amitriptyline therapy (25 mg/d) for IC/BPS for 12 weeks showed an obvious decrease in low urinary tract symptoms and pelvic pains. Therefore, amitriptyline is a commonly used and effective oral drug for the treatment of IC/BPS. In the present study, the combination of amitriptyline and hydrodistension for 3 months improved all parameters significantly better than before treatment and hydrodistension alone. However, at the 6th month after amitriptyline withdrawal, only AIS maintained its effect. Therefore, amitriptyline, as an adjunct to hydrodistension, could be used more quickly and effectively in short-term treatment to improve LUTS, pain, anxiety and other related symptoms in IC/BPS patients. Amitriptyline could significantly improve sleep disorders by relieving pain and urinary urgency.

IC/BPS patients always show decreased maximal capacity of the functional bladder. In addition to being a diagnostic method, hydrodistension has a certain therapeutic effect on IC/BPS patients. Homma reported that bladder water dilatation effectively improved the symptoms of IC/BPS patients, and this treatment has been the pillar of IC patients [20]. The therapeutic principle of bladder dilatation may be due to the destruction of nerve endings of muscle input. In this study, all parameters significantly improved after 6 months of hydrodistension, even when amitriptyline was discontinued. It has been reported that the impact of water expansion is limited [21]. In this study, high pressure (>80 cm H2O) and prolonged (>10 min) hydrodistension under general anesthesia were more beneficial. Repeated water dilation might lead to bladder fibrosis, but this was only a case report; however, evidence of repeated water dilation was still valid [22].

In this study, amitriptyline plus hydrodistension did not significantly increase the maximum urination volume, which indicated that the bladder compliance of IC/BPS patients was poor. Two studies confirmed that the application of botulinum toxin A (BTX-A) in patients with IC/BPS could relieve pain, increase bladder capacity, reduce the number of urinations during the day and night, and thus improve quality of life [23,24]. The main pharmacological action of BTX-A is mainly to inhibit the release of acetylcholine in the presynaptic membrane of nerve endings, which could quickly combine with the neuromuscular endplate, block the release of neurotransmitters, and produce a local denervation effect to play a role, thereby alleviating the pain symptoms of patients [25]. Manecksha et al [26] found that detrusor combined with triangular injection could significantly improve the frequency and urgency of urine, and detrusor combined with triangular injection did not lead to a higher incidence of complications. Therefore, hydrodistension

combined with bladder detrusor BTX-A injection may be an effective method to increase the maximum urination volume of the bladder.

In this study, all patients had no serious complications. The adverse events of amitriptyline including sedation, drowsiness, dizziness, and nausea are very common (affecting up to 80% of patients) [27]. In this study, the incidence of adverse events from high to low was sleepiness, nausea, dry mouth and constipation, which is mild to moderate and tolerable. Chen et al suggested that taking amitriptyline before bed could not only maintain its effects but also reduce adverse events. The mean terminal half-life of amitriptyline was 4.33 hours following oral administration [28]. Therefore, the adverse effects of taking amitriptyline before bed may be significantly less than during the day. In this study, the main complication of hydrodistension was gross hematuria, and the incidence was 46.05%. No special treatment was needed, and indwelling catheters were needed for only 1-2 days. No serious complications, such as bladder rupture and sepsis, should occur when the speed of saline infusion is controlled and the volume of bladder infusion is less than 700 ml.

Conclusion

Hydrodistension could effectively relieve symptoms of IC/BPS patients for at least 6 months; moreover, amitriptyline was useful in both maintaining and improving the effectiveness of hydrodistension in patients with IC/BPS, and the adverse events were tolerable. More work is needed to improve the maximum urination volume of the bladder.

Conflict of Interest

None declared.

Data availability statement

Data are available on reasonable request. Deidentified participant data.

Contributions

Weiguo Chen and Junjun Zhang conceived and designed the experiments; Chengyuan Wang, Xi Zhang, Yifan Chen and Xiaojie Ang collected the data with the help of Weiguo Chen; Junjun Zhang analyzed the data.

Ethics approval

Institutional board of the First Affiliated Hospital of Soochow University. Number approval: 2020032.

Consent for publication

Not applicable.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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