

Role of Bladder Hydrodistention and Intravesical Sodium Hyaluronate in the Treatment of Interstitial Cystitis

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Purpose: To evaluate the clinical efficacy of bladder hydrodistention and intravesical sodium hyaluronate in the treatment of interstitial cystitis (IC).

Materials and Methods: Twenty-one patients with IC received intravesical sodium hyaluronate therapy under nerve block or intravenous anesthesia. Bladders were perfused with 100 cmH₂O perfusion pressure and expanded for 10 min and were later injected with 40 mg/50 mL sodium hyaluronate through the catheter. After 1 h, the perfusion fluid was released. Perfusion was applied once per week, 4 to 6 times as a course of treatment.

Results: Under anesthesia, the average bladder capacity was 191.62 ± 88.67 mL, and after bladder expansion, the bladder capacity reached 425.33 ± 79.83 mL ($P = .000$). There were 2 suspected bladder ruptures after bladder expansion at 6.5 min and 7.2 min. After 10 min of bladder expansion, there were 19 cases of significantly gross hematuria. After treatment, the catheters of 17 patients were removed at 24 h; for the 2 cases of hematuria, catheters were removed at 72 h and for the 2 cases of suspected bladder rupture, catheters were removed after 4 days. After catheter removal, the pain threshold significantly decreased, and the maximum urinary output increased slightly. Compared with values before treatment, the day before the second injection of sodium hyaluronate, the frequency of urination decreased significantly (32.8 vs. 18.5 times/24 h), the maximum urinary output increased significantly (86.7 vs. 151.9 mL), the pain decreased significantly (8.7 vs. 3.0), and the O'Leary-Sant IC score and quality of life score were significantly decreased (30.0 vs. 17.0 and 5.9 vs. 2.4, respectively) ($P = .000$).

Conclusion: Bladder hydrodistention under anesthesia for patients with severe intractable IC produces immediate effectiveness; sodium hyaluronic infusion can alleviate frequent urination and pain, and the efficacy was positively correlated with the duration of treatment.

Keywords: anesthesia; cystitis, interstitial; therapy; female; prospective studies; urinary bladder; dilatation; methods; treatment outcome; lower urinary tract symptoms; etiology.

INTRODUCTION

The etiology of interstitial cystitis (IC) is highly complex, and at present, no treatment has shown good efficacy. Different from cardiovascular disease or cancer, IC will not directly lead to death. However, the suffering resulting from the poor quality of life (QoL) can make patients end their life decisively.⁽¹⁾ It is notably difficult to cure IC, and the current purpose of treatment is to alleviate its symptoms and improve the QoL. Using bladder hydrodistention and intravesical sodium hyaluronate under anesthesia to treat 21 cases with severe stubborn IC, we achieved good clinical efficacy, as reported below.

MATERIALS AND METHODS

Study Subjects

The mean age of the 21 patients (19 women and 2 men) was 50 years (range 18 to 74 years). The mean duration of symptoms was 32 months (12 to 72 months). The typical symptom was pain or discomfort of the perineum and pelvic cavity related to bladder filling. In addition, this symptom was usually accompanied by urgency, frequency and intermittent gross hematuria of different degrees. The quality of sleep and life of these patients was obviously decreased. All 21 patients had a history of multiple courses of antibiotic therapy and symptomatic analgesia.

After admission, urinalysis, urine culture, urine cytology and urinary acid-fast bacilli, color Doppler ultrasound examination and determination of residual urine

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volume were performed to eliminate the diagnosis of urinary tract infection, tuberculosis, urinary calculi, cancer and other diseases. Examination by computed tomography (CT), intravenous urography (IVU) or magnetic resonance hydrography was performed if necessary, and cystoscopy and bladder biopsy under anesthesia were also available. The protocol of the study was approved by the ethics committees of our hospital and was fully explained to the patients before informed consent was obtained.

Treatment Methods

1. Therapeutic method: Nerve blocking or intravenous anesthesia was performed. The residual urine volume was again determined by cystoscopy, and a conventional cystoscopy check was performed. If findings were suspicious, multiple bladder biopsies were taken. The bladder capacity was measured. Under normal pressure (usually 60 cmH₂O pressure), the bladder was continuously expanded for 2 min, the bleeding point of the bladder mucosa was observed, the cystoscope was removed, and three-way urethral Foley catheters were inserted. For patients without biopsies, the perfusion fluid was allowed to flow by gravity (100 cmH₂O pressure) until it slowed down, and hydrodistention was maintained for 10 min. The perfusion fluid could be observed going into the bladder, and pressure was assessed by a water column, connected to the catheter, that moved up and down with the fluctuation in respiration. After 10 min, the perfusion was stopped, the perfusion fluid was released, and bladder capacity was measured after expansion. The bladder was rinsed through the three-way urethral Foley catheter until there was no active bleeding. Sodium hyaluronate (Xi Shitai, Bioniche Life Sciences Inc. Ontario, Canada) 40 mg/50 mL was infused, and after 1 h, the perfusion fluid was released. The urinary canal was retained for 24 h then removed. Perfusion was applied once a week for 4 to 6 weeks as a course of treatment. For patients with biopsies, the above process was performed one week after excluding the possibility of other diseases.

2. Monitoring indicators: Clinical symptom scores were evaluated with a voiding diary before and after treatments during the 1st week, 2nd week, 5th week, 3rd month, and 6th month. The voiding diary registered consecutive records for 3 days, and the pain was evaluated by the visual analogue scale (VAS); the O'Leary-Sant IC questionnaire score was applied;⁽²⁾ QoL was evaluated using a benign prostatic hyperplasia (BPH)-specific, symptoms-based QoL questionnaire.

Statistical Analysis

Statistical Package for the Social Science (SPSS Inc,

Chicago, Illinois, USA) version 13.0 was used for the statistical analysis. Data are expressed as means \pm SD. The paired *t*-test was used to compare continuous variables. The Kolmogorov-Smirnov test was used to address continuous variables. The Wilcoxon signed-rank test and Pearson chi-square test were used for the preoperative and postoperative comparison. The Mann-Whitney *U* test was used to assess the degree of pain. $P < .05$ was considered significant.

RESULTS

Cystoscopy and the Results of the Water Expansion

By cystoscopic examination, we found that 15 cases had typically congestive erythema and small globular bleeding. Of these cases, 8 also had findings of small fountain-like active bleeding at scattered in the bladder mucosa, and 4 cases had typical Hunner's ulcers. Diagnostic expand the 19 cases bladder under 80 cmH₂O pressure for 2 min. All 19 cases with gross hematuria were found to have typical congestive erythema and small globular bleeding, and 12 of these cases were severe. Pathological reports of 5 cases with biopsies of the muscular layer and mucosa showed that there was inflammatory cell infiltration in the muscular layer and mucous, and the bladders displayed a chronic inflammatory response state. Only one case had a typical mast cell infiltration. Under anesthesia, the average bladder capacity was 98~382 (191.62 \pm 88.67) mL, and after 10 min of bladder expansion under 100 cmH₂O, bladder capacity reached 320~575 (425.33 \pm 79.83) mL ($P = .000$). There were 2 suspected bladder ruptures after bladder expansion at 6.5 min and 7.2 min resulting from the sudden increase in perfusion speed. The urinary canal was opened, and the perfusion fluid was released, and after three days, sodium hyaluronate was perfused. The catheter was retained for 1 day and then removed. There was 1 case of significantly gross hematuria after 10 min of bladder expansion.

Changes in Symptoms in Patients Before and After Treatment

After treatment, the catheters of 17 patients were removed at 24 h; the catheters in 2 cases of hematuria were removed at 72 h; the catheters in 2 cases of suspected bladder rupture were removed after 4 days. After removal of the catheter, the pain threshold was significantly reduced and the maximum urinary output increased slightly. Compared to values before treatment, the day before the second injection of sodium hyaluronate, the frequency of urination decreased significantly (32.8 vs. 18.5 time/24 h), the maximum urinary output

Table. The comparison of clinical symptoms and scores between the before and after bladder hydrodistention and intravesical sodium hyaluronate of 21 cases with interstitial cystitis.*

Time	24 h Urinary Frequency	Maximum Voided Volume (mL)	VAS Scores	O'Leary-Sant Scores	QoL Scores	P Value
Before treatment	32.8 ± 10.4	86.7 ± 37.9	8.7 ± 1.1	30.0 ± 4.2	5.9 ± 0.3	.000
After treatment						
1st week	18.5 ± 8.0	151.9 ± 72.2	3.0 ± 0.8	17.0 ± 4.4	2.4 ± 0.9	.000
2nd week	13.6 ± 7.3	190.5 ± 84.2	2.2 ± 1.0	13.8 ± 3.9	1.6 ± 1.0	.000
5th week	10.2 ± 4.0	209.5 ± 98.2	2.8 ± 1.1	12.1 ± 4.2	1.9 ± 1.0	.000
3rd month	15.1 ± 5.4	203.8 ± 94.6	3.3 ± 1.0	15.8 ± 3.5	2.1 ± 1.0	.000
6th month	17.8 ± 6.9	165.7 ± 79.2	4.5 ± 1.2	19.0 ± 6.5	2.8 ± 1.1	.000

Abbreviations: VAS, Visual Analog Scale; QoL, quality of life.

* Data are presented as mean ± SD.

increased significantly (86.7 vs. 151.9 mL), and the pain reduced significantly (8.7 vs. 3.0). After the third treatment, the symptoms continued to improve; in the fifth week, during which the sixth injection of sodium hyaluronate was performed, the treatment effects were optimal. Although the time of follow-up was limited to 6 months, at the time of the sixth month, symptom rebounded, but the changes from baseline to the end of study had great significance ($P < .0001$) (Table).

The changes in Questionnaire Scores of Patients before and after Treatment

The O'Leary-Sant IC questionnaire score of the patients and was calculated, and QoL was evaluated in a short time after treatment. Similar to the improved clinical symptoms, after removal of the urinary canal, both declined obviously ($P = .000$) compared with before treatment. The score was lowest during the fifth week, after the sixth perfusion. At the sixth month, both the O'Leary-Sant score and QoL rebounded slightly; however, compared with the value before treatment, the difference remained statistically significant ($P = .000$) (Table). The treatment efficacy over time is shown in Figure using a Kaplan-Meier curve.

Comparing the first week and the second week, no parameter was significantly different except the VAS score ($P = .008$). Comparing the fifth week and the third month, no parameter was significantly different, except 24 h frequency ($P = .002$) and the O'Leary-Sant score ($P = .04$). Comparing the 3rd month and the 6th month, no parameter was significantly different except the VAS score ($P = .01$). Compared with assessments before treatment, odynuria, frequency of urination, maximal urine volume, O'Leary-Sant IC score and QoL showed a tendency to decline over time.

DISCUSSION

About the Definition of IC

IC is a clinical diagnosis based on symptoms of urinary urgency, urinary frequency and suprapubic pain related to bladder filling. To relieve these symptoms, the efforts of many doctors have been directed toward determining its pathophysiology and treatment.⁽³⁾ Currently, however, the great controversy concerning IC is its definition.^(4,5) The American urological Association (AUA) guidelines recommend that a diagnosis be made according to the bladder pain syndrome based on urinary tract symptoms including urgency, odynuria and frequent pelvic pain together with the finding of typical bleeding and/or ulceration of the bladder mucous membrane observed by bladder endoscopy. At present, China does not have published IC diagnosis and treatment guidelines, and in recent literature, IC has been generally regarded as an interchangeable concept.⁽⁵⁻⁹⁾ Of the 21 patients in the

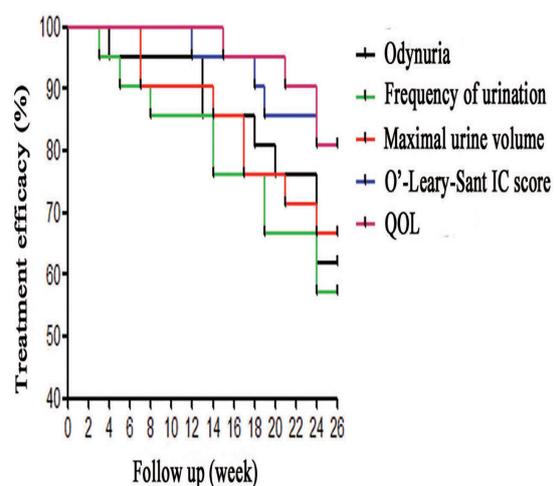


Figure. Kaplan-Meier curve of treatment efficacy.

Abbreviations: IC, interstitial cystitis; QoL, quality of life.

group, pain was the main complaint and was also the main cause of repeated visits to a doctor .

The Timing of Cystoscopy and Pathologic Findings

For patients with IC, cystoscopy is necessary. It is better when performed under general anesthesia because local anesthesia can aggravate patients' pain and fear, making patients uncooperative with the inspection and causing suspicious inspection results. After anesthesia, the bladder mucosa is inspected first. If this reveals an abnormal finding, especially a highly suspected bladder tumor, multiple biopsies for pathological examination should be taken. One week after the diagnosis of IC is confirmed, bladder expansion therapy is conducted. Before this study, 3 patients with symptoms of IC were ultimately diagnosed with bladder cancer. Two of them had bladder cancer in situ and were treated for a bladder tumor. However, these cases were not included in this study. If a bladder tumor is not detected, cystoscopy can also result in satisfactory analgesic effects, and most patients do not require painkillers in the week before bladder expansion therapy.

Although cystoscopy can eliminate the possibility of bladder cancer, it is necessary to obtain biopsies of suspicious areas.⁽¹⁰⁾ Of the 8 cases with biopsies, only one was found to have a typical mast cell infiltration. The remaining biopsy results were nonspecific except for inflammatory cell infiltration in the mucosa and muscularis mucosa, and only two of 21 cases had typical Hunner's ulcers. We believe that punctate hemorrhage has important diagnostic significance for IC. If a patient with symptoms of IC has punctate hemorrhage, the diagnosis of IC can be confirmed. Injection of tiny bleeding usually appeared in typical cases by cystoscopy inspection. However, spot bleeding is more common 2 min after expansion of the bladder. Also, 2 min after expansion, 16 cases (76.2%) were found to have obvious gross hematuria, which might be related to the fact that all cases of this group were refractory.

Measure of Bladder Capacity

Cystoscopy should be carried out before 2 minutes of diagnostic bladder expansion because there is a high rate of punctate hemorrhage during diagnostic bladder expansion, and hemorrhage will affect the results of cystoscopic examination. The determination of bladder capacity should be carried out after the biopsy under general anesthesia. Although the measure of bladder capacity during anesthesia cannot represent the bladder capacity during physiological conditions, the bladder capacity of patients with IC was obviously decreased. Among 21 patients, only 4 had a bladder capacity > 300

mL, 10 had a capacity < 100 mL, and the average capacity was 191.6 ± 88.7 mL; 10 min after the expansion, 5 cases had a capacity > 500 mL, only 1 case had a capacity < 350 mL, and the average capacity increased to 425.3 ± 79.8 mL, which is close to the average capacity of a normal bladder. After expansion, bladder capacity increased significantly compared with before treatment.

Height and Time of the Bladder Hydrodistention

The pressure of bladder hydrodistention generally settled at below 80 cmH₂O. Diagnostic expansion requires 2~3 min.⁽¹¹⁾ Therapeutic expansion requires 8 min. According to this method, we expanded the bladders of 3 cases, but the effect was not satisfactory. Therefore, we increased the pressure to 100 cmH₂O for 10 min, and the effect appeared better. When the flow slowed down, we began the perfusion. After beginning the perfusion, the perfusion continued into the bladder, and its effect was evaluated by a water column, which moved up and down with fluctuating respiratory frequency in order to receive a maximum capacity of expansion and monitor for rupture of the bladder. There were 2 suspected bladder ruptures after expansion at 6.5 min and 7.2 min. However, these 2 cases achieved a cure that lasted until six months without using any painkillers and without further complications. This might be related to the expansion to maximum volume. Bladder expansion alone can immediately relieve the pain, but the long-term effect is not satisfactory and also cannot significantly alleviate the frequency of urination.

Bladder endoscopy and bladder hydrodistention are the gold standard of diagnosis and treatment. The treatment method is simple and effective. The volume of bladder hydrodistention should be increased to a maximum in order to achieve the best treatment efficacy; next, we increased the distension height to 100 cm and increased the time to 10 min from the basic level (distension height 80 cm and distension time 8 min). Although we achieved a satisfactory efficacy, the potential risk of bladder rupture should not be ignored.

Intravesical Sodium Hyaluronate

The etiology of IC is complex and can lead to typical comprehensive symptoms through various ways.⁽¹²⁾ Parsons found that the bladder epithelial glycosaminoglycan (GAGs) layer of patients with IC was decreased significantly.⁽¹³⁾ The GAGs can adjust the permeability of the bladder mucosa and have an anti-adhesion function that can prevent bacteria from contacting the urinary tract epithelium. Any cause of damage to the GAG layer of the urinary tract epithelium will result in an increased permeability of the bladder mucosa and the penetration of chemical substances into the submu-

cosa. This can lead to injury and inflammation of the bladder, which can make the body produce pain through stimulating the sensory nerves. Hyaluronic acid (a type of GAG) has the possible ability to cover and repair the bladder mucosa to relieve and even cure the symptoms of IC. Foreign researchers believe that intravesical sodium hyaluronate might be a useful therapeutic option for patients with IC, whereas a domestic report indicated that it could be used in conjunction with the therapeutic effect of bladder hydrodistention.^(14,15) Other authors suggest that the dosage is not a critical factor for the effectiveness of hyaluronic acid. The dose of sodium hyaluronate did not have an apparent effect on efficacy because the package model is consolidated to 50 mL/40 mg, and we used one at a time.

The O'Leary-Sant IC questionnaire and a BPH QoL questionnaire were used to evaluate the patients' urination over the past month. However, during the weeks after treatment, asking patients to evaluate urination of the days before investigation can also be an objective index, especially when the patients are in the hospital or have just been discharged. Patients can carefully respond to the questionnaires, and the results are also statistically valuable.

Our results show that bladder hydrodistention under anesthesia for patients with severe intractable IC is rapidly effective; intravesical sodium hyaluronate can alleviate frequent urination and pain, and the efficacy was positively correlated with the duration of treatment. The combination of the two treatments has a better short-term effect and is worthy of clinical promotion.

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CONFLICT OF INTEREST

None declared.

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