Intravesical Instillation of Hyaluronic Acid Prolonged the Effect of Bladder Hydrodistention in Patients With Severe Interstitial Cystitis

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OBJECTIVES To evaluate the efficacy of intravesical instillation of hyaluronic acid (HA) after hydrodistention for the treatment of patients with interstitial cystitis (IC) having small bladder capacity.

METHODS A total of 47 patients with IC (aged 27-76 years) whose functional bladder capacity was less than 200 mL received bladder hydrodistention. Thereafter, 20 patients received intravesical instillation of 40 mg HA weekly in the first month and then monthly in the following 2 months. Sixteen patients received intravesical heparin instead and 11 patients received hydrodistention alone as the control. Mean voids per day, visual analog scale for pain, and functional bladder capacity were measured before hydrodistention and 3 and 6 months after hydrodistention in all 3 groups and 9 months after hydrodistention in HA and heparin groups.

RESULTS Two patients in the HA group and 1 in the heparin group failed to complete the treatment. Three months after hydrodistention, there was no improvement in the control group. Six and 9 months after hydrodistention, rate of improvement was significantly higher in the HA group than in the heparin group (77.8% vs 33.3%, $P < .05$; 50% vs 20%, $P < .05$). At 9 months, heparin treatment did not show any improvement. Improvement in voids per day (-1.8 ± 2.5, $P < .01$), visual analog scale (-0.9 ± 1.1, $P < .01$), and bladder capacity (16 ± 18 mL, $P < .01$) was still significant in the HA group.

CONCLUSIONS Intravesical instillation of HA may obviously prolong the effect of bladder hydrodistention in patients with severe IC. Its effect was better than heparin. UROLOGY xx: xxx, xxxx. © 2009 Elsevier Inc.

Interstitial cystitis/painful bladder syndrome (IC/PBS), a treatable but essentially incurable condition manifested by chronic pelvic pain and urinary frequency occurring in the absence of any known etiology, remains an enigma in the urological firmament. IC encompasses a major portion of the "painful bladder" disease complex, which includes a large group of patients with bladder and/or urethral and/or pelvic pain, irritative voiding symptoms (urgency, frequency, nocturia, dysuria), and sterile urine cultures.[1] Because the etiology, diagnosis, and treatment of IC are confusing many urologists and physicians do not pay enough attention on this disease. To date, the prevalence and incidence of IC in the mainland of China still remains unknown. Only few urologists in large medical centers can provide appropriate diagnosis and treatment of IC/PBS. A bladder capacity of less than 200 mL in a patient under anesthesia would not bode well for the likelihood of success of medical therapy.[1] Hydrodistention of the bladder with the patient under anesthesia, although technically a surgical treatment, is frequently the first therapeutic modality employed, often as a part of the diagnostic evaluation. Most favorable responses were brief; however, with the exceptional patient noting improvement for 6 months, thus being a candidate for repeat therapeutic distention.

Parsons hypothesized and popularized the concept that IC in a subset of patients is the result of some defect in the epithelial permeability barrier of the bladder surface glycosaminoglycan (GAG).[2] The major classes of GAGs include hyaluronic acid (HA), heparin sulfate, heparin, chondroitin 4-sulfate and chondroitin 6-sulfate, dermatan sulfate, and keratan sulfate. Urinary HA levels increased 3- to 4-fold in patients with IC. Urine uronate, GAG profile, and HA levels significantly correlated with the severity of IC.[3] The GAG layer functions as a permeability and antiadherence barrier. When impaired, its functions can be duplicated by exogenous GAG.[4] The nonsulfated GAG HA has also been used intravesically.

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Trials using 40 mg dissolved in 40 mL of normal saline solution weekly for 4-6 weeks, and then monthly treatments thereafter, have had response rates varying from 71% to 30%.[5,6] But the efficacy of hydrodistention combined with intravesical HA in patients with severe IC still remains uncertain. Because of the inconvenience and cost of cystoscopy under anesthesia, we analyzed a series of patients with severe IC whose functional bladder capacity was less than 200 mL by cystoscopy under local anesthesia to detect whether intravesical instillation of HA can prolong the efficacy of hydrodistention of the bladder.

MATERIAL AND METHODS

This is a prospective open-label controlled trial from May 2003 to September 2008. A total of 47 female patients with IC were included, with a median age of 55 years (27-76 years). Diagnosis was made by National Institutes of Diabetes and Digestive and Kidney Diseases diagnostic criteria for IC. All our patients followed the same diet control (no caffeine, alcohol, or beverages that might acidify the urine, such as cranberry juice or orange juice) during their treatment and follow-up. Their voids per day, visual analog scale (VAS) of pain, and functional bladder capacity were measured before therapy as baseline. Cystoscopy was done under urethral mucosa anesthesia using lidocaine gel. All patients had functional bladder capacity less than 200 mL and glomerulation could be seen in more than three-fourths quadrant of bladder mucosa. Hydrodistention of the bladder was performed in every patient under subarachnoid anesthesia. Hydrodistention was produced twice for 8 minutes under the pressure of 100 cm H_2O. Afterward, 20 patients received intravesical instillation of 40 mg HA (Bioniche, Canada) weekly in the first month and then monthly in the following 2 months. Sixteen patients used intravesical heparin 12 500 U with 100 mg lidocaine weekly in the first month and then monthly in the following 2 months. The remaining 11 patients received hydrodistention alone as the control. All patients receiving hydrodistention and HA or heparin therapy signed consent forms before their treatment. Mean voids per day and VAS for pain were measured before and 3, 6, and 9 months after hydrodistention. Bladder capacity was measured 3, 6, and 9 months after hydrodistention by cystoscopy under the same local anesthesia as was done before therapy. Improvement in symptoms was defined as decrease of voids per day $\geq$ 25% or decrease of VAS $\geq$ 2.

The statistical analysis software used was SPSS 16.0.

RESULTS

All 47 patients received cystoscopy, and bladder hydrodistention and Hunner ulcers were found in 2 patients. Forty-four patients completed this study while 2 patients in the HA group and 1 in the heparin group failed to complete the treatment and lost contact. Our analysis included those 44 patients who completed their treatment and follow-up. Their voiding frequency per day ranged from 12.3 to 33 (median, 19.5), VAS ranged from 5 to 9 (median, 7), and bladder capacity ranged from 70 to 170 mL (median, 105 mL). The age, voiding frequency per day, VAS, and bladder capacity at baseline had no statistical difference among these 3 groups. Bladder rupture occurred in 2 patients during hydrodistention but both recovered after 7 days of catheterization. No obvious side effect of intravesical HA was recorded. Three months after hydrodistention, 17 of 18 patients in the HA group, all patients in the heparin group, and 2 of 11 patients in the control group showed improvement in their symptoms. Six months after hydrodistention, 14 of 18 patients (77.8%) in the HA group, 5 of 15 patients (33.3%) in the heparin group, and 1 of 11 patients (9.1%) in the control group still maintain some improvement. The percentage of improvement was significantly higher in the HA group ($P < .05$). Nine months after hydrodistention, 9 of 18 patients (50%) in the HA group still had improvement, while 2 of them required continuous HA instillation monthly to maintain the effect afterward (Table 1).

Table 1. Improving rate after hydrodistention in HA and heparin groups

	Time After Hydrodistention (mo)		
	3	6	9
Improving rate (%)			
HA	93.3 (17/18)	77.8* (14/18)	50* (9/18)
Heparin	100 (15/15)	33.3 (5/15)	20 (3/15)
Control	18.2 (2/11)	9.1 (1/11)	—

P value was determined using the Fisher exact test for proportions.

P value refers to the comparison of improving rate between HA and heparin groups.

* $P < .05$.

Table 2 shows change in frequency, VAS, and functional bladder capacity in 18 patients receiving hydrodistention and intravesical HA. Table 3 shows change in the 3 criteria in 15 patients receiving hydrodistention and intravesical heparin. Table 4 shows change in the 3 criteria in those 11 patients receiving hydrodistention alone. Because most patients in this control group had recurrence or progression of symptoms 6 months after hydrodistention, we stopped observation and transferred to other treatment.

Three months after hydrodistention, mean voids per day, VAS, and bladder capacity did not show improvement in control group and at 6 months, mean voids per day and VAS were even higher than those before hydrodistention. Three and 6 months after hydrodistention, mean voids per day, VAS, and bladder capacity were all significantly improved from baseline in HA and heparin groups. Nine months after hydrodistention, all 3 parameters showed no improvement in the heparin group. But in the HA group, these 3 parameters were still significantly improved from baseline.

COMMENT

Treatment of IC is a relatively tough challenge in urology. Owing to the unknown etiology of the disease pro-

Table 2. Change in voiding frequency, VAS, and bladder capacity after hydrodistention in HA group (mean ± SD)

Time After Hydrodistention	0 (Baseline)	3 m	6 m	9 m
Voids per day				
Change from baseline	19.3 ± 4.7	11.1 ± 2.1 −8.2 ± 3.9*	14.6 ± 3.5 −4.8 ± 2.9*	17.5 ± 4.5 −1.8 ± 2.5**
VAS				
Change from baseline	7.1 ± 1.1	3.4 ± 1.0 −3.7 ± 1.2*	4.9 ± 1.1 −2.2 ± 1.0*	6.1 ± 1.1 −0.9 ± 1.1**
Bladder capacity (mL)				
Change from baseline	115 ± 29	173 ± 28 58 ± 19*	142 ± 27 27 ± 18*	130 ± 28 16 ± 18**

P value was determined using paired *t* test.
P value refers the comparison of voiding frequency, VAS, and bladder capacity between baseline and indicated months after hydrodistention.
* $P < .001$; ** $P < .01$.

Table 3. Change in mean voids per day, VAS, and bladder capacity after hydrodistention in heparin group (mean ± SD)

Time After Hydrodistention	0 (Baseline)	3 m	6 m	9 m
Voids per day				
Change from baseline	19.7 ± 6.0	12.1 ± 2.7 −7.6 ± 3.9*	18.3 ± 6.1 −1.4 ± 1.6**	19.7 ± 6.0 −0.03 ± 1.3***
VAS				
Change from baseline	7.2 ± 0.9	3.9 ± 0.8 −3.3 ± 1.3*	6.5 ± 1.1 −1.0 ± 0.6**	7.1 ± 0.9 −0.3 ± 0.6***
Bladder capacity (mL)				
Change from baseline	107 ± 26	163 ± 31 56 ± 20*	117 ± 28 9.7 ± 10.9**	108 ± 28 1.1 ± 8.2***

P value was determined using paired *t* test.
P value refers the comparison of voiding frequency, VAS, and bladder capacity between baseline and indicated months after hydrodistention.
* $P < .001$; ** $P < .01$; *** $P > .05$.

Table 4. Change in voiding frequency, VAS, and bladder capacity after hydrodistention in control group (mean ± SD)

Time After Hydrodistention	0 (Baseline)	3 m	6 m
Voids per day			
Change from baseline	18.5 ± 3.7	18.4 ± 2.9 −0.1 ± 2.0*	19.7 ± 3.8 1.1 ± 1.1**
VAS			
Change from baseline	7.1 ± 1.0	6.6 ± 0.7 −0.5 ± 1.3*	7.5 ± 1.0 0.4 ± 0.5**
Bladder capacity (mL)			
Change from baseline	109 ± 27	110 ± 23 0.5 ± 11.1*	104 ± 27 −5.0 ± 8.4*

P value was determined using paired *t* test.
P value refers the comparison of voiding frequency, VAS, and bladder capacity between baseline and indicated months after hydrodistention.
* $P > .05$; ** $P < .05$.

cess, several treatments have been proposed. Current treatment choices include oral therapy (eg, Elmiron), intravesical therapy, which may include the use of dimethyl sulfoxide or heparin, and even surgical interventions.[7] Intravesical treatment with HA has been used in patients with IC in previous studies. Morales et al[5] reported that in patients with IC who received intravesical HA treatments for up to 1 year, 71% showed a complete or partial response to therapy after 12 weeks of treatment; however, beyond week 24 there was a moderate decrease in the effectiveness of the medication. Kallestrup et al[8] reported 20 patients suffering from IC/PBS who received weekly bladder instillations of HA for 1 month and monthly instillations for further 2 months. All patients had mean decreases in nocturia and pain of 40% and 30%, respectively, and decrease in analgesic use. Thirteen patients (65%) responded to treatment (responders) and continued therapy, and 4 complete responders (30%) ceased therapy after a strong positive response (36%, 60%, and 81% decreases compared with baseline in daytime voids, night-time voids, and scores, respectively), which was maintained in the absence of continuous therapy, while after 3 years 7 partial responders (35%) were still on therapy. Riedl et al[9] used weekly instillations of 40 mg sodium hyaluronate in the treatment of 126 patients with IC/PBS. The majority (101, 84%) reported

significant improvement in their quality of life. Intravesical therapy had to be initiated again with success in 43 patients (34.5%) as symptoms recurred after discontinuation of treatment, while the rest stayed free of symptoms for up to 5 years. They suggested that timely hyaluronan instillation therapy may lead to complete symptom remission or even cure in part of the patients with IC/PBS, while some responders need continuous intravesical therapy. The evidence provided earlier showed that intravesical HA therapy can provide continuous benefit to patients with IC.

Patients with IC having bladder capacity less than 200 mL are considered severe cases. Treatment for these cases seems to be much more difficult on whatever therapeutic method they received. Hydrodistention of the bladder can show immediate benefit in releasing the pain and frequency of voiding in these patients. But its effect gradually decreases after the therapy. Ahmad et al[10] reported sequential hydrodistention and intravesical instillation of HA treatment may be considered for patients with resistant IC, especially those who cannot tolerate the instillation procedure under local anesthesia. Our study suggested that intravesical HA and heparin might maintain or prolong the effect of hydrodistention in patients with IC whose functional bladder capacity is less than 200 mL. We instilled lidocaine intravesically with heparin and lidocaine may be effective for providing sustained amelioration of symptoms of IC/PBS.[11] The effect in heparin group should be combination of heparin and lidocaine, although it was less significant than HA.

In the present study, the improvement due to hydrodistention disappeared within 3 months. Response of hydrodistention was well with intravesical HA or heparin in the first 6 months. But 6 months after hydrodistention, rate of improvement was significantly higher in HA patients. At 9 months after hydrodistention, the mean voids per day, VAS, and bladder capacity returned to baseline in the heparin group. In the HA group, improvement in all 3 parameters were maintained at 9 months, although the effect had some decrease because few patients continued HA therapy monthly after 3 months mostly due to the cost of medication. There was significant difference in rate of improvement between HA and heparin groups 6 and 9 months after hydrodistention. These findings demonstrated that intravesical HA could prolong the effect of hydrodistention better than heparin, and thus reduce the number of repeated hydrodistention. Continuous HA instillation may maintain the effect even better. The surgical therapy of IC is an option after all trials of conservative treatment have failed. In patients with severe IC having functional bladder capacity less than 200 mL, hydrodistention and intravesical HA treatment may avoid surgical intervention in some patients.

The bladder wall in patients with IC can be very thin, and the possibility of perforation or rupture must always be kept in mind and discussed with the patient.[12] Two patients in our study suffered from bladder rupture and were treated with indwelling of urethral catheterization for 1 week. Both patients had good recovery.

CONCLUSIONS

Intravesical instillation of HA can obviously prolong the effect of bladder hydrodistention in patients with severe IC whose functional bladder capacity is less than 200 mL. Its effect might be better than heparin and lidocaine. Hydrodistention and subsequent intravesical instillation of HA may replace part of surgical intervention in the treatment of patients with severe IC.

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