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Original Article

The effect of intravesical hyaluronic acid therapy on urodynamic and clinical outcomes among women with interstitial cystitis/bladder pain syndrome

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ABSTRACT

Objective: Treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) is often delayed because of a lack of objective data during diagnosis. This study was conducted to determine the clinical validity of using urodynamic studies to investigate the effect of intravesical hyaluronic acid (HA) treatment among women with IC/BPS.**Materials and methods:** Thirty patients with IC/BPS undergoing 6-month intravesical instillation of HA were recruited. Pretreatment evaluation involved a urinalysis and urinary culture, urinary cytology, a 3-day voiding diary, and cystoscopy with hydrodistention of the bladder. Urodynamic study was performed before and after HA treatment. Symptomatic changes were assessed using a questionnaire covering lower urinary tract symptoms, the O'Leary-Sant symptom index and problem indexes (ICSI and ICPI), and the visual analog scale for pain and urgency. Patient demographics, urinary symptoms, ICSI/ICPI scores, pain and urgency scores, and urodynamic results before and after HA treatment were compared.**Results:** Urinary frequency, nocturia, urgency, pelvic pain, bladder capacity, ICSI, and ICPI were significantly improved after HA treatment. Comparing urodynamic parameters, the volumes at first desire to void (FDV) and maximum cystometric capacity were significantly increased after HA treatment. Before HA treatment, a negative correlation existed between the ICSI and ICPI and urodynamic parameters, including maximum flow rate and bladder capacity, but there were no significant correlations after treatment. Before HA treatment, a negative correlation was discovered between nocturia and FDV. However, after HA treatment, there were no significant correlations between urinary symptoms and urodynamic parameters.**Conclusions:** Our results indicate that the improvement of urinary symptoms of IC/BPS after HA treatment is associated with increased FDV and maximum cystometric capacity. The value of FDV and the frequency of nocturia after treatment may become useful objective indicators for prognosis of IC/BPS.© 2020 Taiwan Association of Obstetrics & Gynecology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Interstitial cystitis (IC), or so called bladder pain syndrome (BPS) [1,2], is a multifactorial, chronic bladder disease that negatively affects quality of life [3,4]. The symptoms of IC/BPS are high urinary frequency, urgency, and pelvic pain, pressure, or discomfort upon filling of the bladder in the absence of other pathological findings

[1,2]. The prevalence of IC/BPS ranges from 2% to 17.3% among the general population [5]. The pathogenesis of IC/BPS is not completely clear but may involve a defective glycosaminoglycan layer of the bladder urothelium [6]. Hyaluronic acid (HA) is a large mucopolysaccharide that has the crucial function of reconstructing glycosaminoglycan and protecting the surface of the bladder [7]. Intravesical HA instillation is considered a third-line treatment option for IC/BPS [8]. Several studies have shown that intravesical HA treatment results in a high rate of symptom relief in patients with IC/BPS [4,7,9]. However, IC/BPS is often difficult to diagnose, resulting in delayed treatment, because its clinical symptoms are

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similar to those of various urological and gynecological diseases, such as overactive bladder, endometriosis, vulvar pain, and chronic pelvic pain [10,11]. The role of urodynamic study in the diagnosis of IC/BPS has been controversial, but some studies have demonstrated that urodynamic results are significantly different between IC/BPS and other irritative voiding symptoms [10–12]. Urodynamic study combined with clinical symptoms may provide sufficient information to confirm a diagnosis of IC/BPS [13–17]. To date, only a few studies have evaluated the urodynamic results of women with IC/BPS after treatment [9,18]. Therefore, the purpose of this study was to determine the clinical validity of using urodynamic studies to investigate the effect of intravesical HA treatment among women with IC/BPS.

Materials and methods

This retrospective cohort study was conducted in a tertiary teaching hospital from July 2017 to June 2019. Thirty-three consecutive patients with new diagnosis of IC/BPS were enrolled. The diagnosis of IC/BPS followed the European Society for the Study of Interstitial Cystitis guidelines [2] and was based on the characteristic symptoms of high urinary frequency, nocturia, pelvic pain, and cystoscopic findings of glomerulations. Patients with urinary tract infection, urinary retention, stress urinary incontinence, pelvic organ prolapse, or incomplete HA treatment were excluded. The study protocol was approved by institutional review board of the hospital (No. 20200090B0). An informed consent form was signed by every patient before their intravesical HA treatment.

Before treatment, all patients underwent urinalysis, urinary culture, urinary cytology, cystoscopy with hydrodistention of the bladder, and multichannel urodynamic study. Cystoscopic hydrodistention was routinely performed at an intravesical pressure of 80 cm of water under general anesthesia. Using the grading system of Nording et al. [19], we classified the severity of bladder glomerulation as grade 0 = normal mucosa, grade 1 = petechiae in at least two quadrants, grade 2 = extensive submucosal bleeding (ecchymosis), grade 3 = diffuse global mucosal bleeding, grade 4 = mucosal disruption with or without bleeding or edema. The patients received a complete urodynamic study, with all studies performed by a single investigator. The complete urodynamic testing included uroflometry, provocative sitting water cystometry (at a filling rate of 50 mL/min), urethral profilometry at rest, repeated coughing with the bladder at maximum cystometric capacity (MCC) in the sitting position, and a pressure–flow study.

All patients underwent 6-month intravesical HA instillation treatment. The treatment protocol was weekly instillations of 40 mg/50 mL HA solution (Cystistat, Bioniche Teo., Inverin, Co. Galway, Ireland) for 4 weeks followed by monthly HA instillations for 5 months. Patients were asked to avoid voiding for 60 min after each instillation to ensure they retained the HA solution in the bladder. At 3 months after the completion of intravesical HA treatment, the patients underwent a complete urodynamic study to evaluate the objective treatment outcomes.

The bladder symptoms at baseline and 3 months after the completion of HA treatment were assessed at the outpatient department by using a 3-day voiding diary and questionnaires regarding lower urinary tract symptoms [20], the O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) [21], and the 10-point visual analog scale (VAS) for pain and urgency. The 3-day voiding diary—which assessed urinary frequency, nocturia, urgency, urinary leakage, and bladder capacity—was completed at each time point. The lower urinary tract symptoms questionnaire comprised eight questions describing the symptoms of nocturia, diurnal frequency of micturition, urgency, stress urinary incontinence, urgency urinary incontinence, incomplete

emptying, voiding difficulty, and straining [20]. All questions had dichotomous (yes or no) responses. In addition, the ICSI and ICPI scales included four questions assessing the severity of urgency, frequency of urination, nocturia, and level of pelvic pain in the preceding 4 weeks. Each question was rated on a severity scale of 0–5. The total scores for symptoms and problems were then calculated. All the terminology used in this article conforms to the recommendations of the International Continence Society, unless otherwise stated [1].

Clinical data with continuous variables are presented as the mean \pm standard deviation or percentage for categorical variables. To evaluate the effect of the HA treatment, the two-tailed paired *t*-test was employed for before-and-after assessment with repeated-measure continuous variables. Pearson correlation was implemented to measure the degree of association between two continuous variables. A two-tailed test with *p* value less than 0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

A total of 30 patients who completed the 6-month HA treatment were included in the analysis. The demographics of the patients with IC/BPS are shown in Table 1. The mean age of the patients was 46.9 years, and their average body mass index was 22.5 kg/m². The mean duration of IC/BPS symptoms was 4.4 years. Regarding gynecological characteristics, 36.7% (*n* = 11) of the patients were menopausal, and 50% (*n* = 15) had undergone pelvic surgery. The severity of bladder glomerulation was grade 1 in 40% of patients (*n* = 12), grade 2 in 46.7% (*n* = 14), and grade 3 in 13.3% (*n* = 4). In addition, two patients (6.7%) were discovered to have Hunner's patch during cystoscopy.

The urinary symptoms, VAS pain and urgency scores, and ICSI and ICPI scores were significantly different after HA treatment (all *p* < 0.05; Table 2). High urinary frequency, nocturia, urgency, pelvic pain, and bladder capacity were significantly improved after HA treatment.

The urodynamic parameters before and after HA treatment were compared, and the volumes at first desire to void (FDV) and MCC were significantly higher after HA treatment. The difference in

Table 1
Characteristics of patients.

	Mean \pm SD
Age (y)	46.9 \pm 7.2 (range 32–64)
BH (cm)	158.0 \pm 4.6 (range 149–168)
BW (kg)	56.6 \pm 8.0 (range 46–76)
BMI (kg/m ²)	22.5 \pm 3.2 (range 19.3–32.0)
Parity	1.9 \pm 1.0 (range 0–4)
Menopause	36.7% (<i>n</i> = 11)
Hypertension	10.0% (<i>n</i> = 3)
Diabetes mellitus	3.3% (<i>n</i> = 1)
Previous pelvic surgeries	50.0% (<i>n</i> = 15)
Symptoms duration (y)	4.4 \pm 2.9 (range 1–15)
Severity of bladder glomerulation	
Grade 1	40.0% (<i>n</i> = 12)
Grade 2	46.7% (<i>n</i> = 14)
Grade 3	13.3% (<i>n</i> = 4)
Hunner's ulcer	
Yes	93.3% (<i>n</i> = 28)
No	6.7% (<i>n</i> = 2)

SD = standard deviation; BH = body height; BW = body weight; BMI = body mass index. Previous pelvic surgeries include hysterectomy, laparoscopic myomectomy, laparoscopic oophorectomy, laparoscopic cholecystectomy, cesarean section.

Table 2

Clinical symptoms in women with IC/BPS before and after intravesical HA treatment.

Variable	Before HA treatment (Mean \pm SD)	After HA treatment (Mean \pm SD)	Mean difference (after-before)	t-value ^a	p value
Frequency (times)	14.2 \pm 4.6	9.3 \pm 2.3	−4.93	−5.33	<0.0001
Nocturia (times)	3.5 \pm 1.7	1.5 \pm 0.9	−1.97	−5.56	<0.0001
Urgency (times)	2.2 \pm 2.9	0.9 \pm 1.4	−1.30	−2.64	0.0131
Bladder capacity (mL)	94.7 \pm 36.5	146.9 \pm 44.9	52.20	6.04	<0.0001
VAS Pain score	4.8 \pm 2.7	3.7 \pm 2.5	−1.07	−2.74	0.0104
VAS Urgency score	6.0 \pm 3.0	4.2 \pm 2.5	−1.73	−3.63	0.0011
ICSI	14.2 \pm 3.0	10.2 \pm 4.4	−4.00	−7.05	<0.0001
ICPI	13.6 \pm 1.9	10.2 \pm 3.8	−3.33	−5.28	<0.0001

IC/BPS = interstitial cystitis/bladder pain syndrome; SD = standard deviation; HA = hyaluronic acid; VAS = visual analog scale; ICSI = interstitial cystitis symptom Index; ICPI = interstitial cystitis problem index.

^a Two-tailed paired t-test with degree of freedom = 29.

maximum flow rate (Qmax) had borderline significance ($p = 0.0512$; Table 3).

The coefficients of correlation between urodynamic parameters and ICSI and ICPI scores are listed in Table 4. Before HA treatment, negative correlations existed between the ICSI and urodynamic parameters, including Qmax and voided volume. In addition, negative correlations were discovered between ICPI and Qmax before HA treatment. After HA treatment, however, no correlations were found between urodynamic parameters and the ICSI or ICPI.

Table 5 details the correlations between urodynamic parameters and urinary symptoms in the patients with IC/BPS. A negative correlation was discovered between nocturia and FDV ($p = 0.0042$), whereas a positive correlation was identified between bladder capacity and maximal urethral closure pressure ($p = 0.0027$). No correlations were found between urinary symptoms and urodynamic parameters after HA treatment.

Discussion

IC/BPS may have various negative effects on women's quality of life [3], including bladder [22], psychological [4] and sexual [5,22,23] dysfunctions. Intravesical HA instillation is recommended when conservative treatment and oral medications have not been effective [8]. Our previous study demonstrated that based on a global response assessment [24], 70% of patients with IC/BPS had moderate or marked improvement 3 months after receiving 6 months of intravesical HA instillation [4]. Using therapy similar to our HA treatment plan, another study reported that 69% of 29 patients with IC/BPS had improved response at 6 months after HA treatment [9]. Morales et al. [7] used a different intravesical regimen, once weekly for 4 weeks and then once monthly for 12 months, to treat 25 patients with refractory IC/BPS; the positive response rate at 3 months was 71%, and the effect continued until 5

months. Frequency of micturition, bladder capacity, O'Leary-Sant symptom and problem index, and VAS pain and urgency score are commonly used to evaluate the outcomes of IC/BPS [25]. Two articles of systematic reviews reported improvement in urinary frequency, pain score, bladder volume, and O'Leary-Sant symptom and problem index after HA treatment [25,26]. In the present study, diurnal frequency, nocturia, bladder capacity, VAS pain and urgency scores, ICSI, and ICPI were significantly improved 3 months after receiving intravesical HA instillation.

The mean duration of symptoms was 4.4 years in the present study, consistent with a previous report [22]. The lack of objective data regarding IC/BPS diagnosis often delays this diagnosis. Several investigators have suggested that urodynamic testing should play a central role in distinguishing IC/BPS from overactive bladder syndrome [10,12]. Studies have revealed that cystometric parameters and volumes are reduced in patients with IC/BPS [10,12], but few studies have compared the urodynamic results of IC/BPS before and after HA treatment [9,18]. Lai et al. [9] used a bladder diary and uroflowmetry to evaluate HA treatment outcomes and found that Qmax and bladder capacity had improved significantly after 6 months of intravesical HA instillation. In a retrospective study, Figueiredo et al. [18] compared the outcomes of 18 patients with IC/BPS before and 8 months after receiving an 8-week intravesical HA instillation and discovered significant improvement in urodynamic parameters including volume at FDV, normal desire to void, strong desire to void, and MCC [18]. In our study, the volumes at FDV and MCC were significantly increased after intravesical HA treatment, and Qmax had increased with borderline significance. Because HA significantly suppresses the secretion of proinflammatory cytokines and boosts the secretion of sulfated glycosaminoglycan to protect the surface of bladder [27], it can be reasonably expected that after HA treatment, improvement will be observed subjectively in patients' questionnaire responses and also

Table 3

Urodynamic results in women with IC/BPS before and after intravesical HA treatment.

Variable	Before HA treatment (Mean \pm SD)	After HA treatment (Mean \pm SD)	Mean difference (after-before)	t-value ^a	p value
Qmax (mL/sec)	13.2 \pm 6.2	15.6 \pm 8.5	2.40	2.03	0.0512
VV (mL)	257.1 \pm 136.6	240.6 \pm 120.2	−16.43	−0.60	0.5561
RU (mL)	55.8 \pm 73.0	38.0 \pm 59.1	−17.78	−1.74	0.0926
FDV (mL)	110.3 \pm 56.8	134.1 \pm 44.5	23.80	2.20	0.0359
MCC (mL)	254.7 \pm 71.0	300.4 \pm 84.3	45.73	2.87	0.0076
MUCP (cmH ₂ O)	80.0 \pm 25.6	76.3 \pm 22.0	−3.70	−1.29	0.2082
FL (mm)	29.5 \pm 4.8	28.5 \pm 4.7	−0.97	−1.01	0.3197
Pdet Qmax (cmH ₂ O)	38.0 \pm 38.4	34.0 \pm 28.2	−3.97	−0.7	0.4923

IC/BPS = interstitial cystitis/bladder pain syndrome; SD = standard deviation; HA = hyaluronic acid; Qmax = maximum flow rate; VV = voided volume; RU = residual urine volume; FDV = first desire to void; MCC = maximum cystometric capacity; MUCP = maximal urethral closure pressure; FL = functional urethral length; Pdet Qmax = detrusor pressure at maximum flow.

^a Two-tailed paired t-test with degree of freedom = 29.

Table 4

Correlation between ICSI/ICPI score and urodynamic parameters in women with IC/BPS before HA treatment.

Variable	Before HA treatment				After HA treatment			
	ICSI		ICPI		ICSI		ICPI	
	r	p value	r	p value	r	p value	r	p value
Qmax (mL/sec)	−0.4601	0.0105	−0.4528	0.0120	0.0714	0.7076	0.0003	0.9987
VV (mL)	−0.4148	0.0227	−0.0415	0.8278	−0.1046	0.5823	−0.1848	0.3282
RU (mL)	−0.1573	0.4064	0.1134	0.5506	−0.2473	0.1876	−0.2038	0.2801
FDV (mL)	−0.2692	0.1503	0.1279	0.5005	−0.0302	0.8740	−0.0864	0.6498
MCC (mL)	−0.2229	0.2363	0.1294	0.4954	−0.1466	0.4396	−0.1238	0.5144
MUCP (cmH ₂ O)	−0.0161	0.9329	0.1359	0.4741	−0.0696	0.7148	−0.0535	0.7789
FL (mm)	−0.1756	0.3534	−0.1113	0.5581	−0.2218	0.2387	−0.0591	0.7565
Pdet Qmax (cmH ₂ O)	−0.1987	0.2926	−0.3383	0.0675	−0.0126	0.9475	0.0138	0.9424

ICSI = interstitial cystitis symptom Index; ICPI = interstitial cystitis problem index; IC/BPS = interstitial cystitis/bladder pain syndrome; Qmax = maximum flow rate; VV = voided volume, RU = residual urine volume; FDV = first desire to void; MCC = maximum cystometric capacity; MUCP = maximal urethral closure pressure; FL = functional urethral length; Pdet Qmax = detrusor pressure at maximum flow.

Table 5

Correlation between symptoms and urodynamic parameters in women with IC/BPS.

Treatment	Frequency		Urgency		Nocturia		Urgency score		Pain score		Bladder capacity	
	r	p	r	p	r	p	r	p	r	p	r	p
Before treatment												
Qmax (mL/sec)	0.0878	0.6444	−0.0918	0.6294	−0.1109	0.5597	0.0564	0.7673	0.0818	0.6675	−0.1336	0.4814
VV (mL)	0.0385	0.8401	−0.0200	0.9164	0.1234	0.5161	0.2209	0.2409	0.2481	0.1861	−0.0088	0.9634
RU (mL)	0.0435	0.8192	−0.0851	0.6546	−0.0872	0.6468	−0.0348	0.8552	−0.2442	0.1935	−0.0548	0.7736
FDV (mL)	0.3355	0.0700	−0.0103	0.9570	−0.5071	0.0042	0.2652	0.1567	−0.0387	0.8389	−0.1662	0.3800
MCC (mL)	0.1979	0.2945	0.2153	0.2532	0.2140	0.2563	0.1936	0.3053	0.1093	0.5652	0.0606	0.7504
MUCP (cmH ₂ O)	0.0037	0.9844	−0.0807	0.6718	−0.0879	0.6443	−0.0955	0.6158	−0.1112	0.5586	0.5281	0.0027
FL (mm)	0.0183	0.9236	0.0117	0.9511	−0.0865	0.6494	0.1657	0.3815	0.0450	0.8133	0.2236	0.2350
Pdet Qmax (cmH ₂ O)	0.2842	0.1280	−0.2852	0.1266	0.0748	0.6947	0.0270	0.8876	0.0854	0.6537	−0.1980	0.2942
After treatment												
Qmax (mL/sec)	0.0609	0.7493	−0.1893	0.3165	0.1093	0.5645	0.0094	0.9608	−0.1247	0.5114	−0.2870	0.1241
VV (mL)	−0.0579	0.7612	0.1245	0.5121	−0.0925	0.6270	0.2564	0.1714	0.0813	0.6693	−0.0408	0.8307
RU (mL)	0.0382	0.8411	0.2912	0.1185	0.0554	0.7711	−0.0225	0.9060	−0.1539	0.4168	0.0239	0.9001
FDV (mL)	−0.1043	0.5835	0.1681	0.3746	−0.1893	0.3165	0.1794	0.3430	−0.0855	0.6533	−0.2161	0.2514
MCC (mL)	0.1498	0.4296	0.2992	0.1083	0.1046	0.5823	0.1570	0.4074	−0.0938	0.6221	−0.2101	0.2652
MUCP (cmH ₂ O)	0.1678	0.3753	0.2669	0.1539	0.0246	0.8975	−0.3021	0.1047	−0.2288	0.2238	0.2920	0.1174
FL (mm)	−0.0681	0.7206	−0.0161	0.9329	0.0948	0.6184	−0.1339	0.4805	−0.0149	0.9375	0.1275	0.5018
Pdet Qmax (cmH ₂ O)	0.0204	0.9147	−0.1522	0.4222	0.1423	0.4532	0.1873	0.3216	0.2599	0.1655	0.1779	0.3469

IC/BPS = interstitial cystitis/bladder pain syndrome; Qmax = maximum flow rate; VV = voided volume, RU = residual urine volume; FDV = first desire to void; MCC = maximum cystometric capacity; MUCP = maximal urethral closure pressure; FL = functional urethral length; Pdet Qmax = detrusor pressure at maximum flow.

objectively in urodynamic parameters related to the storage symptoms associated with IC/BPS such as FDV and MCC. In addition, patients with IC/BPS are highly likely to have hypertonic pelvic floor dysfunction with levator muscle pain and bladder outlet obstruction [28,29]. Painful voiding often worsens bladder outlet obstruction and causes a decrease in Qmax. Therefore, after HA treatment, Qmax may be higher due to alleviation of bladder pain.

Our results indicated a negative correlation between nocturia and FDV. In addition, a positive correlation was discovered between maximal urethral closure pressure and bladder capacity. Studies have confirmed that IC/BPS symptoms can be objectively measured through urodynamic testing [13,15,16]. Kirkemo et al. [13] found a correlation between diurnal and nocturnal frequency and both FDV and MCC. Sastry et al. [15] reported significantly lower median volume at FDV, strong desire to void, and at MCC in patients with IC/BPS and high pain, ICSI, and ICPI scores. Kuo et al. [16] demonstrated that the mean volume at FDV, strong desire to void, MCC, and voided volume were inversely correlated with ICSI and ICPI scores. In our series, changes in urodynamic parameters including Qmax and volumes at FDV and MCC have indicated that intravesical instillation of HA has a therapeutic effect on the urinary symptoms of patients with IC/BPS. We also observed negative correlations of the O'Leary-Sant index with Qmax and voided volume before HA treatment. After HA treatment, however, no significant correlations

were found between urodynamic parameters and the O'Leary-Sant index or urinary symptoms of IC/BPS. The correlation between FDV and nocturia before HA treatment became insignificant may be due to the increase in FDV value and improvement in nocturia after treatment.

The limitations of this study include its small sample, retrospective study design, and relatively short follow-up. In addition, a single dosage of HA was used; higher dosage and more instances of HA intravesical instillation may have had superior effects in the IC/BPS treatment. Furthermore, this study did not compare the urodynamic parameters of Hunner lesion and non-Hunner lesion groups, because only two of our patients had Hunner IC/BPS. One study demonstrated that the mean volume at FDV, strong desire to void, and MCC in the Hunner IC/BPS group was significantly lower than those in the non-Hunner IC/BPS group [17]. In the future, more patients will be recruited for further investigation of Hunner IC/BPS. Despite these weaknesses, our data reflect the associations between urodynamic parameters and the clinical symptoms of IC/BPS. In addition, we compared the urodynamic results before and after treatment, which have rarely been reported.

In conclusion, although not all the storage urodynamic parameters had significantly changed after treatment, urodynamic study may nonetheless play a role in evaluating the effect of HA treatment. Our results indicate that the improvement of clinical

symptoms of IC/BPS after 6-month intravesical HA instillation is associated with the increase of FDV and maximum cystometric capacity. The value of FDV and the frequency of nocturia after treatment may become useful objective indicators for prognosis of IC/BPS. Future prospective investigations are warranted.

Declaration of Competing Interest

None.

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