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Original Article

Hyaluronic acid improves pain symptoms more than bladder storage symptoms in women with interstitial cystitis

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ABSTRACT

Objective: Intravesical hyaluronic acid (HA) therapy is one of acceptable methods to treat bladder pain and storage symptoms (i.e., urgency, frequency and nocturia) of interstitial cystitis/bladder pain syndrome (IC/BPS). We aim to assess the impacts of intravesical HA on bladder pain and storage symptoms, respectively, and to investigate their associated factors in patients with IC/BPS.**Materials and methods:** In this prospective, multicenter study, 103 women with refractory IC/BPS undergoing a standard protocol of intravesical HA therapy were enrolled. A pain Visual Analog Scale (VAS) and the Interstitial Cystitis Symptom and Problem Index (ICSI & ICPI) were used to assess symptoms and bother associated with IC/BPS. The Scaled Global Response Assessment (GRA) was used to evaluate patients' perception of overall changes in bladder pain and storage symptoms, respectively, after treatment.**Results:** Mean age of participants was 43.6 ± 11.8 years. The average duration of symptoms was 5.1 ± 5.0 years. Significant improvements in pain VAS, ICSI and ICPI scores were observed after treatment. However, patients reported significantly different rates of moderate/marked improvement in bladder pain and storage symptoms (73.8% vs. 47.6%; $P < 0.001$) on the GRA, respectively. "Lower pain VAS score" and "reduced functional bladder capacity" were found to be the factors that adversely affected the treatment responses of bladder pain and storage symptoms, respectively, after repeated statistical analyses.**Conclusion:** Bladder instillation of HA seemed more efficient in improving bladder pain than storage symptoms associated with IC/BPS. The persistence of bladder storage symptoms after treatment might result from a reduced functional bladder capacity.© 2019 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

Bladder-related painful sensation accompanied by urinary storage symptoms (i.e., urgency, frequency and nocturia) are the

main complaints of patients with interstitial cystitis/bladder pain syndrome (IC/BPS). Further typical cystoscopic and histological features are needed to confirm the diagnosis of IC [1]. The etiology and pathogenesis of IC/BPS remains obscure [2]. Injury or dysfunction of the glycosaminoglycan (GAG) layer on the urothelium and diffusion of urine toxins leading to sensory nerve activation, bladder inflammation and detrusor fibrosis are the potential mechanisms that result in painful sensation and urinary storage symptoms in women with IC/BPS [3].

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Bladder instillation of hyaluronic acid (HA) is part of GAG replacement therapy and has become an acceptable treatment for IC/BPS. Although invasive, the treatment has been used as a first-as well as a second-line therapy because of a very good safety profile [2,4–11]. However, varying degrees of success in treatment outcomes have been reported in the literature, which may result from variations in disease severity, protocol of instillation, or methods of outcome measure, etc. [2,4–11]. Notably, studies conducted by Riedel et al. that used pain outcome as single measurement had the highest response rates of 85–86% [2,4–6]. When using IC symptoms and bother scores, such as the Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI), lower response rates of 30–78% were noted [2,7–11]. Based on these results and our clinical observation, we postulate that intravesical HA therapy for treating women with IC/BPS might have better effects in improving bladder pain than storage symptoms. Unfortunately, no comparison has been made in the same cohort to evaluate responses of bladder pain and storage symptoms, respectively, to the treatment with the exception of a study conducted by Kallestrup et al. [10]. Kallestrup et al. reported that bladder instillation of HA was more effective for reduction of bladder pain than urinary frequency, however, the measurement was not specified.

In this study, a homogeneous patient group with cystoscopically diagnosed IC/BPS was enrolled and treated with a standard protocol of intravesical HA therapy to evaluate the responses of bladder pain and storage symptoms to the treatment, respectively. Further, we assessed predisposing factors that may affect treatment outcomes.

Materials and methods

Study design

This was the secondary analysis of results obtained from a prospective, multicenter study conducted at six tertiary referral hospitals in our country [12]. Approval for this clinical trial was obtained from an Institutional Review Board and Ethics Committee (10MMHIS183). The inclusion and exclusion criteria were detailed in our previous report [12]. In brief, the diagnosis of IC/BPS was based on symptoms, cystoscopic findings, and the exclusion of other diseases according to European Society for the Study of Interstitial Cystitis (ESSIC) criteria [1]. Bladder biopsy was not routinely performed but was done for ruling out suspicious bladder pathology. All patients included were previously treated with oral medications, with or without bladder hydrodistention, and were refractory to treatment that necessitated referral. These oral medications included pentosan polysulfate, non-steroid anti-inflammatory drugs, tri-cyclic antidepressants and anti-cholinergics, etc.

Clinical assessment

All patients underwent a cystoscopy with hydrodistention of the bladder under anesthesia. Urodynamic study was optionally performed according to the methods, definitions and units described in official guidelines [13]. The standardized composite questionnaire that contains a 10-point pain visual analog scale (VAS), the Interstitial Cystitis Symptom Index (ICSI) and the Interstitial Cystitis Problem Index (ICPI) [14] was used for pretreatment evaluation and outcomes measures. All participants were interviewed by trained research assistants.

Intravesical HA therapy and outcome measures

The treatment protocol and methods used to determine treatment results are detailed in our previous report [12]. In brief, All

patients gave informed consent for and underwent a standard, 6-month bladder instillation of HA therapy. Treatment started at four weeks after the cystoscopic diagnosis. The treatment was performed with four weekly bladder instillations of 40 mg/50 ml of a commercial HA solution (Cystistat®, Mylan Institutional, Galway, Ireland) followed by five monthly instillations. Any oral medication that may have therapeutic effects on IC/BPS was limited during the study period to prevent bias.

Treatment results were obtained by comparing various clinical parameters (pain VAS, ICSI and ICPI) at baseline, and at 4 weeks after the fourth (one-month) and the ninth (6-month) instillation, respectively. In addition, a 7-point scaled Global Response Assessments (GRA) [15] was used to assess patients' perception of overall changes in bladder pain and storage symptoms, respectively, 4 weeks after the 6-month intravesical HA therapy. The patient-reported GRA indicated changes of symptoms such as "markedly worse, moderately worse, mildly worse, same, slightly improved, moderately improved, or markedly improved" after intravesical HA therapy. Patients who reported moderate/marked improvement on the GRA were generally considered as treatment responders.

Statistical analysis

Changes in the pain VAS, ICSI, and ICPI scores before and after treatment were analyzed by univariate analysis. Important clinical variables were also compared between response and non-response groups by univariate analysis. Additional multivariate logistic regression analysis and a group discriminate analysis were conducted to evaluate the association of important clinical variables with treatment outcomes. $P < 0.05$ was considered as a significantly statistical difference. The SAS 9.2 statistical software (SAS, Cary, NC, USA) was used for statistical analyses.

Results

Patient characteristics

In total, 110 patients with refractory IC/BPS were recruited into this study. Seven (6.4%) patients could not finish the 6-month treatment plan due to personal reasons and were thus excluded from analysis. Patient characteristics are presented in Table 1. These patients were characterized by having advanced stages of IC/BPS combined with functional bladder impairment.

Therapeutic results

There were no severe adverse events related to the treatment in these 103 (93.6%) patients who completed the 6-month treatment course. Significant improvement in scores for bladder pain, urinary symptoms and bother were noted after one month and six months (Table 2). After the 6-month treatment, the majority of patients reported some degree of improvement in bladder pain and storage symptoms (Fig. 1). A successful treatment outcome for bladder pain and storage symptoms on the GRA was noted in 73.3% (76/103) and 47.2% (49/103) of patients, respectively, and the rates were significantly different ($P < 0.001$). The correlation coefficient was ≥ 0.6 (good) with related changes in pain VAS, ICSI and ICPI scores.

We found that intravesical HA therapy is a safe and effective treatment for IC/BPS but was more efficient in improving bladder pain than storage symptoms. Although the average pain VAS score improved from 6.3 to 3.3 after the 6-month treatment plan, there were still a high percentage (59.2%; 61/103) of patients reporting more than mild pain (pain VAS score > 2).

Table 1
Patient characteristics (N = 103).

Patient characteristics	Value	Range
General data		
Mean age (years)	44.3 ± 11.5	(22–69)
% with menopause	32.0	(33/103)
Mean symptomatic years	5.1 ± 5.0	(0.5–30)
Mean functional bladder capacity (ml)	228.6 ± 70.8	(80–400)
^aUrodynamic (filling & voiding cystometry) results		
Mean volume at first sensation to void (ml)	134.7 ± 53.0	(53–296)
Mean maximum cystometric capacity (ml)	258.6 ± 93.0	(87–615)
Mean bladder compliance at urgency (ml/cmH ₂ O)	89.2 ± 107.7	(1–464)
Mean voided volume (ml)	259.2 ± 116.0	(73–663)
Mean maximum flow rate (ml/sec)	15.3 ± 6.2	(5–30)
Mean average flow rate (ml/sec)	6.6 ± 3.5	(2–19)
Mean voiding pressure (cmH ₂ O)	30.2 ± 19.3	(2–108)
Mean residual urine amount (ml)	24.6 ± 26.6	(0–148)
% with bladder oversensitivity	49.4	(38/77)
% with detrusor overactivity	11.7	(9/77)
% with dysfunctional voiding	32.5	(25/77)
Cystoscopic findings with hydrodistention		
Mean anesthetic bladder capacity (ml)	506.3 ± 198.2	(200–1000)
% with advanced (grade II & III) glomerulations	93.2	(96/103)
% with Hunner's ulcers	13.6	(14/103)

^a Urodynamic study was performed in 77 (74.8%) of the 103 patients.

Outcome associations

A comparison of clinical data of treatment responders and non-responders of bladder pain and storage symptoms on the GRA are presented in Tables 3 and 4, respectively. Bladder pain responders appeared to report a significantly higher pain score at baseline compared to non-responders (7.0 vs. 5.0; $P < 0.05$) (Table 3). Conversely, bladder storage symptom responders reported a significantly higher functional bladder capacity (the maximum voiding volume on a 3-day voiding diary; 255.6 vs. 212 ml; $P < 0.05$) before treatment (Table 4). Although anesthetic bladder capacity (547.2 vs. 484.9 ml) also seemed different between groups, there was no statistical significance ($P = 0.210$).

Multivariate analysis revealed that baseline “pain VAS score” ($P = 0.026$) and “functional bladder capacity” ($P = 0.003$) were significantly and positively correlated with improvement of bladder pain and storage symptoms according to the GRA, respectively. These results were supported by a group discriminate analysis, which disclosed baseline “pain VAS score” and “functional bladder capacity” were the most relevant variables to treatment responses categorized on the GRA. Our findings suggested that patients who had a higher pain VAS score and larger functional bladder capacity before treatment might be more likely to benefit from the therapy and vice versa.

Table 2
Changes in assessment scores after intravesical HA therapy (N = 103).

	Baseline	1 month	6 months	P-value
Pain VAS	6.3 ± 2.7	4.3 ± 2.5	3.3 ± 2.2	<0.001
ICSI	14.2 ± 3.8	10.3 ± 3.9	7.8 ± 4.0	<0.001
Urgency	3.5 ± 1.4	2.6 ± 1.3	1.9 ± 1.3	<0.001
Frequency	4.3 ± 1.1	3.1 ± 1.2	2.3 ± 1.3	<0.001
Nocturia	3.5 ± 1.3	2.7 ± 1.2	2.2 ± 1.3	<0.001
Bladder Pain	2.9 ± 1.7	1.9 ± 1.4	1.3 ± 1.2	<0.001
ICPI	13.0 ± 3.3	9.9 ± 3.3	8.4 ± 4.3	<0.001
Frequency	3.2 ± 0.9	2.7 ± 1.0	2.2 ± 1.2	<0.001
Nocturia	3.4 ± 0.9	2.7 ± 1.0	2.3 ± 1.4	<0.001
Urgency	3.1 ± 1.0	2.4 ± 1.1	2.0 ± 1.3	<0.001
Bladder pain	3.1 ± 1.2	2.3 ± 1.2	1.6 ± 1.2	<0.001

VAS: visual analog score (range 0–10); ICSI: interstitial cystitis symptom index (range 0–20); ICPI: interstitial cystitis problem index (range 0–16).

Discussion

The impacts of intravesical HA on bladder pain and storage symptoms in patients with refractory IC/BPS were evaluated, respectively, in this study. Our results suggested the treatment is more efficient in improving bladder pain than storage symptoms associated with IC/BPS. Meanwhile, two statistically significant factors, i.e., “lower pain VAS score” and “reduced functional bladder capacity”, were found to adversely affect the treatment effectiveness of intravesical HA therapy.

In this study, intravesical HA therapy was well tolerated by all patients and was noted to improve symptoms and bother significantly as early as one month and six months after treatment. Bladder instillation of HA is thought to provide a direct protection on damaged urothelium and, therefore, relieve bladder symptoms efficiently [2]. However, there was a discrepancy between treatment effectiveness of intravesical HA therapy on bladder pain and storage symptoms in this study. A significant improvement of bladder pain was noted in 73.3% of patients by the GRA, while less than half (47.2%) were satisfied with the treatment effects on bladder storage symptoms. Specifically, bladder instillation of HA seemed more efficient in improving bladder pain than storage symptoms in patients with refractory IC/BPS. Other investigators

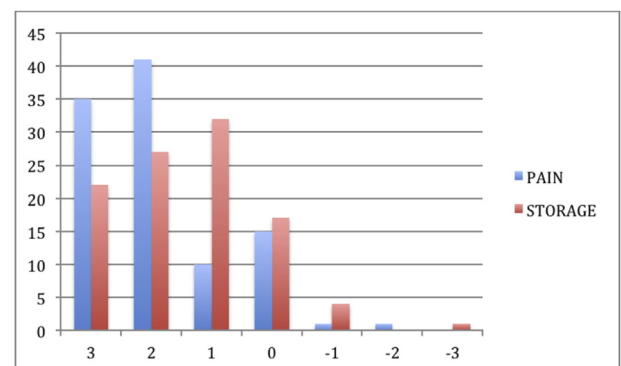


Fig. 1. Distribution of responses of bladder pain and storage symptoms to intravesical HA therapy on the GRA.

Table 3

Comparison of patient characteristics between responders and non-responders of “bladder pain” symptoms to intravesical HA therapy.

Parameters	Responders (n = 76)		Non-responders (n = 27)		P-value
	Value	Range	Value	Range	
General data					
Mean age (years)	45.0 ± 11.5	(25–68)	41.7 ± 12.5	(22–60))	0.307
Mean symptomatic years	5.4 ± 5.8	(0.5–30)	4.0 ± 2.5	(1–9)	0.760
Mean functional bladder capacity	230 ± 65	(90–350)	237.2 ± 83.4	(80–350)	0.617
Mean Pain VAS scores	7.0 ± 2.5	(1–10)	5.0 ± 2.8	(0–10)	0.005
Mean ICSI scores	14.3 ± 4.0	(1–20)	13.4 ± 3.9	(1–18)	0.298
Mean ICPI scores	12.9 ± 2.9	(4–17)	11.9 ± 3.3	(2–16)	0.274
^a Urodynamic results					
First desire to void	137.0 ± 55.9	(53–296)	137.9 ± 58.7	(58–257)	0.977
Mean cystometric capacity (ml)	255.9 ± 96.8	(106–615)	275.5 ± 102.8	(87–522)	0.357
Mean bladder compliance	84.5 ± 106.2	(1–464)	123.7 ± 131.0	(6–380)	0.204
Mean voided volume	253.3 ± 120.8	(88–663)	300.1 ± 118.8	(120–493)	0.076
Mean maximum flow rate	15.6 ± 7.1	(5–30)	15.2 ± 5.0	(7.5–27.5)	0.951
Mean average flow rate	6.1 ± 2.8	(2–12)	7.5 ± 4.7	(2–19)	0.503
Mean voiding pressure (cmH2O)	30.9 ± 20.7	(2–108)	28.5 ± 17.2	(2–76)	0.880
Mean residual urine	25.8 ± 29.2	(0–148)	13.7 ± 17.3	(0–50)	0.137
% with bladder oversensitivity	53.8	28/52	40.0	10/25	0.176
% with detrusor overactivity	11.5	6/52	12.0	3/25	0.585
% with dysfunctional voiding	32.7	17/52	32.0	8/25	0.566
Cystoscopic findings					
Mean anesthetic bladder capacity	528.2 ± 199	(250–1000)	485.5 ± 201.3	(200–900)	0.422
Mean Grade of glomerulation	2.7 ± 0.5	(2–3)	2.4 ± 0.8	(2–3)	0.261
% with Hunner's ulcers	14.5	(11/76)	11.1	(3/27)	0.615

^a Urodynamic study was performed in 77 (74.8%) of the 103 patients.

also had similar findings [10,16]. Kallestrup et al. found bladder instillation of HA reduced bladder pain to a higher degree than urinary frequency symptoms of IC/BPS [10]. Kim et al. found that most (77.2%) patients with IC/BPS had bladder pain improvement after three months of conventional treatment (including bladder instillation of HA), but about half of these patients showed persistent urinary frequency. They also found “marked urinary frequency”, “low voiding volume and flow rates on uroflowmetry”, and “small functional bladder capacity” may contribute to the persistence of urinary frequency after treatment. Besides, this condition was not effectively treated with anti-muscarinics [16].

Anti-muscarinic agents are widely used for controlling storage symptoms associated with an overactive bladder; however, these medications are not efficacious for treating similar symptoms in IC/BPS patients [17,18]. The qualitative difference in storage symptoms experienced by IC/BPS patients and those with an overactive bladder may indicate a different pathogenesis of these two conditions [18,19]. In this study, after repeated statistical analyses, we found “reduced functional bladder capacity” was the only statistically significant predisposing factor for an unsatisfactory treatment for bladder storage symptoms by intravesical HA therapy. This finding is consistent with the results reported by Lim et al. They found that patients with characteristics suggesting a reduced

Table 4

Comparison of patient characteristics between responders and non-responders of bladder storage symptoms to intravesical HA therapy.

Parameters	Responders (n = 49)		Non-responders (n = 54)		P-value
	Value	Range	Value	Range	
General data					
Mean age (years)	45.4 ± 10.9	(26–67)	43.1 ± 13.6	(22–68))	0.387
Mean symptomatic years	5.2 ± 6.7	(0.5–30)	5.0 ± 2.9	(1–15)	0.090
Mean functional bladder capacity	255.6 ± 70.8	(138–400)	212 ± 56.8	(80–340)	0.038
Mean Pain VAS scores	6.7 ± 2.8	(1–10)	6.3 ± 3.0	(1–10)	0.505
Mean ICSI scores	14.4 ± 4.3	(1–20)	13.9 ± 3.2	(1–20)	0.485
Mean ICPI scores	12.8 ± 3.2	(2–16)	12.6 ± 2.3	(4–17)	0.672
^a Urodynamic results					
Mean First desire to void	145.3 ± 56.5	(76–296)	133.5 ± 50	(53–288)	0.415
Mean Cystometric capacity (ml)	263.2 ± 90.6	(138–615)	264.3 ± 102.2	(87–526)	0.995
Mean bladder compliance	96.7 ± 96.8	(1–265)	98.0 ± 128.1	(6–464)	0.865
Mean Voiding volume	262.9 ± 127.4	(91–663)	277.3 ± 100	(88–638)	0.444
Mean maximum flow rate	16.3 ± 7.4	(5–30)	15.2 ± 5.0	(7–29)	0.522
Mean average flow rate	7.5 ± 2.8	(3–12)	6.5 ± 2.1	(2–19)	0.144
Mean Voiding pressure (cmH2O)	30.8 ± 21.8	(2–108)	26.6 ± 13.1	(2–59)	0.637
Mean residual urine	29 ± 32.6	(0–148)	17.6 ± 16.6	(0–60)	0.084
% with bladder oversensitivity	51.5	17/33	47.7	21/44	0.568
% with detrusor overactivity	9.1	3/33	13.6	6/44	0.157
% with dysfunctional voiding	39.4	13/33	27.3	12/44	0.393
Cystoscopic findings					
Mean anesthetic bladder capacity	547.2 ± 207.8	(250–1000)	484.9 ± 181.2	(200–900)	0.210
Mean grade of glomerulations	2.6 ± 0.6	(1–3)	2.6 ± 0.6	(2–3)	0.906
% with Hunner's ulcers	13.0	(6/46)	14.0	(8/57)	0.385

^a Urodynamic study was performed in 77 (74.8%) of the 103 patients.

bladder capacity are more likely to have treatment failure by bladder instillation of a DMSO cocktail [20]. These features included marked daytime frequency, nocturia, and small functional and anesthetic bladder capacity. One possible explanation for the above findings is that when detrusor fibrosis and bladder shrinkage have occurred as a result of the progressive inflammation process of IC/BPS then, intravesical therapy may be less helpful.

Bladder (detrusor) fibrosis is a special histological finding of IC/BPS, but not of an overactive bladder, and has been included in the histological diagnosis criteria suggested by the ESSIC [1]. A recent study conducted by Kim et al. disclosed the severity of fibrosis in the bladder wall of patients with IC/BPS had close correlations with increased frequency and decreased volume recorded on a voiding diary [21]. Conversely, basic research conducted by Richter et al. has shown that the cellularity of inflammatory cells (i.e., YKL-40 and mast cells) at bladder biopsies was negatively correlated with bladder volume of IC/BPS patients. These findings suggest an ongoing inflammation in the bladder of IC/BPS patients and that may result in a fibrotic bladder and shrinkage [22]. Besides, in one of our previous studies, “detrusor underactivity”, which might be the functional presentation of bladder (detrusor) fibrosis, was identified as a risk factor for an unsatisfactory treatment of IC/BPS by bladder instillation of DMSO cocktail [23]. Unfortunately, routine bladder biopsy was not performed in this study; therefore, no further conclusion could be drawn if a “reduced functional bladder capacity”, which was shown to adversely affect the treatment of bladder storage symptoms by bladder instillation of HA, had associations with any bladder histopathology.

Intravesical HA therapy, either used as a first- or second-line treatment, was noted to be efficacious in improving bladder-related pain in patients with IC/BPS [2,4–11]. Data summarized in a systematic review revealed the average pain scores after bladder instillation of HA was stably around 2.0–3.5 despite the initial scores whether high or low (around 3.28–8.5) [2]. The data was helpful for interpretation of our findings that patients who had a higher pain VAS score before treatment are more likely to appreciate the pain reduction from intravesical HA therapy. On the contrary, patients who reported a vague painful sensation before treatment were less likely to sense the difference. Although bladder pain was effectively treated by intravesical HA therapy, a high percentage (59.2%) of our patients still reported more than mild pain (pain VAS score > 2) after six months of treatment. We do not know whether a longer-term instillation could have further improved symptoms because of a lack of follow-up. However, a long-term follow-up study, which was conducted by Engelhardt et al., showed a marked reduction in pain scores from an average of 8.15 to 2.14 at five year after intravesical HA therapy. While 50% of their patients had complete symptom remission, 41.7% of the patients went on continued instillation to control symptoms [6]. These results suggest bladder pain in a considerable number of IC/BPS patients was improved but not cured by intravesical HA therapy and, therefore, should be treated as a chronic disease [24].

The current study had limitations. One limitation was that we did not have a placebo arm, and the relatively short-term (six months) treatment results may not be generalized to a longer-term treatment outcome. Another limitation was the results of intravesical HA therapy may be confounded by the cystoscopy with bladder hydrodistention under anesthesia. However, we believe the confounding effect is minimal, if any, because a diagnostic (short) rather than therapeutic (prolonged) hydrodistention [25] with an interval of at least four weeks to subsequent therapy was adopted in this study. On the other hand, we did not perform bladder biopsies as a routine procedure, therefore, no further information could be drawn on the potential correlations of bladder histology with treatment outcomes and other clinical parameters.

In conclusion, our results suggested intravesical HA therapy is a safe and effective treatment for patients with refractory IC/BPS combined with advanced stages of diseases. However, it seemed more efficient in improving bladder pain than storage symptoms of IC/BPS after a relatively short-term (six months) treatment. The discrepancy between the impacts of intravesical HA on bladder pain and storage symptoms of IC/BPS might contribute to the variation in success rates reported in the literature because of methods of outcome measure. Meanwhile, our study as well as others that revealed a “reduced (functional) bladder capacity” might affect the treatment efficacy of bladder storage symptoms by intravesical HA therapy is a stimulating finding. Since there is a lack of effective treatment for the annoying persistent storage symptoms of IC/BPS, more basic and clinical research is required.

Conflicts of interest

None.

Acknowledgements

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