CEOG Clinical and Experimental Obstetrics & Gynecology

The efficacy of intravesical hyaluronic acid instillation in resistant bladder pain syndrome

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Summary

Purpose: In this study the authors aimed to assess the efficacy of intravesical hyaluronic acid (HA) instillation in patients with resistant painful bladder syndrome (PBS). *Materials and Methods*: A series of 32 women with PBS received intravescical instillation of HA once-a-week for eight weeks and then once monthly for four months for a total of 12 doses. The authors considered scale (VAS) pain scores ≥ 4 and total scores (symptom and bother scores) ≥ 13 on the pelvic pain and urgency/frequency (PUF) questionnaire. An efficacy of the HA instillation was evaluated by comparing the mean changes in the scores of the VAS and questionnaires from baseline to eight weeks of treatment. Improvement was defined as a ≥ 2 decrease in the VAS. *Results*: The authors compared the responses at baseline and after treatment: there were 22 patients (63.0%) with positive response rate at week 8, which was maintained until 12 months. Specifically, both VAS and PUF score decreased significantly after treatment. *Conclusion:* The present results showed that intravesical HA therapy is an effective treatment for patients with PBS who had inadequate response to conservative treatment.

Key words: Painful bladder syndrome (PBS); Hyaluronic acid (HA).

Introduction

Painful bladder syndrome (PBS) is a chronic inflammatory condition of the bladder wall characterized by bladder and pelvic pain, urinary urgency, frequency, and nocturia in the absence of other identified causes for the symptoms and has a negative impact on quality of life [1]

The etiology of PBS is still not well understood and different hypotheses have been suggested, including infection, dysfunctional urothelium, mast cell activation, neuronal inflammation, autoimmune processes, exposure to toxins or dietary elements, and psychosomatic factors [2, 3].

While there is no general agreement on the precise pathophysiology of this disease, a disorder at the level of the urine–tissue barrier of the bladder seems to be the underlying mechanism behind the functional, anatomical, and symptomatic manifestations in a considerable number of cases [4]. In fact, it has been hypothesized that PBS could be pathophysiologically related to a defect of the glycosaminoglycan (GAG) layer of the bladder mucosa [5].

The glycosaminoglycan layer is secreted by the transitional epithelium and is also bound to its surface, consists of long, linear, and highly negatively charged polysaccharides composed of a variable number of repeating disaccharide units. The layer can protect the bladder wall from injury, toxins, and microorganisms.

GAGs are classified in four structural families [6]: heparin and heparan sulfates, chondroitin and dermatan sulfates, hyaluronan, and keratan sulfate.

Some drugs that aim at improving the integrity of the GAG layer and functioning of the urothelial barrier have [7] been evaluated for PBS, such as pentosan polysulfate, heparin sulfate, HA, chondroitin sulfate (CS), or a combinations of these drugs [8], and have been used during the last few decades as intravesical instillations for GAG substitution therapy, with the benefit of delivering high concentrations of the therapeutic agent at the target tissue with a low risk of systemic side effects [9]. In particular, an important part of the GAG layer is composed by HA and instillation provided positive effects for patients with PBS according to the physiological function; early repair of the glycosaminoglycan layer may help avoid subsequent chronic bladder inflammation by improving the integrity and function of the bladder lining. As one of the relevant components of the glycosaminoglycan layer, HA has been reported to be effective in a number of studies in the treatment of PBS [10].

Despite many treatment strategies of PBS, there are no standard treatment guidelines. Treatment modalities are oral drugs, intravesical drug instillation, neuromodulation. Many drugs and procedures are empirically used, though only a few have been studied in randomized controlled tri-

Revised manuscript accepted for publication November 7, 2017

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLV, n. 2, 2018
doi: 10.12891/ceog4568.2018

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als [11].

Intravesical instillation of hyaluronic acid (HA) may regenerate the damaged GAG layer of the bladder in patients with PBS [7]. Several studies reported that HA instillation is an effective treatment for PBS [12] and the efficacy of HA instillation was reported to have 30–70% of improvement rates [13]. Furthermore, intravesical HA instillation is recommended as a therapeutic option in recent guidelines [14]. Even though several treatments have been proposed for PBS, this syndrome shows recurrent and refractory characteristics. In this study the authors aimed to assess the efficacy of intravesical hyaluronic acid (HA) instillation in patients with resistant painful bladder syndrome (PBS).

Materials and Methods

The authors conducted a prospective study from January 2016 to September 2017 on 32 female PBS patients who were refractory to common treatments. The protocol was approved by the local Ethics Committee and an informed written consent was obtained from each woman before enrollment. Inclusion criteria were: women, Age > 20 < 75 years, Long-term symptom of PBS (> 12 months), Urinary urgency, increased urinary frequency, and suprapubic bladder area pain aggravated by delayed urination and diminished after voiding, Refractory to previous treatments, visual analogue scale (VAS) pain score ≥ 4, pelvic pain and urgency/frequency (PUF) questionnaire and ≥13, negative cytology and cystoscopy, a sterile urine culture, and a negative urine pregnancy test. Exclusion criteria were: history of cancer, bladder stones, recurrent urinary tract infection or history of bacterial cystitis during the previous four months, previous history of HA instillation, sexually transmitted infection, history of current genitourinary tuberculosis, endometriosis, history of neurogenic bladder, radiation cystitis, and urethral diverticulum.

Patients were previously treated conservatively as patient education (as change lifestyle), with adequate water supply dietary restrictions, oral therapy with tricyclic antidepressants, antihistamines, anti-muscaranic (anticholinergic) agents, pentosanpolysulphate, or analgesics.

The authors used their institution protocol of HA instillation: each patients received intravesical instillations of a sterile solution of HA once weekly for eight weeks and once monthly for four months for a total of 12 doses. Solutions were administered by hydrophilic 12 Fr Foley catheters and performed by the urologist.

Before treatment and one month following treatment, all patients were asked to complete a three-day voiding diary (24-hour frequency/nocturia, mean voided volume) so they could evaluate the voiding frequency and functional bladder capacity. Any adverse events were recorded at each treatment session.

The authors evaluated the efficacy by determining the mean changes in the VAS pain score from baseline to eight weeks of HA treatment. Outcomes measured included scale (VAS) pain scores ≥ 4 and total scores (symptom and bother scores) ≥ 13 on the pelvic pain and urgency/frequency (PUF) questionnaire and ≥13.

The efficacy of the HA instillation was evaluated by comparing the mean changes in the scores of the VAS and questionnaires from baseline to eight weeks of treatment. Improvement was defined as a ≥ 2 decrease in the VAS. Secondary end points included comparison of daily urinary frequency/nocturia changes in the PUF scores, from baseline to week 12. Improvement was considered to be if ≥ 2 decrease in VAS. The patients were followed prospectively and the data were analyzed retrospectively.

Continuous variables are presented as median with interquartile ranges (IQR, 25th and 75th percentiles), and categorical variables are presented as frequencies and percentages. The statistical significance of the changes from baseline was assessed using the paired *t*-test. All tests were completed using SPSS v. 19 software. For all statistical comparisons, significance was considered as $p < 0.05$.

Results

Between January 2016 and September 2017 a total of 32 female patients with typical findings on PBS (who were refractory to common treatments) received treatment with the intravesical HA. In the total cohort of 32 patients, the mean age of the women was 54.0 ± 1.8 (range, 28–75) years. Table 1 shows the baseline and the demographic characteristics of the entire cohort of the patients.

Following bladder catheterisation, the patients received a dose of 40 mg of HA, weekly for eight weeks, and then monthly for four months. Response to therapy was evaluated by comparing the pre-treatment and post-treatment symptom scores and voiding diaries.

The authors compared the responses at baseline and after treatment: there were 22 patients (63.0%) with positive response rate at week 8, which was maintained until 12 months.

As shown in Table 2 at baseline, the mean VAS score was 6.5, the PUF score was 13.5; after treatment the authors observed a significant reduction in pain intensity versus baseline; the change in the VAS pain score was –2.5 ($p < 0.001$) and PUF-total score (–3.8, $p < 0.001$). Specifically, both VAS [6.5 to 4 ($p < 0.001$)] and PUF-symptom score decreased significantly after treatment [13.5 to 8.2 ($p < 0.001$)].

No significant local or general side effects were registered during the course of treatment. The intravesical administration of HA was well tolerated in all cases.

Discussion

In this study the authors considered PBS patients who were refractory to common treatments. PBS is a challenge to the urologist because of its unknown etiology and the unpredictable effects and durability of conventional treatments including oral therapies, intravesical therapies, and surgical interventions. For these reasons, various therapeutic modalities have been attempted. GAG layer replacement therapy is widely accepted as therapy for patients with PBS who have poor or inadequate response to conventional therapy. There are four different commercially available products for GAG replacement, including CS, heparin, HA, and pentosan polysulfate. HA represents an important portion of the GAG layer, and several studies have reported that HA instillation provided positive effects for patients with PBS [10]. Intravesical treatment with various agents has been

Table 1. — *Baseline characteristics of the patients.*

	n=32
Age (years), median (IQR)	54.00 (28.00-75.00)
VAS score	6.5 (4.9-7.2)
PUF symptom score	13.5 (13.1-14.3)
Voiding frequency	16.2 ± 4.3
Nocturia (/night)	3.9 ± 1.1
Mean voided volume (ml)	145.00 ± 21.1

IQR= interquartile range; VAS Score (Visual Analogue Scale); PUF-symptom score (pelvic pain and urgency/frequency).

Table 2. — *Comparison of assessments before and after treatment with hyaluronic acid for painful syndrome(n=32).*

	Before treatment	After treatment	*p* value
VAS score	6.5 (4.9-7.2)	4 (3.8-4.2)	< 0.001
PUF score	13.5 (13.1-14.3)	8.2 (9.3-7.9)	< 0.001
Voiding frequency	16.2 ± 4.3	9 ± 2.3	< 0.001
Nocturia (/night)	3.9 ± 1.1	2.3 ± 0.5	< 0.001
Mean voided volume (ml)	145.00 ± 21.1	155.00 ± 30.4	< 0.001

IQR= interquartile range; VAS score (Visual Analogue Scale); PUF-score (pelvic pain and urgency/frequency).

reported, and response rates after initial instillation therapy were 45% for CS, 56% for heparin, and 44% for pentosane polysulfate [4, 15-17]. Other authors reported respectably higher response rates with intravesical HA therapy, and the beneficial effect was maintained for more than three years [18,19].

Intravesical HA was the first GAG substance used for PBS. The first study was published by Morales *et al.* in 1996 [20] who found a complete or partial response rate of 71% for up to one year. HA is widely studied and has shown a wide range of symptom improvement, from 30% to 85% [21]. Engelhardt *et al.* [22] reported their long-term results of intravesical HA therapy and they observed a 50% complete bladder symptom remission at the five-year follow-up without any additional therapy, while 41.7% with symptom recurrence improved with HA maintenance therapy.

HA is considered a good candidate for GAG substitution and used in the treatment of patients with recurrent cystitis, hemorrhagic cystitis, and interstitial cystitis in urology field [19]. One study reported a satisfactory response of PBS patients to intravesical HA instillation for eight weeks [20]. Another study showed acute remission and long-term HA efficacy in the treatment of PBS and HA instillation was considered to improve functional bladder capacity, symptom scores, pain, and quality of life.

To date, the optimal intravesical instillation regimen with HA has not been defined. However, most studies adopted a treatment strategy consisting of weekly treatment for several weeks followed by maintenance treatment. In the literature, several different protocols have been described for instillation. Many uncontrolled studies used 40-mg HA dissolved in 40 mL of normal saline solution weekly for four to six weeks and then monthly [11, 20, 21].

In the present study, instillation protocol was once weekly intravesical instillations of HA for eight weeks and four more instillations were performed monthly according to patient consultation.

The present authors focused treatment of HA in refractory PBS patients and they showed that HA instillation improved VAS pain score and PBS questionnaire scores in refractory PBS patients; in particular the VAS score significantly decreased from baseline to eight weeks of treatment (–2.7) and the PUF questionnaires showed significant improvements after eight weeks of HA instillation. The rate of improvement was 63%, which was slightly higher than that of the previous reported study [22].

Regarding tolerability of intravesical HA instillation, no adverse event for HA instillation was reported in the present study. There were no adverse reactions over the whole treatment period with a total of 1,521 instillations; mild adverse events were reported such as urinary tract infection (0-17.4%), temporary worsening of storage symptoms (0-11.3%), and events related to catheterization [10]. The duration of the follow-up period and the number of patients were limited in this study, but comparable to other series.

Conclusion

The present results showed that intravesical HA therapy is an effective treatment for patients with PBS who had inadequate response to conservative treatment. HA instillation induced an improvement in pain, urgency symptoms, and quality of life in patients with PBS. Thus, HA treatment could be considered as a component of therapeutic strategy for a good treatment of PBS.

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