Review Article

Interstitial cystitis/bladder pain syndrome and glycosaminoglycans replacement therapy

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Abstract: Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic disease characterized by discomfort or recurrent abdominal and pelvic pains in the absence of urinary tract infections. Its symptomatology includes discomfort, increased bladder pressure, sensitivity and intense pain in the bladder and pelvic areas, increased voiding frequency and urgency, or a combination of these symptoms. For these reasons, this pathology has a very negative impact on quality of life. The etiology of IC/BPS is still not well understood and different hypotheses have been formulated, including autoimmune processes, allergic reactions, chronic bacterial infections, exposure to toxins or dietary elements, and psychosomatic factors. The finding of an effective and specific therapy for IC/BPS remains a challenge for the scientific community because of the lack of a consensus regarding the causes and the inherent difficulties in the diagnosis. The last recent hypothesis is that IC/BPS could be pathophysiologically related to a disruption of the bladder mucosa surface layer with consequent loss of glycosaminoglycans (GAGs). This class of mucopolysaccharides has hydrorepellent properties and their alteration expose the urothelium to many urinary toxic agents. It has been hypothesized that when these substances penetrate the bladder wall a chain is triggered in the submucosa. In order to improve the integrity and function of the bladder lining, GAG layer replenishment therapy is widely accepted as therapy for patients with IC/BPS who have poor or inadequate response to conventional therapy. Currently, Chondroitin sulfate (CS), heparin, hyaluronic acid (HA), and pentosan polysulfate (PPS), and combinations of two GAGs (CS and HA) are the available substances with different effectiveness rates in patients with IC/BPS. There are four different commercially available products for GAG replenishment including CS, heparin, HA and PPS. Each product has different concentrations and dosage formulations. Recently, a combination of CS and HA is the latest commercially available product with promising results.

Keywords: Bladder pain syndrome; interstitial cystitis (IC); glycosaminoglycan replacement (GAG replacement); multimodal therapy

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Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic syndrome characterized by discomfort or recurrent abdominal and pelvic pains in the absence of urinary tract infections. Its symptomatology includes discomfort, increased bladder pressure, sensitivity and intense pain in the bladder and pelvic areas, increased voiding frequency and urgency, or a combination of these symptoms. The pain often worsens during menstruation and may intensify during intercourse [National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)]. It also worsens with bladder filling and is relieved after bladder emptying (1).

For these reasons, this pathology has a very negative impact on quality of life (2).

This condition has a prevalence rate of 2.71% and 1.22% in women and men, respectively, although these rates depend on the definitions used (3). The etiology of IC/BPS is still not well understood and different hypotheses have

been formulated, including autoimmune processes, allergic reactions, chronic bacterial infections, exposure to toxins or dietary elements, and psychosomatic factors (4,5).

The finding of an effective and specific therapy for IC/BPS remains a challenge for the scientific community because of the lack of a consensus regarding the causes and the inherent difficulties in the diagnosis. The last recent hypothesis is that IC/BPS could be pathophysiologically related to a disruption of the bladder mucosa surface layer with consequent loss of glycosaminoglycans (GAGs). This class of mucopolysaccharides has hydrorepellent properties and their alteration expose the urothelium to many urinary toxic agents. It has been hypothesized that when these substances penetrate the bladder wall a chain is triggered in the submucosa. Here nerve terminals produce inflammatory mediators causing mast cell degranulation and histamine secretion with consequent vasodilatation and inflammatory exudate. The consequence of this inflammatory response is the stimulation of C fibers with mast cell activation and histamine release. This produce consequent bladder pain and release of neuropetides with a consequent damage to the mucosa and fibrosis of the submucosa (6-8). The major classes of GAG include hyaluronic acid (HA), heparin sulphate, heparin, chondroitin 4-sulphate, chondroitin 6-sulphate, dermatan sulphate and keratan sulphate (9). In order to improve the integrity and function of the bladder lining, GAG layer replenishment therapy is widely accepted as therapy for patients with IC/BPS who have poor or inadequate response to conventional therapy (10). Currently, chondroitin sulfate (CS), heparin, HA, and pentosan polysulfate (PPS), and combinations of two GAGs (CS and HA) are the available substances with different effectiveness rates in patients with IC/BPS.

There are four different commercially available products for GAG replenishment including CS, heparin, HA and PPS. Each product has different concentrations and dosage formulations. Recently, a combination of CS and HA is the latest commercially available product.

Sodium pentosan polysulfate (PPS)

PPS is a semi-synthetic, sulfated polysaccharide, which is chemically and structurally similar to heparin and GAG. A proposed mechanism is that the drug replaces the damaged parts of the GAG layer that lines the bladder (11). It has been reported that PPS reduces bladder permeability based on the potassium sensitivity test (12). Currently, PPS is the only oral therapy approved by the FDA for IC/PBS (13). However, randomized controlled trials (RCTs) have shown mixed results in its efficacy. Mulholland and Parsons separately reported significantly improved pain and urgency symptoms from baseline at 3-month follow-up (14,15). La Rock and Sant (16) suggested that in comparison with oral therapy, intravesical sodium pentosan polysulphate (SPP) therapy promotes direct absorption of the drug by the bladder. Conversely, Holm-Bentzen *et al.* failed to demonstrate any difference at 4-month follow-up compared to placebo (17). Increasing treatment doses does not appear to improve efficacy from the 100 mg 3 times a day (TID) dosing. Diarrhea, abdominal pain, and rectal bleeding are the most common side effects and have been found to be dose-related. Alopecia was also noted in 5% of patients in one study (18). High-quality evidence demonstrates mixed support for this therapy. Therefore, given the moderate side effect profile, PPS is recommended as a second-line therapy for IC/PBS (19).

Hyaluronic acid (HA)

Intravesical HA was the first GAG substance used for IC/PBS. Morales *et al.* published the first study in 1996; they found a complete or partial response rate of 71% for up to 1 year (20). In patients with IC/BPS, the concentration of this acid is decreased and urothelial permeability toward potassium compounds is increased, causing an increase in bladder pain. HA inhibits leukocyte chemotactic and phagocytic functions, and reduces the permeability of the synovial membrane (21). HA acts on urothelial cells in three distinct ways: by increasing secretion of GAG enzymes; this leads to increased GAG secretion, leading to restored homoeostasis and eventual normal GAG barrier production. HA through a direct physicochemical interaction with the cells' surface decreases the permeability of the urothelium. HA acts on the third pathway by decreasing secretion of pro-inflammatory cytokines IL-6 and IL-8 from the urothelial cells, decreasing immune cell infiltration to the urothelium and decreasing inflammation (22). HA has been the subject of multiple studies and has shown a wide range of symptom improvement, from 30% to 85% (23-25). In 2011 Engelhardt and his collaborators reported their long-term results of intravesical HA therapy; they observed a 50% complete bladder symptom remission at the 5-year follow-up without any additional therapy, while 41.7% with symptom recurrence improved with HA maintenance therapy (26).

Not all the studies have shown a significant effect of

HA. For example in a double-blind, placebo-controlled, multicentre clinical study with this GAG in different preparations (40 or 200 mg/cc), no significant efficacy of sodium hyaluronate compared to placebo was found for interstitial cystitis (IC) patients. However, further details, including patient selection, inclusion/exclusion criteria, definition of improvement/success, are not available (27). In the study of Daha *et al.* hydrodistention in combination with HA with potassium chloride (KCl), in addition to sodium chloride (NaCl), were used as a treatment of IC/BPS. With the combined use of KCl and NaCl, pain was improved by 62.5% and 71.48% respectively (28). HA does not provide immediate relief of symptoms, as some time is required before the onset of regeneration of the GAG layer. By contrast, lidocaine (a local anesthetic) can reduce sensory ending excitability in the bladder and help with the control and immediate relief of pain and voiding frequency. For this reason, Lv proposed a combined therapy that may lead to an immediate relief of symptoms by addicting lidocaine to HA. With this treatment, voiding frequency was reduced by 67.25% and pain was reduced by 70.82% (29).

Chondroitin sulfate (CS)

CS is another natural proteoglycan present in the GAG layer of the bladder epithelium. Like HA, intravesical instillation of this molecule has been proposed as a treatment for patients with IC/BPS, to promote regeneration of GAG in the bladder urothelium. Results from a recent experiment revealed good control of urinary symptoms and pain, suggesting that the use of this drug in IC/BPS may be of benefit. Intravesical CS therapy efficiency was evaluated by Steinhoff and colleagues in an open-label 12-month study. In this study, the authors treated 18 patients with 40-mL instillations of CS 0.2% weekly for 4 weeks and then monthly for 12 months. They found a response rate for symptom improvement of 67% (30).

In an uncontrolled open multicenter study of 53 IC patients, instillations of CS 2% produced a 60% response rate at 6 months (31).

In contrast, a recently published RCT failed to show superiority of CS 2.0% over control after 6 weeks of treatment. In that study, most patients reported a clinical benefit, but the difference between treatment and control group was not statistically significant (32).

According to the 2012 data of the Brazilian Ministry of Health, the production of intravesical HA was stimulated by instillation of CS; a substance that blocks the action of lytic enzymes and stimulates proteoglycan synthesis by inducing increased HA levels, thus reconstituting the urothelium.

Nickel *et al.* conducted an interventional study by using bladder hydrodistention with 20 mL of saline associated with 2% CS, and found an improvement in pain and urinary urgency of 47% and a decrease in voiding frequency by 51.8% (33).

CS and HA

A combination of two GAG contains CS (2.0%) and low molecular weight HA (1.6%) is the latest available substance for the GAG replenishment therapy.

In an open-label single arm study by Porru and colleagues, the efficiency of intravesical CS/HA combination therapy was evaluated in IC/PBS patients. Twenty-two patients with IC/BPS received intravesical instillations (40 mL) of sodium HA 1.6% and CS 2.0% in 0.9% saline solution (IALURIL®) (IBSA, Lugano, Switzerland) once weekly for 8 weeks, then once every 2 weeks for the next 6 months. Parameters included visual analogue scale (VAS) for pain and urgency, number of void per day, mean voiding volume, Interstitial Cystitis Symptom Index (ICSI) and Pain Urgency Frequency (PUF) questionnaire.

The score for urgency was reduced from 6.5 to 3.6 (P=0.0001), with a reduction in pain scores from an average of 5.6 to 3.2 (P=0.0001). The average urine volume increased from 129.7 to 162 mL (P<0.0001), with a reduction in the number of voids in 24 hours, from 14 to 11.6 (P<0.0001). The IC Symptom and Problem Index decreased from 25.7 to 20.3 (P<0.0001), and the PUF score, from 18.7 to 12.8 (P<0.0001) (34).

Cervigni and colleagues reported the long-term results of intravesical CS/HA therapy in 12 IC/BPS patients refractory to other treatments. They used a combination of HA 1.6% and CS 2.0% over a period of 3 years assessing symptoms and quality of life using a visual analogue scale, 3-day voiding diaries and validated questionnaires. Improvements in bladder function were sustained for 3 years (mean number of daily voids decreased from 17.8 at baseline to 15.5 at 9 months and 11.9 at 3 years, and mean volume per void from 136.8 mL at baseline to 143.9 mL at 9 months and 180.9 mL at 3 years). Quality of life assessments confirmed these improvements (35).

Ömer Gülpınarite studied 53 BPS IC patients with inadequate clinical response after 6 months of conservative treatment comparing for the first time intravesical HA/CS combination and intravesical HA. In total, 53 patients met

the study criteria. There were 30 patients in the HA-CS group (mean age: 48.47 years old) and 23 patients in the HA group (mean age: 49.61 years old) (P>0.05). The initial PST was positive in 71.7% patients (38/53) overall with no difference between groups (P>0.05). Responses for VAS, ICSI, Interstitial Cystitis Problem Index (ICPI), 24-hour frequency/nocturia statistically improved in both groups at 6 months. There was no significant difference in symptomatic improvement (P>0.05). Eight patients had mild adverse events (36).

Conclusions

HA and HA/CS therapy are effective treatment options for patients with IC/BPS who had inadequate response to conservative treatment, in the short term.

IC/PBS remains a prevalent, but untreated disease with a poorly understood pathophysiology. Nonetheless, research suggests that (I) disruption of the bladder GAG/proteoglycan layer, (II) upregulated immune/inflammatory response, (III) neural upregulation, and (IV) pelvic floor dysfunction may all play a role in the pathophysiology of the disease.

However, further randomized controlled studies with a larger number of patients and a longer follow-up period are needed to confirm these encouraging results and to optimize the treatment protocol for a sustained long-term therapeutic effect.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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