Clinical comparison of intravesical hyaluronic acid and chondroitin sulfate therapies in the treatment of bladder pain syndrome/interstitial cystitis

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Introduction: Intravesical glucosaminoglycan (GAG) replacement therapies are commonly used in the treatment of bladder pain syndrome (BPS)/interstitial cystitis (IC). Different intravesical glucosaminoglycan products are currently available. In this prospective study, clinical efficacy of chondroitin sulfate and hyaluronic acid are compared in patients with BPS/IC.

Methods: Patients were randomized to CS and HA groups. All patients were evaluated for visual analogue pain scale (VAS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), voiding diary for frequency/nocturia, and mean urine volume per void at the beginning of the therapy and after 6 months. All patients had a potassium sensitivity test (PST) initially. Wilcoxon and Mann-Whitney U tests were used for statistical analysis.

Results: There were 21 patients in both groups. Mean age of patients in CS and HA groups were 47.10 and 48.90, respectively ($P > 0.05$). Before treatment, Parson’s test was positive in 64.3% of patients (27/42) with no difference between groups. VAS of pain, ICSI, ICPI, frequency at 24 h and nocturia results have improved significantly at both treatment arms. Intravesical CS was also found superior to intravesical HA in terms of 24 h frequency, nocturia and ICPI ($P < 0.05$). No severe adverse effects were reported.

Conclusions: Data comparing clinical efficiencies of different GAG therapies are very limited. In this study, intravesical CS was found superior to intravesical HA in terms of 24 h frequency, nocturia and ICPI in patients with BPS/IC in short term follow-up. To provide a definitive conclusion on superiority of one GAG therapy to others, further evaluation with long term follow up is required.

1 | INTRODUCTION

Bladder pain syndrome/Interstitial cystitis (BPS/IC) is the occurrence of persistent or recurrent pain perceived in the urinary bladder region, accompanied by at least one other symptom, such as pain worsening with bladder filling and day-time and/or night-time urinary frequency, in the absence of proven urinary infection or other obvious local pathology. Wide variation of prevalence rates have been reported in literature due to different definitions accepted in the studies and different study designs. But recent modern prevalence...
studies showed higher rates than previous estimations. A population based epidemiological study revealed prevalence rates in females and males as 2.7% and 1.9%, respectively.2,3

Although etiology of bladder pain syndrome/interstitial cystitis is not clearly identified and probably has a multifactorial cause, it is a widely accepted theory that such clinical conditions may arise from a primary defective urothelium lining or from a damage of its glycosaminoglycan (GAG) component.4 The loss of the watertight function of the urothelium may allow both the normal and abnormal constituents of urine to directly contact the subepithelial layers, resulting in inflammation and delayed healing of the damaged urothelial layer. Consequently, some noxious substances in urine may activate submucosal nerve filaments, thus accounting for symptoms of pain, urgency, and urinary frequency.5

To improve the integrity and function of the bladder lining, exogenous intravesical GAG replacement therapies are one of the treatment options for patients with BPS/IC, generally refractory to conventional therapy.6 Intravesical heparin with or without lidocain and sodium bicarbonate, sodium pentosan polysulfate (PPS), hyaluronic acid (HA), chondroitin sulphate (CS), and HA-CS combinations are available products currently used as intravesical GAG replacement therapies.

In literature, there are some placebo-controlled and uncontrolled studies showing success rates of these products but data comparing these substances in BPS/IC patients is very limited. This causes difficulty for physicians to choose optimal GAG replacement therapy for their patients. In this study, we compared the clinical efficacy of HA and CS in patients with BPS/IC who had no benefit from previous conservative and medical treatment.

2 METHODS

A total of 42 female patients with BPS/IC were included to the study. Patients with complaints of chronic pelvic pain related to bladder filling accompanied by voiding frequency ≥8 times/24 h, nocturia ≥2 times per night or persistant urge for at least 24 weeks, an average pain score of ≥4 (VAS: 0 no pain, 10 unbearable pain), a negative pregnancy test, a sterile urine culture and inadequate clinical response after 6 months of conservative and medical treatment were included to the study. Patients with positive pregnancy test, current urinary infection or sexually transmitted disease, chemical cystitis, tuberculous or radiation cystitis, urolithiasis, urological malignancy, endometriosis, urethral diverticulum, and breastfeeding women were excluded from the study. Data were collected prospectively and evaluated retrospectively. Hospital ethical committee approval and informed consents of patients were obtained.

Patients were randomized for intravesical therapy with 50 mL/120 mg sterile sodium HA (HYACYST®—Molecular weight:152 kDa) or 40 mL/80 mg sodium CS (GEPAN INSTILL®). Intravesical instillations were administered to patients using 12F hydrophilic Foley catheters. Patients were instructed to try not to urinate for the next 60 min. Intravesical instillations were done weekly in first month, once in 15 days in second month and monthly in third and fourth months as a total of eight intravesical doses. Patients were evaluated for visual analog scale score (VAS) for pain, 3 day voiding diary (24 h frequency, nocturia, median voided volume), symptom index score (ICSI) and problem index score (ICPI) at the beginning of the therapy and after 6 months. A reduction less than two on VAS of pain was considered as non-response to treatment. Among responders; a reduction of more than 50% of VAS score was considered as strong benefit and less than 50% of VAS score was considered as limited benefit. All patients had a potassium sensitivity test (PST) initially.

The primary outcome of the study was the change of pain VAS score from baseline compared to week 24. Secondary outcomes included comparison of daily urinary frequency/nocturia, ICSI, and ICPI scores and mean voided volume from baseline to week 24.

Baseline factors were compared with the t-test and the Mann-Whitney rank sum test, and differences between treatment outcomes were calculated with the Mann-Whitney rank sum test. Proportions of responders were calculated with the Fisher exact test; P < 0.05 was considered significant. Statistical analysis was performed with SPSS, v.16.0 statistical software (SAS Institute, Cary, NC).

3 RESULTS

Between January 2012 and February 2014, a total of 42 patients were randomized. Twenty-one patients with a mean age of 47.10 randomized for CS group and 21 patients with a mean age of 48.90 randomized for HA group (P > 0.05). PST was positive for 14 patients (66.7%) and 13 patients (61.9%) in CS and HA groups respectively (P > 0.05). Total positiveness rate of PST was 64.3% (27/42). There was no statistically significant difference between the pretreatment findings of the two groups (Table 1).

Former treatments in CS group were dietary restrictions and analgesics (n = 10), dietary restrictions and hydroxyzine hydrochloride (n = 5), dietary restrictions and amitriptyline (n = 3) and oral pentosanpolysulfate (n = 3). Dietary restrictions and analgesics (n = 12), dietary restrictions and amitriptyline (n = 4), and oral pentosanpolysulfate (n = 5) were the former treatments of the HA group.

We compared results at baseline and 6 months. In both groups VAS of pain decreased significantly at both groups (nine to four in HA group and eight to five in CS group,
TABLE 1  Pretreatment characteristics of the two groups

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hyaluronic acid (HA), n = 21</th>
<th>Chondroitin sulfate (CS), n = 21</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>48.90 ± 17.18</td>
<td>47.10 ± 10.70</td>
<td>0.684</td>
</tr>
<tr>
<td>VAS of pain</td>
<td>9 (min:4-max:10)</td>
<td>8 (min:5-max:10)</td>
<td>0.615</td>
</tr>
<tr>
<td>Micturition frequency (24 h)</td>
<td>13.90 ± 5.69</td>
<td>16.48 ± 5.08</td>
<td>0.130</td>
</tr>
<tr>
<td>Nocturia</td>
<td>2 (min:0-max:12)</td>
<td>3 (min:1-max:6)</td>
<td>0.479</td>
</tr>
<tr>
<td>Mean voided volume (mL)</td>
<td>148 (min:26-max:369)</td>
<td>136 (min:29-max:355)</td>
<td>0.320</td>
</tr>
<tr>
<td>ICSI</td>
<td>16 (min:4-max:20)</td>
<td>17 (min:11-max:20)</td>
<td>0.630</td>
</tr>
<tr>
<td>ICPI</td>
<td>13 (min:6-max:16)</td>
<td>14 (min:8-max:16)</td>
<td>0.779</td>
</tr>
<tr>
<td>PST positivity rate</td>
<td>61.9%</td>
<td>66.7%</td>
<td>0.747</td>
</tr>
</tbody>
</table>

HA, hyaluronic acid; CS, chondroitin sulfate; VAS, visual analog scale; ICSI, interstitial cystitis symptom index; ICPI, interstitial cystitis problem index; PST, potassium sensitivity test.

According to changes in VAS scores, patients were categorized into three groups such as non-response, limited benefit and strong benefit. No statistically significant difference was found between treatment arms (Table 2) ICSI, ICPI, frequency at 24 h, nocturia results have improved significantly at both treatment arms. CS was also found to increase mean urine volume per void, but not for HA (Fig. 1). Intravesical CS was also found superior to intravesical HA in terms of 24 h frequency, nocturia, and ICPI (P < 0.05) (Fig. 2). But there was no statistically significant difference between treatment arms in VAS scores and mean urine volume per void (P > 0.05) (Table 3). No severe adverse effects were reported.

4 | DISCUSSION

Hursts’ proposal, defects of glucosaminoglycan layer can cause symptoms of BPS/IC, is a widely accepted theory. Intravesical GAG replacement therapy is indicated in patients who have poor or inadequate response to conventional therapy. Intravesical heparin with or without lidocain and sodium bicarbonate, sodium pentosan polysulfate (PPS), HA, CS, and HA-CS combinations are available products currently used as intravesical GAG replacement therapies.

Exogenous intravesical HA was the first GAG used to treat BPS/IC. First study evaluating HA use for BPS/IC symptoms was published in 1996 by Morales and colleagues, and they found 71% complete or partial response by week 12. Since than studies reported wide range of response rates, from 30% to 85%. Best results reported by Riedl and colleagues. They have studied on 126 BPS/IC patients with positive modified potassium chloride test and found 85% had symptom improvement (≥2 VAS units) and 84% had significant improvement of their quality of life. In contrast to previously mentioned studies, in 2003 and 2004, two industry sponsored randomized, double-blind, placebo controlled studies of different HA preparations (40 or 200 mg per mL) were completed. No significant efficacy of HA compared with placebo for BPS/IC patients was shown. However, further details, including patient selection, inclusion/exclusion criteria, definition of improvement/success, are not available.

Previous studies has shown a deficit of chondroitin sulfate from lumenal surface may play a role in the pathophysiology of BPS/IC. Based on this point, intravesical CS treatment has been suggested to be effective in BPS/IC patients. Steinhoff et al evaluated intravesical CS therapy efficiency in an open label 12-month study. In this study, 40-mL instillations of CS 0.2% were administered to 18 patients with interstitial cystitis and positive potassium chloride test. They found a response rate for symptom improvement of 67%. An uncontrolled open multicenter study of 53 IC patients, found 60% response rate to CS 2% at 6 months.

In contrast to previous results, a prospective randomized and controlled 12 week trial (6 weeks treatment period, 6 weeks follow up) by Nickel et al failed to show superiority of CS 2% over control. In this study, twice as many patients reported a clinically significant benefit with intravesical chondroitin sulfate treatment compared with control treatment, but difference was not enough to maintain statistical significance. In a latter study by Nickel et al, minor improvements in BPS/IC related symptoms and pain were
achieved with intravesical CS treatment. But again, these differences were found statistically insignificant.\textsuperscript{17}

CS-HA combination (2% CS-low molecular weight 1.6% HA) is the latest available substance for intravesical treatment and good results have been reported in uncontrolled studies. In an open-label, single arm study, Porru et al evaluated efficiency of CS/HA combination therapy in 20 patients with BPS/IC. After treatment, weekly for 8 weeks, then once every 2 weeks for the next 6 months, results showed statistically significant improvement in all parameters including VAS for pain and urgency, mean voiding volume, average number of voids in 24 h, ICSI, and Pain Urgency Score (PUF).\textsuperscript{18} Cervigni et al reported long term outcomes of intravesical CS/HA combination therapy in 12 patients with BPS/IC. They found improvements in symptoms and quality of life evaluation were still apparent at 3-year follow up.\textsuperscript{19} In the most recent study, statistically significant decreases in ICSI, ICPI and PUF questionnaire scores in 20 women with BPS/IC were obtained by Giberti and colleagues.\textsuperscript{20}

Placebo-controlled and uncontrolled studies showing success rates of these products were mentioned above. But info comparing these substances to each other is very limited. Previously, intravesical HA/CS combination and intravesical HA were compared in 53 patients with BPS/IC who had inadequate clinical response after 6 months of conservative treatment. Improvements in parameters such as VAS for pain, 24-h frequency/nocturia, ICSI and ICPI were observed in both treatment arms. However no statistically significant difference in any parameter was found between CS/HA combination therapy and HA therapy at the 6-month evaluation.\textsuperscript{21}

Our study is the first study in the literature comparing intravesical CS and HA therapies and the first study finding statistically significant difference between two intravesical GAG substances in the treatment of BPS/IC. We compared intravesical CS and HA in patients with BPS/IC who had inadequate response after 6 months of conservative treatment. Statistically significant

![FIGURE 1 Increased mean voided volume in CS group](image)

| TABLE 3 Pretreatment and 6 months findings of the patients treated with CS and HA |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Hyaluronic acid (HA)**                          | **Chondroitin sulfate (CS)**                      | **HA versus CS** |
| **Initial visit**                                 | **6 months**                                     | **P** value  | **Initial visit** | **6 months** | **P** value  | **P** value |
| VAS of pain                                       | 9 (min:4-max:10)                                 | <0.001      | 8 (min:5-max:10) | 5 (min:0-max:8) | 0.000      | 0.842       |
| 24 h frequency                                    | 13.90 ± 5.69                                    | 0.018       | 16.48 ± 5.08     | 10.57 ± 3.61  | <0.001     | <0.001      |
| Nocturia                                          | 2 (min:0-max:12)                                 | 0.002       | 3 (min:1-max:6)  | 1 (min:0-max:4) | <0.001     | 0.029       |
| Mean voided volume (mL)                           | 148 (min:26-max:369)                             | 0.555       | 136 (min:29-max:355) | 155 (min:64-max:369) | <0.001     | 0.102       |
| ICSI                                              | 16 (min:4-max:20)                                | 0.003       | 17 (min:11-max:20) | 9 (min:4-max:18) | <0.001     | 0.096       |
| ICPI                                              | 13 (min:6-max:16)                                | <0.001      | 14 (min:8-max:16) | 7 (min:1-max:13) | <0.001     | 0.045       |

HA, hyaluronic acid; CS, chondroitin sulfate; VAS, visual analog scale; ICSI, interstitial cystitis symptom index; ICPI, interstitial cystitis problem index.
improvements in parameters including VAS for pain, average number of voids in 24 h, nocturia, ICSI and ICPI scores were obtained in both treatment arms. CS was found to increase in urine volume per void unlike HA. Intravesical CS was also found superior to intravasical HA in terms of 24 h frequency, nocturia, and ICPI in patients with BPS/IC in short term period.

Natural GAG layer consists sulfated GAGs like chondroitin sulfate, dermatan sulfate and non-sulfated GAGs such as hyaluronic acid. About 80-90% of the total surface GAG is bound as integral membrane proteins, with 55% of the protein bound GAG being heparan sulfate, 26% being CS, and the remainder either not identified or dermatan sulfates.22 Previous studies also demonstrated that a deficit of chondroitin sulfate from lumenal surface may play a role in the pathophysiology of BPS/IC.13 Considering relative abundance of CS compared to HA in the natural GAG layer of bladder surface and results of previously mentioned studies showing the possible role of CS deficit in the pathophysiology of BPS/IC, it can be reasonable to suggest that CS may be more efficient than HA in the treatment of IC/BPC. To have a definitive conclusion on whether there is a superiority of intravesical CS to other intravesical GAG therapies, we need further research with large prospective RCTs with long-term follow up.

Cost-effectiveness of intravesical GAG therapies is certainly an important aspect for physicians to choose optimal treatment for their patients and should be mentioned. In a recently published meta-analysis; cost efficacy was found less than 25% for CS compared with HA. In this meta-analysis; mostly results of CS 2% and HMW (high molecular weight) HA were compared. Number needed to treat for a treatment response was found 1.31 for HMW-HA and 5.51 for CS 2%.23 But our results showed similar response rates for both therapies and also similar costs. Further studies comparing cost efficacies of LMW-HA and CS 0.2% are required to have a conclusion on the issue.

Lack of control group is the important limitation of our study. But it was difficult to form a control group since patients with BPS/IC were suffering from severe pain and were desperate for treatment. The duration of the follow-up period and number of patients included to our study were also limited, but comparable to other series in literature.

5 | CONCLUSION

Intravesical GAG replacement therapy is a standard treatment in patients with inadequate response to conservative treatment. Both CS and HA are shown as effective treatments in patients with BPS/IC. Data comparing intravesical GAG therapies are very limited. To our knowledge, this is the first study in literature finding statistically significant difference between two intravesical GAG substances in the treatment of BPS/IC. Further research with large prospective RCTs with long-term follow up is required to have a definitive conclusion on any possible superiority of CS to other intravesical GAG replacement therapies.

REFERENCES


