EFFECT OF INTRA VESICAL HYALURONIC ACID TREATMENT ON BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

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ABSTRACT

Purpose: Our study aims to evaluate the efficacy of hyaluronic acid (HA) on interstitial cystitis patients admitted to our clinic with the diagnosis of bladder pain syndrome/interstitial cystitis (BPS/IC).

Material and methods: The pre- and post-treatment symptom scores the severity of symptoms, and cystoscopic and pathologic findings of 23 patients diagnosed with BPS/IC were prospectively evaluated between 2009-2013. The O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI) Scale, and Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUFSS) were used as questionnaire forms. 40 mg HA was administered intravesically for 6 weeks. Results were reviewed in patients who completed the treatment.

Results: Two patients discontinued the treatment, 21 patients were enrolled in the study. The mean age was 48 (33-78). 20 patients underwent cystoscopy surgery. While 8 of them showed nonspecific changes in the trigonum area, 12 had no pathologies. While the mean ICSI score of the 21 patients who filled out the ICSI/ICPI and PUFSS questionnaire forms was 15.6 (12-20) pre-treatment and 9.2 (1-18) post-treatment (p<0.01), the mean ICPI score was 13.1 (7-16) pre-treatment, and 7.8 (0-16) post-treatment (p<0.01). The mean PUFSS score was 23.9 (14-35) pre-treatment, and 16.4 (5-31) post-treatment (p<0.01). While the mean PUF symptom score was 16.1 (10-23) pre-treatment, and 10.9 (3-19) post-treatment (p<0.01), the mean PUF quality of life score was 7.8 (4-12) pre-treatment, and 5.5 (1-12) post-treatment (p<0.01). No side effects were found in the patients.

Conclusion: Intravesical HA therapy is a safe treatment option in the treatment of BPS/IC. While it has a certain degree of efficacy, further prospective, randomized, placebo-controlled studies with a larger study population are required.

Key words: Cystitis, Interstitial, Glycosaminoglycans, Hyaluronic Acid.

Introduction

Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) is a chronic intermittent clinical syndrome characterized by a constellation of symptoms that include bladder/pelvic pain associated with urinary urgency, frequency and dysuria⁴. There are cystoscopic and histologic features which are said to be typical but in many cases the diagnosis is one of exclusion in order to rule out specific causes such as infection and malignancy.

The underlying pathophysiology of this disease is still unknown. A loss of the glycosaminoglycans (GAG) ’’water-tight’’ function at the epithelial surface of the bladder, possibly due to an infective or other inflammatory insult is thought to be important as this exposes the bladder subepithelium to substances present in urine (normal substances such as Na+, K+, H+, Cl- and abnormal substances such as cytotoxic drugs and toxins)⁶. Once these irritating substances come into direct contact with the subepithelial layers, they are causing inflammation and delayed healing of the damaged urothelial layer and GAGs⁶. This is also thought to be important along with sensory nerve upregulation and enhanced mast cell activation⁶. The end result of this process is a form of regional neuropathy that can have other gynaecological and gastrointestinal manifestations as well as pain and voiding symptoms⁶.

Hyaluronic acid (HA) is a major mucopolysaccharide found widely in the epithelial, neural and connective tissues. HA is used in different ways in
the treatment of patients. It is used in certain orthopedic and ophthalmologic procedures\(^{(6,7)}\); in cosmetic regeneration and reconstruction tissue\(^{(6)}\); and in vesicoureteral reflux\(^{(9)}\). In urothelium it constitutes a protective barrier\(^{(10)}\) and has an inhibitory action on mast cell activation which is considered a crucial step in the pathogenesis of BPS/IC\(^{(11)}\). In light of these findings, the early repair of the GAG layer by HA might avoid the chronic evolution of bladder inflammation.

The aim of this study was to determine whether hyaluronic acid instillation had an impact on the urinary frequency, nocturia, life quality in patients diagnosed with BPS/IC.

**Material and methods**

A total of 23 patients diagnosed with BPS/IC between 2009-2013 were recruited for this open, prospective, unblinded, uncontrolled study. All patients were chosen from among patient who did not benefit from the previous oral medication, life behavioral changes and dietary recommendations. Diagnosis was made based on criteria defined by European Society for the Study of Interstitial Cystitis criteria\(^{(4)}\).

Patients were included in the study if they had chronic pelvic pain, pressure, or discomfort, perceived to be related to the urinary bladder accompanied by at least one other urinary symptom, such as persistent urge to void or frequency. Exclusion criteria included age under 18 years; pregnancy or breastfeeding; vesical urethral pathologies (as infective or actinic cystitis, neurogenic bladder, urethral diverticula, bladder or urethral cancer, urinary stones, urge/ stress incontinence, pelvic prolapses) or nonvesical pathologies (vaginitis, uterine, vaginal or cervical cancers, endometriosis) not related to IC/BPS.

All patients undergone physical examination, full blood count, urine analyses, urinary tract ultrasonography (USG), and urinary tuberculosis (TBC) analyses. TBC analyses were made by EZN (Ehrlich-Ziehl-Nielsen) staining and where possible by adding the PCR (Polymerase Chain Reaction) method. A 3-day voiding diary form was filled out for each patient. 16 patients underwent urodynamic evaluation. Cytologies and cytoscopic examination were carried out for patients who had hematuria in urine analyses and bladder wall thickening in ultrasonic images. Concurrent “hydroadisstention+bladder capacity measurement” was performed during cystoscopy, and biopsy samples were received from suspicious areas. This procedure were performed under general anesthesia in dorsal lithotomy position. The saline was put 70-80 cm above the suprapubic area and the bladder was filled passively with saline. The bladder was distended for 1-5 minutes when the urine stream to the bladder was stopped. Then the bladder was slowly emptied, and the total drained volume was recorded as the maximum bladder capacity. The bladder was refilled to perceive changes in the bladder surface (glomerulation).

Cold-cup biopsy samples were obtained from patients who had suspicious areas after hydroadisstention: 1 sample from the suspicious area and 1 sample randomly from any area of the bladder.

The O’Leary-Sant (OLS) Interstitial Cystitis Symptom Index (ICSI) and Interstitial Cystitis Problem Index (ICPI) scale, and Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUFSS), (overall PUFSS score, PUFSS symptom score, and PUFSS quality of life score) forms were filled out for each patient both pre-treatment and 15 days after post-treatment\(^{(12,13)}\).

Complete Urine Analysis (CUA) was performed before each instillation, and urine culture and antibiogram was performed in the event of any findings of infection in CUA. Appropriate antibiotic treatment was performed in the event of urinary tract infection, and instillation was delayed. A 8F silicon catheter was inserted to empty the bladder, 40mg HA 1.6% (800 mg/50 ml) was dilueted in saline and was administered intravesically as a 50cc solution under sterile urine conditions weekly for six weeks. The patients were instructed to retain the hyaluronic acid in their bladders at least for 2 hours after the instillation. 15 days after the final administration, the voiding diary, the ICSI and ICPI scales and PUFSS forms were filled out again in order to asses the response to therapy.

All patients provided written informed consent prior the treatment and this study was approved by the ethics committee of our hospital.

The SPSS® software was used for statistical analysis. The variables were compared using the Wilcoxon rank sum test. Data were expressed as mean ± standard deviation. p<0.05 was considered to be statistically significant.

**Results**

Of the 23 patients diagnosed with BPS/IC 2 patients (8.7%) discontinued the treatment after 2 sessions claiming to have gained no benefits from
the treatment, these two patients were excluded from the study and 21 patients were enrolled in the study. Patients characteristics are shown in Table 1. None of the patients had any bacteria in their urinary cultures.

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (M/F)</td>
<td>19-Feb</td>
</tr>
<tr>
<td>Age, years ± SD</td>
<td>48 ±12.19 (33-78)</td>
</tr>
<tr>
<td>BMI, kg/m2 ± SD</td>
<td>25.2± 3.2</td>
</tr>
<tr>
<td>Parity, n</td>
<td>2.5</td>
</tr>
<tr>
<td>Menopausal, n (%)</td>
<td>11 (52%)</td>
</tr>
<tr>
<td>Time since BPS/IC diagnosis, years</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Table 1: Patients characteristics (mean values).

<p>| BMI: body mass index; BPS/IC: Bladder pain syndrome/Interstitial cystitis; SD: standard deviation |</p>
<table>
<thead>
<tr>
<th>Pretreatment questionnaire scores, mean (SD)</th>
<th>Post-treatment questionnaire scores, mean (SD)</th>
<th>p value (t test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICSI 15.6±4.3 (12-20)</td>
<td>9.2 ±4.0 (1-18)</td>
<td>0.0005</td>
</tr>
<tr>
<td>ICPI 13.1 ± 2.19 (7-16)</td>
<td>7.8 ± 1.83 (0-16)</td>
<td>0.0065</td>
</tr>
<tr>
<td>Overall PUFSS scores 23.9±14 (14-55)</td>
<td>16.4 ±2.62 (5-31)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Mean PUFSS symptom score 16.1±10 (10-23)</td>
<td>10.9±2.30 (3-19)</td>
<td>0.0066</td>
</tr>
<tr>
<td>Mean PUFSS quality of life score 7.8±6.1 (4.12)</td>
<td>5.5±0.83 (1.12)</td>
<td>0.0078</td>
</tr>
<tr>
<td>Number of voids Day time 10.5±7.3 (6-15)</td>
<td>7.5±0.92 (5-15)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Night time 3±1.21 (1-7)</td>
<td>1.9±0.89 (0-5)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mean urine volume per void 117.3±30.1 (78-153)</td>
<td>153±37.4 (98-186)</td>
<td>0.0056</td>
</tr>
</tbody>
</table>

Table 2: Results from the patient questionnaires pre and post treatment.

ICPI: Interstitial Cystitis Problem Index; ICSI: Interstitial Cystitis Symptom Index
PUFSS: Pelvic Pain and Urgency/Frequency Patient Symptom Scale; SD: standard deviation

All of the patients underwent cystoscopy. Of these two had bladder wall thickening in the USG (9.5%). During cystoscopy 8 of 21 patients showed nonspecific changes in the trigonum area(38%), 13 had no pathologic findings. After hydrodistention glomerulations were observed in 11 of all patients (52%). Biopsy samples were obtained from suspicious areas in 9 patients who underwent cystoscopy (43%). “Partial desquamation of the superficial epithelium, chronic active cystitis, mononuclear cellular infiltra-
tion” were found in 6 of them (29%). Three patients had no specific pathologic abnormalities.

Thirteen patients had hematuria (62%). All of these patients underwent urine cytologic analysis. Of these 12 had no pathological findings in their cytology results. Atypical cells were found in 1 patient. Biopsy was performed for this patient and no specific pathologic abnormalities were found.

16 patients underwent urodynamic evaluation (76%). Three of them had involuntary bladder contractions (18.7%), 13 had normal detrusor activity.

Voiding diaries were kept for all patients. The mean pretreatment day time voiding frequency and mean nocturia frequency decreased from 10.5 (6-15) to 7.5 (5-15) (p<0.01) and from 3 (1-10) to 1.9 (p<0.01) respectively. Mean urine volume per void increased from 117.3 to 153 ml (p<0.01).

Results from the patient questionnaires are shown in table 2. Pre and post-treatment mean ICSI score was 15.6 (12-20) and 9.2 (1-18) respectively (p<0.01). The mean pre-treatment ICPI score was 13.1 (7-16) and post-treatment 7.8 (0-16) (p<0.01).

When analyzing the mean values of the overall PUFSS score, PUFSS symptom score, and PUFSS quality of life score, a statistically significant change after treatment was reported compared with baseline. The overall PUFSS mean values decreased from 23.9 (14-35) to 16.4 (5-31) (P<0.01), mean PUFSS symptom score decreased from 16.1 (10-23) to 10.9 (3-19) (P<0.01) and the mean PUFSS quality of life score decreased from 7.8 (4-12) to 5.5 (1-12) (P<0.01).

The mean follow up was 4 months (range 2–7 months) from the end of the instillation protocol. No cases of intolerance, side effects or complications were observed.

Discussion

BPS/IC is a chronic bladder condition that negatively affects a patient’s quality of life. It occurs mostly in women and the estimated ratio of women to men is 9:1(14).

The exact etiology of BPS/IC is still controversial and various pathophysiology theories have been proposed. The most recent one is based on a disruption in the GAGs layer of the bladder mucosa. This results in the loss of the normal permeability barrier and allows transfer of substances from urine to the bladder interstitium, which finally causes a cascade of reactions and disease progression(25).
Diagnosis of BPS/IC is based on symptoms and exclusion of other painful bladder conditions that resemble BPS/IC but have a different identifiable cause. A variety of tools are available to help eliminating all other possibilities and identify BPS/IC\(^{15}\). Besides laboratory and radiological evaluations we used cystoscopy with hydrotension, bladder biopsy, urodynamic testing, voiding diaries and symptom surveys in order to exclude confusable diseases.

Although cystoscopy with hydrotension is no longer considered mandatory for the diagnosis of BPS/IC, cystoscopic findings can be helpful to rule out bladder cancer, stones or foreign bodies as causes of urinary urgency and frequency symptoms\(^{16-18}\). It also allows photodocumentation of the bladder inflammation (glomerulations, submucosal hemorrhages, ulcers), determination of the bladder capacity under anesthesia and definition of the degree and type of microscopic inflammation if biopsies are performed\(^{19}\). Furthermore, in a study it has been shown that approximately half of patients experience short-term therapeutic benefit following hydrotension\(^{18}\). But still there are controversies about the therapeutic affect of bladder hydrotension. Hanno et al. showed that BH provides symptoms relief at 6 months only in 0-7% of treated patients\(^{20}\). After hydrotension Hunner’s lesion and glomerulations can be seen. Today it has been shown that glomerulations are not specific for BPS/IC and they can be seen in defunctionalized bladders, after intravesical chemotherapy and in up to 40% of normal women undergoing tubal ligation\(^{20-22}\).

All of the patients in our study underwent cystoscopy with hydrotension in order to exclude confusable diseases and none of them had Hunner lesions or other confusable diseases but all patients had submucosal ectasias in at least three bladder quadrants.

Bladder biopsy is not essential for the diagnosis of IC and is often not indicated\(^{23}\). Biopsy can be used to rule out other diseases, especially carcinoma in situ. Although there are no pathognomonic histological features for BPS/IC, biopsy findings can establish the degree of chronic inflammation, the presence of inflammatory cells and the presence of vasodilatation in the mucosal layers\(^{24,25}\).

In our case series, biopsy samples were obtained from 9 patients who had suspicious areas during cystoscopy. “Partial desquamation of the superficial epithelium, chronic active cystitis, mononuclear cellular infiltration” were found in 6 of them. Three patients had no specific pathologic abnormalities.

Urodynamic testing is not required for a diagnosis of BPS/IC, but it may help eliminate other bladder disorders such as detrusor instability, stress urinary incontinence and bladder outlet obstruction\(^{16,24,25}\). The Interstitial Cystitis Data Base (ICDB) study reported involuntary bladder contractions in 14.6% of IC patients\(^{26}\). In our study 16 patients underwent urodynamic testing study and 3 (18.7%) patients had involuntary bladder contractions.

Symptom surveys and voiding diaries are very useful in screening for BPS/IC and in the follow-up evaluation of patients with BPS/IC\(^{16,24}\). ICSI, PUFSS and ICPI are the most commonly used symptom surveys\(^ {14,15}\). Both surveys ask the patient about urinary urgency, frequency, nocturia and pain and the impact of these symptoms on daily life. The PUFSS evaluates sexual dysfunction as well. The PUFSS, ICSI, ICPI are simple to administer and may clarify symptoms that the patient failed to explain during history taking\(^{27}\). We also used voiding diaries, PUFSS and ICSI in order to understand and standardise the symptoms and to evaluate the outcomes of the treatment.

Many different kinds of therapies have been proposed for the treatment of BPS/IC. Intravesical therapy options such as HA, heparin sulfate and chondroitin sulfate aims to restore the GAG layer and to reduce inflammation, mast cell activation and in addition repair the damaged urothelial lining.

HA is an important component of GAG layer. It is reported that instillation of HA provides long-term improvement for patients with BPS/IC\(^ {28}\). HA is not only a regenerating factor for the defected GAG layer but it is also able to attach to several cellular receptors that are overexpressed in inflammatory conditions and by this way can inhibit release of pro-inflammatory molecules from mast cells and alleviate the inflammatory process\(^ {29}\).

Some trials proved the efficacy of HA in the treatment of BPS/IC. Leppilahiti and colleagues administered four weekly intravesical instillations of 40mg HA after BH in 11 patients and observed a decrease in urinary frequency (less than 75%) and in a visual analogue scale (VAS) pain score (less than 26%)\(^ {29}\).

Morales reported a 71% response to the treatment with HA after 12 weeks\(^ {30}\). In another study the long-term efficacy of intravesical HA therapy
was proved. 68.6% of patients responded after a mean follow-up of 4.9 years, 50% reported complete remission without any additional therapy and 41.7 % patients with recurrences were improved with HA maintenance therapy\(^{(31)}\). Kallestrup at al reported a 65% of positive response rate after four weekly plus two monthly bladder instillations of 40mg HA in 20 patients with BPS/IC\(^{(32)}\).

Cervigni and colleagues showed a statistically significant improvement in ICSI/ICPI and PUFSS andVAS score after 20 weekly and 3 monthly intravesical instillations of 40mg HA and CS over 8 months of follow up, with no cases of complications after intravesical instillation of HA and CS in a group of 23 patients\(^{(33)}\). Similar results were reported by Porru and colleagues, 6 months after treating 20 patients with a combination of HA and CS\(^{(34)}\).

Our study was based on a protocol using ICSI/ICPI and PUFSS questionnaires. There were statistically significant reductions in pre and post treatment ICSI/ICPI and PUFSS scores. There was also a significant increase in urine volume per void, and decrease in frequency of daily voiding. In addition, intravesical combination therapy with HA was well tolerated and there were no adverse effects.

Although this study was a prospective study, still it has some limitations which are mainly represented by the small sample size, the short follow up and the lack of a placebo control group. However, the encouraging results of this study will give countenance to researchers on making future multicentral, randomized and controlled studies on a larger population.

**Conclusions**

Despite the limitations of this study, our findings verifies that the role of intravesical treatment with HA is a safe and effective option for the treatment of BPS/IC. It produced improvement in symptoms and there were no known side effects. Nevertheless, 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 longterm therapeutic effect.

**References**


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Abbreviations
HA: Hyaluronic acid
BPS/IC: Interstitial Cystitis/Bladder Pain Syndrome
ICSI: The O’Leary-Sant Interstitial Cystitis Symptom Index
ICPI: Problem Index Scale
PUFSS: Pelvic Pain and Urgency/Frequency Patient Symptom Scale
GAG: Glycosaminoglycans
VAS: Visual Analogue Scale

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