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ORIGINAL ARTICLE

A combined intravesical therapy with hyaluronic acid and chondroitin for refractory painful bladder syndrome/interstitial cystitis

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Abstract The aims of this study were to evaluate the efficacy and tolerability of intravesical instillations of high-molecular-weight hyaluronic acid (HA) 1.6% and chondroitin sulfate (CS) 2.0% in patients with refractory painful bladder syndrome/interstitial cystitis (PBS/IC) and to observe their impact on Quality of Life. Twenty-three women were enrolled. They received bladder instillations with HA and CS weekly for 20 weeks and then monthly for 3 months. Mean follow-up after completion of therapy was 5 months. We observed a significant improvement in urinary symptoms on voiding diaries and Visual Analogue Scale for frequency (p=0.045), urgency (p=0.005), and pain (p=0.001). The O'Leary–Sant Interstitial Cystitis Symptom Index and Interstitial Cystitis Problem Index resulted in a significant improvement in both scores (p= 0.004 and 0.01, respectively). The Pelvic Pain and Urgency/Frequency Symptom Scale only showed significant improvement in the symptom score (p=0.001). This promising experience seems to offer an additional therapeutic option in patients with refractory PBS/IC.

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Introduction

Painful bladder syndrome/interstitial cystitis (PBS/IC) is a chronic clinical syndrome characterized by pelvic pain, urinary frequency, nocturia, and urgency. The exact etiology of this disease is still unknown, and various hypotheses have been postulated. There are several suggested causes for PBS/IC, among which include infections, immunologic factors, alteration of the glycosaminoglycan (GAG) layer in the bladder wall, toxic substances, neurogenic inflammation, and activation of mast cells [1–6].

The most likely etiology involves disruption of the bladder mucosa surface layer. This layer is formed by GAGs, a class of mucopolysaccharides with hydrorepellent properties covering the internal bladder wall, which make it impermeable to urinary solutes. For partially unknown reasons, the GAG layer tends to lose its function, causing increased bladder permeability. A reduced GAG production by the urothelium worsens this increase in permeability even further, exposing the bladder submucosa to various toxic urinary substances. Once those substances penetrate the bladder wall, a chain reaction is triggered in the submucosa, where nerve terminals (unmyelinated C fibers) produce inflammatory mediators (vasoactive intestinal peptide, substance P, acetylcholine) causing mast cell degranulation and histamine secretion. Histamine secreted through mast cell degranulation causes hyperemia, vasodilatation and an inflammatory exudate. Such inflammatory response stimulates C fibers, with consequent bladder pain [7] and with release of neuropeptides producing secondary damage to the mucosa and fibrosis of the submucosa [8].

Among the several therapies described for PBS/IC, a few are aimed at improving the function of the urothelial barrier, with wide variation in efficacy among them. Heparin sulfate, hyaluronic acid (HA), and chondroitin sulfate (CS) are all either part of the urothelial barrier or very similar in structure to GAGs. These substances are administered orally [9], intravesically [10–12], or both, with the aim of restoring the integrity of the GAG layer. Therapy protocols utilized with these medications vary among different authors, and the optimal mode of treatment has not been established yet.

The primary outcome of this study was to assess the efficacy and tolerability of the intravesical instillation of CS and HA in patients with PBS/IC refractory to conventional therapies. The secondary outcome was to evaluate the impact of this therapy on Quality of Life (QoL).

Materials and methods

IC diagnosis was performed conforming to NIDDK criteria [13]. All patients had failed several previous oral therapies including: pentosan polysulfate, cimetidine [14], and DMSO. With regard to intravesical therapies, two patients had undergone intradetrusorial administration of botulinum toxin A without symptomatic improvement.

All women had failed intravesical instillations of HA at low concentration (i.e., 0.08%), using weekly doses of 40 mg of HA for 4 weeks and then monthly for 2 months [12].

The wash-out period from all previous therapies was at least 1 month. All patients underwent the following evaluation before therapy, monthly during the treatment protocol and at the end of the study:

- 3-day voiding diary
- structured symptom questionnaire
- Visual Analogue Scale (VAS) for pain, frequency and urgency, scored from 0 to 10
- Questionnaires: O'Leary–Sant Interstitial Cystitis Symptom Index (ICSI) and Problem Index (ICPI) [15]; Pelvic Pain and Urgency/Frequency Symptom Scale (PUF symptom scale) [16]
- complete urinalysis and urine culture.

A complete urodynamic study was performed in all patients before the beginning and at the end of the study. Diagnostic cystoscopy was carried out in all women before treatment but only in 11 patients after completing therapy.

The treatment protocol included intravesical instillations (40 ml) with sodium HA (high molecular weight) 1.6% and CS 2.0% (Patent Cooperation Treaty by IBSA Institut Biochimique SA, Lugano, Switzerland). The instillation was carried out, after bladder emptying, with an 8-French Nelaton catheter weekly for 20 weeks, then every 2 weeks for 4 weeks, and then monthly for 3 months. The solution was left to act in the bladder for 1 h.

The study was approved by the ethics committee of our hospital, and the patients gave their written informed consent before taking part in the study. The statistical analysis was performed using the *t* test for dependent samples. We considered $p<0.05$ as statistically significant.

Results

Twenty-three women were enrolled in our study. Ages ranged from 20 to 65 years (mean 46.68, SD 13.63), and median parity was 1 (0–2 deliveries). Thirteen women (56.5%) were post-menopausal. The mean time since PBS/IC initial diagnosis was 2.4 years.

Mean follow-up was 5 months (range 3 to 8 months) from the end of the instillation protocol. There was no drop-out of patients from treatment and all completed the entire protocol. No cases of intolerance, side effects, or complications were observed.

Data from the analysis of questionnaires are reported in Tables 1 and 2 and data from the analysis of voiding diaries in Table 3. Data regarding VAS analysis are shown in Table 4 while urodynamic data are reported in Table 5. In two patients we found a pre-treatment high cystometric capacity at enrolment: it was the effect of previous botulinum toxin type A (BTX-A) therapy, as previously reported in the literature [17]. So, we decided to exclude these two patients in the evaluation of urodynamic data.

Cystoscopic evaluation pre- and post-treatment was carried out only in 11 patients. At the last follow-up visit, submucosal vascular ectasia had disappeared in eight patients, and there was a marked reduction in hyperemia of the bladder mucosa in ten patients.

Discussion

Numerous intravesical drugs have been proposed for the treatment of PBS/IC. The effect of some of those agents is

Table 1 O'Leary–Sant Interstitial Cystitis Symptom Index and Problem Index

	Pre-treatment	Post-treatment	*p*
Symptom index	8–23 (mean 13.87, SD 3.67)	6–20 (mean 11.22, SD 3.75)	0.004
Problem index	7–16 (mean 11.52, SD 2.15)	4–16 (mean 10.13, SD 3.14)	0.01

Table 2 Pelvic Pain and Urgency/Frequency Symptom Scale

	Pre-treatment	Post-treatment	*p*
Symptom score	8–19 (mean 13.70, SD 3.35)	3–25 (mean 11.61, SD 4.60)	0.001
Bother score	2–21 (median 8.57, SD 3.55)	2–12 (mean 6.04, SD 2.85)	0.06
Total	10–31 (mean 22.26, SD 5.18)	6–31 (mean 17.39, SD 6.19)	0.004

based on their anti-inflammatory action. Another group of substances is supposed to act as GAG substitutes, on the basis of the urothelial dysfunction theory.

Among the anti-inflammatory agents, the first drug used was dimethyl sulfoxide (DMSO), which is now considered a first-line treatment for PBS/IC [18]. Its mechanism of action is only partially understood and is based on its anti-inflammatory, analgesic, muscle relaxing, collagen-dissolving, and mast cell inhibitor effects [11, 12]. On the basis of experimental studies which showed the positive effect of BTX-A on visceral pain with a short latency period, this agent has been described for the treatment of PBS/IC, with conflicting results [19]. Intravesical therapy with other anti-inflammatory agents for PBS/IC has been reported, among them resiniferatoxin and RDP-58 [18].

Several agents with a GAG substitution action have been described. Heparin, a sulfated polysaccharide with a structure similar to heparan sulfate, a GAG component, has been used for intravesical treatment of PBS/IC. This therapy has been shown to be effective in about 50% of patients [20], but symptomatic improvement takes long to occur. Parsons proposed the association of heparin (40,000 IU) with lidocaine for better short-term symptom relief. To allow better absorption of lidocaine by the lipid urothelial membrane, the addition of 3 ml of 8.4% sodium bicarbonate, suspended in a total volume of 15 ml, was suggested. Lidocaine gives an immediate analgesic effect, while heparin down-regulates bladder sensory nerves [21].

HA, a glycosaminoglycan present in the bladder mucosa, plays an important protective role on the underlying urothelium. HA inhibits adherence of immune complexes to polymorphonuclear cells, leukocyte migration, and aggregation. It also binds to lymphocytes and endothelial cells, blocking the ICAM-1 receptors and alleviating the inflammatory process [22].

Table 3 Voiding diary

	Pre-treatment	Post-treatment	*p*
Number of voids	12–39 (mean 15.52, SD 7.40)	7–33 (mean 13.91, SD 7.57)	0.012
Mean voiding volume	43–250 ml (mean 143.13, SD 56.83)	40–500 ml (mean 191.26, SD 96.43)	0.006

Table 4 VAS for pain, frequency, and urgency

	Pre-treatment	Post-treatment	*p*
Pain	1–9 (mean 5.65)	0–9 (mean 3.83)	0.001
Frequency	4–10 (mean 7.43)	2–10 (mean 5.45)	0.045
Urgency	1–10 (mean 6.23)	1–8 (mean 3.63)	0.005

A few studies on HA in PBS/IC are available in the literature: Morales et al. reported a 71% partial or complete response to treatment with HA after 12 weeks, with a subsequent relapse after 24 weeks [10]. A lower response rate of only 30% was demonstrated by another author on a small group of PBS/IC patients, achieving improvement in both pain and frequency [11].

Kallenstrup et al. reported a positive response to treatment in 65% of patients, with a follow-up of 3 years. A significant reduction in pain score was noted (2.2-fold decrease in pain score after 3 months and 5.2-fold decrease after 3 years), while reduction in urinary frequency was not observed [12].

Similar results on pain emerge from the study by Daha et al. [23]. The greatest symptomatic improvement observed in this study was achieved in a selected group of patients, whose bladder showed a 30% reduction in maximum bladder capacity following cystometry done with KCl as compared to NaCl (p=0.003).

Two other groups reported the use of HA intravesical instillation combined with hydrodistension under general anesthesia. Leppilahti et al. reported complete or partial response in eight patients out of 12 with this technique [22]. Ahmad et al. recently reported their experience on 23 patients: they obtained a response rate of 74% with an average follow up of 15.8 months [24].

Table 5 Urodynamic data

	Pre-treatment	Post-treatment	*p*
First sensation of bladder filling	34–158 ml (mean 75 ml, SD 54.21)	34–146 ml (mean 81 ml, SD 50.23)	0.14
Maximum cystometric capacity	92–290 ml (mean 240 ml, SD 56.23)	118–306 ml (mean 265 ml, SD 33.12)	0.07
Detrusor pressure at maximum flow	2–69 cm H_2O (mean 26, SD 19.13)	5–46 cm H_2O (mean 21, SD 11.39)	0.81
Maximum flow	8–41 ml/s (mean 16, SD 9.35)	7–25 ml/s (mean 14, SD 8.33)	0.77

In a different study, HA was used in combination with CS, another component of the GAG layer, which was administered systemically with promising results in patients with refractory PBS/IC. Flavonoid quercetin, which has anti-inflammatory properties and inhibits mast cell activation, was added. Using this combination, the global assessment scale was reduced from 9.0±2.9 to 4.3±2.1, with a statistically significant reduction in ICSI and ICPI ($p<0.05$) [12].

Based on those promising results, we decided to administer combined HA and CS by intravesical instillation to maximize their protective effect on the urothelium. Furthermore, we increased the concentration of HA to 1.6% as compared to 0.08% in previous studies on intravesical HA.

Our open, prospective, unblind, and uncontrolled study showed a statistically significant improvement in urinary symptoms following therapy. The voiding diaries reported a reduction in the number of voids ($p=0.012$) and an increase in mean voiding volume ($p=0.006$). These objective results were supported by subjective data: VAS score showed a reduction in urinary frequency ($p=0.065$), urgency ($p=0.0005$), and pain ($p=0.001$). The improvement of pain in PBS/IC is in our opinion an important achievement, as in our experience pain has great negative impact on PBS/IC patients' Quality of Life.

A more accurate evaluation of quality of life was carried out using ICSI/ICPI and PUF symptom scale. Specifically, the results from ICSI and ICPI demonstrated a statistically significant improvement in symptoms ($p=0.004$) and problems ($p=0.01$), respectively.

On the other hand, the PUF symptom scale showed a statistically significant improvement both globally and in the symptom score ($p=0.001$) while the bother score was not significantly changed ($p=0.06$).

No significant changes were observed in urodynamic parameters following therapy. The absence of statistically significant changes in urodynamic data is probably due to the effects of long-standing disease on those patients' bladder. Possibly, a longer treatment protocol may be necessary to obtain on urodynamic performance the positive effects seen on voiding diaries and symptom questionnaires.

Conclusions

Despite the study's limitations, mainly the lack of placebo control, our experience with combined HA and CS seems a promising option for the treatment of refractory PBS/IC which, in recent years, has not benefited from effective new therapies. Further controlled studies, a greater number of patients, and a longer follow-up are required to confirm these initial encouraging results.

Conflicts of interest None.

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