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Combined intravesical sodium hyaluronate/chondroitin sulfate therapy for interstitial cystitis/bladder pain syndrome: a prospective study

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Abstract:
Objectives: The aim of this study was to verify the efficacy and safety of intravesical treatment combining sodium hyaluronate (HA) and chondroitin sulfate (CS) in patients with interstitial cystitis/bladder pain syndrome (IC/BPS).
Methods: Between February 2010 and May 2011, 20 consecutive women with IC/BPS were treated with intravesical instillations containing sodium HA (1.6%; 800 mg/50 ml) and sodium CS (2%; 1 g/50 ml) weekly for the first month, biweekly for the second month, and then monthly for at least 3 months. Before and after treatment, all patients filled in the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI), the Patient Health Questionnaire 9 and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF). Treatment efficacy was assessed by comparing the pre- and post-treatment mean scores of the three questionnaires using Student's *t* test (p value <0.05 was considered significant).
Results: Statistically significant mean decreases in ICSI (from 13.0 to 9.3; $p = 0.0003$), ICPI (from 11.35 to 8.85; $p = 0.0078$) and PUF (from 20.0 to 15.75; $p = 0.0007$) questionnaire scores were seen. No cases of side effects or complications were observed. The mean follow up was 5 months.
Conclusions: Despite the limitations of this study, the outcomes confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment of IC/BPS. Further randomized controlled studies with a higher number of patients and a longer follow-up period are needed to confirm these results.

Keywords: chondroitin sulfate, hyaluronic acid, interstitial cystitis, intravesical administration, painful bladder syndrome

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a chronic clinical syndrome characterized by bladder/pelvic pain and urinary dysfunction, such as increased frequency and urgency, with a strongly negative impact on patients' quality of life [Neuhaus *et al.* 2011; Nordling *et al.* 2012; Vij *et al.* 2012]. 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 [Giannantoni *et al.* 2012; Mahmoud, 2011]. Both the lack of a general consensus regarding the causes and the inherent difficulties in the diagnosis have dramatically affected the development of an effective and specific therapy for IC/BPS. This remains a challenge for the scientific community.

It has been hypothesized that IC/BPS could be pathophysiologically related to a disruption of the bladder mucosa surface layer with consequent loss of glycosaminoglycans (GAGs), a class of mucopolysaccharides with hydrorepellent properties, exposing the urothelium to many urinary toxic agents. Once these substances penetrate the bladder wall, a chain reaction is thought to be triggered in the submucosa, where nerve terminals produce inflammatory mediators causing

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mast cell degranulation and histamine secretion with consequent vasodilatation and inflammatory exudate. This inflammatory response stimulates C fibers with consequent bladder pain and release of neuropetides, producing damage to the mucosa and fibrosis of the submucosa [Bassi *et al.* 2011; Iavazzo *et al.* 2007; Parsons, 2003]. Based on these aspects, the early repair of the bladder mucosal layer with intravesical application of GAGs, such as hyaluronic acid (HA) or chondroitin sulfate (CS), has been proposed as possible treatment [Damiano *et al.* 2011; Iavazzo *et al.* 2007; Nickel *et al.* 2012]. Very few clinicians are experienced in the combined intravesical instillation of HA and CS in the treatment of IC/BPS. However, preliminary evidence suggests that this combination therapy provides better efficacy than the individual compounds on the urothelium [Cervigni *et al.* 2008; Porru *et al.* 2008, 2012].

The aim of this study is to investigate efficacy and tolerability outcomes of an intravesical treatment combining both HA and CS in patients with IC/BPS.

Methods

Patients

Between February 2010 and May 2011, 20 consecutive women with IC/BPS according to European Society for the Study of Interstitial Cystitis criteria [van de Merwe *et al.* 2008] were enrolled into the study. All subjects gave written consent for participation and agreed to comply with the study protocol. The study procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional).

Patients were included in the study if they had chronic (for at least 6 months) 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; severe comorbidities (such as neurological pathologies, diabetes mellitus); previous treatments for IC/BPS during the 3 months before enrollment.

Study design and endpoints

The patients were subjected to medical history, objective examination, routine blood tests, urinalysis, urine culture, urinary ultrasonography, and cystoscopy with hydrodistension at least 1 month before starting the treatment protocol. Bladder biopsy was not routinely performed.

The treatment protocol required weekly intravesical instillations of a sterile solution, containing sodium HA 1.6% (800 mg/50 ml) and sodium CS 2% (1 g/ 50 ml) in 50 ml water with calcium chloride (Ialuril®, IBSA, Pambio-Noranco, CH) for the first month, biweekly for the second month, and then monthly for at least 3 months.

According to the study protocol, the patients underwent three medical visits. At the first visit, patient enrolment and drug prescription were carried out. The second visit took place 2 weeks after the beginning of the treatment to evaluate potential adverse events. The third visit was carried out 5 months after the beginning of the treatment. After the third visit, the patients were followed every 2 months for the first year.

Before and after the therapy, all patients were asked to fill in three different questionnaires: the Interstitial Cystitis Symptom Index and Problem Index (ICSI/ICPI) [O'Leary *et al.* 1997], the Patient Health Questionnaire 9 (PHQ-9) [Kroenke and Spitzer, 2002] and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale (PUF) [Brewer *et al.* 2007].

The primary endpoint of this study was to evaluate the efficacy of this protocol by comparing the pre- and post-treatment mean scores from the three questionnaires.

Statistical analysis

Statistical analysis of the patient questionnaire data was performed using the Student's t test for dependent samples. A p value less than 0.05 was considered to be statistically significant.

Results

All patients completed the entire protocol. Patients' baseline characteristics are shown in Table 1. On

examining cystoscopic findings, some glomerulations were observed in only 8 out of 20 patients (40%). A biopsy was performed in only 4 out of 20 patients (20%).

All patients completed the ICSI, ICPI, and PUF questionnaires before and after the treatment, while the PHQ-9 questionnaire was incomplete for two patients. On analyzing the mean values of the ICSI, ICPI, and PUF questionnaires, a statistically significant change after treatment was reported compared with baseline. In particular, the ICSI mean values decreased from 13.0 to 9.3 (p = 0.0003), the ICPI mean values decreased from 11.35 to 8.85 (p = 0.0078), and the PUF mean values decreased from 20.0 to 15.75 (p = 0.0007), demonstrating a subjective perception of improvement in urinary symptoms and pain. No significant changes were seen before and after treatment in PHQ-9 questionnaire values (Table 2).

The mean follow up was 5 months (range 2–10 months) from the end of the instillation protocol. The median follow up was 5.5 months. No cases of intolerance, side effects or complications were observed.

Table 1. Baseline patient characteristics.

Patients, *n*	20
Age, years ± SD	60.2 ± 13.2
BMI, kg/m^2 ± SD	22.9 ± 3.2
Parity, *n*	0.6
Menopausal, *n* (%)	14/20 (70%)
Time since IC/PBS diagnosis, years	2.1

Age, BMI, parity and time since IC/PBS diagnosis are reported as mean values.
BMI, body mass index; IC/PBS, interstitial cystitis/bladder pain syndrome; SD, standard deviation.

Discussion

There is no consensus in the literature regarding the etiology and the physiopathology of IC/BPS. Moreover, many different kinds of therapies have been proposed for the treatment of this condition. To date, there is a general agreement on the administration of some oral or intravesical agents, as indicated by both the European Association of Urology and American Urological Association guidelines [Fall *et al.* 2010; Giannantoni *et al.* 2012; Hanno *et al.* 2011]. With regard to intravesical therapy, the application of GAGs has been proposed recently based on the urothelial dysfunction theory, which describes the loss of the GAGs mucous layer as the first step of a chain reaction producing chronic urothelial and neurogenic inflammation [Bassi *et al.* 2011; Damiano and Cicione, 2011; Iavazzo *et al.* 2007; Parsons, 2003]. In this setting, the intravesical instillation of HA or CS has been supposed to prevent this process, promoting the regeneration of the GAGs and inhibiting mast cell degranulation [Iavazzo *et al.* 2007; Nickel *et al.* 2009]. In accordance with this assumption, some papers published on the use of HA or CS in the treatment of IC/PBS have confirmed promising results in terms of pain and quality of life improvements [Ahmad *et al.* 2008; Gupta *et al.* 2005; Nickel *et al.* 2009; Riedl *et al.* 2008; Shao *et al.* 2010]. These studies also suggested that a combination treatment with HA and CS would provide better and longer-lasting outcomes than using the individual compounds due to a more protective effect on the urothelium. However, there are very few publications regarding GAG combination therapy [Cervigni *et al.* 2008; Porru *et al.* 2008, 2012]. Cervigni and colleagues demonstrated a statistically significant improvement in ICSI/ICPI and PUF symptom scales and visual analog scale score, with no cases of intolerance, side effects or complications after intravesical instillation of HA and CS in a group of 23 patients with a follow up of 5

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

	Pretreatment questionnaire scores, mean (SD)	Post-treatment questionnaire scores, mean (SD)	*p* value (*t* test)
ICSI (*n* = 20)	13.0 (3.71)	9.3 (4.51)	0.0003
ICPI (*n* = 20)	11.35 (3.23)	8.85 (4.31)	0.0078
PUF (*n* = 20)	20.0 (5.55)	15.75 (5.55)	0.0007
PHQ-9 (*n* = 18)	9.95 (5.77)	8.28 (5.63)	0.2335

ICPI, Interstitial Cystitis Problem Index; ICSI, Interstitial Cystitis Symptom Index; PHQ-9, Patient Health Questionnaire 9; PUF, Pelvic Pain and Urgency/Frequency Patient Symptom Scale; SD, standard deviation.

months [Cervigni *et al.* 2008]. Similar results were reported in a study by Porru and colleagues 6 months after treating 20 patients with GAG combination therapy [Porru *et al.* 2008]. Our study was based on a similar protocol using ICSI/ICPI and PUF questionnaires. The PHQ-9 scale was also included to evaluate the influence of any psychosomatic factors on IC/BPS symptoms. In fact, it has been shown previously that women with IC/BPS may experience depressive symptoms [Novi *et al.* 2005; Watkins *et al.* 2011], and that clinically relevant symptoms of depression in IC/BPS may be correlated with patients' quality of life [Tripp *et al.* 2009].

Findings from our study showed a statistically significant decrease in ICSI/ICPI and PUF mean scores after treatment compared with the respective baseline values, confirming the subjective perception of improvement in urinary symptoms and pain which has already been reported in the literature [Cervigni *et al.* 2008; Damiano and Cicione, 2011; Porru *et al.* 2008, 2012]. In our opinion, this improvement in pain-related symptoms is a relevant achievement considering the negative impact of this factor on the quality of life of patients with IC/BPS. However, the nonsignificant variation of the mean PHQ-9 questionnaire scores, which remained very low before and after the treatment, showed no influence of any depression on patients' status or of GAG combination therapy on patients' depressive symptoms. Finally, intravesical combination therapy with HA and CS was well tolerated and produced no adverse reactions.

This study 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, these aspects are understandable if we consider the 'real' incidence of interstitial cystitis based on the strict criteria for a pathologic diagnosis.

Conclusion

Despite the limitations of this study, our outcomes confirmed the role of combination therapy with HA and CS as a safe and effective option for the treatment of IC/BPS. 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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Conflict of interest statement

The authors declare that there are no conflicts of interest.

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