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Original Article

The short-term efficacy of intravesical instillation of hyaluronic acid treatment for bladder pain syndrome/interstitial cystitis

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ABSTRACT

Objective: The aim of the study was to evaluate the short term efficacy of intravesical instillation of hyaluronic acid in patients with Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC).

Material and methods: The study included 54 women with BPS/IC who received intravesical instillation of hyaluronic acid treatment (120 mg/50 mL) for 6 weeks. Visual Analogue Scale (VAS), The O'Leary Sant Questionnaire (ICSI/ICPI) forms of the patients were filled by the clinician and the health technician separately before and 3 months after the treatment. Demographic characteristics of the patients were recorded, and effectiveness of the treatment was investigated according to these data.

Results: Decrease in mean VAS and mean total scores of ICSI and ICPI was observed after three months of intravesical instillation of hyaluronic acid treatment (55%, $p<0.05$ and 48.5%, $p<0.05$ and 45.5%, $p<0.05$, respectively). In most of the patients, all scores of VAS, ICSI and ICPI improved (minimum: 75.9%, maximum: 94.4%). Mostly the symptoms of nocturia and pollakiuria were seen, and treated after the instillation treatment.

Conclusion: It has been observed that in the short-term follow-up of intravesical instillation of hyaluronic acid treatment, the symptoms have highly improved. Also, Turkish versions of ICSI and ICPI forms were reliable and comprehensible.

Keywords: Bladder pain syndrome; hyaluronic acid; ınterstitial cystitis; ıntravesical treatment.

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Introduction

As defined by the European Society for the Study of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC), BPS/IC is a chronic (>6 months) pelvic pain, pressure, or discomfort perceived related to the urinary bladder accompanied by at least one other urinary symptom such as persistent urge to void or frequency.[1,2] The prevalence of BPS/IC ranges from 10 up to 510 cases per 100,000 population.[3] No generally accepted laboratory tests have been found to aid in the diagnosis, although some new urine markers have been suggested for clinical use. No specific histologic or clinical features have been found, and the diagnosis is based largely on the elimination of other known diseases.[4-6] BPS/IC is frequently a diagnosis of exclusion.[3] The healthy urothelium possesses biochemical and anatomic mechanisms to defend itself against urinary pathogens.[7,8] Many etiologic factors have been suggested for this condition, including autoimmune response, mast cell activation, neuropathic changes, occult infection, toxic substances in the urine, and a primary defect in the glycosaminoglycan (GAG) layer of the bladder mucosa.[9-12] It has been suggested that a defect in GAG layer allows access of different components of urine, such as ions, microorganisms, and toxic molecules into the bladder urothelium and urinary hyaluronic acid levels correlate with interstitial cystitis.[13,14] The most consistent finding in BPS/IC is that, at least in some patients, this mucin/GAG layer seems to be defective. [9,15] Hyaluronic acid is a major mucopolysaccharide found widely in the connective, epithelial, and neural tissues. It is one of the main compo-

nents of the extracellular matrix that contributes significantly to cell proliferation and migration. In this study, we evaluated the efficacy of intravesical instillation of hyaluronic acid in patients with BPS/IC.

Material and methods

During a 4-year-period, between February 2013 and December 2017, the study included 54 women with BPS/IC who received intravesical instillation of hyaluronic acid treatment, and the outcomes of the treatment were analyzed retrospectively following approval of the Ethics Committee of Mersin University. The patients had been diagnosed according to European Society for the Study of Interstitial Cystitis (ESSIC) criteria. Carcinoma and carcinoma in situ, infection, urethral diverticulum, urogenital prolapse, endometriosis, vaginal candidiasis, cervical cancer, uterine cancer, ovarian cancer, overactive bladder, and pelvic floor muscle-related pain are considered in the differential diagnosis. These diseases had been excluded or diagnosed by using cystoscopy and biopsy, routine bacterial culture, special cultures, physical examination, medical history, uroflowmetry and ultrasound, urodynamics and imaging modalities. We have translated O'Leary Sant Questionnaire [Interstitial Cystitis Symptoms Index (ICSI), Interstitial Cystitis Problem Index (ICPI)] into Turkish language.[16] The ICSI contains 4 items that measure urgency and frequency of urination, nighttime urination, and pain or burning in bladder. ICPI contains 4 items that measure the magnitude of problems related to the 4 items contained in ICSI questionnaire. Visual Analogue Scale (VAS) is usually a horizontal line, 100 mm in length. The patient marks the point on the line that they feel represents their perception of their current state. The VAS score is determined by measuring the length in millimetres/centimetres from the left hand end of the line to the point that the patient marks. ICSI, ICPI and VAS tests were recorded before the treatment through interviewing patients by the clinician and medical assistant, individually. All patients had undergone physical examination, received oral or intravesical treatments, urinanalysis, uroflowmetry, post-voiding residual urine volume tests, and finally cystoscopy with hydrodistension under general anesthesia. During the cystoscopy procedure, the saline was instilled into bladder at a height of 80-100 cm from pubic symphysis and the bladder was distended under gravity. Then the bladder mucosa was inspected for glomerulations and Hunner's lesion before and after this procedure, and bladder biopsies were obtained for histopathological evaluation. Intravesical instillation treatment was started after the results of pathologic evaluation were reported. In all patients, hyaluronic acid 120 mg/50 mL (Hyacyst®) was applied intravesically weekly for 6 weeks one week following cystoscopy. Instillations were applied with catheter adaptors (Pre-Filled Syringes) mounted to urethral catheters. We have advised the patients to keep the Hyacyst® intravesically for one hour. The patients were followed closely for urinary tract infection (UTI). The questionnaires and VAS test were applied in the same way at 3rd month following the last instillation again. The patients were divided into subgroups according to median age, median parity, menopause, sexual activity and concomitant medication to compare rates of improvement in each group.

Statistical analysis

Cronbach's Alpha Reliability Analysis test was applied in order to measure the intraclass consistency of the questions in the Turkish versions of the ICSI and ICPI forms, used in our study. Kappa Measure of Agreement test was applied to measure the comprehensibility and coherence. The mean scores of pretreatment and three months after the last instillation were calculated, and these were compared with Wilcoxon Signed Rank Test. Rates of improvement were calculated. The improvements in mean scores of subgroups were compared with the Student's t test or Mann-Whitney U test. The comparison and correlation analysis were performed for the total scores of ICSI and ICPI. Univariate analyses using various parameters were performed for predicting significant improvements (≥median improvement ratio) in ICSI-TS and ICPI-TS. A p-value less than 0.05 was considered to be statistically significant. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences Statistics (IBM SPSS Corp.; Armonk, NY, USA) program package version 21.

Results

Table 1 shows the demographic data of 54 patients. Some (42.6%) patients, drugs had received amitriptyline, hydroxyzine, cimetidine, gabapentin and pentosan polysulfate sodium as concomitant medications in varied combinations. The patients continued their concomitant medications during instillations and three months following the last instillation. Cronbach's Alpha Reliability Analysis test was applied in order to measure the intraclass consistency of the questions in the Turkish versions of the ICSI and ICPI forms, used in our study (Table 2). Kappa Measure of Agreement test was applied to measure the comprehensibility and coherence. Meaningful results were observed (p=0.000) (Table 3). The Wilcoxon Signed Rank Test was performed to compare pre-and post treatment results in forms which were filled by the clinician. The biopsy pathology results indicated squamous metaplasia in two patients, Hunner ulcer in one, leukoplakia in another patient and chronic inflammation in others. The mean VAS value decreased by 55%, and improvement was observed in 92.6% of the patients. Significant decreases in mean total scores of ICSI and ICPI were observed after the treatment (48.5%, $p<0.05$ and 45.5%, $p<0.05$, respectively). In the most of patients, all scores of ICSI and ICPI improved. Further-

more, decreases in mean total score of ICSI and mean total score of ICPI were comparable, and there was significant association between each other (Table 4 and Table 5). The rates of improvement in mean scores classified according to subgroups were seen in Table 6. The treatment was more effective in the patients aged ≥51.5 (median value) years, in menopausal women and the those who had no sexual activity. Parity (≥2) and concomitant medication did not affect the effectiveness of treatment. In univariate analysis, none of the parameters was predictive for improvement in mean total scores of ICSI and ICPI (Table 7).

Table 1. Demographic characteristics of the patients

Parameter	n
# of patients	54
Age (year, range)	55* (18-87)
Parity, range	2* (0-9)
Menopause (+/-)	28/26
Sexual activity (+/-)	36/18
Concomitant medication (+/-)	23/31

*median value

Discussion

Bladder pain syndrome/interstitial cystitis is a disease which can be diagnosed and treated with difficulty. Although the disease can be treated with short-term regimen, it could recur over the time. Many alternative treatment modalites are available to treat BPS/IC. Intravesical agents provide higher concentration with lower side effects.

Intravesical instillation of hyaluronic acid exhibits a variety of properties that might contribute to its prophylactic mechanism. These are inhibition of adherence of immune complexes to polymorphonuclear cells, inhibition of leukocyte migration and aggregation, depending on viscosity, regulation of fibroblast and endothelial cell proliferation and enhancement of connective tissue healing. To restore the GAG layer is becoming the main aim of new therapies for the treatment of chronic cystitis and PBS/IC. Preliminary experiences with GAG replenishment for different pathological conditions involving the lower urinary tract have been reported. Exogenous intravesical GAGs have been used for the treatment of PBS/IC.[17] In the present study, the mean VAS decreased from pretreatment level of 7.9 to 3.6 after 3 months of teatment (55% decrease, $p<0.05$). The mean

Table 2. The reliability test of questionnaires

Test (Clinician)	Cronbach's Alpha	p	Test (Medical assistant)	Cronbach's Alpha	p
ICSI (pre-treatment)	0.778	0.000	ICSI (pre-treatment)	0.593	0.000
ICSI (post-treatment)	0.918	0.000	ICSI (post-treatment)	0.927	0.000
ICPI (pre-treatment)	0.779	0.000	ICPI pre-treatment)	0.636	0.000
ICPI (post-treatment)	0.934	0.000	ICPI (post-treatment)	0.945	0.000

ICSI: Interstitial Cystitis Symptoms Index; ICPI: Interstitial Cystitis Problem Index

Table 3. Kappa measure of agreement test

Score (pre-treatment)	Kappa Measure of Agreement (Clinician-Medical assistant)	p	Score (post-treatment)	Kappa Measure of Agreement (Clinician-Medical assistant)	p
VAS	0.573	0.000	VAS	0.612	0.000
SI-q1	0.943	0.000	SI-q1	1.000	0.000
SI-q2	1.000	0.000	SI-q2	1.000	0.000
SI-q3	1.000	0.000	SI-q3	1.000	0.000
SI-q4	0.949	0.000	SI-q4	0.959	0.000
SI-TS	0.929	0.000	SI-TS	0.967	0.000
PI-q1	1.000	0.000	PI-q1	1.000	0.000
PI-q2	0.949	0.000	PI-q2	1.000	0.000
PI-q3	1.000	0.000	PI-q3	1.000	0.000
PI-q4	1.000	0.000	PI-q4	1.000	0.000
PI-TS	0.954	0.000	PI-TS	1.000	0.000

TS: total score, q: question; VAS: visual analogue scale SI: Symptoms Index, PI: Problem Index

Table 4. The pretreatment and post-treatment scores with improvement ratios (recorded by clinician)

	Pre-treatment mean score ± SD	Post-treatment mean score ± SD	p*	Improvement (score) ratio %	Improvement (patient) ratio (%)
VAS	7.9±1.4	3.6±2.4	0.00	55.0	50/54 (92.6)
SI-q1	4.3±0.9	2.4±1.3	0.00	44.7	48/54 (88.9)
SI-q2	4.1±1.0	2.1±1.5	0.00	50.0	45/54 (83.3)
SI-q3	3.2±1.3	1.7±1.5	0.00	48.3	44/54 (81.5)
SI-q4	3.3±0.8	1.6±1.2	0.00	50.0	43/54 (79.6)
SI-TS	15.0±3.2	7.9±5.0	0.00	48.5	51/54 (94.4)
PI-q1	3.6±0.6	2.0±1.4	0.00	44.4	42/54 (77.8)
PI-q2	3.2±1.0	1.7±1.4	0.00	46.4	41/54 (75.9)
PI-q3	3.5±0.7	2.0±1.3	0.00	43.7	41/54 (75.9)
PI-q4	3.7±0.5	2.0±1.3	0.00	46.1	44/54 (81.5)
PI-TS	14.0±2.2	7.7±4.8	0.00	45.5	47/54 (87.0)

*Wilcoxon Signed Rank Test. TS: total score; VAS: visual analogue scale SI: Symptoms Index, PI: Problem Index

Table 5. The comparison and correlation of improvements in total scores of ICSI and ICPI

Questionnaire	Improvement in total score mean (%)	p*	Correlation**
ICSI-TS	48.5	0.000	r=0.947
ICPI-TS	45.5		(p=0.000)

ICSI: Interstitial Cystitis Symptoms Index; ICPI: Interstitial Cystitis Problem Index
*Student's t test, **Pearson correlation test TS: total score

total scores of ICSI and ICPI decreased significantly after the treatment (48.5% and 45.5%, respectively). In addition, there was a significant association between decreases in total scores of ICSI and ICPI (Table 5). Morales et al.[18] reported 25 patients who received intravesical instillation of hyaluronic acid weekly for 4 times, and monthly for a long time, and they compared pre-, and posttreatment symptom scores and VAS scores. Fifty-six percent of the patients demonstrated improvements at 4, and 71% of them at 12 weeks of treatment, and treatment efficacy decreased after 24 weeks of the therapy. Riedl et al.[19] included 126 patients who received hyaluronan treatment, and the mean VAS scores decreased from 8.5 to 3.5 in other words 55% decrease after the treatment. Cervigni et al.[20] reported on 23 women who received intravesical instillation of hyaluronic acid and chondroitin sulphate treatment per week for 20 weeks and then monthly for 3 times. They observed a significant improvement in urinary symptoms on voiding diaries and VAS for frequency (p=0.045), urgency (p=0.005), and pain on urination (p=0.001). In addition to these findings, ICSI and ICPI decreased significantly (p=0.004 and p=0.01, respectively). In a study by Engelhardt et al.[21] on long-term effect of intravesical instillation of hyaluronic acid treatment, 70 patients had undergone the treatment for 10 weeks. While pre-treatment median VAS score was reported as 8.15, while they were 2,71 at immediate post-treatment, 2.70 at 6 months and 2.41 at 5 years after the treatment. Kallestrup et al.[9] reported 20 patients who had received intravesical instillation of hyaluronic acid treatment weekly for 4 weeks and monthly for 2 times. At 3 years after the treatment, they found 40% decrease in nocturia and 30% decrease in bladder pain. In our study, frequency of nocturnal urination (ICSI form q:3) decreased 48.3% compared to pre-treatment. There was also 50% decrease in the frequency of bladder pain and burning (ICSI form q:4) after the treatment. As shown in Table 4, all scores significantly improved after the treatment. In a meta-analysis of 10 published studies, including 390 patients, Pyo et al.[22] found significant improvements in fixed-effects of mean VAS (mean difference-3.654) ICSI (mean difference-3.223) and ICPI scores (mean difference-2.941). In our study, hyaluronic acid treatment was more effective in the patients aged ≥51.5 relative to <51.5 years (p=0.033). Decreases in mean total scores of ICSI and ICSI were similar in each age group (p>0.05). After the treatment, the mean VAS, mean total scores of ICSI and ICPI were lower than the pretreatment levels in the presence of menopause, however, these decreases were not significant. The mean VAS scores decreased significantly (p=0.018), while mean total scores of ICSI and ICSI decreased insignificantly (p>0.05) in the patients who had no sexual activity. Gardella et al.[23] suggested that the association between vulvodynia and IC/BPS, a chronic, debilitating disease of unknown etiology, might involve sex hormone-dependent mechanisms regulating vulvo-vaginal health. It was suggested that IC/BPS and vulvodynia are chronic pain syndromes that appear to be intertwined from the perspectives of embryology, pathology and epidemiology.[24] In the present study, positive response to the treatment in the patients with no sexual activity might be explained with the association between vulvodynia and BPS/IC. Bogart et al. [25] reported that sexual

Table 6. Comparison of rates of improvement in mean scores, classified according to subgroups

Parameter	VAS %	SI-q1 %	SI-q2 %	SI-q3 %	SI-q4 %	SI-TS %	PI-q1 %	PI-q2 %	PI-q3 %	PI-q4 %	PI-TS %
Age ≥51.5*	62.9	50.4	57.1	49.0	57.7	54.0	51.8	46.6	48.4	54.0	50.8
Age <51.5*	47.2	38.8	42.1	47.5	41.9	42.9	37.0	46.3	38.9	38.3	40.2
p**	0.033	0.101	0.088	0.084	0.082	0.129	0.128	0.976	0.331	0.076	0.222
Parity-n ≥2*	56.5	45.8	50.7	47.9	50.7	49.5	46.5	48.0	43.0	47.4	46.6
Parity-n <2*	49.0	36.8	41.0	43.8	44.0	41.0	31.0	36.3	37.5	38.7	36.2
p**	0.390	0.260	0.334	0.713	0.534	0.312	0.152	0.306	0.618	0.402	0.288
Menopause (+)	59.8	46.2	52.1	47.0	52.5	50.0	49.0	43.5	44.4	48.8	47.2
Menopause (-)	48.9	40.3	43.7	46.7	45.0	44.1	35.0	46.3	38.3	41.0	40.1
p**	0.161	0.409	0.344	0.970	0.428	0.427	0.144	0.783	0.531	0.398	0.414
Sexual activity (+)	49.0	41.0	45.5	49.3	45.0	45.6	41.4	45.0	42.1	41.2	42.6
Sexual activity (-)	67.4	52.1	57.9	46.2	60.0	54.3	50.5	49.5	46.8	56.0	51.5
p**	0.018	0.134	0.185	0.760	0.124	0.262	0.385	0.665	0.658	0.116	0.333
Concomitant medication (+)	54.8	42.1	44.4	50.2	51.1	47.1	39.1	42.0	40.6	45.6	42.1
Concomitant medication (-)	55.2	46.65	53.4	46.9	49.0	49.5	48.4	49.8	46.0	46.5	48.1
p**	0.951	0.547	0.314	0.735	0.816	0.742	0.350	0.449	0.589	0.925	0.499

VAS: visual analogue scale; *Median value, **Student's t test or Mann-Whitney U test SI: Symptoms Index, PI: Problem Index TS: total score

Table 7. The univariate analysis with various parameters for predicting significant improvement in ICSI-TS and ICPI-TS

Parameter	Improvement in ICSI – TS (≥median)			Improvement in ICPI – TS (≥median)		
	OR	95% CI	p	OR	95% CI	p
Age (≥51.5)	2.07	0.17-24.40	0.560	7.42	0.82-66.62	0.073
Parity (≥2)	6.16	0.51-74.17	0.167	1.10	0.18-6.44	0.916
Menopause (+)	2.26	0.19-26.60	0.517	1.52	0.30-7.60	0.608
Sexual activity (+)	0.00	0.00-0.00	0.998	0.00	0.00-0.00	0.998
Concomitant medication (+)	1.51	0.13-17.82	0.740	0.99	0.19-4.91	0.998

ICSI: Interstitial Cystitis Symptoms Index; ICPI: Interstitial Cystitis Problem Index TS: total score

dysfunction specific to BPS/IC was significantly associated with more severe BPS/IC symptoms, younger age, worse depression symptoms, and badly perceived general health. In the present study, parity (≥2) and additional medicine use were not predictive for improvement in the mean VAS and mean total scores of ICSI and ICPI (p>0.05). No study was found in the literature to report the relationship between parity, menopause and sexual activity on the efficacy of intravesical instillation of hyaluronic acid treatment.

In the light of our findings, the possibility of the presence of confusable diseases have been excluded and the high dose (120 mg/50 ml) of intravesical hyaluronic acid may be used in further studies. In addition, this treatment modality has some advantages such as monthly maintenance, if necessary, and repeatable instillations with very low rate of side effects.

Ethics Committee Approval: Ethics committee approval was received fort his study from the Ethics Committee of Mersin University (Date: 12/22/2016 and number: 376).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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