

Assessment of long-term intravesical hyaluronic acid, chondroitin sulfate and combination therapy for patients with bladder pain syndrome

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Introduction The aim of this study was to evaluate the efficacy, safety and tolerability of intravesical hyaluronic acid (HA), chondroitin sulfate (CS) and combination therapies (HA+CS) for patients with bladder pain syndrome (BPS) – interstitial cystitis (IC) during a 24 months follow-up period.

Material and methods The study was conducted with a prospective, randomized and double-blinded design. A total of 72 patients were divided into three groups as HA, CS and combination group. Outpatient visits were performed at the beginning of the study and at every 3rd month thereafter. Both objective parameters included in 3 day micturition diary such as number of micturitions per 24 hours, volume voided in each micturition and self-reported questionnaires such as Patient Perception of Bladder Condition Scale, Visual Analog Scale, Pain Urgency Frequency Questionnaire, Interstitial Cystitis Symptom and Problem Index, Health Related Quality of Life (HRQoL) were used to assess the efficacy of three different agents. Safety was defined as any adverse event beginning or worsening in the study and reported in each visit.

Results All groups showed a significant improvement both in the parameters included in the 3 day micturition diary and self-reported questionnaires compared to the baseline values or scores recorded at the beginning of the study. Our primary end point was improvement in HRQoL score. The combination therapy was superior to both of the monotherapies in terms of improvement in HRQoL score and the difference was statistically significant ($p = 0.02$).

Conclusions Combination therapy provides better results than the monotherapies to obtain symptomatic relief in patients with BPS/IC. Meta-analysis of different well-designed studies are required for more definitive results.

Key Words: bladder pain syndrome ↔ chondroitin sulfate ↔ hyaluronic acid
↔ interstitial cystitis ↔ intravesical therapy

INTRODUCTION

Bladder pain syndrome (BPS) is characterized by persistent pelvic pain related to the bladder, worsening in case of bladder filling and accompanied by at least one of overactive bladder (OAB) symptoms such as nocturia, frequency, urgency or urinary incontinence. Any other disease which may lead to these symptoms must be excluded for the definitive diagnosis of BPS. The term of interstitial cystitis (IC) could be used if cystoscopic findings such

as Hunner ulcers or glomerulations are recognized in BPS patients.

The duration of symptoms is also important in the diagnosis of BPS. They should persist for at least 6 weeks; symptoms lasting less time are commonly associated with other conditions such as urinary tract infection (UTI), stone formation, bladder tumor or neurogenic bladder.

Conservative approaches such as adjusted diet, optimal hydration and changing micturition habits constitute the first-line treatments of BPS. If these

conservative treatment options fail despite being performed firmly for 6 months, analgesics and oral pentosan polysulfate therapy are considered as the second step of BPS treatment.

Intravesical glycosaminoglycan (GAG) replenishment therapy provides higher efficacy and tolerability compared to oral pentosan polysulfate (PPS). Adverse effects limit the long-term use of pentosan polysulfate. So, intravesical therapy as the third step of BPS treatment is performed in most patients. Hyaluronic acid (HA) and chondroitin sulfate (CS) are essential GAGs in bladder layers. Drugs containing these GAGs are used to relieve symptoms of BPS, particularly pelvic pain. Gülpınar et al. [1] compared intravesical HA and CS therapies in a randomized study including 42 patients with a follow-up period of 6 months. The study concluded that CS was superior to HA in terms of frequency and nocturia. Porru et al. [2] discussed the efficacy of intravesical HA and CS combination therapy in a single arm study. Significant improvements were reported in the Pain Urgency Frequency (PUF) score. Although efficacy of intravesical HA [3], CS [4] and combination therapies have been defined, follow-up period of the studies was relatively short (6 months) and comparison of combination therapy with both of the single therapies has not been evaluated yet.

Our study aims to compare efficacy, safety and tolerability of HA, CS and combination therapies in the long-term treatment of BPS and associated symptoms.

MATERIAL AND METHODS

The study was conducted at Şanhurfa Research and Training Hospital with a prospective, randomized and double-blinded design and in accordance with ethical principles derived from The Declaration of Helsinki and Good Clinical Practice. An ethical approval was obtained from the local ethical committee and all patients who participated provided written informed consent.

A total of 72 patients with definitive diagnosis of BPS were enrolled. First, all patients were evaluated with a detailed medical history and physical examination. Then, urinalysis, urine culture, complete blood count, serum electrolytes, creatinine and liver enzymes, and ultrasonography examination of the abdomen were performed. Moreover, prostate-specific antigen (PSA) testing and digital rectal examination (DRE) for males and pregnancy test for females were performed. All patients underwent cystoscopy to rule out bladder tumor or stone. Computed tomography (CT) examination was performed in cases with suspicion of ureteric stone. A history of tuberculosis,

endometriosis, urinary cancer, pelvic radiotherapy, current UTI or urinary stone, untreated sexually transmitted disease or urethral diverticulum, any suspicious finding in DRE, PSA ≥ 2.5 ng/ml, positive pregnancy test and breastfeeding were exclusion criteria (Figure 1). Patients who had persistent pelvic pain arising from the bladder, deteriorating with bladder filling, lasting longer than 6 weeks, additionally suffering from at least one of OAB symptoms and not benefited from prior treatments were included in the study (Table 1). It was mandatory to meet all the inclusion criteria and none of the exclusion criteria to be involved in the study. Although all prior intravesical therapies were accepted as a reason for exclusion, prior oral PPS therapy was not defined as a criteria for exclusion. Inclusion – exclusion assessment of patients was performed by one physician. The 72 patients were randomly divided into three groups by block randomization according to different intravesical GAG replenishment therapies, Group 1 was administered hyaluronic acid (HA) and Group 2 chondroitin sulphate (CS) whereas Group 3 received a combination of HA and CS. No placebo group was included.

Follow-up period of the study was 24 months. Out-patient visits were performed at the beginning of the study and then at every 3 months thereafter (9 visits in total). Patients who were lost to follow-up were excluded from the study. Treatment schedules for the three drugs used are listed in Table 2.

The efficacy of the treatments was assessed by the parameters included in the micturition diaries, additionally by the scores of self-reported questionnaires (PPBC Scale: Patient Perception of Bladder Condition Scale, VAS: Visual Analog Scale, PUF: Pain Urgency Frequency Questionnaire, ICSI and ICPI: Interstitial Cystitis Symptom Index and Problem Index, HRQoL: Health Related Quality of Life).

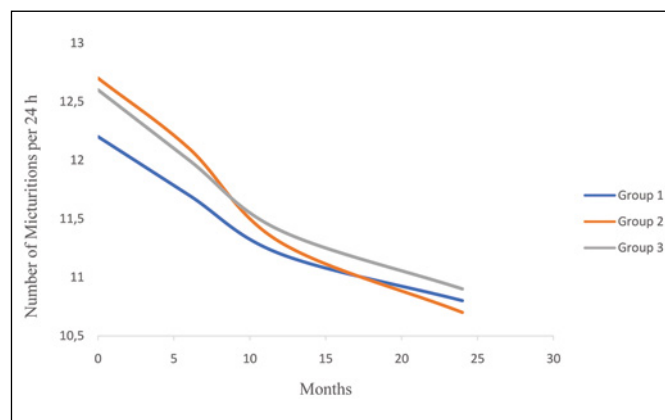


Figure 1. Improvement in urinary frequency during follow-up period of 24 months.

Table 1. Inclusion-exclusion criteria of the study

Exclusion criteria
Any defined neurological disease affecting pelvic nerves
Heart failure, NYHA class III or IV
Chronic obstructive pulmonary disease, GOLD 3 or 4
Defined urologic malignancy or any cancer with a urinary metastasis
Liver enzymes higher than upper limit
Creatinine level ≥ 1.2 mg/dl
History of tuberculosis
History of endometriosis
History of radiotherapy including pelvis
Untreated UTI, STD or urinary stone
Urethral diverticulum
Positive pregnancy test
Breastfeeding
Suspicious DRE or PSA ≥ 2.5 ng/ml
Prior intravesical GAG replacement therapy such as HA, CS, heparin or PPS
Inclusion criteria
Persistent pelvic pain related to the bladder
Pain worsening with bladder filling
At least one OAB symptom: frequency, urgency, urgency incontinence, nocturia
Duration of symptoms longer than 6 weeks
Not benefited from conservative approaches or prior drugs

NYHA – New York Heart Association; GOLD – Global Initiative for Chronic Obstructive Lung Disease; UTI – urinary tract infection; STD – sexually transmitted disease; DRE – digital rectal examination; PSA – prostate-specific antigen; GAG – glycosaminoglycan; HA – hyaluronic acid; CS – chondroitin sulfate; PPS – pentosan polysulfate; OAB – overactive bladder

Table 2. Treatment schedules of the drugs used in the study

Hyaluronic acid 50 ml/120 mg	Via intravesical route, once a week for 6 weeks, then twice a month for 6 months, then continued once a month until 24 th month.
Chondroitin sulphate 40 ml/80 mg	Via intravesical route, once a week for 6 weeks, then twice a month for 6 months, then continued once a month until 24 th month.
Hyaluronic acid and chondroitin sulfate combination (half dose of each)	Via intravesical route, once a week for 6 weeks, then twice a month for 6 months, then continued once a month until 24 th month.

Table 3. The patient perception of bladder condition scale

Which of the following statements describes your bladder condition best at the moment? Please mark X in one box only
<input type="checkbox"/> My bladder condition does not cause me any problems at all.
<input type="checkbox"/> My bladder condition causes me some very minor problems.
<input type="checkbox"/> My bladder condition causes me some minor problems.
<input type="checkbox"/> My bladder condition causes me some moderate problems.
<input type="checkbox"/> My bladder condition causes me severe problems.
<input type="checkbox"/> My bladder condition causes me many severe problems.

The micturition diary included 3 day recordings of numbers of micturitions per 24 hours, number of urgency, incontinence and nocturia episodes per 24 hours, and additionally volume voided during each micturition. PPBC (Table 3) is a validated scale in which patients report their perceived bladder condition on a 6-point scale ranging from 1 ‘no problems at all’ to 6 ‘many severe problems’. Micturition diaries and questionnaires were completed at each visit. Safety was defined as any adverse event beginning or worsening during the study. To assess safety; evaluation of vital signs (fever, heart rate and blood pressure), electrocardiogram (ECG) and laboratory tests (urinalysis, complete blood count, electrolytes, renal-hepatic function tests) were performed at each visit of the study. Serious adverse events (Table 4) such as recurrent febrile UTIs, symptomatic cardiac arrhythmias, significant nephrotoxicity or hepatotoxicity were regarded as causes requiring discontinuation of treatment.

Efficacy and safety were assessed by one physician. All adverse events were reported at each visit. The primary end point was improvement in HRQoL.

Any drug used by the participants for comorbidities was recorded at the beginning of the study. In addition, some patients used a type of antimuscarinic (solifenacin, tolterodine, propiverine) or mirabegron for OAB symptoms.

Results starting from the first visit until the final visit for all groups were analyzed by using analysis of covariance model (ANCOVA) to obtain adjusted means. SPSS Version 22.0 [5] was used for all statistical analyses. A p-value of <0.05 was accepted for statistical significance.

RESULTS

Table 5 provides an overview of the baseline values and general characteristics of the study population. Each group included 24 patients. Mean age was 37.2 years and it was not different between the three groups. A total of 10 (13%) of the participants were male, 20 (27%) patients were Syrian. There was no significant difference between the three groups in male or Syrian ratio.

Parameters recorded in the 3 day micturition diary at the first visit showed similar results for the three groups. Mean volume voided during each micturition was 136.6 ± 3.7 ml ($p:0.84$) and mean number of micturitions per 24 hours was 12.5 ± 1.3 for all patients ($p = 0.73$). Number of episodes of urgency, incontinence and nocturia were 3.5 ± 1.3 , 2.7 ± 0.9 , 3.3 ± 0.6 , respectively, for the study population. Variations of these parameters amongst the three groups presented insignificant differences ($p > 0.4$).

Baseline PPBC score was obviously high in all groups, varying from 5.1 to 5.3. VAS scores were over 8.5 in each group which indicated the severity of pain of the participants. PUF questionnaire symptom score and bother score were 22.5 ± 1.5 and 12.7 ± 0.5 , mean ICSI score and ICPI score were 17.7 ± 1.3 and 14.5 ± 1.2 , respectively. The primary endpoint of our study, HRQoL, was highest with a score of 64.2 ± 2.3 in Group 1 and lowest with a score of 63.9 ± 2.1 in Group 2. As in other parameters, HRQoL score did not differ significantly in any group ($p = 0.9$). All drugs used provided a significant improvement in parameters recorded by micturition diaries at the end of the study compared to baseline values ($p < 0.05$). However, as post-treatment values of

three groups were compared, no significant differences ($p > 0.65$) were obtained (Table 6). Number of micturitions per 24 hours were significantly decreased in all groups (Figure 1). Mean volume voided in each micturition was slightly higher in Group 3 with a value of 157.3 ± 4.8 ml though the difference was not clinically significant.

Evident improvements were recorded at the end of the study in all groups compared with the baseline values of the scores of self-reported questionnaires ($p < 0.05$). PPBC score presented a remarkable decrease from a baseline value of 5.2 to 4.0. The most prominent recovery in perceived bladder condition was seen in the HA+CS group with a decreased score of 1.5. However, final PPBC scores of the study groups did not differ significantly ($p = 0.36$). Mean VAS score was 6.3 ± 0.6 in Group 3, which represented better pain relief than the other groups though the difference was not significant ($p = 0.15$). PUF questionnaire symptom score and bother score was significantly lower in Group 3 ($p = 0.04$ for PUF symptom score, $p = 0.03$ for PUF bother score). Mean ICSI and ICPI scores were lower in Group 3, however, the difference was statistically insignificant ($p = 0.07$ for ICSI score, $p = 0.05$ for ICPI). The primary end point of our study, improvement in HRQoL score, was significantly better in Group 3 (Figure 2) compared with Groups 1 and 2 after 24 months of follow-up ($p = 0.02$).

Table 4. Adverse events requiring discontinuation of treatment

Elongation in QT interval
Symptomatic cardiac arrhythmia
2 times the upper limit of liver enzymes
An increase of ≥ 0.4 mg/dl in creatinine level
Decrease in consciousness
Peripheral neuropathy
Intolerable gastrointestinal side effects such as vomiting, diarrhoea, dyspepsia
Persistent macroscopic hematuria or febrile urinary tract infections

Table 5. Baseline values and characteristics of the study population

	Group 1	Group 2	Group 3	P value	Total
Mean age (years)	37.1	37.4	37.2	0.52	37.23
Patients excluded (n)	3	3	3	–	9
Patients included (n)	24	24	24	–	72
Male / total ratio %	16% (4/24)	12% (3/24)	12% (3/24)	0.67	13% (10/72)
Ethnicity, Syrian / Syrian+Turkish ratio	29% (7/24)	29% (7/24)	25% (6/24)	0.71	27% (20/72)
Mean number of micturitions per 24 hr	12.2 ± 1.2	12.7 ± 1.3	12.6 ± 1.4	0.73	12.5 ± 1.3
Mean volume voided in each micturition (ml)	135.7 ± 3.9	136.8 ± 3.7	137.4 ± 3.6	0.84	136.6 ± 3.7
Number of urgency episodes per 24 hr	3.5 ± 1.3	3.4 ± 1.2	3.6 ± 1.4	0.43	3.5 ± 1.3
Number of urgency incontinence episodes per 24 hr	2.8 ± 0.93	2.6 ± 0.88	2.9 ± 0.91	0.41	2.7 ± 0.9
Number of nocturia episodes per 24 hr	3.2 ± 0.6	3.3 ± 0.7	3.4 ± 0.5	0.48	3.3 ± 0.6
Mean PPBC Scale Score	5.3 ± 0.8	5.1 ± 0.6	5.3 ± 0.8	0.56	5.2 ± 0.7
Mean VAS Score	8.8 ± 0.7	8.9 ± 0.6	8.9 ± 0.5	0.62	8.8 ± 0.6
Mean PUF Questionnaire Symptom Score	22.8 ± 1.6	22.4 ± 1.5	22.3 ± 1.4	0.74	22.5 ± 1.5
Mean PUF Questionnaire Bother Score	12.9 ± 0.6	12.8 ± 0.5	12.5 ± 0.6	0.83	12.7 ± 0.5
Mean ICSI Score	17.9 ± 1.4	17.6 ± 1.2	17.8 ± 1.3	0.69	17.7 ± 1.3
Mean ICPI Score	14.5 ± 1.2	14.3 ± 1.3	14.8 ± 1.1	0.73	14.5 ± 1.2
Mean HRQoL Questionnaire Score	64.2 ± 2.3	63.9 ± 2.1	64.1 ± 2.2	0.91	64.0 ± 2.2

PPBC – Patient Perception of Bladder Condition Scale; VAS – Visual Analog Scale; PUF – Pain Urgency Frequency Questionnaire; ICSI – Interstitial Cystitis Symptom Index; ICPI – Interstitial Cystitis Problem Index; HRQoL – Health Related Quality of Life

Table 6. Results of three groups at the end of the study

	Group 1	Group 2	Group 3	P value	Total
Mean number of micturitions per 24 hr	10.8 ±1.5	10.7 ±1.4	10.9 ±1.3	0.83	10.8 ±1.4
Mean volume voided in each micturition (ml)	152.8 ±4.6	154.1 ±5.0	157.3 ±4.8	0.66	154.7 ±4.8
Number of urgency episodes per 24 hr	2.7 ±1.3	2.8 ±1.4	2.9 ±1.4	0.91	2.8 ±1.3
Number of urgency incontinence episodes per 24 hr	1.6 ±0.5	1.5 ±0.6	1.5 ±0.7	0.89	1.5 ±0.6
Number of nocturia episodes per 24 hr	2.5 ±0.6	2.7 ±0.7	2.6 ±0.5	0.95	2.6 ±0.6
Mean PPBC Scale Score	4.3 ±0.7	4.1 ±0.6	3.8 ±0.5	0.36	4.0 ±0.6
Mean VAS Score	7.6 ±0.5	7.7 ±0.6	6.3 ±0.6	0.15	7.0 ±0.5
Mean PUF Questionnaire Symptom Score	18.4 ±1.2	17.9 ±1.1	16.1 ±0.9	0.04	17.4 ±1.0
Mean PUF Questionnaire Bother Score	10.5 ±0.9	10.2 ±0.8	8.7 ±0.7	0.03	9.8 ±0.8
Mean ICSI Score	15.3 ±0.9	15.1 ±1.0	13.4 ±1.1	0.07	14.6 ±1.0
Mean ICPI Score	12.4 ±1.0	12.1 ±0.8	10.3 ±0.8	0.05	11.6 ±0.8
Mean HRQoL Questionnaire Score	72.8 ±3.3	73.6 ±3.0	88.5 ±1.5	0.02	78.3 ±2.3

PPBC – Patient Perception of Bladder Condition Scale; VAS – Visual Analog Scale; PUF – Pain Urgency Frequency Questionnaire; ICSI – Interstitial Cystitis Symptom Index; ICPI – Interstitial Cystitis Problem Index; HRQoL – Health Related Quality of Life

No serious adverse event requiring discontinuation of treatment was seen in any of the participants during the 24 months follow-up period. A total of 5 patients presented with UTIs which were not severe and did not recur, so they were treated with appropriate antibiotic therapy. Transient macroscopic hematuria due to traumatic catheterization was seen in 3 patients, however this did not require intervention and resolved in 2 to 4 days. None of the patients in the study quit due to the side effects of the drugs, so tolerability was good in all groups during the 24 months follow-up period.

DISCUSSION

BPS is one of the demanding diseases in urology. Persistent complaints, decreased quality of life and several side effects of different treatment modalities lead to low patient satisfaction rates. Therefore, good management of BPS is one of the most important goals in functional urology.

Persistent pelvic pain is the most irritating symptom that causes patients to report to the physician. OAB symptoms such as frequency, urgency or nocturia are accompanying symptoms that worsen patients' quality of life. Therefore, the main goal of BPS treatment focuses on relief of pelvic pain at first and then its accompanying symptoms.

Intravesical GAG therapies constitute the main treatment option in most of the patients with BPS. Oral supplements of GAGs have a lower efficacy. Although oral replacement therapy are recommended in the guidelines, most patients benefit from intravesical therapy. Different agents and treatment

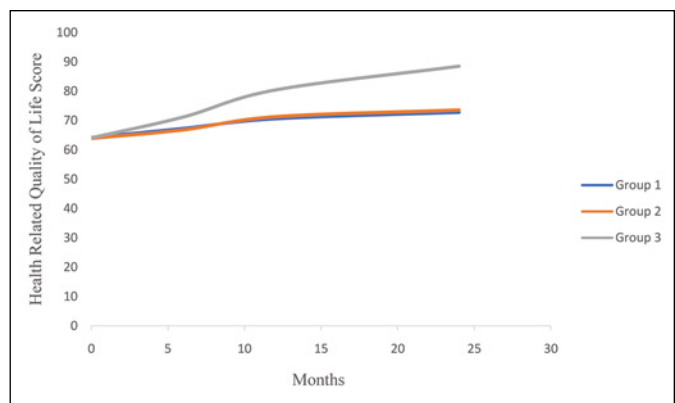


Figure 2. Improvement in HRQoL score during follow-up period of 24 months.

schedules are defined and it should be patient-adjusted to improve treatment satisfaction.

Urologic literature has a limited amount of well-designed studies comparing these agents for efficacy and safety. Gülpınar et al. [6] compared HA with HA and CS combination in a randomized study including 53 patients and concluded that there was no significant difference between the two groups although both groups had significant improvement compared to the beginning of the study. Cervigni et al. [7] reported the long term results of HA and CS combination therapy in 12 BPS patients refractory to other treatments. They concluded that combination therapy was safe and effective during a 3 year follow-up period.

Our study had similar results to the literature. The results showed no difference between HA and CS.

However, combination of HA and CS provided better results, particularly in HRQoL questionnaire. We think that the main reason for this result depends on possible decreased levels of both GAGs in the impaired bladder layers. Each GAG has a specific role in bladder physiology so that lack of any GAG may cause significant changes in bladder layers that would lead to complaints in the lower urinary tract. The reason why vesical layers are impaired is the point of interest in BPS. Recurrent cystitis or vaginitis due to sexually transmitted infections, radiotherapy including the pelvic field, some chemotherapeutic agents such as cyclophosphamide, neurological or systemic diseases (diabetic pelvic neuropathy) affecting pelvic nerves and psychological pathologies such as major depression are blamed factors leading to or accompanying BPS. However, the underlying pathophysiological mechanism is still under research. Recent studies have found that the disorganisation of bladder layers leads to the contact of urine with the submucosal field. This contact causes irritation of the nerves located in the lamina propria and submucosa. Replenishment of GAGs provides symptomatic relief at first in 65% to 87% of BPS patients. However, associated symptoms, particularly pelvic pain, recur in 47% of the patients in 3 to 6 months.

Repeated doses improve symptoms in 53% of BPS patients. Our study takes attention into this topic with its 24 months follow-up. Those who suffer from persistent OAB symptoms may benefit from antimuscarinics or mirabegron. Lack of antimuscarinic or mirabegron as an add-on therapy is a limitation of our study.

Another limitation of the study is lack of periodic cystoscopic examinations. Regular cystoscopy and bladder biopsy would contribute to our knowledge about the histologic alterations of vesical layers in BPS patients under intravesical GAG therapy. In addition, this may reveal treatment failures and guide future treatment approaches.

CONCLUSIONS

Intravesical HA and CS have adequate and similar response rates in the treatment of BPS. A combination of these agents presents better results than their respective monotherapies. In order to provide more definitive recommendations, a meta-analysis of several randomized prospective trials is required.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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