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ORIGINAL ARTICLE

Outcomes of intravesical chondroitin-sulfate and combined hyaluronic-acid/chondroitin-sulfate therapy on female sexual function in bladder pain syndrome

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Abstract

Introduction and hypothesis Our aim was to determine the efficacy of intravesical chondroitin sulfate (CS) and combined hyaluronic acid/chondroitin sufate (HA/CS) treatment and their effects on sexual function of females with interstitial cystitis/bladder pain syndrome (IC/BPS).

Methods A total of 68 female patients with IC/BPS between 2012 and 2018 were reviewed. Thirty-three patients were treated with combined HA/CS and 28 patients were treated with CS. Instillations were performed weekly for the first month, biweekly for the second month, and monthly in the third and fourth months. Before and after the sixth month of the treatment, all patients were evaluated with the Female Sexual Function Index (FSFI), visual analog pain scale (VAS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), and voiding diary, and changes were recorded.

Results A statistically significant improvement was determined for FSFI, VAS, ICSI, and ICPI scores after treatment in both groups. Among baseline characteristics, a weak but significant negative correlation was determined only between the ICSI score improvement and age (rho: −0.38; $p = 0.03$) on statistical analysis. Compared with CS, combined HA/CS treatment was superior in terms of ICSI, ICPI, and daytime and nighttime frequency improvement (0.042, 0.038, 0.039, and 0.045; respectively). All domains of the sexual function index were significantly improved at the sixth month of intravesical therapy in both groups. A statistical difference was not found between the two groups.

Conclusions Although it seems that intravesical HA/CS combination is superior to CS alone in terms of symptom reduction, both of them have beneficial effects on sexual function.

Keywords Interstitial cystitis · Sexual function · Chondroitin sulfate · Hyaluronic acid

Introduction

Interstitial cystitis/bladder pain syndrome (IC/BPS) is defined by the International Continence Society (ICS) and The European Society for the Study of Interstitial Cystitis (ESSIC) as a chronic inflammatory pain syndrome characterized by suprapubic pain related to bladder filling and urinary symptoms such as urgency and frequency [1, 2]. Diseases with similar symptoms such as urinary tract obstructions or stones, bladder tumor, or bladder infection must be ruled out before making a precise diagnosis [3]. The estimated prevalence rates of IC/BPS were reported as 2.7–6.5% and 1.9–4.2% for women and men [4, 5]. Although it has been hypothesized that various factors such as autoimmunity, infectious processes, toxins, and activation of mast cells are responsible, the etiology of IC/BPS is poorly understood [6]. There is a wide consensus that clinical signs and symptoms are related to the disruption of the bladder mucosa surface layer and the damage of its glycosaminoglycan (GAG) component. Due to the loss of watertight function, the subepithelial layer is exposed to various urinary toxic agents, which results in neurogenic inflammation and chronic bladder epithelial damage [7].

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Female sexual dysfunction is a significant health problem related to age, education, and psychological and medical conditions, and it consists of loss of sexual desire, dyspareunia, and decreased arousal and orgasm frequency [8]. IC/BPS is known to exert a considerable negative effect on female sexual function and quality of life in women [1, 9]. Because of this, improving sexual function should be one of the main goals in the multidisciplinary treatment of women with IC/BPS. Various treatment modalities such as oral pentosan polysulfate (PPS) or amitriptyline and bladder instillation of heparinoids [PPS, hyaluronic acid (HA), chondroitin sulfate (CS), and hyaluronic acid/chondroitin sulfate combination (HA/CS)] are recommended for IC/BPS after conservative management [10]. However, studies in the literature that investigate the effects of treatment on sexual function are limited. The impact of chondroitin sulfate and/or hyaluronic acid/chondroitin sulfate combination on female sexual function has not been evaluated yet.

Materials and methods

A total of 68 female patients with IC/BPS who attended a urogynecology outpatient clinic between 2012 and 2018 were reviewed in this study after institutional review board approval. Data were collected prospectively, but evaluation was performed retrospectively. After excluding specific diseases and conditions (e.g., pregnancy, urinary tract infection or malignancy, urolithiasis, incontinence, neurological pathologies, and breast feeding), patients were diagnosed with IC/BPS on the basis of symptoms and cystoscopic findings (including hydrodistension procedure) according to the European Society for the Study of Interstitial Cystitis criteria [2]. Of the 68 patients, 7 were excluded from the study because of insufficient data (1 patient) and improvement after the hydrodistension procedure (6 patients). Patients who are not sexually active were also excluded from this study. All 61 patients were contacted for the use of their data, and their informed consent was obtained retrospectively.

After conservative and oral treatments (analgesics, anticholinergics, and antidepressants) failed, intravesical treatment as a second-line therapy was performed. Thirty-three patients were treated with 800 mg/50 ml sodium hyaluronate (1.6%) and 1 g/50 ml sodium chondroitin sulfate (2%) (iAluRil, Aspire Pharma, UK) and 28 patients were treated with 40 ml/80 mg sodium chondroitin sulfate (Gepan Instill). To avoid bias, medication preference (CS alone or combined with HA) was made according to the order of application to the outpatient clinic. Intravesical instillations were performed weekly for the first month, biweekly for the second month, and monthly in the third and fourth months. Before and after the sixth month of the treatment, all patients were evaluated with the Female Sexual Function Index (FSFI) [11], visual analog pain scale (VAS), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI) [12], and 3-day voiding diary, and changes were recorded. Additionally, for excluding vulvodynia in patients with dyspareunia, a moistened cotton swab was used to palpate the vestibule and identify any painful areas (Q-type touch test).

A total of 56 patients were required to achieve 80% power with a two-sided type 1 error of 0.05. Statistical analyses were performed using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Categorical variables expressed as numbers or percentages were compared with chi-square or Fisher's exact test, and continuous variables were compared using Wilcoxon or Mann-Whitney U test. Spearman's correlation coefficient was used to assess the associations between ICSI score improvement and baseline characteristics including age, parity, BMI, drug intake, and bladder capacity. For all statistical tests, differences were considered statistically significant when $p < 0.05$.

Results

Twenty-eight patients with a median age of 32 (19–54) years in the CS group and 33 patients with a median age of 35 (21–52) years in the HA/CS group were compared. Baseline characteristics of the study cohort are summarized in Table 1. There were not any statistical differences between the CS and HA/CS groups in terms of age, parity, body mass index, smoking history, menopausal situation, bladder capacity under general anesthesia, and pre-treatment VAS, ICSI, ICPI, and FSFI scores. Of those 61 patients, 59, 55, 27, and 4 patients were taking anticholinergics, analgesics, antidepressants, and oral contraceptives before intravesical treatment, respectively. A total of only two patients continued to use medications during the instillations (one patient in the CS group used an oral contraceptive and one patient in the HA/CS group used an antidepressant).

Changes in daytime and nighttime frequency episodes, mean voided volume, pain, symptom, and sexual function scores for CS and HA/CS groups are presented in Table 2. A statistically significant improvement was determined for post-treatment daytime and nighttime frequency episodes, VAS, ICSI, ICPI, and total FSFI scores in both the CS and HA/CS groups. Among parameters including age, parity, BMI, drug intake, and bladder capacity, a weak but significant negative correlation was determined only between the ICSI score improvement and age (rho: –0.38; $p = 0.03$) on statistical analysis. Compared with CS, intravesical HA/CS treatment was superior in terms of ICSI, ICPI, and daytime and nighttime frequency improvement (0.042, 0.038, 0.039, and 0.045, respectively).

Table 1 Characteristics of patients who underwent intravesical therapy

	CS group $n = 28$	HA/CS group $n = 33$	p value
Median age (years)	32 (19–54)	35 (21–52)	0.328
BPS type, n (%)			0.905
• Classical (ulcerative)	1 (3.6%)	1 (3.1%)	
• Non-lesion	27 (96.4%)	32 (96.9%)	
Smoking history (%)	25.0%	27.2%	0.841
Median parity (n)	2 (0–5)	2 (0–6)	0.744
Body mass index (kg/m^2)	23.1	22.0	0.180
Mean bladder capacity (ml)	215	227	0.682
Menopause (%)	17.8%	15.1%	0.776
Drug intake, n(%)			
• Anticholinergic	27 (96.4%)	32 (96.9%)	0.905
• Analgesic	24 (85.7%)	31 (93.9%)	0.282
• Antidepressant	12 (42.8%)	15 (45.4%)	0.818
• Oral contraceptive	2 (7.1%)	2 (6.1%)	0.727
Pre-treatment VAS	8.7 ± 2.0	8.5 ± 1.6	0.711
Pre-treatment ICSI	14.1 ± 2.9	14.6 ± 2.8	0.768
Pre-treatment ICPI	12.5 ± 2.7	13.8 ± 2.6	0.396
Pre-treatment FSFI	21.6 ± 5.4	21.4 ± 5.0	0.814

BPS bladder pain syndrome, *CS* chondroitin sulfate, *FSFI* Female Sexual Function Index, *HA/CS* hyaluronic acid/chondroitin sulfate combination, *ICSI* Interstitial Cystitis Symptom Index, *ICPI* Interstitial Cystitis Problem Index, *VAS* visual analog pain scale

Changes in all domains (desire, arousal, lubrication, orgasm, satisfaction, and pain) for sexual function assessment are presented in Table 3. All domains were significantly improved at sixth months of intravesical therapy in both the CS and HA/CS groups. A statistical difference was not found between the CS and HA/CS groups. Pre- and post-treatment Q-type touch test scores in patients with dyspareunia were determined as 1.2 vs. 1.4, $p = 0.615$, for the CS group and 1.3 vs. 1.4, $p = 0.712$, for the HA/CS group. A statistical difference was not found between the two groups.

Discussion

IC/BPS is a chronic clinical syndrome with non-specific symptoms and has a detrimental effect on patients' quality of life. It is usually thought that defects of the GAG layer coating the bladder urothelium may play an essential role in the development of IC/BPS. The major classes of GAG include heparin sulfate, chondroitin 4-sulfate, chondroitin 6-sulfate, dermatan sulfate, keratan sulfate, and non-sulfated GAGs such as heparin and hyaluronic acid [13]. HA is an anionic, non-sulfated glycosaminoglycan distributed widely

Table 2 Changes of the questionnaire scores and voiding parameters after intravesical therapy

	CS group $n = 28$			HA/CS group $n = 33$			CS and HA/CS
	Pre-treatment	Post-treatment	p value	Pre-treatment	Post-treatment	p value	p value
Daytime frequency	12.1 ± 4.6	9.2 ± 3.0	**0.044**	12.7 ± 4.2	7.4 ± 3.2	**< 0.001**	**0.039**
Nighttime frequency	3.3 ± 1.4	2.3 ± 1.3	**0.039**	2.9 ± 1.1	1.5 ± 1.0	**< 0.01**	**0.045**
Mean voided volume (min–max)	138 ml (35–240)	162 ml (60–252)	0.258	146 ml (40–265)	168 ml (54–270)	0.361	0.882
VAS	8.7 ± 2.0	4.9 ± 1.9	**0.021**	8.5 ± 1.6	4.5 ± 1.7	**0.018**	0.691
ICSI	14.1 ± 2.9	10.0 ± 3.8	**0.035**	14.6 ± 2.8	7.7 ± 3.4	**< 0.001**	**0.042**
ICPI	12.5 ± 2.7	8.1 ± 3.2	**0.032**	13.8 ± 2.6	7.2 ± 3.1	**< 0.001**	**0.038**
FSFI	21.6 ± 5.4	27.9 ± 7.6	**0.030**	21.4 ± 5.0	29.2 ± 6.9	**0.035**	0.212

CS chondroitin sulfate, *FSFI* Female Sexual Function Index, *HA/CS* hyaluronic acid/chondroitin sulfate combination, *ICSI* Interstitial Cystitis Symptom Index, *ICPI* Interstitial Cystitis Problem Index, *VAS* visual analog pain Scale

Statistically significant values are indicated in bold

Table 3 Changes of the FSFI scores for each domain after intravesical therapy

	CS group $n = 28$			HA/CS group $n = 33$			CS and HA/CS
	Pre-treatment	Post-treatment	p value	Pre-treatment	Post-treatment	p value	p value
Desire	3.2 ± 0.6	3.7 ± 0.8	**0.043**	3.3 ± 0.7	4.1 ± 1.0	**0.046**	0.920
Arousal	3.5 ± 0.7	4.4 ± 1.2	**0.024**	3.3 ± 0.8	4.5 ± 1.2	**0.027**	0.811
Lubrication	3.4 ± 1.1	3.9 ± 1.5	**0.038**	3.5 ± 1.2	4.3 ± 1.5	**0.031**	0.916
Orgasm	3.8 ± 1.3	4.9 ± 1.4	**0.018**	3.7 ± 1.1	5.0 ± 1.2	**0.012**	0.774
Satisfaction	4.3 ± 0.9	5.5 ± 1.2	**0.022**	4.4 ± 0.5	5.8 ± 1.1	**0.019**	0.791
Pain	3.4 ± 0.8	5.2 ± 1.5	**0.042**	3.2 ± 0.7	5.5 ± 0.9	**0.028**	0.052
Total score	21.6 ± 5.4	27.9 ± 7.6	**0.030**	21.4 ± 5.0	29.2 ± 6.9	**0.035**	0.212

CS chondroitin sulfate, *HA/CS* hyaluronic acid/chondroitin sulfate combination

Statistically significant values are indicated in bold

throughout epithelial, neural, and connective tissues. It may reduce the permeability of bladder mucosa and decrease the leukocyte functions such as chemotaxis and phagocytose [3, 14]. CS is also an important molecule which was discovered in the cartilage of cows and constitutes approximately one-third of the total muco-polysaccarides on the bladder surface [15]. Based on the urothelial damage theory, intravesical CS alone or combined with HA treatments has been suggested to restore this process.

Steinhoff et al. and Nickel et al. reported 67 and 60% response rates for symptom improvement in studies investigating the efficacy of single-agent CS, respectively [16, 17]. Similarly, in a recently published article, Gulpinar et al. reported that instillation of CS in patients with IC/BPS results in a statistically significant improvement in pain, ICSI, and ICPI scores [18]. Several studies evaluated HA and CS combination as the newest intravesical treatment in IC/BPS, and favorable results have been reported. Porru and colleagues demonstrated that the HA/CS combination is an efficacious treatment model for IC/BPS and improves all parameters including VAS, ICSI, and ICPI scores [19]. A meta-analysis by Pyo et al. also confirmed that HA combined with CS may provide significant effects on symptoms and quality of life [20]. In our study, significant improvements were found for the VAS score ($p = 0.021$ and 0.029), ICSI score ($p = 0.035$ and < 0.001), and ICPI score ($p = 0.032$ and < 0.001) in both the CS and HA/CS groups, respectively. It has been also revealed that improvements in urgency and pain symptoms were the most important parameters contributing to the ICSI score decrease. We demonstrated that intravesical HA/CS combination is superior to CS treatment in terms of ICSI ($p = 0.042$) and ICPI ($p = 0.038$) in accordance with Cervigni et al. who reported that HA/CS combination may provide better therapeutic effects than CS or HA alone [21]. We hypothesized that a combination treatment with HA and CS would provide better outcomes than using the CS alone because of a more protective effect on the urothelium.

Women with IC/BPS mostly abstain from sexual intercourse, which is accepted as an important trigger for IC/BPS flares. It has been shown in several studies that IC/BPS is related to significant impairment in female sexual function, which is a substantial predictor of quality of life. In a study by Gardella et al. including 47 IC/BPS patients and 188 controls, the FSFI score of the IC/BPS group was found significantly lower than that of the control group (16.8 ± 8.7 vs. 27.3 ± 6.4) [22]. In another study evaluating female sexual dysfunction in IC/BPS, Ottem et al. reported that the baseline FSFI score was significantly higher in IC/BPS patients compared with controls (20.2 ± 9.6 vs. 29.9 ± 6.3) [23]. When compared, we found that the mean baseline FSFI score of our 61 IC/BPS patients was slightly higher than those in studies in the literature (21.5 ± 5.1). Although previous limited studies have shown that changes of the sexual function index scores (FSFI), Pelvic Organ Prolapse/Urinary Incontinence Sexual Function Questionnaire (PISQ-9), and the Medical Outcomes Study Sexual Functioning Scale (MOS SexFn) are negatively correlated with IC/BPS symptom scores after treatment, there were not any placebo-controlled studies in the available literature [24, 25]. Hung and colleagues evaluated the changes in sexual function of 87 sexually active women with IC/BPS by comparing PISQ-9 after intravesical HA instillation. A statistically significant improvement was found in the total PISQ-9 score and three of the nine domain scores (dyspareunia, negative reactions, and intensity) [24]. In another randomized study of 32-week oral pentosan polysulfate 300 mg/day, Nickel et al. assessed the sexual function of 128 patients. All patients were followed with MOS SexFn at baseline and at 8, 16, 24, and 32 weeks. They found that MOS SexFn scores progressively improved with treatment, and the mean change from baseline to the end of the study was statistically significant [25]. They also suggested that it would be better to use FSFI, which is accepted as the most reliable questionnaire nowadays instead of MOS SexFn. In our study, we demonstrated that all the domains and total FSFI scores were significantly improved after CS and HA/CS treatment, but there was not any statistical difference between the two

treatment groups. However, compared with other domains, a satisfactory improvement was observed in pain scores for the CS and HA/CS groups ($p = 0.052$; +1.8 vs. +2.3, respectively).

We used the FSFI questionnaire for our study, which is a validated tool with excellent psychometric properties evaluating sexual function during a 4-week period on a 5-point scale. This self-administered multidimensional scale assesses six individual domain scores (desire, arousal, lubrication, orgasm, satisfaction, and pain), and then the full-scale scores (ranging from 2 to 36) were calculated [11]. It has been reported in the literature that a total FSFI score of 26.0 has been established as a cutoff score for indicating possible female sexual dysfunction [26]. However, the scoring of the FSFI is problematic because 15 of the 19 items of the FSFI have a 5-point response scale with a zero value for "no sexual activity" or "did not attempt intercourse." Clearly, a woman may have a variety of reasons other than sexual dysfunction that explain a 4-week period without "sexual activity or intercourse." So we argue that it is not possible to determine a certain normal value for the FSFI score. Additionally, because our analysis revealed an important increase in FSFI scores in both treatment arms (21.6 to 27.9 in the CS group and 21.4 to 29.2 in the HA/CS group), we suggested that both CS and HA/CS have beneficial effects on female sexual function. Although there is a statistically significant increase in FSFI scores, we think that the main point is to observe the clinical improvement in the patient. For this reason, while the FSFI form was filled by the patient, we simultaneously evaluated the patients' psycho-sexological well-being.

Due to the lack of control group, it is impossible to know whether the improvements in sexual function are related to intravesical treatment or other factors. We know that multiple factors contributing to sexual dysfunction (including biopsychosocial comorbidities such as stress, abuse, or chronic illness) can be present in women with IC/BPS, and it is also important to consider that some typical IC/BPS treatments, such as antidepressants and opioids used to manage symptoms, can exacerbate female sexual dysfunction. So, we cannot rule out that the high rate of sexual impairment in our study population may be also related to the frequent use of antidepressant agents (44.2%), and the improvements noted in FSFI may be associated with discontinuation of antidepressant use.

To the best of our knowledge, this is the first study in the literature that compares the efficacy of intravesical CS and HA/CS treatment and their effects on female sexual function in IC/BPS. Small sample size, retrospective design, lack of randomization, short follow-up span, and lack of a control group were the limitations of our study. Although it seems that intravesical HA/CS combination is superior to CS alone in terms of symptom reduction, both of them have beneficial effects on the sexual function of females with IC/BPS.

Compliance with ethical standards

Conflicts of interest None.

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