Original Article

ISSN 2465-8243(Print) / ISSN: 2465-8510(Online)
https://doi.org/10.14777/uti.2022.17.2.36
Urogenit Tract Infect 2022;17(2):36-41

Pilot Study of Cystochon® (Cranberry Extract, Chondroitin Sulfate, and Hyaluronic Acid Complex) in Interstitial Cystitis/Bladder Pain Syndrome

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Purpose: This study examined whether Cystochon® (cranberry extract, chondroitin sulfate, and hyaluronic acid complex) effectively improves the symptoms and problems of interstitial cystitis/bladder pain syndrome (IC/BPS) patients.
Materials and Methods: From December 2021 to May 2022, the medical records of IC/BPS patients who visited St. Vincent's Hospital, Kyung Hee University Medical Center, or Gachon University Gil Medical Center were collected. For the treatment of IC/BPS, the patients were given pentosan polysulfate (PPS) for 12 weeks, with Cystochon® then added and maintained for an additional eight weeks. The O'Leary–Sant symptom and problem index (Interstitial Cystitis Symptom Index [ICSI], Interstitial Cystitis Problem Index [ICPI]) was used to measure the treatment response.
Results: After 12 weeks of PPS treatment, ICSI and ICPI improved in all patients. After adding Cystochon® for eight weeks, the ICSI and ICPI indicators improved further. In the ICSI category, significant improvement in symptoms was confirmed in the total ICSI score, particularly in the Q4 (pain-related) questionnaire after adding Cystochon®. In the ICPI category, significant problem improvement was confirmed in the total ICPI score, particularly in the Q1 (frequent urination) and Q4 (pain-related) questionnaires. Although not statistically significant, the remaining indicators generally tended to improve.
Conclusions: The orally administered combination of cranberry extract, chondroitin sulfate, and hyaluronic acid (Cystochon®) may have a clinically positive effect in patients with IC/BPS. Better clinical improvement can be expected when it is added to the PPS treatment, especially in the category of bladder pain.

Keywords: Interstitial cystitis; Bladder pain syndrome; Cranberry; Chondroitin sulfates; Hyaluronic acid

Received: 4 August, 2022
Revised: 18 August, 2022
Accepted: 18 August, 2022

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INTRODUCTION

Interstitial cystitis (IC) or bladder pain syndrome (BPS) accompanies lower urinary tract symptoms, such as frequency, urgency, nocturia, and dysuria that persist for more than six weeks without infection or other identifiable cause. It is characterized as a discomfort sensation, including pain, pressure, or burning sensation in the urinary bladder. Its diagnosis and treatment have not been standardized, and the terms IC, BPS, and IC/BPS are also used interchangeably.

Several causes have been suggested, but none have been clarified. IC/BPS occurs frequently in women after middle age, and the disease persists for a long time and recurs repeatedly, causing deterioration of the quality of life. It is a kind of syndrome with a broad spectrum of symptoms rather than a specific disease. As an initial treatment, stress management, pain control, and patient education are performed. Medical treatment, such as oral administration or intravesical injection, can be applied. Hydrodistension or neuromodulation may be considered for patients who do not respond to these treatments. Surgical therapies may be considered, such as transurethral resection or fulguration for Hunner lesions and immunosuppressive agents.

Among those methods suggested to improve IC/BPS symptoms, cranberry extract is also used to prevent subclinical recurrent cystitis. Cranberries have been tested for their clinical relevance in many different conditions. Although they have been deemed ineffective for treating urinary tract infections (UTIs), there is evidence suggesting that cranberry juice may reduce the number of symptomatic UTIs [1]. In addition, the intravesical instillation of hyaluronic acid and chondroitin sulfate is widely used, which relieves pain by replenishing the bladder mucosal glycosaminoglycan (GAG) layer damaged by inflammation [2-4]. This treatment reduces pain and protects the bladder wall from external irritants, such as urine and waste products. On the other hand, there are few reports on the use results of oral-type formulations of hyaluronic acid and chondroitin sulfate.

Cystochon® is a dietary supplement available in South Korea as an oral capsule with cranberry extract 500 mg/day, chondroitin sulfate 600 mg/day, and hyaluronic acid 40 mg/day. This study examined whether Cystochon® is effective in improving the symptoms and problems of IC/BPS patients.

MATERIALS AND METHODS

A retrospective study utilizing medical records was conducted. From December 2021 to May 2022, the medical records of IC/BPS patients who visited St. Vincent's Hospital, Kyung Hee University Medical Center, or Gachon University Gil Medical Center were collected. The diagnosis of IC/BPS was based clinically on evidence, such as symptoms including suprapubic pain during bladder filling without infectious origin and referring to characteristic cystoscopy findings. For the treatment of IC/BPS, patients were given pentosan polysulfate (PPS) first for 12 weeks with Cystochon® added and maintained for an additional eight weeks. PPS was maintained at the standard dose of 100 mg three times a day, and the Cystochon® regimen was twice daily in the morning and evening, two capsules at a time. The O'Leary–Sant symptom and problem index (Interstitial Cystitis Symptom Index [ICSI], Interstitial Cystitis Problem Index [ICPI]) was used to measure the treatment response. The score of each questionnaire at the first visit, at the time of 12 weeks of PPS completion, and after eight weeks of Cystochon® add-on treatment was compared and statistically analyzed. Twenty-two medical records that met the selection criteria were enrolled. Descriptive analysis and a paired t-test were performed on the ICSI and ICPI changes before and after Cystochon® add-on to confirm the effect of supplementation. This study was approved by the Institutional Review Board of The Catholic University of Korea (VC22RIDI0171).

RESULTS

Twenty females and two males, with an average age of 55.5 years (42 to 72), were enrolled in this study. After 12 weeks of administering PPS to clinically diagnosed IC/BPS patients, ICSI and ICPI improved in all patients. The ICSI and ICPI indicators were improved after adding Cystochon® for eight weeks (Tables 1, 2). The paired t-test results before and after Cystochon® add-on to confirm the effect are as follows. In the ICSI category, significant improvement in symptoms was confirmed in Q4 (During the past month, have you experienced pain or burning in your bladder?) after the Cystochon® add-on. Although the remaining Q1, Q2, and Q3 did not reflect statistical significance, an overall improvement trend was shown, and the total ICSI score showed a significant decrease after Cystochon® add-on (Table 3). In the ICPI category, a statistically significant level of problem improvement was confirmed in the Q1 (Frequent urination during the day) Q4 (Burning, pain, discomfort, or pressure in your bladder) questionnaires after the Cystochon® add-on, and the total ICPI score also showed a significant decrease (Table 4). Overall, Cystochon® had additional effects on the bladder pain-related indicators. Although not statistically significant, the remaining

Table 1. Observation of symptom score by ICSI before Tx, after PPS, and after PPS+CT (n=22)

Variable		Score					
		0	1	2	3	4	5
Q1	Before TX	1 (4.5)	2 (9.1)	6 (27.3)	5 (22.7)	6 (27.3)	2 (9.1)
	PPS	2 (9.1)	9 (40.9)	7 (31.8)	4 (18.2)	0 (0)	0 (0)
	PPS+CT	2 (9.1)	10 (45.5)	7 (31.8)	3 (13.6)	0 (0)	0 (0)
Q2	Before TX	0 (0)	3 (13.6)	2 (9.1)	9 (40.9)	4 (18.2)	4 (18.2)
	PPS	3 (13.6)	3 (13.6)	10 (45.5)	4 (18.2)	2 (9.1)	0 (0)
	PPS+CT	3 (13.6)	5 (22.7)	9 (40.9)	5 (22.7)	0 (0)	0 (0)
Q3	Before TX	1 (4.5)	2 (9.1)	4 (18.2)	11 (50.0)	3 (13.6)	1 (4.5)
	PPS	3 (13.6)	7 (31.8)	8 (36.4)	4 (18.2)	0 (0)	0 (0)
	PPS+CT	4 (18.2)	6 (27.3)	8 (36.4)	4 (18.2)	0 (0)	0 (0)
Q4	Before TX	0 (0)	0 (0)	2 (9.1)	9 (40.9)	8 (36.4)	3 (13.6)
	PPS	0 (0)	8 (36.4)	11 (50.0)	2 (9.1)	1 (4.5)	0 (0)
	PPS+CT	3 (13.6)	10 (45.5)	8 (36.4)	1 (4.5)	0 (0)	0 (0)

Values are presented as number (%).
Q1, During the past month, how often have you felt the strong need to urinate with little or no warning?
0-not at all, 1-less than one time in 5, 2-less than half the time, 3-about half the time, 4-more than half the time, 5-almost always.
Q2, During the past month, have you had to urinate less than 2 h after you finished urinating?
0-not at all, 1-less than one time in 5, 2-less than half the time, 3-about half the time, 4-more than half the time, 5-almost always.
Q3, During the past month, how often did you typically get up at night to urinate?
0-none, 1-once, 2-2times, 3-3times, 4-4 times, 5-5times.
Q4, During the past month, have you experienced pain or burning in your bladder?
0-not at all, 1-less than one time in 5, 2-less than half the time, 3-about half the time, 4-more than half the time, 5-almost always.
ICSI: O'Leary–Sant Interstitial Cystitis Symptom Index, Tx: treatment, PPS: pentosan polysulfate, CT: Cystochon, Q1-4: question 1-4 of ICSI.

Table 2. Observation of symptom score by ICPI before Tx, after PPS, and after PPS+CT (n=22)

Variable		Score				
		0	1	2	3	4
Q1	Before TX	1 (4.5)	8 (36.4)	3 (13.6)	4 (18.2)	6 (27.3)
	PPS	3 (13.6)	11 (50.0)	2 (9.1)	5 (22.7)	1 (4.5)
	PPS+CT	6 (27.3)	8 (36.4)	4 (18.2)	4 (18.2)	0 (0)
Q2	Before TX	2 (9.1)	4 (18.2)	6 (27.3)	3 (13.6)	7 (31.8)
	PPS	3 (13.6)	9 (40.9)	5 (22.7)	3 (13.6)	2 (9.1)
	PPS+CT	4 (18.2)	8 (36.4)	6 (27.3)	3 (13.6)	1 (4.5)
Q3	Before TX	1 (4.5)	9 (40.9)	4 (18.2)	5 (22.7)	3 (13.6)
	PPS	6 (27.3)	8 (36.4)	4 (18.2)	2 (9.1)	2 (9.1)
	PPS+CT	6 (27.3)	9 (40.9)	3 (13.6)	4 (18.2)	0 (0)
Q4	Before TX	0 (0)	2 (9.1)	2 (9.1)	5 (22.7)	13 (59.1)
	PPS	0 (0)	10 (45.5)	5 (22.7)	5 (22.7)	2 (9.1)
	PPS+CT	3 (13.6)	8 (36.4)	8 (36.4)	3 (13.6)	0 (0)

Values are presented as number (%).
During the past month, how much has each of the following been a problem for you?
Q1, Frequent urination during the day?
Q2, Getting up at night to urinate?
Q3, Need to urinate with little warning?
Q4, Burning, pain, discomfort, or pressure in your bladder?
0-no problem; 1-very small problem; 2-small problem; 3-medium problem; 4-big problem.
ICPI: O'Leary–Sant Interstitial Cystitis Problem Index, Tx: treatment, PPS: pentosan polysulfate, CT: Cystochon, Q1-4: question 1-4 of ICPI.

indicators showed a tendency to improve. In some cases, a dramatic pain relief effect was noted.

DISCUSSION

IC or BPS, evaluated as a subtype of chronic pelvic pain, is a clinical syndrome with chronic recurrent suprapubic pain, frequent urination, and nocturia without infection or other etiologies. It has a negative effect on emotional and sexual disorders and even sleep disorders. Although the etiology of IC/BPS is not completely understood, autoimmune mechanisms, preceding infection, stress, mast cell activation, neurogenic changes, toxic substances in urine, genetic predisposition, central nervous system

Table 3. Score of ICSI - Treatment of PPS and PPS+CT

Variable		Mean	SD	p-value
Q1	PPS	1.59	0.908	0.162
	PPS+CT	1.50	0.859	
Q2	PPS	1.95	1.133	0.135
	PPS+CT	1.73	0.985	
Q3	PPS	1.59	0.959	0.665
	PPS+CT	1.55	1.011	
Q4	PPS	1.82	0.795	0.013
	PPS+CT	1.32	0.780	
Total	PPS	6.95	3.184	0.034
	PPS+CT	6.09	3.206	

A paired t-test comparing the response of patients treated with PPS and PPS+CT.
ICSI: O'Leary–Sant Interstitial Cystitis Symptom Index, PPS: pentosan polysulfate, CT: Cystochon, Q1-4: questions1-4 of ICSI, SD: standard deviation.

Table 4. Score of ICPI - Treatment of PPS and PPS+CT

Variable		Mean	SD	p-value
Q1	PPS	1.55	1.143	0.030
	PPS+CT	1.27	1.077	
Q2	PPS	1.64	1.177	0.329
	PPS+CT	1.50	1.102	
Q3	PPS	1.36	1.255	0.378
	PPS+CT	1.23	1.066	
Q4	PPS	1.95	1.046	0.015
	PPS+CT	1.50	0.913	
Total	PPS	6.50	4.149	0.032
	PPS+CT	5.50	3.864	

Apaired t-test comparing the response of patients treated with PPS and PPS+CT.
ICPI: O'Leary–Sant Interstitial Cystitis Problem Index, PPS: pentosan polysulfate, CT: Cystochon, Q1-4: questions1-4 of ICPI, SD: standard deviation.

mechanisms, and psychosomatic mechanisms have been mentioned. Damage to the GAG layer of the urinary bladder epithelium disrupts the barrier of the bladder mucosa, and exposure of the submucosal tissue to toxic substances is suggested as the main cause of IC/BPS.

In the diagnosis and treatment of IC, the systematic diagnostic criteria that can measure changes in the patient's symptoms and quality of life are very important. O'Leary et al. [5] first developed the 'ICSI' and the 'ICPI' as diagnostic criteria for IC in 1997. It has since been actively used in various clinical studies, as well as in the diagnosis and treatment of IC/BPS. The ICSI consists of four items asking about urgency, frequent urination, nocturia, and pain, and the ICPI consists of four items asking how problems, such as frequency, nocturia, urgency, and bladder pain or discomfort, are perceived as serious problems.

Cranberry is known for its anti-inflammatory effects, but despite several studies, the exact mechanisms behind UTI protection are unclear [6-8]. Cranberry consumption is widely recommended for UTI prophylaxis. On the other hand, there is a debate about whether the effects are significant [9]. Moreover, it is unclear how much IC/BPS is affected by recurrent UTIs, but clinically, many patients are taking cranberries to improve their symptoms [1].

Chondroitin sulfate is a major component of the GAG layer and is effective in improving pain and urinary frequency when intravesical instillation is performed in IC/BPS [2-4]. It has also been found to help improve symptoms in patients with recurrent UTI [10,11]. On the other hand, only studies on 'intravesical' treatment have been conducted, and the effect of oral administration has not been clearly identified. Nevertheless, oral chondroitin sulfate is effective in improving pain in arthritis [12]. Hyaluronic acid is also a natural GAG component, and the GAG layer supplementation therapy in IC/BPS has been studied extensively [13]. Oral supplements using hyaluronic acid and chondroitin sulfate are available in a few countries. It has been reported to be effective in preventing recurrent UTIs [14]. In the field of IC/BPS, it has been reported that the oral dietary supplement, CystoProtek, contains chondroitin sulfate and sodium hyaluronate and reduces the O'Leary/Sant Symptom Index [15,16]. Therefore, the effects of oral formulations of natural GAG components, chondroitin sulfate and hyaluronic acid, on IC/BPS should be studied. Furthermore, the implementation of dietary supplementation, such as Cystochon® used in this study, will also be meaningful in improving the quality of life of patients. In particular, Cystochon® contains a cranberry extract, chondroitin sulfate, and hyaluronic acid, which will help patients with recurrent UTI and IC/BPS.

This study had several limitations. First, it was a retrospective study based on medical record analysis, and it is a simple observational study that cannot exclude the effect of the existing PPS treatment. In addition, there is a decisive problem that cranberry extract, chondroitin sulfate, and hyaluronic acid complex are not specified for each component and interaction. On the other hand, it is significant because it is the first review of oral formulations reported in South Korea for IC/BPS patients. In the future, several more rigorously designed long-term clinical studies with objective diagnosis and evaluation indicators should be conducted by extracting each component individually.

These efforts may provide clinical evidence for the effects of oral formulations of cranberry extract, chondroitin sulfate, and hyaluronic acid on IC/BPS.

CONCLUSIONS

The orally administered combination of cranberry extract, chondroitin sulfate, and hyaluronic acid (Cystochon®) may have a clinically positive effect in patients with IC/BPS. Better clinical improvement can be expected when added to the PPS treatment, especially in the category of bladder pain. In the future, it will be necessary to prove its effectiveness through detailed research for each component and interaction in large-scale clinical studies.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHORS CONTRIBUTIONS

K.T.K. participated in data collection and wrote the manuscript. J.W.L. participated in data collection and coordination and helped to draft the manuscript. H.S.C. participated in the study design and data collection, performed the statistical analysis and wrote the manuscript. All authors read and approved the final manuscript.

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