

Efficacy of Pentosan Polysulfate Treatment in Patients with Interstitial Cystitis/Bladder Pain Syndrome

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Abbreviation used: PPS, Pentosan Polysulfate; IC, Interstitial Cystitis; BPS, Bladder Pain Syndrome; ICSI, Interstitial Cystitis Symptom Index; ICPI, Interstitial cystitis problem index; QoL, quality of life; GAG, glycosaminoglycan

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ABSTRACT

Objectives: Pentosan Polysulfate (PPS) is the only oral treatment for interstitial cystitis (IC)-bladder pain syndrome (BPS) approved by the World Health Organization. Self-evaluation scales can provide more objective results on pre- and post-treatment satisfaction. The aim of this study was to investigate the effect of pentosan polysulfate treatment on symptoms in IC-BPS patients.

Methods: This study included 37 adult male and female patients with IC-BPS who reported pain, urinary urgency, polyurea, and nocturia without urinary tract infection for a minimum of six months prior to the study and were taking 300 mg/day oral pentosan polysulfate. Pre- and post-treatment symptoms, Interstitial Cystitis Symptom Index (ICSI) Scores, quality of life (QoL) scores (1–4), and satisfaction conditions were examined.

Results: Following the application of inclusion and exclusion criteria, mean age of 37 suitable patients was 46.0±11.9 years and 27% (10 individuals) of the patients were male. Pre-treatment, ICSI scores, and measures of satisfaction degree and QoL increased significantly after the treatment ($p<0.001$). Adverse reaction was detected in two patients (5.4%) among the patients treated with pentosan polysulfate.

Conclusions: Oral pentosan polysulfate for the treatment of interstitial cystitis/bladder pain syndrome treatment could achieve recovery in symptoms, increase Interstitial Cystitis Symptom Index score and improve quality of life and patient satisfaction.

Keywords: Bladder Pain Syndrome, Efficacy, Interstitial Cystitis, Pentosan Polysulfate, Treatment

INTRODUCTION

Interstitial cystitis (IC)/bladder pain syndrome (BPS) is a disease that presents with dysuria, urinary frequency, and a feeling of suprapubic discomfort due to full bladder-related pain and pressure. It tends to last for over six weeks without any proven urinary system infection or other proven pathology [1,2]. IC/BPS prevalence has been reported to stand at 2.7–12% [3–6].

The lack of a clear etiopathogenesis and classification has required that the diagnosis of interstitial cystitis should be made through clinical exclusion [7]. To provide the most objective measurement possible, survey methods have been developed to aid in diagnosis, including the interstitial cystitis symptom index (ICSI) and the interstitial cystitis problem index (ICPI),

among others [8]. Furthermore, the UPOINT (urinary symptoms, psychosocial function disorder, organ-specific findings, infection, neurological function disorder, and tenderness of muscles) system was developed to help create the most suitable treatment plans for different clinical presentations of the disease [9,10].

Staged treatments that have been used for IC/BPS include lifestyle changes, oral treatments [*e.g.*, amitriptyline, hydroxyzine, and pentosan polysulphate sodium (PPS)], Botox, sacral neuromodulation, and major surgeries, such as cystoplasty [5,7]. IC/BPS symptoms are thought to be related to the degradation of either the apical cell layer in the urothelium or the glycosaminoglycan (GAG) layer (which is believed to regulate the passage of cations in a healthy bladder and protect the urothelium against harmful effects). Because PPS allows for the regeneration of the

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GAG layer, it is prescribed predominantly [11,12]. Moreover, PPS is the only oral treatment approved by the World Health Organization for IC-related bladder pain and discomfort [7,13]. Although literature data are conflicting regarding oral PPS, it was nevertheless categorized in the strong suggestion level in the EAU 2022 Guidelines [1,12,14–16]. High-cost treatments (Botox, neuromodulation, etc.), with undeniable benefits, have been developed in recent years to treat persistent cases [17], but PPS may still be advantageous in terms of the profit/loss rate. This study was undertaken to clarify these issues and support literature.

Self-evaluation scales can provide more objective results on pre- and post-treatment satisfaction. Furthermore, such self-assessment questionnaires may be useful regarding the pathology of diseases such as IC/BPS that have a wide range of patient complaints and clinical admissions [3]. Thus, studies have been conducted on the relationship between IC/BPS treatments and patient satisfaction [3].

Based on these data, this study aimed to investigate the effect of pentosan polysulfate treatment on symptoms in patients with IC-BPS.

MATERIALS AND METHODS

Demographic, clinical, laboratory and cystoscopic data of the patients who were admitted to our clinic between January 2019 - September 2022 and diagnosed with IC/BPS were examined retrospectively.

The study included 37 adult male and female IC/BPS patients who reported pain, urinary urgency, polyuria, and nocturia without urinary tract infection for a minimum of six months prior to the study and were taking oral PPS at 300 mg/day. Exclusion criteria included: allergic reaction to PPS, intravesical instillation (bladder distension, dimethyl sulfoxide) within three months of starting the treatment, use of agents effective on symptoms (*e.g.*, antidepressants, antihistamines, antispasmodics, and/or anticho-

linergics) within a month, pregnancy, having received urethral catheterization, having urinary tract anomalies, urolithiasis, kidney failure, urothelial carcinoma, immunosuppression, stage II or higher pelvic organ prolapses, bladder outlet obstruction, stress incontinence, and positive urinary culture. Pre- and post-treatment symptoms, ICSI scores, quality of life (QoL) scores (on a 1–4 point scale), and satisfaction conditions were compared.

This study, which was approved with 10.01.2023-37 number ethics board consent of Hisar Intercontinental Medical Ethic and Research Board under the guidance of Helsinki Declaration, was registered at clinicaltrials.gov (NCT05744908) on 17 February 2023.

Statistical method

SPSS 25.0 software package was used for statistical analysis. Categorical measurements were expressed as number and percentage and constant measurements were presented as mean and standard deviation (median and minimum-maximum when required). Upon checking of distributions in the comparison of variables and pain duration, Kruskal Wallis test or Mann Whitney U test was used since the distribution was non-parametric based on the number of variables. Wilcoxon test was employed for constant variables and Mc-Nemar test was utilized for categorical variables. Statistical significance level was set at 0.05 in all tests.

RESULTS

Against the inclusion and exclusion criteria, a total of 37 eligible patients were included. They had a mean age of 46.0 ± 11.9 years, and 10 of them (27%) were male and 20 (63%) were female. The demographical and clinical data of the patients are listed in **Tables 1** and **2**. Urine cultures of bacteria yielded negative results.

In general, a statistically significant recovery was found in after treatment. Compared to pre-treatment findings, ICSI score, measures in satisfaction degree and QoL were increased significantly following the treatment ($p < 0.001$) (**Table 3**).

Table 1 Distribution of Demographical Data

	N	Mean \pm SD	Median	Min-Max
Age (year)	37	46.0 \pm 11.9	47	24-70
BMI* (kg/m ²)	37	26.8 \pm 3.1	27.1605	19.8-32.5
Bladder wall thickness (mm)	37	5.2 \pm 1.1	5.5	3.4-7.0
Duration of use (month)	37	6.0 \pm 3.1	6	1-12

*BMI; Body-Mass Index

A statistically significant positive correlation was found between wall thickness and frequency ($r=0.42$, $p=0.010$). The frequency before the treatment was found to be raised statistically significantly after treatment as the wall thickness of the patient increased.

Presence of Hunner's ulcer in the patients in the study did not bear a statistically significant relationship with pre- and post-treatment ICSI, urgency, nocturia, frequency, incontinence, satisfaction degree and quality of life.

Adverse reactions were observed in two patients, with a preva-

lence rate of 5.4% in the patients receiving PPS. Treatment could not be continued due to diarrhea in week 1 in one patient. In another patient, the treatment was withdrawn because of blurred vision in the third month (The patient was not diagnosed with maculopathy.). No clinically significant change was detected in urine analysis, histopathological, ultrasonographic findings and physical examinations.

Table 2 Distribution of Demographic and Clinical Data

	n	%
USG*		
Increased bladder wall thickness	29	78.4
Normal	8	21.6
Hunner's Ulcer		
No	27	73.0
Yes	10	27.0
Histopathology		
Mild Chronic Cystitis	17	45.9
Chronic Cystitis	10	27.0
Chronic Cystitis, Mild Dysplasia	6	16.2
Average Dysplasia	4	10.8
Adverse Effect		
None	34	91.9
Blurred Vision	1	2.7
Diarrhea	1	2.7
Cystectomy	1	2.7

*USG; ultrasonography

DISCUSSION

This study showed that IC/PBS patients who were treated with 300 mg/day oral PPS for an average time of six months reported improvement in all symptoms, as indicated by the ICSI scores. Self-evaluation by patients also showed increase in QoL and satisfaction.

In general, symptom recoveries are supported by the literature. For example, in prior studies, patients reported a 28–32% recovery in post-treatment complaint scale investigations [12, 16]. In our study, in which the ICSI, a validated evaluation tool, was used for subjective evaluation, patients reported a general symptom recovery of 66%. Because IC/BPS was pathologically complicated and involves a wide array of symptoms, changes in less bothersome symptoms may go unnoticed, as patients tend to focus on the most significant or challenging ones. Therefore, by using an objective symptom evaluation tool, more reliable results can be obtained. Similar to our study, Sand *et al.* found that patients with moderate ICSI scores reported improvements of over 30% [3].

Two previous randomized controlled studies reported no significant recovery of IC/BPS symptoms after PPS treatment [7,15]. This might be ascribed to the fact that these studies did not exclude patients with related conditions, such as irritable bowel disease, depression, and pelvic base dysfunctional disease, or those who had indefinite symptoms and/or no cystoscopic findings, in contrast to the strict application of inclusion/exclusion criteria in our study.

A meta-analysis by Hwang *et al.* revealed that PPS was effective in easing pain and urgency but had no effect on nocturia [16], whereas in our study, significant recovery was observed in all symptoms, including nocturia. This discrepancy might be attributed to the difference in treatment duration. In the study by Hwang *et al.*, treatment lasted for three months, and, as a result, while recovery was observed in faster-responding symptoms, such as pain and urgency, other symptoms that might take months to resolve, such as nocturia and abnormal urination pattern, remained unchanged. This difference has been highlighted in studies featuring treatments continuing for up to three years [3, 16]. The recovery period has been reported to be approximately one year for bladders that have suffered from impaired function and volumetric capacity and recovery from urination symptoms via detrusor rehabilitation takes longer time [12]. This major difference, therefore, should be covered in multiple dimensions. Patients limiting or increasing their fluid intake during inflammation periods may also experience changes in urination frequency and volume, which may imitate IC/BPS symptoms.

Considering the IC/BPS formation mechanism, symptoms caused by the degradation of apical cell layers of the urothelium and/or GAG layer degradation are related to chronic inflammatory phases [5]. This may cause long-term pain, nocturia, dysuria symptoms, and mucosal ulcers (Hunner's ulcers) that might subject bladder to vesical laceration or rupture when the bladder swells [18]. Hunner's ulcers were reported to be more common in elderly patients and patients with long-term symptoms [5]. One study showed that PPS treatment was more effective in IC/BPS patients with Hunner's ulcers [18]. Our study detected no correlation between Hunner's ulcers and post-treatment symptom recovery, although we believe this difference might be related to the fact that these types of ulcers can take 8–9 years to resolve but our study lasted only for 4 years.

IC/BPS symptoms cause physical and emotional problems, social constraints and sleep disorder and they are major contributors to the lowered QoL [3]. Studies evaluating patient satisfaction and QoL can be considered as a contributing factor for treatment options. QoL and patient satisfaction are also starting to stand out in IC/BPS symptom evaluations [19].

Satisfaction of patients who received different treatment options for IC/BPS was evaluated in a previous study and patients with recovering symptoms reported their satisfaction with their treatments [20]. Improvement in patient satisfaction and QoL was found to be correlated with the recovery rate in symptoms and ICSI scores in patients taking oral PPS in our study and findings

made by Sand *et al* were supportive of our results [3]. EAU 2022 guidelines also reported that oral PPS improved QoL score [21].

According to literature, the most common side effects of oral PPS were nausea (1.4–7.9%), diarrhea (1–14.9%) and headache (1–2.9%), and less common side effects included rash (3%), liver function abnormalities (1–2%), drowsiness (1.6%) and rectal bleeding (4%) [7,22,23]. In addition to these side effects, PPS-related maculopathy was reported, with an occurrence rate between 16–23% [24]. Side effects and treatment discontinuation due to side effects were low at the dosage of daily 300 mg oral PPS in our series: *i.e.*, two (5.4%) patients in total. Treatment

was stopped due to diarrhea in week 1 in one patient, and, due to blurred vision in the third month (The patient was not diagnosed with maculopathy.) in another patient. Maculopathy, which is a relatively more severe side effect was reported as a cumulative dystrophic effect upon long-term (nearly 10 years) and dose-dependent (over 1500 mg) use in a previous study [24]. In our study, withdrawing the medicine after noticing mild symptoms, such as blurred vision, may have prevented maculopathy. Thus, it is important to follow up patients on regular basis in order to prevent severe side effects and to inform patients about side effects.

Table3 Before and after treatment symptoms, ICSI scores, QoL scores and satisfaction conditions

	Pre-treatment		Post-treatment		p
	Mean±SD	Median (Min-Max)	Mean±SD	Median (Min-Max)	
Frequency	9.0±1.6	8(7-15)	5.2±1.7	5(3-12)	0.0001
Nocturia	1.4±1.1	1(0-4)	0.7±0.5	1(0-2)	0.0001
	n	%	n	%	
Urgency					
No	0	0.0	23	62.2	0.0001
Yes	37	100.0	14	37.8	
Nocturia					
0	8	21.6	12	32.4	
1	13	35.1	24	64.9	
2	10	27.0	1	2.7	0.0001
3	5	13.5	-	-	
4	1	2.7	-	-	
Incontinence					
No	26	70.3	28	75.7	0.500
Yes	11	29.7	9	24.3	
ICSI*	5.9±1.4	6(3-9)	2.1±1.3	2(0-6)	0.0001
Unsatisfied/Very Unsatisfied					
Unsatisfied	29	78.4	9	24.3	0.0001
Satisfied	8	21.6	28	75.7	
Quality of Life**					
1	1	2.7	0	0.0	0.0001
2	20	54.1	0	0.0	
3	16	43.2	12	32.4	
4	0	0.0	25	67.6	

*ICSI; Interstitial Cystitis Symptom Index, **QoL; quality of life

Strengths and limitations

Main limitations of our study were limited sample size and its retrospective nature. Low number of patients may not have correctly reflected the rate of side effects. Lack of a validated evaluation tool for satisfaction and quality of life constitutes

another limitation of our study. On the other hand, use of an objective tool such as ICSI was a strength of the study.

CONCLUSION

Oral PSS in IC/BPS treatment could achieve recovery in symptoms, increase ICSI scores and also improve the quality of life and patient satisfaction. In addition, periodic follow-ups are required to detect irreversible side effects early.

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Clinical trial registration and ethical approval

Pentosan Polysulfate Treatment's Effectiveness, NCT05744908 (17 February 2023)

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