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FUNCTIONAL UROLOGY

Safety and efficacy of pentosan polysulfate in patients with bladder pain syndrome/interstitial cystitis: a multicenter, double–blind, placebo–controlled, randomized study

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Introduction Bladder pain syndrome/interstitial cystitis (BPS/IC) is a condition that is characterized by urgency, frequency and/or pelvic pain. The disease occurs mainly in women. BPS/IC can be severe enough to have a significant impact on patients' quality of life, but it can also be associated with moderate symptoms that are equally debilitating.
The aim of this article was to evaluate the possibility of the use of pentosan polysulfate sodium in patients in the complex treatment of BPS/IC.
Material and methods A multicenter, double-blind, placebo-controlled, randomized study was conducted in parallel groups in 7 Russian medical centers.
Results Efficacy and safety have been established as the main criteria. A total of 93 patients were screened. Statistical analysis was performed. It has been shown that pentosan therapy is more effective than in the placebo. Average change in the number of points on the scale O'Leary-Santa Interstitial Cystitis Symptom Index compared to baseline data in the pentosan group 4.93 ±3, 03, in the placebo group 1.66 ±3.19 (p = 0.014), and the adverse events and safety of pentosan are comparable to the placebo group.
Conclusions Oral glycosaminoglycan (pentosan polusulfate sodium) is an effective and safe drug and should be included in the complex treatment of patients with bladder pain syndrome/interstitial cystitis.

Key Words: pentosan polysulfate ‹› bladder pain syndrome ‹› interstitial cystitis

INTRODUCTION

Bladder pain syndrome/interstitial cystitis (BPS/IC) is a condition that is characterized by urgency, frequency and/or pelvic pain [1, 2, 3]. The disease occurs mainly in women and, according to epidemiological data, is detected in 0.01% to 0.5% of the population [1, 4]. BPS/IC can be severe enough to have a significant impact on patients' quality of life, but it can also be associated with moderate symptoms that are equally debilitating [5]. A variety of IC treatment methods are available, but it is generally assumed that the results are quite disappointing, and only a few have been thoroughly clinically evaluated. [6]. Pentosan polysulfate sodium (PPS) is an oral analogue of glycosaminoglycan indicated for the treatment of bladder pain or discomfort associated with BPS/IC. PPS was evaluated as a drug for BPS/IC treatment in five randomized, multicenter, double-blind, placebo-controlled trials [7–11], four of which showed better results with pentosan than with placebo (P = 0.03, P = 0.01, P = 0.02, P = 0.06) [7, 8, 9, 11]. The purpose of trial is to evaluate the efficacy and safety of PPS, 100 mg capsules in comparison with placebo in patients with BPS /IC.

MATERIAL AND METHODS

This study is a phase III trial and was conducted as a multicenter, double-blind, randomized, placebo-controlled, parallel group study in Russian medical centers. The primary evaluation criterion was the clinical efficacy of the drug in patients with BPS/IC. Secondary criteria were safety analysis and adverse event data analyses and evaluation.

Patients who successfully passed the screening and met the inclusion/exclusion criteria were randomized to one of the treatment groups 1:1 – drug or placebo: Group I: Pentosane polysulfate (Miropentan™, Pride-Pharme), 100 mg, orally 1 capsule, 3 times a day; Group II: placebo, capsules, 100 mg, orally 1 capsule, 3 times a day.

At the stage of preparation for the clinical trial, patients were randomized by assigning a number and the corresponding drug for each patient. The corresponding randomization list was generated in a statistical program using a random number generator. The list was not sent to research centers. The drug and placebo were delivered in research centers in the package, having the patient randomization number and containing the inscription 'Only for a clinical trial'. The study also provided blinding of patients and researchers.

The primary criteria for efficacy evaluation was the average O'Leary-Sant Interstitial Cystitis Symptom Score (ICSI) points change in comparison with initial data. The second part of this questionnaire was used as criteria for the secondary quality of life assessment. The study included patients with a diagnosis of bladder pain syndrome/interstitial cystitis of both gender, aged 18–55 years, who completed the ICSI questionnaire, had a score of at least 8 in the first part, and more than 1 point for any question from the ICSI second part. Complaints must not have been associated with urinary tract infections (a negative screening result of bacterial urine culture), and bladder pain must have presented for longer than 6 months prior to the study. Other inclusion criteria were: frequency ≥10 times a day (≥30 voiding during 3 consecutive days); nocturia ≥1 time. The results of the cytological examination of urine during screening must have been negative. Endoscopic criteria of bladder pain syndrome/interstitial cystitis were petechial hemorrhages or Hunner's lesions of the bladder during a cystoscopic examination conducted during the 6 months preceding the screening visit, but not earlier than 6 weeks preceding the screening visit. Patients of reproductive age were required to use contraception. All patients signed an informed consent to participate.

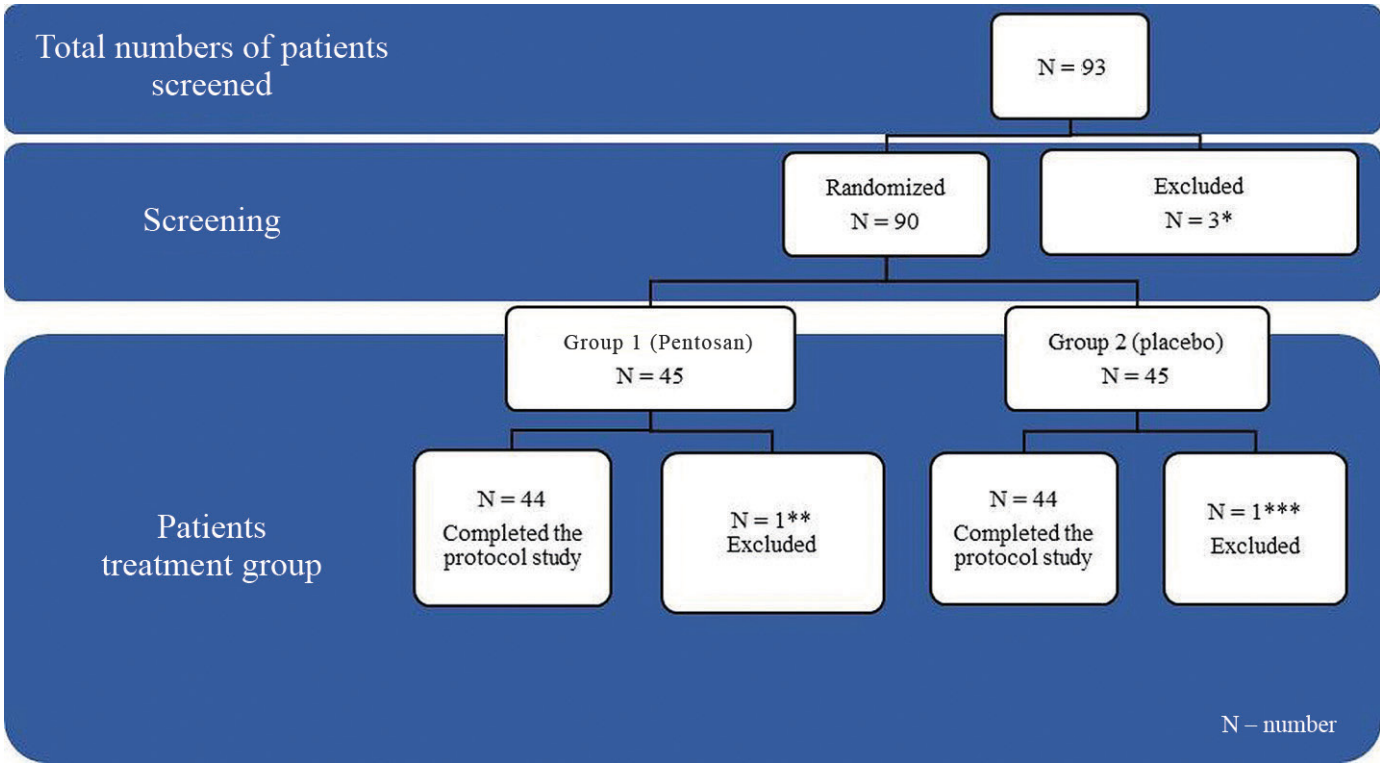

Figure 1. *Groups of patients in a clinical study: * Discovered criteria for non-inclusion in the study; ** The patient excluded from study prematurely; *** The patient excluded from study prematurely.*

The non-inclusion criteria were:
- hypersensitivity to pentosan polysulfate sodium;
- frequency ≥25 per day;
- bladder capacity >350 ml;
- BPS/IC therapy in the form of intravesical drug instillation in the period 1 month before the start of the study;
- oral therapy for BPS/IC in the period 1 month before the study;
- use of any type of anticoagulant in the period 7 days prior to screening;
- any concomitant somatic diseases or conditions at the time of screening or in the anamnesis that, according to the researcher, made it difficult to interpret the results of treatment or made it impossibile to perform procedures in this clinical study that are dangerous for the patient during his participation in the study;
- breastfeeding;
- pregnancy.

Statistical analysis

Patients were randomized using an adaptive design with three interim analyses (25%, 50%, 75% information received). At the first stage, it was planned to analyze data for at least 41 patients in each group. If superiority was proven at a significance level of 0.017, the study would be terminated due to sufficient justification for accepting the hypothesis of the drug over placebo superiority. The results of the first phase of tests were enough to confirm the alternative hypothesis and to complete the study at this stage (according to the Pocock correction, the required significance level corresponds to $p = 0.017$)
Null hypotheses were tested using Student's t-test, Mann-Whitney test or χ^2 test to test the hypothesis about the initial homogeneity of groups. Fisher's exact two-sided test was applied if the prerequisites for applying the χ^2 criterion were not met. The primary variable for efficacy was O'Leary-Sant – interstitial cystitis symptom score (ICSI) points change in comparison with initial data. Analysis of variance for independent groups was used to analyze changes in ICSI from baseline with repeated measures. Secondary variable for efficacy were analyzed similarly to the primary performance variable.
Secondary performance variables were analyzed similarly to the primary performance variable. Comparison of categorical variables between groups was performed using the χ^2 criterion.

Table 1. *The baseline features of the study participants*

	Miropentan	Placebo	P-Value
Gender	Female 43 (95.56%) Male 2 (4.44%)	Female 38 (86.36) Male 6 (13.64)	0.157[3]
Age	36.93 ±10.60	35.43 ±10.15	0.495[1]
Height	165.60 ±5.26 cm	166.95 ±5.95 cm	0.258[2]
Weight	22.95 ±3.48 kg	22.93 ±4.08 kg	0.870[1]
BMI	22.95 ±3.48	22.93 ±4.08	0.870[1]
OLS (ICSI)	12.02 ±2.87	12.18 ±2.58	0.692[1]
Frequency	14.7 3 ±3.38	14.56 ±3.77	0.722[1]
Frequency of nocturia	2.78 ±1.38	2.86 ±2.35	0.453[1]
Bladder capacity	224.2 ±73.87	225.42 ±69.51	0.937[2]

[1]Mann-Whitney U-test; [2]Student T-test; [3]Fisher's exact tests
BMI – body mass index; OLS (ICSI) – O'Leary-Sant Interstitial Cystitis Symptom Score

RESULTS

A total of 93 patients were screened during the study, 90 of them were randomized, 3 patients were excluded from the study during the screening stage: 2 patients were not admitted to further participation in the study due to non-compliance with the inclusion/exclusion criteria, 1 patient withdrew their informed consent to participate in the study. Two patients completed the study prematurely: connection with the patients was lost. The study was completed at the first stage, since in the course of the statistical analysis of the data obtained after the first stage of the study, an alternative hypothesis with the calculated level of significance was confirmed (Figure 1).

The average values of age, body weight, height, body mass index (BMI), ICSI, frequency, bladder capacity, frequency of nocturia were comparable in both groups and both populations, when analyzing initial data. There were no statistically significant differences between the pentosan and placebo groups ($p = 0.05$) (Table 1).

Efficiency evaluation

According to the study protocol, the primary efficacy criteria is the average O'Leary-Sant Interstitial Cystitis Symptom Index (Symptom Index) scale change points in comparison with initial data. Analysis of variance for independent groups with repeated measures was used to analyze changes in ICSI from baseline. Analysis of variance for independent groups with repeated measures showed that the treatment in the pentosan group was significantly more effective than the placebo group ($P = 0.014$). The study of secondary criteria showed that the mean value changes on scale quality evaluation index of life in patients with interstitial cystitis O'Leary-Sant (Problem Index) at the end

of treatment compared with the original data in pentosan treatment group was 5.47 ±4.16, group placebo – 2.77 ±3.83 (Tables 2 and 3).

Safety assessment

All reported adverse events were analyzed and grouped according to frequency, severity and their relationship to study medicine usage. A total of 299 adverse events were reported 159 in the study medicine pentosan group and 140 in the placebo group] during this clinical study. Total adverse events were observed in 76 patients (38 patients in the group taking the drug pentosan and 38 patients in the placebo group). Statistically significant differences between the number of patients with adverse events identified in the comparison of pentosan group and placebo were not detected ($p > 0.05$). Serious adverse events during the study were not reported.

DISCUSSION

Interstitial cystitis/BPS is a severe disease that significantly reduces patients' quality of life. The etiology of IC is still unclear. Despite the large number of treatment options available, few have received rigorous clinical evaluation. One of the drugs that have undergone clinical evaluation is pentosan polysulfate sodium (PPS). Based on the results of our study, it was concluded that the efficacy and a similar safety profile of pentosan polysulfate sodium 100 mg capsule was made versus placebo in patients with IC. The role of PPS has also been studied by other researchers.

Nickel et al. in their randomized, double-blind study evaluated the dose-response effect of pentosan polysulfate sodium in patients with IC. The recommended dose (300 mg) was compared with doses two (600 mg) and three (900 mg) times higher. A 32-week study included 380 adult patients diagnosed with IC. The diagnosis of IC was made by a positive cystoscopic examination (Hunner's lesions, petechial hemorrhages) in combination with bladder pain and urgency or in patients with a history of IC symptoms for at least 6 months. Efficiency assessment was carried out using Patient's Overall Rating of Improvement of Symptoms (PORIS), O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI). These instruments were used throughout the study to assess the dynamics of the patient's symptom status. Pentosan polysulfate sodium had already shown efficacy at an early stage of treatment (4 weeks). At the same time, the dosage of the drug and the severity of symptoms did not affect the onset of the effect. The response to treatment increased over the remaining time points. Most of the adverse effects were mild and resolved without intervention or consequences. The researchers showed that a clinically significant but similar

Table 2. *Average change in the number of points on the scale O'Leary-Sant Interstitial Cystitis Symptom Index compared to the initial data*

Indicator	Miropentan	Placebo
Number of valid values	45	44
Average value	4.93	1.66
Confidence interval -95%	4.02	0.69
Confidence interval +95%	5.84	2.63
Median	4	1.5
Dispersion	9.15	10.18
Standard deviation	3.03	3.19
Minimum	0	-4
Maximum	10	13
Interquartile range	6	3
Lower quartile	2	0
Upper quartile	8	3
P	0.014	
1 ANOVA for Independent Repeated Groups (Repeated Measures ANOVA)		

ANOVA – analysis of variance

Table 3. *Average change in the number of points on the scale O'Leary-Sant Interstitial Cystitis Problem Index compared to the initial data*

Indicator	Miropentan	Placebo
Number of valid values	45	44
Average value	5.47	2.77
Confidence interval-95%	4.22	1.61
Confidence interval +95%	6.72	3.94
Median	5	1
Dispersion	17.35	14.69
Standard deviation	4.16	3.83
Minimum	0	-2
Maximum	15	13
Interquartile range	8	4.75
Lower quartile	1	0
Upper quartile	9	4.75
Shapiro – Wilk criterion of normality	0.923	0.815
Probability of normality matching p(W)	0.006	0.000
P[1]	0.001	

[1]Mann-Whitney U-test

response was demonstrated for all three doses. It has been noted that duration of therapy appears to be a more important component of efficacy than dosage [12].

Davis EL et al. in their double-blind, placebo-controlled study, concluded that the combined use of PPS: oral + intravesical, was safe and more effective than oral PPS alone in the treatment of IC. This was an 18-week randomized study in which 41 women took part. Both groups underwent treatment for 6 weeks: in the control group, patients took oral PPS + intravesical instillation of PPS, in the placebo group, patients took oral PPS + intravesical placebo. All patients continued to receive PPS orally for another 12 weeks. The primary criterion for assessing effectiveness was the change in the O 'Leary-Sant Interstitial Cystitis Symptoms / Problem Index score from baseline at 6, 12, 18 weeks. Additional criteria were used: the changes in Pelvic Pain and Urgency Frequency questionnaire, Health Related Quality of Life Index: SF-36, pain scale, urgency scale, voiding log, patient global assessment, and sexual function scales.

The change in the overall O'Leary-Sant Interstitial Cystitis Symptoms/Problems Index score from baseline at 12 weeks was significantly greater than in the placebo group. At week 18, the control group showed statistically significant improvement in all areas of quality of life, while the placebo group showed significant improvement in only 3 areas. The authors concluded that pentosan polysulfate sodium therapy is effective and safe for patients with IC, and combination therapy with PPS (oral + intravesical) has advantages over monotherapy (oral) [13].

Hwang et al. conducted a meta-analysis on the effectiveness of PPS in patients with IC. The data sources were Medline, Excerpta Medica, International Pharmaceutical Abstracts (IPA). The investigators conducted a blind selection of materials that met the inclusion criteria: prospective placebo-controlled comparative studies lasting at least 8 weeks; PPS dosage not less than 300 mg/day; adults of a patient with ≥1 symptom, including pain, urgency, frequency, and nocturia; symptoms for at least 12 months, normal urinalysis, negative urine culture and cytology. The meta-analysis included 4 studies for a total of 448 subjects. The overall effectiveness of PPS for pain was 37%, for urge to urinate 28%, for urinary frequency 54%, for nocturia 48%. The results in the control group were significantly higher compared to placebo in terms of pain, urgency to urinate, urinary frequency. With regard to nocturia, the effectiveness of PPS was not significantly different from placebo. According to the authors, this may be due to the short duration of the study: a change in the urination profile can take many months [14].

The limitation of our study is the complexity of the comparative assessment of the effectiveness of PPS in the group of patients with the presence of Gunner's lesions compared with the group of patients without Gunner's lesions.

CONCLUSIONS

Our study reliably confirms the improvement of the quality of life and the regression of interstitial cystitis symptoms in the treatment with pentosan polysulfate sodium (PPS). PPS at a dosage of 300 mg per day is an effective and safe drug for patients with bladder pain syndrome/interstitial cystitis (BPS/IC). We are convinced that the PPS should be included in the complex treatment of patients BPS/ IC. (Appendix)

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Appendix

O'Leary-Sant questionnaire consists of two sections: assessment and evaluation of the symptoms of the patient's quality of life.

INTERSTITIAL CYSTITIS SYMPTOM INDEX

During the past month:

Q1. How often have you felt the strong need to urinate with little or no warning?
0. not at all
1. less than l time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

Q2. Have you had to urinate less than two hours after you finished urinating?
0. not at all
1. less than l time in 5
2. less than half the time
3. about half the time
4. more than half the time
5. almost always

Q3. How often did you most typically get up at night to urinate?
0. none
1. once
2. two times
3. three times
4. four times
5. five or more times

Q4. Have you experienced pain or burning in your bladder?
0. not at all
2. a few times
3. almost always
4. fairly often
5. usually

INTERSTITIAL CYSTITIS PROBLEM INDEX

During the past month, how much has each of the following been a problem for you:

Q1. Frequent urination during the day?
0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

Q2. Getting up at night to urinate?
0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

Q3. Need to urinate with little warning?
0. no problem
1. very small problem
2. small problem
3. medium problem
4. big problem

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

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