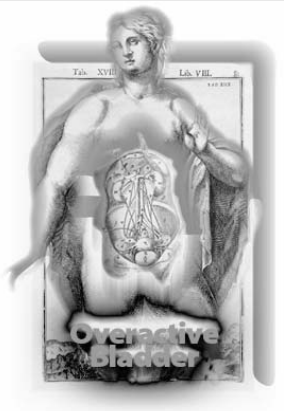

Interstitial cystitis: a retrospective analysis of treatment with pentosan polysulfate and follow-up patient survey

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To evaluate the efficacy and safety of pentosan polysulfate sodium (PPS) in relieving symptoms of interstitial cystitis, the authors retrospectively reviewed charts of 260 patients in whom interstitial cystitis had been diagnosed. Subsequently, they conducted a follow-up phone interview or mail survey of those patients who were treated with PPS to investigate changes in the patients' symptoms, adverse effects, and change in quality of life. The control group consisted of patients whose interstitial cystitis had been diagnosed at cystoscopy and had a duration of at least 1 year and who had taken at least one or more oral medications for their sypmptoms.

The average length of treatment was 9.3 months among the 27 subjects on PPS therapy. The mean length of time that they had diagnosed interstitial cystitis was 35.63 months and 48.78 months for the PPS-treated and control groups, respectively, with no statistically significant difference. Changes in frequency, urgency, and pain were greater in the treatment group and statistically significant (P=.11, P=.49, and P=.004, respectively). No change occurred in the rate of nocturia in the PPS-treated group compared with that in the control group. Symptoms of both groups improved over time, but improvement was statistically significantly greater in the treatment group (P=.001) over the treatment interval. The most common side effect attributable to PPS was diarrhea in 15% of subjects. Pentosan proved to be an efficacious option for reducing the debilitating symptoms of interstitial cystitis.

(Key words: interstitial cystitis, urinary frequency, urinary urgency, nocturia, pentosan polysulfate sodium)

Interstitial cystitis is a chronic, debilitating disorder characterized by urinary frequency (sometimes up to 60 times a day), urinary urgency, nocturia, and pain. Patients have symptoms of interstitial cystitis for an average of 7 years before diagnosis is made.[1] Although anyone can be affected, 90% of the afflicted are women in their fifth and sixth decades of life. Diagnosis of interstitial cystitis is primarily one of exclusion. The disorder does not represent a single disease entity but a disease spectrum, presumably multifactorial. Symptoms often resemble those of patients with overactive bladder. Up to 50% of patients with symptoms of interstitial cystitis will have spontaneous resolution in time.

Typical cystoscopic appearance of the bladder after hydrodistension with the patient under anesthesia demonstrates glomerulations or submucosal pinpoint capillary hemorrhages, and occasionally, a fissure-type lesion known as *Hunner's ulcers*. Inflammation of the bladder is a predominant finding in patients with interstitial cystitis. Patients with interstitial cystitis repeatedly lack evidence of any ongoing bacterial or viral infection.

Several intriguing theories have been suggested as possible etiologic mechanisms for the disorder, including inflammatory/autoimmune effect, mast cell infiltration, urinary toxins, and reflex sympathetic dystrophy. Another hypothesis is that there is a defect in the glycosaminoglycan (GAG) layer of the bladder mucosa. The GAG layer appears to be a critical defensive layer of the urothelium, normally preventing diffusion of toxins, bacteria, and irritating components of urine through the underlying bladder wall. Loss of the GAG layer is postulated to be the inciting cause of the symptom complex of interstitial cystitis.

In 1996, the US Food and Drug Administration approved release of pentosan polysulfate sodium (PPS) (Elmiron), a semisynthetic sulfated polysaccharide that serves as a synthetic bladder mucosal glycosaminoglycan. It adheres to the bladder surface, reinforcing the defective GAG layer.[2] Additionally, PPS has a weak heparin-like effect, stabilizing mast cells and inhibiting histamine release.[3] Originally used as a bladder instillation treatment, PPS was found to have reportedly low toxicity and good tolerance when taken orally.

Minor adverse reactions to the drug include nausea, diarrhea, headache, dizziness, skin rash, peripheral edema, and hair loss. Rarely, severe thrombocytopenia, increased anticoagulant activity, and elevated transaminase levels are reported. Intestinal absorption of PPS is approximally 3%. It is taken daily for at least 2 to 3 months to assess efficacy.

A significant number of patients in our population with interstitial cystitis have been started on treatment with PPS. The objective of our study was to evaluate the efficacy and safety of oral PPS in relieving recurring symptoms of interstitial cystitis through retrospective chart review and detailed follow-up interview of patients.

Materials and methods

Study design and patient selection

Control and PPS treatment groups were eligible for the study if they had had interstitial cystitis diagnosed at least 1 year previously and had persisting symptoms of frequency, nocturia, urgency, or pain, either singly or in combination. They were required to have undergone at least one cystocopy/hydrodistension procedure with anesthesia and to have had negative urine cultures. The PPS-treated group had to be on PPS therapy at least 8 weeks to be included in the treatment arm. Control group patients had to be taking at least one oral medication as a treatment for their symptoms of interstitial cystitis. Exclusion criteria were age less than 18 years, PPS therapy for less than 8 weeks, interstitial cystitis diagnosed for less than 1 year, no previous cystoscopy/hydrodistension, and inability to complete the questionnaire.

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Charts of 260 patients with interstitial cystitis from seven metropolitan Detroit area urology clinics were reviewed. As of May 1998, 27 patients with interstitial cystitis treated with PPS and 27 control group patients met the criteria for the study. The same investigator (M.G.W.) asked all patients to answer a questionnaire documenting their disease-related symptoms, which included frequency, nocturia, urgency, pain or discomfort, and overall change over time. The responses to the questionnaire provided the data for the quantitative evaluation presented here. Both groups were compared demographically in relation to average age, age range, length of time with the diagnosis of interstitial cystitis, and average number of previous drug treatments (*Table 1*).

Evaluation

All patients had undergone a complete history and comprehensive physical assessment with baseline laboratory studies (complete blood cell count with platelet and differential counts and electrolyte, blood urea nitrogen, and serum creatinine levels, prothrombin time, partial thromboplastin time, and urine cultures). Complete treatment histories were obtained, including previous experimental modes of therapy, over-the-counter medications or herbal products, and intravesical instillation with such agents as dimethyl sulfoxide (DMSO), chromium, chlorpactin, and heparin. Most of the patients underwent bladder biopsy during at least one cystoscopy/hydrodistension procedure. Biopsy results, when available, were categorized and calculated in relation to those typically found in interstitial cystitis, but no correlations were made with patients' symptoms. Bladder capacity was recorded in all patients.

The detailed questionnaire was adapted from a study by Hanno[4] in 1997. Patients on PPS therapy provided information based on symptoms just before starting therapy and up to current use or at the point of cessation of therapy. Control group patients were asked to report change in symptoms during the 12 months preceding the time of interview. Responses to the questionnaire provided the quantitative data. Patients were asked to report any adverse effects regardless of what medication had been prescribed for them. All adverse effects attributed to PPS were categorized and calculated over the entire study. Any causes for discontinuance of treatment with PPS were calculated and categorized.

Statistics

Length of participation was calculated as the length of time on PPS therapy for the treatment arm and the changes in symptoms during the preceding year up to time of interview in the control arm group. Because four means (frequency, urgency, pain, and overall change) and one covariant (interval of change) were identified, the Fischer test was used for statistical analysis. In order to test whether the PPS intervention group did better than the control group, a repeated measures analysis of covariance model was run.[5] This model allowed examination and comparison of the changes in the mean scores from pretest to posttest in the intervention and the control group.

Results

Of the 260 charts reviewed, 27 patients with interstitial cystitis who were taking PPS and 27 control patients with interstitial cystitis met the criteria for the study. The average age of PPS-treated patients was 43.9 years (range, 23 to 83 years), while the average age for the control group patients was 45.3 years (range, 18 to 72 years), with no statistically significant difference between the two groups. The length of time the patients had had the diagnosis of interstitial cystitis was 35.63 months and 48.78 months for the PPS-treated and control groups, respectively, with no statistically significant difference. The number of previous drug treatments for both groups was identical (2.3).

Urinary frequency

Although urinary frequency in both groups improved over time, the PPS-treated group demonstrated a larger change (5.9 vs 2.7), with the difference of improvement being statistically significant (P=.11). Frequency in both groups was nearly identical initially.

Nocturia

Control group patients had slighly more nocturia than the PPS-treated patients initially. Patients' levels of nocturia, representing the number of voids per night, dropped 2.2 points in the PPS-treated group versus 1.2 points in the control group, but the difference was not statistcally significant (P=.054).

Urgency

Similar to frequency, the change in urgency was better in the PPS-treated group compared with that in the control group, barely reaching statistical significance (P=.049). Severity of urgency was worse in the PPS-treated group than in the control group initially.

Pain or discomfort

Both the PPS-treated and the control groups were similar at the onset, with the patients treated with PPS having closest to severe pain levels. Change in pain or discomfort over time was greater in the PPS-treated study group, with strong statistical significance (P=.004). This represented the largest change in the four study parameters.

Overall change

We asked patients about their complete change in all parameters over time, with 1 being worse up to 6 representing total improvement or complete abatement (or both) of symptoms. Although both groups improved over time, there was a strong statistically significant change in the PPS-treated group versus the control group (P=.001).

Previous treatments

Table 2 lists and compares the previous medical treatments of both study groups. Six (22%) of the patients in each group were given intravesical DMSO during their course of therapy. Spasmolytics were given more frequently in the PPS-treated group (74%) than in the control group (44%); whereas tricyclic antidepressants had been used in 30% of patients in the control versus only 4% of the patients in the PPS-treated group. A transcutaneous electrical nerve stimulation (TENS) unit had been placed in one patient of each study group but had been subsequently removed. One patient had received full-course intravesical bacille Calmette-Guérin (BCG) vaccine as part of a study that has since been published.[6] None of the control group patients had received heparin bladder instillation.

Concomitant medications

We investigated the use of concomitant medication in our study cohort (*Table 3*). Spasmolytics were being used more frequently in the PPS-treated group (88%) versus in the control group (48%). An equal number of patients in each group were using phenazopyridine (30%) to treat their symptoms, while slightly more control group patients were taking tricyclic antidepressants (33%) or selective serotonin-reuptake inhibitors (26%) than

Table 1
Demographic Data: Group Treated with Pentosan Polysulfate Versus Control Group

Variable	Group treated with pentosan	Control group
☐ Average age, y	43.96	45.30
☐ Age range, y	23 to 38	18 to 72
☐ Mean time having diagnosis, mo	35.63	48.78
☐ Mean time on pentosan therapy	9.3	NA*
☐ Average No. of previous treatment modalities	2.3	2.3

*NA = not applicable.s

Table 2
Treatment Modalities Previously Used in Group Treated with Pentosan Polysulfate and in Control Group

Treatment modality	Treatment group	Control group
☐ Dimethyl sulfoxide, No. (%)	6 (22)	6 (22)
☐ Spasmolytics, No. (%)	20 (74)	12 (44)
☐ Tricylic antidepressants, No. (%)	1 (4)	8 (30)
☐ Transcutaneous electrical, nerve stimulation, No. (%)	1 (4)	1 (4)
☐ Bacille Calmette-Guérin vaccine, No. (%)		1 (4)
☐ Chromium instillation, No. (%)		1 (4)
☐ Heparin instillation, No. (%)	3 (11)	
☐ Steroids, No. (%)	1 (4)	2 (7)
☐ Other, No. (%)	10 (37)	13 (48)

Table 3
Concomitant Oral Medication: Group Treated with Pentosan Polysulfate Versus Control Group

Type of medication	Treatment group	Control group
☐ Spasmolytics, No. (%)	24 (88)	13 (48)
☐ Tricyclic antidepressants, No. (%)	6 (22)	9 (33)
☐ Selective serotonin-inhibitors, No. (%)	3 (11)	7 (26)reuptake
☐ Phenazopyridine, No. (%)	8 (30)	8 (30)
☐ Anxiolytics, No. (%)		2 (7)
☐ Antibiotics, No. (%)	1 (3)	3 (11)
☐ Antihistamines, No. (%)	3 (11)	1 (4)
☐ α-Blockers, No. (%)	2 (7)	2 (7)
☐ Herbal or other products, No. (%)	10 (37)	7 (26)

the PPS-treated group (11%). α-Blockers were used in 7% of patients in each participant group. Ten (37%) of the PPS-treated patients and 7 (26%) of the control group patients were using herbal products or over-the-counter remedies.

Because PPS is a relatively new drug, we inquired as to whether the PPS study group had any side effects develop during their course of treatment. Most prevalent was diarrhea, with mild cases developing in 4 (15%) of the 27 PPS-treated patients after initiating therapy (*Table 4*). The second most frequent side effect was hair thinning. Three (11%) of the patients reported some degree of hair thinning or fallout. One stopped therapy because of persistent hair fallout. Eight percent of patients had abdominal cramping. One patient reported weight gain, while two patients had neurolgic symptoms including paresthesias or visual disturbances. Other side effects included shortness of breath in a nonasthmatic patient and generalized morbilliform rash in another.

In all, 27% of patients on PPS therapy had gastrointestinal symptoms or weight gain during their course of treatment.

A number of patients discontinued PPS during their course of treatment, but not all discontinuations were due to negative factors. Four patients (15%) stopped taking the drug because of the previously listed side effects (*Table 5*). Symptoms worsened in 9% of the patients, forcing discontinuance. One patient's symptoms totally abated on PPS therapy, and she stopped use of PPS before the interview. One male patient had a myocardial infarction during his course of treatment, and administration of the drug was stopped although the incident was not related to the drug use. Finally, one patient stopped taking PPS for a planned pregnancy. In all, 33% of patients stopped taking PPS during their course of treatment.

Cystoscopy/bladder biopsy results

To be part of the study cohort, all patients were required to have had at least one cystoscopy/hydrodistension with bladder mucosal biopsy. Hunner's patch was identified in two (7.4%) of the PPS-treated patients and in only one (4%) of the patients in the control group (*Table 6*). No fissures were found during cystoscopic evaluation in either group. Glomerulations were similarly prevalent in both study groups, with 81% of the PPS-treated group and 74% of the control group having glomerulations. Similarly, bloody effluent was slightly more prevalent in the PPS-treated group (74%) compared with the control group (66%), but this difference was not statistically significant. Average bladder capacity was measured in both groups and found to be similar at 540 mL and 574 mL in the PPS-treated and control groups, respectively.

Discussion

Of the 260 charts reviewed, 27 patients with interstitial cystitis taking PPS and 27 control patients with interstitial cystitis met the criteria for the study. Criteria

used to enter patients into the study were strict so as to stratify both groups and reduce confounding variables. Although some investigators do not require cystoscopy for diagnosis of interstitial cystitis, we required all patients to have undergone at least one hydrodistension and bladder biopsy. This requirement was to ensure that each patient had a similar baseline treatment (hydrodistension) and ruled out carcinoma in situ, other neoplasms, diverticula, or stones as a potential cause of their symptoms.

Because it is well established that PPS takes up to 6 weeks or more to exert any symptomatic relief, the PPS-treated patients had to have been taking the drug for at least 8 weeks. Average length of use of PPS was 9.3 months among the 27 subjects which provides more long-term results compared with studies evaluating patients at 3 months. Because the PPS-treated patients were taking at least one drug (PPS), we stratified the control group by selecting only those patients who were currently taking at least one oral medication. All patients had to have established interstitial cystitis diagnosed no less than 1 year previously.

Patients treated with PPS on average were younger than the the control group patients, but not statistically significantly so. The PPS-treated patients had a shorter duration of diagnosed interstitial cystitis, but the difference was not statistically significantly different. Both groups had the same average number of previous drug treatments. Cystoscopic evaluation revealed Hunner's patch in two (7.4%) of the PPS-treated patients, but in only one control group patient (4.0%), comparing closely with the rate found in studies by Koziol (7.0%)[7] and Messing and colleagues (11.3%).[8] As in the latter study, the rate of glomerulations (91% of patients) was similar in both study groups (81% of the PPS-treated group and 74% of the control group). Although bloody effluent was slightly more prevalent in the PPS-treated group compared with the control group, this difference was not statistically significant and was nearly identical to the findings of Messing and colleagues.[8] Average bladder capacity was measured in both groups and found to be similar in both groups.

Interestingly, mean symptoms in both groups improved over time (*Table 7*). The PPS-treated group demonstrated a statistically significant (P=.11) improvement in urinary frequency on the analog scale over time, with the frequency in both groups being nearly identical initially (15.3 vs 16.4). Patients treated with PPS had nearly 6 voids fewer per day compared with just less than 3 fewer voids per day for the control group. Frequency in both groups improved over the time interval.

Control group patients had slightly more nocturia than the PPS-treated patients initially, but both groups improved over the time interval. Nocturia, representing the number of voids per night, dropped 2.2 points in the PPS-treated group versus 1.2 points in the control group, but the difference was not statistically significant (P=.054). Our results are consistent with those of most studies, but not with those of Parsons and coworkers,[9] who found a 50% or greater reduction in nocturia in PPS-treated patients.

As with urinary frequency, the change in urgency was better in the PPS-treated group compared with that in the control group, barely reaching statistical significance (P=.049). Severity of urgency was worse in the PPS-treated group than the control group initially. Severity of urgency was worse in the PPS-treated group than in the control group initially.

Both PPS-treated and control groups had similar pain levels at the onset, with the PPS-treated patients being closest to severe pain levels. Change in pain or discomfort over time was greater in the PPS-treated study group with strong statistical signifi-

Table 4
Adverse Effects of Pentosan Polysulfate: Nature and Incidence

Side effect	No.	%
☐ Diarrhea	4	15
☐ Hair thinning	3	11
☐ Abdominal cramping	2	8
☐ Weight gain	1	4
☐ Shortness of breath	1	4
☐ Visual disturbances	1	4
☐ Rash	1	4
☐ Paresthesias	1	4

Table 5
Discontination of Pentosan Polysulfate Treatment

Cause	No.	%
☐ Side effects*	4	15
☐ Worsening of symptoms	2	9
☐ Remission of symptoms	1	4
☐ Myocardial infarction	1	4
☐ Planned pregnancy	1	4
☐ **Total**	**9**	**33**

*Includes diarrhea, abdominal cramping, nausea, hair thinning.

Table 6
Results of Cystoscopy and Biopsy for Group Treated with Pentosan Polysulfate and Control Group

Finding	Treatment group	Control group
☐ Hunner's patch, No. (%)	2 (7.4)	1 (4.0)
☐ Fissures, No. (%)	0 (0)	0 (0)
☐ Glomerulations, No. (%)	22 (81.0)	20 (74.0)
☐ Blood effluent, No. (%)	20 (74.0)	18 (66.0)
☐ Bladder capacity, mL	540	574

Table 7
Improvement in Interstitial Cystitis Symptoms in Pentosan Polysulfate (PPS)–Treated and Control Groups

Parameter	Group	
	PPS-treated	Control
Frequency, No. of voids		
Pretest	15.3	16.4
Posttest	9.4	13.7
Change	−5.9	−2.7
Nocturia, No. of voids		
Pretest	4.7	5.8
Posttest	2.5	4.5
Change	−2.2	−1.3
Urgency, severity*		
Pretest	2.3	2.2
Posttest	1.4	1.6
Change	−0.9	−0.6
Pain, severity*		
Pretest	6.6	6.2
Posttest	3.3	4.7
Change	−3.3	−1.5

*Change in all parameters over time, with 1 being the worst up to 6, representing total improvement or complete abatement of symptoms (or both).

cance (P=.004). This represented the largest change in the four study parameters.

We asked patients about their complete change in all parameters over time, with 1 being the worst up to 6, representing total improvement or complete abatement of symptoms (or both). Although both groups improved over time, there was a strong statistically significant change in the PPS-treated group versus the control (P=.001).

Twenty-two percent of patients in each group were given intravesical DMSO during their course of therapy. Spasmolytics were given more frequently in the PPS-treated group (74%) than in the control group (44%), while tricyclic antidepressants had been used in 9 (33%) of the patients in the control group versus only 1 patient (4%) of the PPS-treated group. A TENS unit had been placed in one patient of each study group but had been subsequently removed. One patient had received full-course intravesical BCG as part of a study that was published in mid-1998.[6] She admitted to having improved symptoms. None of the control group patients had received bladder instillation of heparin.

As PPS is a relatively new drug, we inquired as to whether the PPS study group had any side effects develop during their course of treatment. Most prevalent was diarrhea, with mild cases developing in 4 (15%) of the 27 PPS-treated patients after initiating therapy. The second most frequent side effect was hair thinning. 3 (11%) of patients reported some degree of hair thinning or fallout. One stopped therapy due to persistent fallout. Eight percent of patients experienced abdominal cramping. One patient reported weight gain, while two patients experienced neurolgical symptoms, including paresthesias or visual disturbances. Other side effects included shortness of breath in a nonasthmatic patient and generalized morbilliform rash in another.

In all, 27% of patients on PPS therapy had gastrointestinal symptoms or weight gain during their course of treatment. This compares poorly with the PPS package insert, which states that approximately 5% of patients will experience such symptoms.

As interstitial cystitis is a difficult, chronic disease to treat, patients often require multimodal approach to alleviate their symptoms. Most studies investigating PPS involve patients taking PPS exclusively, but in a day-to-day clinical setting, it makes sense to us to evaluate the use of PPS as an additional medication to a regimen providing marginal results.

Regarding the use of concomitant oral medications in our study cohort, it is interesting to note that 10 PPS-treated patients (37%) and 7 (26%) control group patients were using herbal products and over-the-counter remedies. Although this fact could create a bias in the study results, both groups were essentially equal in their use of such agents. The pattern of herbal use among patients, including specific types, did not appear to greatly affect the outcome of the patients' symptoms. No patients were found to taking only an herbal remedy.

Although 9 patients discontinued taking PPS during their course of treatment, 3 of them did so for reasons not related to negative causative factors. Four patients (15%) stopped taking the drug because of side effects, mostly gastrointestinal disturbances and hair thinning. According to the package insert,[10] approximately 4% of patients taking PPS will have hair thinning or alopecia. Hanno[4] noted alopecia in 3.91% of study subjects. Interestingly, we found nearly three times the rate of hair thinning in our patients compared with that of other investigators. This difference may be due to our use of a stricter definition of hair loss in our patients.

Symptoms of interstitial cystitis actually worsened in 9% of the patients, forcing discontinuation of the drug's use. One patient's symptoms totally abated on PPS therapy, and she stopped use of PPS before the interview. It is unknown whether her symptoms have returned since cessation of the drug. A second patient was contemplating discontinuation because of marked improvement of symptoms, as well.

A male patient's myocardial infarction during his course of treatment was not related to use of the drug, although use of the drug was stopped. The patient's symptoms were returning at the time of interview. To date, it is unknown whether the patient who stopped taking PPS for a planned pregnancy plans to resume PPS therapy postpartum.

This study, which compares highly selected, treatment-stratified patients with interstitial cystitis, is useful to the clinician because it is difficult, indeed rare, to find a group of patients of this cohort type who respond only to one drug and are willing to stay on one therapy regardless of symptoms. Realistically, many patients with interstitial cystitis require several medications or modes of therapy (or both) to control their debilitating

symptoms. This study confirms that PPS is an effective, viable choice for patients with interstitial cystitis and can provide measurable improvement even when added to a patient's current medical regimen.

Comment

The response to oral PPS varied widely in patients from worsening symptoms to complete ablation. Pentosan polysulfate significantly hastened the decline in the scores for urinary frequency, urgency, and pain between the two groups. There was, however, no significant change in the urgency parameter between the two groups.

Perception of overall improvement was better in PPS-treated patients as compared with those patients in the control group, although both groups improved over time. Compared with agents used by the control patients, PPS provides modest efficacy in treating symptoms of interstitial cystitis and should be considered a useful drug in the armamentarium of treatments for the patient in whom interstitial cystitis is diagnosed.

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