Safety and Efficacy of the Use of Intravesical and Oral Pentosan Polysulfate Sodium for Interstitial Cystitis: A Randomized Double-Blind Clinical Trial

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Purpose: We examined the safety and the efficacy of a combination of intravesical and oral pentosan polysulfate sodium in comparison to only oral pentosan polysulfate sodium in treating interstitial cystitis.

Materials and Methods: A total of 41 females diagnosed with interstitial cystitis were randomized to receive a combination of intravesical pentosan polysulfate sodium plus oral pentosan polysulfate sodium (21 in treatment group) or intravesical placebo plus oral pentosan polysulfate sodium (20 in placebo group) for 6 weeks. All subjects continued to receive oral pentosan polysulfate sodium for another 12 weeks. The primary outcome was the change in the O'Leary-Sant Interstitial Cystitis Symptoms/Problem Index from baseline to week 6, 12, and 18. Other outcomes included: 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.

Results: The change in the total score of O'Leary-Sant Interstitial Cystitis Symptoms/Problems Index from baseline to week 12 among the treatment group (median −12 or approximately a 46% reduction) was significantly greater compared to the placebo group (median −5.5 or approximately a 24% reduction, $p = 0.04$). At week 18 the treatment group showed statistically significant improvement in all Health Related Quality of Life domains compared to the baseline ($p \leq 0.01$), while the placebo group showed significant improvement in only 3 Health Related Quality of Life domains, ($p \leq 0.05$) compared to the baseline. There were no significant differences within major categories of adverse events between treated and placebo groups.

Conclusions: The use of intravesical pentosan polysulfate sodium simultaneously with oral pentosan polysulfate sodium is a safe and effective therapeutic option. These findings will open a new option for patients with interstitial cystitis to reduce their severely devastating symptoms and to improve their quality of life and well-being.

Key Words: cystitis, interstitial; administration, intravesical; pentosan sulfuric polyester; clinical trials

Interstitial cystitis is a chronic, severely debilitating disease of the urinary bladder characterized by urinary frequency, urgency, nocturia, and pelvic pain in the absence of other obvious bladder pathology.[1] IC has a profound impact on patient quality of life that extends beyond its severe symptoms to include physical, social, as well as emotional functions and well-being.[2] Despite the long-standing recognition of IC, there are still no clear answers to many vital issues (eg etiology, prevalence, diagnostic definition and therapy).[1]

The actual prevalence rate is unknown, and estimates range widely from 67 per 100,000[3] to 575 per 100,000[4] based on the diagnostic criteria and methods used in estimating the rate. The majority of IC cases are females, with a median age at diagnosis of 42 to 46 years old.[3]

At present there is no single etiology of IC, therefore treatment is prescribed on the basis of patient symptoms. Pentosan polysulfate sodium is the only oral therapy approved for IC by the FDA. The mechanism of action of PPS is not completely understood but a widely accepted theory is that it replaces damaged segments of the GAG layer, the mucus of the bladder lining.[5] The GAG layer protects the bladder from the caustic effects of urine and bacteria. PPS safety and efficacy as an oral treatment for IC have been documented in several randomized double-blind clinical trials.[6,7]

A main disadvantage of PPS as an oral therapy is the low concentration of active drug reaching the bladder (1% to 3%) resulting in a long lag time (approximately 3 to 6 months) before clinical improvement can be observed.[7,8]

It would appear that intravesical therapy (the direct instillation of treatment into the bladder using catheter through urethra) compared to oral therapy alone might pro-

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For another article on a related topic see page 359.

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vide the benefit of establishing a higher concentration of therapy directly into the bladder with a minimum risk of systemic side effects.[9] Therefore, PPS instilled directly into the bladder might accelerate a more rapid resolution of IC symptoms.

Dimethylsulfoxide, an anti-inflammatory analgesic agent with muscle relaxing properties, is the only FDA approved intravesical therapy in the United States. It is safe and can provide moderate symptomatic relief.[10] Its unpleasant metabolic bio-product (eg garlic odor) makes it undesirable as a treatment.

The use of intravesical PPS was shown to be an effective and safe option for the treatment of IC in a small clinical trial in the Netherlands.[11] In the United States the only data on intravesical PPS were provided through a limited retrospective study of 17 patients with IC.[12] In this study intravesical PPS was administered to the subjects (average of 13 instillation therapies) during 1 year. The results suggested that intravesical PPS provides a safe and generally effective treatment option for IC while oral PPS therapy takes effect.

Although IC has an incredibly negative impact on patient quality of life, few clinical trials that assessed the efficacy of oral PPS considered health related quality of life as one of its main outcomes.

This study is the first randomized double-blind clinical trial to assess the safety and efficacy of a combined therapy of intravesical and oral PPS compared to intravesical placebo and oral PPS over 18 weeks. Changes in IC symptoms, HRQL and sexual function will be examined.

MATERIALS AND METHODS

Study Design and Setting

This was an 18-week randomized double-blind placebo controlled clinical trial and was conducted in Glendora, California between April 2004 and August 2006. Restricted randomization with a size of 4 per block was used to allocate study subjects into 2 groups. The blinding process was monitored, assessed and recorded by an independent pharmacist, who was responsible for preparing the trial intravesical treatment and placebo for subjects according to an FDA approved method.

A total of 40 subjects were initially allocated into 2 balanced groups: treatment (received intravesical PPS and oral PPS) or placebo (received intravesical placebo [normal saline] and oral PPS). Figure 1 shows a flow

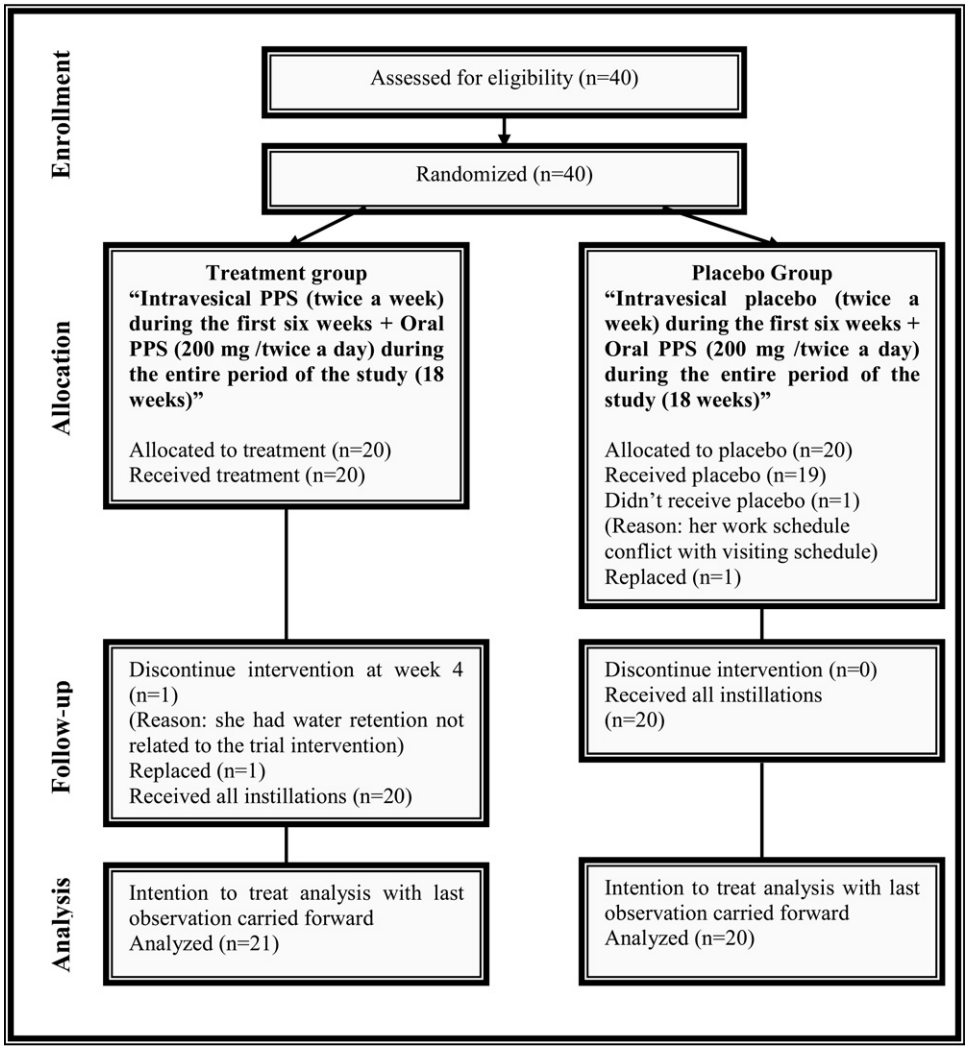

FIG. 1. Flow diagram of subject progress through phases of trial

diagram of subject progress through the phases of the trial. Oral PPS capsules were administered either 1 hour before meals or 2 hours after meals.[8] The study design was approved by the institutional review board of Foothill Presbyterian Hospital, Glendora, California, the institutional review board of the University of Pittsburgh, Pittsburgh, Pennsylvania, the FDA and Ortho-McNeil Pharmaceutical, Inc.

Study Subjects, Exclusion and Inclusion Criteria

Females who were older than 18 years, diagnosed with IC within 1 year of the beginning of the study, and previously untreated with either intravesical or oral PPS were recruited from patients with IC of Citrus Valley Medical Research, Inc. Glendora, California. To be included in the study all subjects had to have the following examination requirements: cystoscopic examination under anesthesia with hydrodistention and photo documentation showing petechial hemorrhage or ulcers, negative urine culture, a score of at least 4 on a 9-point pain scale, 5 on the O'Leary-Sant IC symptom index, and 4 on IC problem index.

Subjects were excluded from the study for bladder capacity greater than 350 ml on an awake cystometrogram, absence of intense urge with bladder filled to 150 ml water on cystometrogram, biphasic involuntary bladder contractions, absence of nocturia, voiding frequency less than 8 times per day (voiding diaries), remission of symptoms by antimicrobials, urinary antiseptics, anticholinergics, or antispasmodics, bacterial cystitis within 3 months, recurrent bladder, genital herpes within 3 months, cervical, vaginal or urethral cancer, chemical, tubercular or radiation cystitis, benign or malignant bladder tumor, vaginitis, vesicle ureteral reflux or urethral diverticula, neurogenic bladder dysfunction, prior urinary diversion, receiving any intravesical treatment at time of enrollment, pregnant or lactating mother. A total of 33 subjects had a cystometrogram (median bladder capacity 131 ml). Subjects lacking this criterion (because it was painful) were entered into the study but they must have met all the other standard criteria for IC.

Procedure for Intravesical Instillation of PPS and Placebo

All instillations were performed in the clinic by either the principal investigator (ED) or a well trained nurse. An 8Fr LoFric® catheter (Astra Tech Inc, Torrance, California) was used in all intravesical instillations (PPS and placebo). Before placing the catheter into the urethra, a preparatory prophylaxis solution (lidocaine hydrochloride jelly, United States Pharmacopeia 2% 100 mg [20 mg/ml]) was applied to the catheter tip first and then to the perineum to prevent urethral spasms and perineal sensitivity. Then the bladder was drained from any post void residual and the intravesical instillation process was performed in 2 consecutive steps as described previously.[12] In brief, a solution of 8 ml 1% lidocaine and 3 ml 8.4% sodium bicarbonate was first instilled into the bladder to eliminate urethral discomfort so that the subject could more easily retain the instilled solution. After 5 minutes the intravesical solution of either PPS (200 mg or 2 capsules mixed with 30 ml sterile normal buffered saline) or placebo (30 ml sterile normal buffered saline) was then instilled, retained for a minimum of 30 minutes to a maximum of 60 minutes and voided (fig. 2).

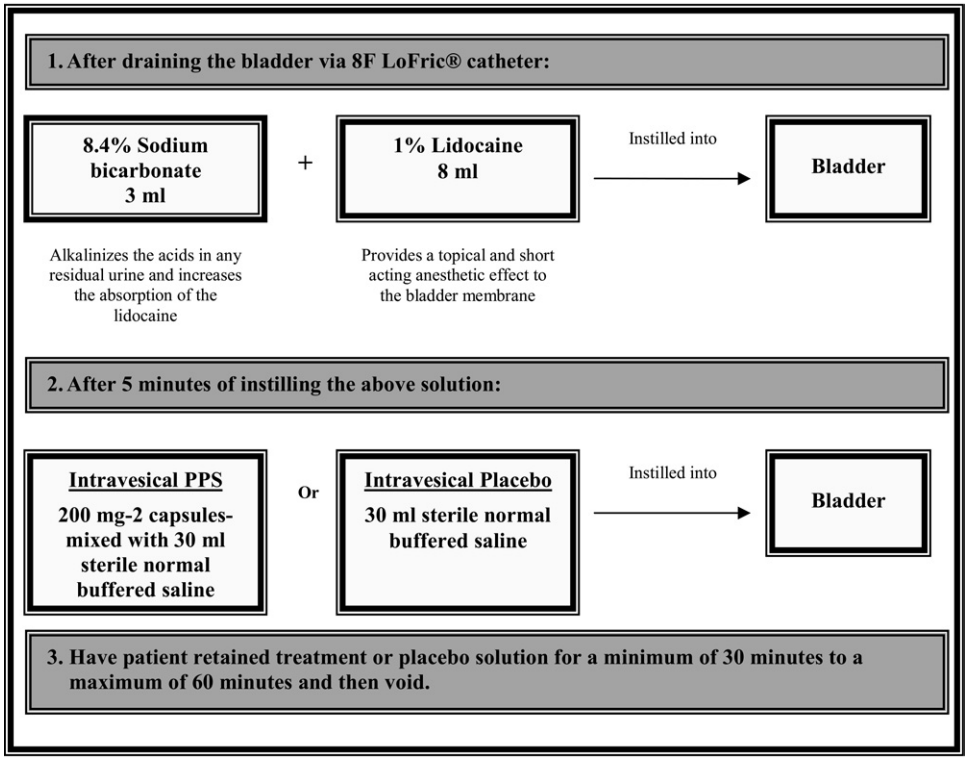

FIG. 2. Procedure for intravesical instillation process of treatment or placebo

Efficacy Outcomes

The primary outcome was the change from baseline to week 6, 12 and 18 in the severity of IC symptoms measured by the O'Leary-Sant IC symptom and problem index (total score = 36).[13] The PUF questionnaire (total score 35),[14] pain assessment scale (range 1 to 9, 1—no pain, 9—severe pain), urgency scale (range 1 to 5, 1—no urgency, 5—severe urgency), and voiding diaries that measure the voiding frequency during waking hours and sleeping hours for a duration of 24 hours were completed at baseline, and weeks 6, 12 and 18 of the trial. The SF-36,[15] a widely used well validated instrument that measures HRQL and includes 8 different domains (score range 0 to 100 for each domain, 0—worse HRQL, 100—excellent HRQL) was completed at baseline, and weeks 4 and 18. The sexual function VAS which assesses sexual desire and sexual arousal through a 10 cm line with none at 1 end and high at the other end, was assessed at baseline, and weeks 4, 6, 12 and 18.

The proportion of responders was determined using a different version of the patient global assessment questionnaire. This version was used in a previous clinical trial (sponsored by Bioniche Life Sciences Inc., Canada, 2003). The Canadian trial assessed the safety and efficacy of Cystistat® (sodium hyaluronate) as a treatment for IC.[16] This version of patient global assessment evaluates the overall change in the IC condition since enrollment in the study. It measures the level of change with: worse, no change, and improved as the possible outcomes. It also measures the level of improvement with: moderate, greatly improved, and completely improved as the possible outcomes. The global assessment also allowed the patients to evaluate the changes in urgency and urinary frequency using the same outcomes as overall change in the IC condition. The subjects completed this instrument at week 18 of the study. Responders were defined as those who reported improved as a possible outcome. This definition, for responders, was chosen based on the design of this version of the patient global assessment, and it reflects all the corresponding outcomes of improvement (moderately, greatly and completely).

Safety Measures

Safety was ascertained through evaluating adverse events during the entire study period, hepatic panel function and blood clotting after each instillation and at week 12, and the development of UTI at baseline, at the first visit from week 1 through week 6 and at followup visits (weeks 12 and 18). The urine specimen must contain more than 10^6 bacteria of single organism to confirm the occurrence of clinically significant UTI (clinically significant positive urine culture). All laboratory tests were performed at a single location to insure quality control and to reduce bias.

Possible Confounders

To be sure that the efficacy results were only related to the trial intervention and not to other factors, demographics at baseline, data about concurrent treatments, medical history, and compliance of oral PPS during the entire period of the study were monitored and assessed. Compli-

TABLE 1. *Baseline demographics and clinical characteristics of the study population*

	Median (25th, 75th percentiles)		
	Treatment	Placebo	p Value*
Age	36.9 (31.9, 45.1)	38.7 (26, 42.7)	0.5
% Race:			0.3
White	76	65	
Not white	24	35	
Presence of Hunner's ulcers (%)	5	25	0.1
Uroflow vol (ml)	149 (67, 231)	174.5 (91, 232)	0.9
Bladder capacity/cystometrogram (ml)*	131 (58, 270)	136 (90.3, 227.5)	0.7
O'Leary-Sant total score (0–36)	26 (18.5, 32)	23 (19.3, 30)	0.4
O'Leary-Sant ICSI score (0–20)	14 (10.5, 17)	12 (10, 16)	0.4
O'Leary-Sant ICPI score (0–16)	13 (8.5, 15)	11.5 (10, 14)	0.2
PUF total score (1–35)	23 (18.3, 25.5)	21.5 (18.3, 26.5)	0.9
PUF symptom score (1–23)	14 (11.5, 17)	14 (12.3, 17)	0.9
PUF bother score (0–12)	8 (6, 9)	7.5 (6, 9.7)	0.8
Pain (1–9)†	4 (4, 5)	4.7 (4, 5.8)	0.3
Ave voiding urgency score (1–5)‡	3.5 (2.6, 3.6)	3 (2.5, 3.2)	0.1
Urinary frequency	12 (9, 16)	14.5 (10, 18.8)	0.3
Nocturia	2 (1, 4)	2 (1, 4)	0.7
SF-36 (0–100)§:			
Physical functioning	65 (45, 85)	65 (36.3, 89.7)	0.9
Role limitation/physical	0 (0, 50)	37.5 (0, 68.8)	0.3
Bodily pain	31 (16, 41)	32 (22, 48.5)	0.5
General health	42 (27.5, 67)	57.3 (40.5, 80.8)	0.1
Vitality	20 (10, 27.5)	32.5 (20, 57.5)	0.06
Social functioning	37.5 (25, 62.5)	56.3 (28.1, 96.9)	0.2
Role limitation/emotional	33.3 (0, 100)	66.7 (33.3, 100)	0.2
Mental health	56 (32, 68)	66 (56, 75)	0.07
Sexual assessment VAS (0–10 cm)‖:			
Sexual desire	1.7 (0.5, 4.5)	3.9 (2.2, 5.5)	0.08
Sexual arousal	2.4 (0.7, 4.9)	3 (1.2, 5.8)	0.5

Cystometrogram was performed in 33 subjects (15 treatment, 18 placebo).
* chi-square or Fisher's exact tests for categorical variables, Mann-Whitney U test for continuous variables.
† Score of 1—no pain, score of 9—severe pain.
‡ Score of 1—no urgency, score of 5—severe urgency.
§ Score of 0—worse health related quality of life, score of 100—excellent health related quality of life.
‖ Score of 0—none, score of 10—high; one missing in placebo group for sexual desire and sexual arousal (19).

ance of oral PPS was calculated for each of the study weeks by dividing the total number of capsules that were administered during a week by 28 capsules (the total number of capsules that the subject should administer during each week).

Statistical Analysis and Sample Size

The projected sample size of 40 subjects was selected to detect a minimum difference of 2.3 in the mean O'Leary-Sant IC symptom index at end point between the 2 groups (based on a 2-sample t test with standard deviation of 2.5, a significance level of 5%, and 80% power). The change of 2.3 in ICSI was chosen based on preliminary data which demonstrated using intravesical instillation of PPS can reduce the O'Leary-Sant Interstitial Cystitis Symptom Index score from 14.3 to 11.1 during a treatment period of approximately 17 weeks.[17]

The primary analysis was intent to treat with LOCF to the end of the trial. A nonparametric approach was used to assess study outcomes and the results of continuous variables were presented as median, 25th and 75th percentiles except for the hepatic panel and blood clotting values which were presented as mean ± SD. Baseline characteristics were compared between groups using Fisher's exact test or chi-square test for categorical variables, and Mann-Whitney U test for continuous variables.

For continuous outcomes, differences from baseline to each end point within each group were assessed through Wilcoxon signed-rank test while differences between changes from baseline to each end point among groups were assessed via Mann-Whitney U test. Differences in proportions of responders between the 2 groups at week 18 were assessed through Fisher's exact test or chi-square test. All statistical tests were 2-sided and performed using a significance level of 5%. SPSS® version 13.0 was used to conduct all statistical analyses.

RESULTS

Figure 1 illustrates the flow diagram of the progress of study subjects through the phases of the trial. Two subjects dropped out. Subject 1 (placebo group) did not start the study because of a conflict with her work schedule. Subject 2 (treatment group) completed 4 weeks of the study and dropped out for medical reasons that were unrelated to the clinical trial. Thus, there was no further followup. Per the study protocol both subjects were not evaluable, therefore 2 additional subjects were recruited. The first received the same intervention that was assigned to subject 1 while the second received the same intervention that was assigned to subject 2. In total, 42 subjects signed an informed consent, of whom 41 were included in the final analysis. Based on intent to treat analysis we included subject 2 who dropped out after 4 weeks of the trial in the treatment group (21). The LOCF method was used to impute all missing data for this subject.

All subjects were females, and the majority was white (71%, 29 of 41) with a median age of 38 years (range 20 to 71). Hunner's ulcers were present in 15% of the study population (6 of 41) and glomerulations in 100%. Except for 1 subject all cases were classified as moderate IC cases (46%, 19 of 41) or severe IC cases (51%, 21 of 41) based on O'Leary-

TABLE 2. *Changes in IC symptoms from baseline*

Outcomes	Median (25th, 75th percentiles) Treatment						Median (25th, 75th percentiles) Placebo					
	Wk 6		Wk 12		Wk 18		Wk 6		Wk 12		Wk 18	
O'Leary-Sant total score (0–36)	−7	(−3, −14.5)*	−12	(−6.5, −16.5)*,†	−12	(−7.5, −16.3)*,‡	−4	(−1.3, −12)*	−5.5	(−3, −9)*	−8	(−3.3, −13)*
O'Leary-Sant ICSI (0–20)	−4	(−1.5, −8)*	−6	(−3, −7.5)*,†	−6	(−3.5, −9)*,‡	−2	(0, −4.8)*	−3	(−1.3, −4)*	−4	(−3, −7.5)*
O'Leary-Sant ICPI (0–16)	−3	(−1.5, −7)*	−6	(−3, −8.5)*,‡	−6	(−3.3, −8.5)*,‡	−2	(−1, −5)*	−3	(−1, −5)*	−4	(−0.3, −5)*
PUF total score (1–35)	−4	(0, −8.9)*	−6	(−3.4, −10.8)*	−7.3	(−4.3, −13.5)*	−3.8	(−1.3, −7.8)*	−5.8	(−3, −10)*	−6	(−3, −13)*
PUF symptom index (1–23)	−3	(0, −5.8)*	−5	(−2, −7)*	−4.5	(−2.5, −8.3)*	−2	(−1, −5.5)*	−4	(−2, −6.5)*	−4.5	(−1.3, −8)*
PUF bother index (0–12)	−1.5	(0, −2.9)*	−2.5	(−1, −3.8)*	−3	(−2, −4.8)*	−1.7	(−1, −3)*	−1.8	(−1, −3.8)*	−2.5	(−1, −5)*
Pain scale (1–9)	−1	(0, −2)*	−2	(−0.5, −3)*	−2	(−1, −3)*	−1.5	(−0.3, −3)*	−1.5	(0, −3)*	−2	(0, −3)*
Urgency scale (1–5)	−0.4	(0.1, −1)*	−0.6	(−0.1, −1)*	−0.6	(0, −1.2)*	−0.2	(0.5, −0.9)	−0.2	(0.4, −1.1)	−0.4	(0.2, −0.9)
Voiding frequency	−1	(3, −2.5)†	−2	(1.5, −3.5)	−1	(0, −3)†	−2.5	(−1, −4.8)*	−2	(−0.3, −4.8)*	−3	(−1, −7)*
Nocturia	0	(0, −1)§	0	(1.5, −1)	−1	(−0.5, −2)*	−0.5	(0.8, −2)	−0.5	(0, −2.8)§	−1	(0.8, −2)*

* Wilcoxon sign rank test (changes from baseline to each end point within each group) $p < 0.05$.
† Mann-Whitney U test (changes from baseline to each end point between treatment groups) $p < 0.05$.
‡ Mann-Whitney U test (changes from baseline to each end point between treatment groups) $0.05 \leq p < 0.1$.
§ Wilcoxon sign rank test (changes from baseline to each end point within each group) $0.05 \leq p < 0.1$.

Sant ICSI cut points of 0 to 6—mild, 7 to 13—moderate and 14 to 20—severe.[13]

There were no significant differences between the study groups at baseline in terms of demographics, IC status, and efficacy primary and secondary outcomes (table 1). Confounders like menopausal status, smoking, concurrent medications, and compliance with oral PPS during the entire study period as well as during the first, second and third 6 weeks of the trial were comparable between the 2 groups ($p > 0.05$).

The treatment group showed greater reduction (greater reduction equates with improvement) in the total score of the O'Leary-Sant and its components (ICSI and ICPI) from baseline to each end point (weeks 6, 12 and 18) compared to the placebo group. The changes in the total score of the O'Leary-Sant instrument and the ICSI score were significantly more among the treatment group compared to the placebo group at week 12 ($p = 0.04$ and 0.03, respectively). At week 18, 13 of 21 in the treatment group (approximately 62%) compared to 5 of 20 in the placebo group (25%) reported changes of 50% or more in their total O'Leary-Sant score since the beginning of the study ($p = 0.02$). Interestingly, changes in urgency scale from baseline to each end point were only significant among the treatment group while changes in voiding frequency (voiding diaries) from baseline to each end point were only significant among the placebo group. The placebo group reported significant reduction in voiding frequency at weeks 6 and 18 compared to the treatment group. There were no significant differences in the changes from baseline to each end point among the study groups in terms of PUF scores, pain scale, urgency scale and nocturia (table 2).

At week 18, the proportion of responders (who reported that their overall IC condition improved in comparison to the baseline) was comparable in the 2 groups. Interestingly, the majority of the responders in the treatment group evaluated themselves as greatly improved (72.2%, 13 of 18), compared to 33.3% (6 of 18) of the responders in the placebo group ($p = 0.04$). By the end of the trial, 100% (21 of 21) of the treatment group vs 80% (16 of 20) of the placebo group evaluated the change in their urinary frequency as well as in urgency as improved in comparison to the baseline ($p = 0.04$) (table 3).

Related to the improvement in HRQL as measured by the SF-36, both groups showed significant improvement in bodily pain at week 4 compared to the baseline ($p < 0.01$). At week 18, the treatment group reported significant improvement in all HRQL domains in comparison to the baseline, while the placebo group showed significant improvement in only 3 HRQL domains compared to the baseline ($p < 0.05$). The unique improvement from baseline to week 18 in general health domain was greater among the treatment group in comparison to the placebo group ($p = 0.05$). Although only the treatment group showed significant improvement in terms of sexual desire (at weeks 6 and 12) and sexual arousal (at week 6) compared to the baseline, no significant differences were reported between the 2 groups at any end point (table 4).

The incidence of adverse events was comparable between the study groups. Approximately 92 different adverse events were reported during the entire study period (range 2 to 15 adverse events per subject). Headache (approximately 66.7%, 14 of 21 in treatment group and 60%, 12 of 20 in the placebo group, $p > 0.05$) and bruise in arms due to blood draw (52.4%, 11 of 21 in treatment group and 55%, 11 of 20 in placebo group, $p > 0.05$) were the most frequently experienced adverse events. Mild hair loss was reported in 3 participants among the treatment group and 1 participant among the placebo group. There were no clinically significant differences between the study groups for any of the laboratory data, and there were no cases with laboratory measures critically outside the normal limits and related to the trial intervention. None of the laboratory measures in any of the 2 study groups required hospitalization or discontinuation of the treatments (table 5).

No clinically significant positive urine culture (UTI) was reported among all the scheduled performed urine cultures during the entire study period in any of the trial groups. Among the unscheduled urine cultures (were performed as a standard of care) in the treatment group, there were 4 clinically significant urine cultures (among 2 subjects). Of the 4 positive cultures 2 (1 per subject) were reported during the intravesical treatment period. Thus, the intravesical treatment infection rate for 488 catheterizations (12 instillations $\times$40 subjects plus 8 instillations for the drop out subject) was 0.41%. The other 2 positive cultures (1 per subject) were performed at least 20 days after catheterization. All significant positive urine cultures were treated with the appropriate antibiotics.

TABLE 3. *Level of improvement among responders at the end of the trial*

Pt Global Assessment[16]	% (No./total No.) Treatment	% (No./total No.) Placebo	p Value*
Improvement in overall condition	85.7 (18/21)	90 (18/20)	0.6
Level of improvement:			
Moderately improved	27.8 (5/18)	61.1 (11/18)	0.04
Greatly improved	72.2 (13/18)	33.3 (6/18)	
Completely improved	0	5.6 (1/18)	
Improvement in urgency	100 (21/21)	80 (16/20)	0.04
Level of improvement:			
Moderately improved	38.1 (8/21)	56.3 (9/16)	0.2
Greatly improved	61.9 (13/21)	37.5 (6/16)	
Completely improved	0	6.3 (1/16)	
Improvement in urinary frequency	100 (21/21)	80 (16/20)	0.04
Level of improvement:			
Moderately improved	38.1 (8/21)	62.5 (10/16)	0.2
Greatly improved	61.9 (13/21)	37.5 (6/16)	
Completely improved	0	0	

* Chi-square test or Fisher's exact test.

TABLE 4. *Changes in HRQL and sexual function from baseline*

Outcomes	Median (25th, 75th percentiles) Treatment				Median (25th, 75th percentiles) Placebo			
	Wk 4	Wk 6	Wk 12	Wk 18	Wk 4	Wk 6	Wk 12	Wk 18
SF-36 (0–100):		Not applicable*	Not applicable*			Not applicable*	Not applicable*	
Physical functioning	0 (−5, 15)			15 (2.5, 24.2)*	7.5 (−5, 18.8)†			5 (0, 25)†
Role/physical	0 (0, 25)			50 (0, 75)*	12.5 (0, 43.2)*			50 (0, 68.8)*
Bodily pain	9 (0, 16)*			29 (15.5, 41.5)*	11 (0, 20)*			21 (10.3, 41.8)*
General health	3 (−3.5, 11)			8 (1.5, 20)*,‡	−1 (−5, 4.9)			0 (−10, 9.1)
Vitality	5 (−2.5, 15)*			20 (10, 35)*	0 (−8.8, 15)			12.5 (−5, 28.8)*
Social functioning	0 (0, 12.5)			25 (0, 43.8)*	0 (0, 12.5)			0 (0, 37.5)†
Role/emotional	0 (0, 33.3)†			17 (0, 66.7)*	0 (0, 0)			0 (−25, 58.3)
Mental health	12 (−10, 18)†			12 (4, 18)*,‡	4 (−4, 11)			2 (0, 15)
Sexual VAS (0–10 cm):								
Sexual desire	0.3 (−0.1, 1.8)	1 (0.2, 2.3)*	1.3 (0.1, 2.7)*	0.7 (−0.1, 3.3)†	0.4 (−0.6, 1.4)	0.3 (−0.8, 3)	1 (−0.6, 2.6)	0.7 (−1.5, 1.5)
Sexual arousal	0.1 (−0.3, 2.7)	0.8 (0.1, 3.3)*	1 (−0.3, 3.5)†	0.2 (−0.8, 3.6)	0.5 (−1.1, 3.2)	0.9 (−0.5, 3.4)†	1.7 (−1.2, 4.1)†	0.6 (−1, 3.5)

* Wilcoxon sign rank test (changes from baseline to each end point within each group) $p < 0.05$.
† Wilcoxon sign rank test (changes from baseline to each end point within each group) $0.05 \leq p < 0.1$.
‡ Mann-Whitney U test (changes from baseline to each end point between treatment groups) $0.05 \leq p < 0.1$.

TABLE 5. *Liver function and blood clotting tests during the entire study period*

	Treatment				Placebo				
	Mean ± SD	No. Tests Performed	% Within Normal Limit	% Out of Normal Range Not Clinically Significant†	Mean ± SD	No. Tests Performed	% Within Normal Limit	% Out of Normal Range Not Clinically Significant†	p Value*
Hepatic panel tests (normal ranges):									
Total bilirubin (0.1–1.5 mg/dl)	0.5 ± 0.33	231	98.7	1.3	0.5 ± 0.28	214	99.1	0.9	1
Alkaline phosphatase (27–142 IU/l)	62.2 ± 21.0	231	99.1	0.9	62.7 ± 20.0	214	98.6	1.4	0.7
Alanine transaminase (serum glutamic pyruvic transaminase) (1–55 IU/l)‡	16.8 ± 9.2	231	100	0	20.0 ± 16.2	214	94.4	5.6	<0.0001
Aspartate transaminase (serum glutamic oxaloacetic transaminase) (1–45 IU/l)‡	17.9 ± 7.5	231	99.1	0.9	21.0 ± 10.1	214	95.8	4.2	0.03
Blood clotting tests (normal ranges):									
Platelet count (150,000–400,000/μl)	268.6 ± 55.9	225	96.9	3.1	292.2 ± 68.9	209	94.3	5.7	0.2
Prothrombin time (9–11.5 secs)	9.1 ± 0.7	225	64.0	36.0	9.4 ± 0.8	208	68.8	31.3	0.3
Partial thromboplastin time (22–34 secs)	26.1 ± 2.6	224	98.2	1.8	26.9 ± 2.1	208	100	0	0.1

* Chi-square test.
† The result of any hepatic panel test and blood clotting test must be 1.5 to 2 times the normal range to be considered clinically significant.
‡ Two results of serum glutamic oxaloacetic transaminase test were 1.5 to 2 times the normal range (1 among treatment and 1 among placebo) and were considered out of normal range not clinically significant because they were related to viral infections (bronchitis and oral herpes, respectively) and not to trial medications. One result of the serum glutamic pyruvic transaminase test was 1.5 to 2 times the normal range (among placebo) and was considered out of normal range not clinically significant because other parameters of the same subject did not change simultaneously or at all.

DISCUSSION

The present study demonstrated that the combined therapy of intravesical and oral PPS medication is a safe and effective therapeutic option for the treatment of moderate and severe cases of interstitial cystitis. Specifically, this randomized clinical trial showed that IC subjects who received a regimen of intravesical and oral PPS had a 2-fold reduction in the severity of IC symptoms compared to those who received the oral regimen of PPS alone ($p = 0.04$). Moreover, at the cessation of the trial, the combined therapy also showed significant improvement in all health related quality of life domains in the treatment group compared to their baseline self evaluation. Therefore, the management of the cascade of symptoms was reflected in the positive outcome responses to questionnaires. Most compelling were the life affirmations responses to the SF-36.

The rationale for using PPS as a treatment option for IC is based on its biochemical nature as a semi-synthetic sulfated polysaccharide which chemically and structurally resembles GAG. PPS may augment the GAG layer of the bladder and protect damaged tissue, therefore, relieving symptoms. Because only 1% to 3% of oral PPS reaches the bladder,[8] the therapeutic efficacy of PPS should be greater when applied intravesically. Furthermore, using intravesical and oral PPS simultaneously for a specific period of time followed by sustained use of oral PPS may accelerate reduction in symptoms compared to oral therapy. This study supports the previous hypothesis. At the end of the trial subjects in the treatment group were significantly more likely to report great improvement in overall condition compared to those in the placebo group.

Changes in O'Leary-Sant as well as patient global assessment instruments were considered to be the most appropriate measure of treatment efficacy. The multifactorial complex nature of the IC condition and the wide variation of individual IC symptoms within and between patients suggest that the significant improvement in IC is the result of improvement in overall condition rather than in a specific symptom. Sharp focusing on each symptom may dilute the expected effect. This may explain why the present study reported significant differences in the change in IC condition when measured by O'Leary-Sant ICSI and ICPI and patient global assessment, but not by pain assessment, urgency scale and/or nocturia between the 2 groups at any end point.

It may surprise the reader that only the placebo group showed significant improvement in voiding frequency at each end point in comparison to the baseline. One suggested explanation is that voiding frequency can be a misleading symptom as it may be affected by other uncontrolled factors. Patients tend to restrict their fluid intake during painful periods and increase their fluid intake when pain is relieved.[7] Thus, it is expected that subjects who experienced greater improvement in their pain will increase their fluid intake and thus will have an increase in their voiding frequency in comparison to those who experienced less improvement.

With regard to the choice of design for this trial, only 1 clinical trial in 1997, in the Netherlands, assessed the efficacy of intravesical PPS compared to a true placebo.[11] PPS (Elmiron®) became FDA approved in 1996 in the United States for oral therapy,[18] and has been widely considered standard of care for the treatment of IC. Therefore, a nontreated (true placebo) IC group was not appropriate.[19]

It was not applicable to make an extensive comparison between the results from this study and the results from the Netherlands study because of the difference in the study design and the outcomes that were used in each study to assess the efficacy of the treatment.[11] In general, this study was consistent with that of Bade et al in that instilling intravesical PPS is an effective and safe treatment option for patients with IC.

The trial results cannot be explained by other factors such as the use of concurrent medications as well as the compliance with oral PPS. Both groups showed comparable use of antihistamines, antispasmodics, antidepressants and analgesics during the entire study period ($p > 0.05$). Furthermore, both groups administered more than 95% of the oral PPS during either the entire study period or the first, second or third 6 weeks of the trial.

It is also unlikely that our results were biased as we adhered to the LOCF method to handle missing data. The same results were found when all the statistical analyses were performed with and without including the drop out subject in the treatment group or applying the LOCF method.

The main limitations of the current study were the small sample size and the lack of external validity. We will not be able to generalize our finding on men or mild IC cases as all our study population were females who were classified, with 1 exception, as either moderate or severe cases. More studies will be required to test the same measures in a larger sample size that represent both genders and the full spectrum of severity.

Other future questions and issues to be addressed are: What is the durability of this dual therapy of intravesical and oral PPS? What is the best dose range and frequency of therapeutic events? Should the medical intervention be based on the severity of symptoms rather than assuming that 1 intervention class works for all? Importantly, if intravesical PPS becomes an accepted therapy option, the production of a liquid product needs to be addressed as well.

CONCLUSIONS

This double-blind placebo controlled trial demonstrated the safety and the efficacy of the use of a combined therapy of intravesical and oral PPS for the treatment of moderate and severe IC cases. The use of intravesical PPS and oral PPS together appears to enhance the proliferation of the GAG layer of the bladder, to produce greater relief and return to normal protective coating when maintained with oral PPS. These findings will open a new option for patients with IC and provide another tool in the arsenal of the urologist in the treatment of this difficult and debilitating condition.

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Abbreviations and Acronyms

FDA	=	Food and Drug Administration
GAG	=	glycosaminoglycan
HRQL	=	health related quality of life
IC	=	interstitial cystitis
ICPI	=	Interstitial Cystitis Problem Index
ICSI	=	Interstitial Cystitis Symptom Index
LOCF	=	Last Observation Carried Forward
PPS	=	pentosan polysulfate sodium
PUF	=	Pelvic Pain and Urgency/Frequency questionnaire
SF-36	=	Short Form 36
UTI	=	urinary tract infection
VAS	=	Visual Analog Scale

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