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PENTOSAN POLYSULFATE SODIUM THERAPY FOR MEN WITH CHRONIC PELVIC PAIN SYNDROME: A MULTICENTER, RANDOMIZED, PLACEBO CONTROLLED STUDY

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ABSTRACT

Purpose: We evaluated the efficacy and tolerability of pentosan polysulfate sodium (PPS) for the treatment of men with chronic pelvic pain syndrome (CPPS), National Institutes of Health (NIH) category III.

Materials and Methods: In a 16-week double-blind study 100 men with a clinical diagnosis of CPPS were randomized to receive 300 mg PPS or placebo 3 times daily. Clinical Global Improvement (CGI) was the primary outcome measure. Additional outcome measures were the NIH-Chronic Prostatitis Symptom Index (CPSI), Subjective Global Assessment and Symptom Severity Index assessment tools.

Results: Significantly more patients receiving PPS experienced moderate to marked improvement based on CGI assessment (18 or 37% vs 8 or 18%, $p = 0.04$). However, mean CGI scores were not significantly different between the PPS group (1.0) and placebo groups (1.0 vs 0.6, $p = 0.107$). All NIH-CPSI domains suggested a positive effect for PPS and for total NIH-CPSI the difference approached statistical significance (-5.9 or 22% vs -3.2 or 12%, $p = 0.068$). The PPS group showed significantly greater improvement in NIH-CPSI quality of life domain scores than the placebo group (-2.0 or 22% vs -1.0 or 12%, $p = 0.031$). Of patients receiving PPS 67% and 80% of those receiving placebo completed the 16-week study. Diarrhea, nausea and headache were the most common adverse events.

Conclusions: Pentosan polysulfate (900 mg daily) was more likely than placebo to provide relief for CPPS symptoms.

KEY WORDS: prostate, prostatitis, pelvic pain, pentosan sulfuric polyester

Chronic pelvic pain syndrome (CPPS), that is National Institutes of Health (NIH) category III prostatitis, historically referred to as nonbacterial prostatitis or prostatodynia, is clinically defined by discomfort or pain in the perineal or pelvic region, without bacteriuria or other known etiology.[1] It is much more common than bacterial prostatitis (NIH categories I and II).[2] Prostatitis in aggregate is the most common urological diagnosis in men under 50 and the third most common diagnosis in men older than 50, accounting for 8% of office visits to urologists annually in the United States.[3] It has been estimated that CPPS symptoms may affect 5 to 10% of the adult male population of North America[4,5] and the prevalence of diagnosed cases[6] further confirms the importance of this condition. In the United States of America, approximately 90% to 95% of men with symptoms of chronic prostatitis have CPPS.[4] Antibiotics, anxiolytics, antispasmodics, anti-inflammatories and α-blockers appear to provide only modest relief in only some patients with category III CPPS.[2,7] Currently there is no Food and Drug Administration approved treatment for category III CPPS.

Like CPPS, interstitial cystitis (IC), a disease predominantly diagnosed in women, is also associated with chronic pain in the pelvic area and/or lower urinary tract, and with voiding dysfunction. A relationship between IC and CPPS has been suggested.[8] Oral pentosan polysulfate sodium (PPS), a plant derived, cross-linked, semisynthetic mucopolysaccharide with a xylan backbone, has been shown to provide a moderate benefit in women with IC.[9–11] The Food and Drug Administration approved dose for IC is 300 mg daily (100 mg 3 times daily). Limited studies have reported benefits of PPS therapy in men diagnosed with CPPS.[12,13] In this multicenter study we used a double-blind, placebo controlled

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design to evaluate the effects of 900 mg PPS (Elmiron, Ortho-McNeil Pharmaceutical, Raritan, New Jersey) daily in men with CPPS.

MATERIALS AND METHODS

This 16-week, randomized, placebo controlled, double-blind, multicenter study was performed at 11 centers in the United States and 1 in Canada. Males 18 to 50 years old with a clinical diagnosis of CPPS at least 3 months in duration were eligible for this study. Participants must have scored 6 or greater on questions 1 to 4 and 3 or greater on question 4 of the NIH-Chronic Prostatitis Symptom Index (CPSI), which was administered at screening. Study exclusion criteria were a history of cystitis with an associated urine culture positive for a uropathogen, prostate, bladder or urethral cancer, genital herpes in the prior year, any sexually transmitted disease in the prior 3 months, inflammatory bowel disease, pelvic radiation or chemotherapy, unilateral orchialgia without pelvic symptoms, active urethral stricture; neurological diseases or disorders of the bladder, surgery on or physical treatment of the prostate, renal failure, pelvic or rectal surgery other than hemorrhoidectomy, hemostasis disorders, occult blood in the stool, anticoagulant use, that is greater than 1 gm aspirin or opioids (United States Schedule II), medication for sexual dysfunction, sensitivity to PPS or capsule components and planned surgery during or within 4 weeks of the study.

The study protocol was reviewed and approved by the sponsor, and by the institutional review or research ethics board at each participating study center, in accordance with the Code of Federal Regulations or Clinical Trial Review and Approval Policy. Each participant was required to read, understand, sign and date an institutional review or research ethics board approved consent form in the presence of a representative of the study center and a witness, who each also signed the consent document. All aspects of the study were explained to each patient prior to consent. Patient confidentiality was maintained at all times.

At the beginning of the study participants completed the certain assessments to establish baseline data, namely the NIH-CPSI[14] and Symptom Severity Index (SSI).[15] Patient demographic characteristics were recorded. A standard lower urinary tract localization study[16] was performed, including microscopy and culture of expressed prostatic fluid and/or post-prostatic massage urine. Physical examination was done to record systolic and diastolic blood pressure, and heart rate. Blood samples were collected and 10 hematological measures were determined per patient. The levels of 17 chemical components of blood, including the enzymes aspartate transaminase (serum glutamic-oxaloacetic transaminase) and alanine transaminase (serum glutamic-pyruvic transaminase [SGPT]) were also determined. An analysis of coagulation parameters and clotting factors was performed in each sample.

Randomization was stratified according to symptom severity at screening, as measured by the SSI.[15] The strata were SSI score less than 45 and 45 or greater. PPS and placebo were administered in identical hard gelatin capsules ingested 3 times daily. Each PPS capsule contained 300 mg PPS. The total daily dose was 900 mg. Study medications were received with water at least 1 hour before or 2 hours after the morning, midday and evening meals.

At weeks 4, 8, 12 and 16 evaluations were administered, that is Clinical Global Improvement (CGI), NIH-CPSI, Subjective Global Assessment (SGA) and SSI. CGI data were patient ratings of "the overall effect of study medication on your CPPS (chronic prostatitis) since you began taking the medication." Choices were "markedly worse," "moderately worse," "slightly worse," "no change," "slightly better," "moderately better" or "markedly better." SGA recorded the patient same day impression of symptom severity on a 0 to 10 scale. Blood samples were collected at weeks 2, 8 and 16, and hematological, coagulation and clotting factor tests were performed. Blood chemistry was analyzed at week 16 and 3 patients underwent an additional analysis at week 2 or 8. Microscopy, and culture of expressed prostatic fluid and post-prostatic massage urine were performed in each patient at week 16.

Randomization stratification and power calculations were based on SSI since we only had longitudinal treatment data with that parameter at the time of study protocol development. However, the primary efficacy parameter was CGI. It was estimated that 43 men would need to be enrolled in each group to allow 90% power to detect a 15 point SSI change with an SD of 22. Additional patients were enrolled in each group to allow for attrition.

The Cochran-Mantel-Haenszel test of the row mean score difference was used in a pairwise test of primary end point treatment effect data (CGI). Parametric data were evaluated using the 2-sample t test, or a 2-way ANOVA or ANCOVA model, including treatment, center and treatment by center interaction effects. The ANCOVA model also included baseline score as a covariate. Final models did not include center and treatment by center as factors because they were found to be not significant at the $\alpha = 0.10$ level. Additional analyses were also performed on CGI data. Counted data (eg the number of responders) were tested for statistical significance using Fisher's exact or the chi-square test. Responders (primary analysis) were patients who reported moderate or marked improvement on the CGI scale. Other nonparametric data (eg time to response) were tested using the log rank and Wilcoxon tests. Analyses were done in the intent to treat population with the last observation carried forward and $p < 0.05$ considered significant.

Adverse events (AEs) were defined as unusual and most often undesirable symptoms or signs that occurred in participants. All reported AEs were recorded. Appropriate treatment was provided for each AE. For each AE the severity and possible relationship to the study drug were determined by the investigator.

RESULTS

Of the 100 participants enrolled 51 were randomized to the PPS treatment group and 49 were randomized to the placebo group (table 1). There were no significant differences in demographic measures or baseline clinical characteristics between the PPS and placebo groups (table 1). However, the group receiving PPS had a higher mean score, equating to more pronounced symptoms, on the NIH-CPSI urinary symptoms domain ($p < 0.081$). Of the enrolled patients 73% completed the 16-week study. Of 27 patients who did not complete the study 11 in the PPS group and 4 in the placebo group discontinued due to adverse events or intercurrent illnesses (table 2).

TABLE 1. *Demographic and baseline characteristics in all randomized patients*

Variable	PPS	Placebo	p Value
No. pts	51	49	
Mean age (range)	40.8 (21–59)	37.5 (25–55)	0.065
Mean wt (kg)	91.8	88.4	0.390
Mean ht (cm)	180.1	178.8	0.346
No. SSI score:			0.686
Less than 45	30	31	
45 or Greater	21	18	
No. time since CPPS diagnosis (mos):			0.811
3–6	12	9	
7–12	3	5	
13–60	22	23	
Greater than 60	14	12	