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CYCLOSPORINE A AND PENTOSAN POLYSULFATE SODIUM FOR THE TREATMENT OF INTERSTITIAL CYSTITIS: A RANDOMIZED COMPARATIVE STUDY

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ABSTRACT

Purpose: In a previous retrospective analysis, cyclosporine A (CyA) was highly efficient in treating patients with interstitial cystitis. A prospective randomized study with this immunosuppressive agent was warranted. We compared CyA to pentosan polysulfate sodium (PPS) in patients with interstitial cystitis.

Materials and Methods: A total of 64 patients with interstitial cystitis meeting the National Institute of Diabetes and Digestive and Kidney Diseases criteria were enrolled in a randomized prospective study. Patients were randomized in a 1:1 ratio to 1.5 mg/kg CyA twice daily (27 women, 5 men) or 100 mg PPS 3 times daily (26 women, 6 men) for a period of 6 months. The primary end point was daily micturition frequency, and secondary end points were mean and maximal voided volume, number of nocturia episodes, O'Leary-Sant symptom and problem indexes, visual analogue scale for pain, and subjective global response assessment.

Results: CyA was superior to PPS in all clinical outcome parameters measured at 6 months. Micturition frequency in 24 hours was significantly reduced in the CyA arm compared to the PPS arm (-6.7 $\pm$ 4.7 vs -2.0 $\pm$ 5.1 times). The clinical response rate (according to global response assessment) was 75% for CyA compared to 19% for PPS ($p < 0.001$). Although there were more adverse events in the CyA arm than in the PPS arm, 29 patients completed the 6-month followup in both groups.

Conclusions: CyA is more effective than PPS in interstitial cystitis.

KEY WORDS: cystitis, interstitial; cyclosporine, pentosan sulfuric polyester, drug therapy

Interstitial cystitis (IC) is a debilitating inflammatory bladder disease characterized by urinary symptoms. Symptoms include urinary urgency, frequency, nocturia, and suprapubic or pelvic pain without any known etiological factor. Thus, there is no target for specific treatment. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has established diagnostic criteria to standardize the diagnosis of IC based on patient symptoms and cystoscopic findings with the patient under anesthesia.[1] Standardized criteria make it possible to compare clinical studies on IC. Multiple treatments have been recorded in the IC database.[2] Previous placebo controlled trials of oral pentosan polysulfate sodium (PPS) on IC have shown varying degrees of efficacy.[3–5] However, the limited efficacy of PPS is considered to be higher than the effect of placebo. By using the data available, the Food and Drug Administration has approved PPS when indicated in treating patients with IC.

The long-term experience with cyclosporine A (CyA) of patients with severe IC showed that CyA treatment was effective and well tolerated.[6] However, retrospective analysis warranted a randomized prospective trial. In the present study we compared CyA with PPS. Followup of 6 months was selected because in that time the clinical effect of the study drugs would be clear. Because both arms of the study had an active drug it was also motivating for patients to enter the study. We tested the efficacy of CyA in comparison to PPS in a randomized open label prospective multicenter study.

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MATERIALS AND METHODS

A total of 64 patients meeting the NIDDK criteria of interstitial cystitis were randomized in a1:1 ratio to cyclosporine A (Sandimmun Neoral®) or to pentosan polysulfate sodium (bene-Arzneimittel GmbH, Munich, Germany) treatment for 6 months. The cyclosporine A dose was 3 mg/kg divided into 2 daily doses, while that of PPS was 100 mg 3 times daily. The first patient was randomized in October 2002 after which enrollment of the 64 patients lasted for 17 months. Seven Finnish urological units participated in this study (see Appendix). Exclusion criteria for the study were history of cancer in the last 10 years, untreated hypertension or renal insufficiency (serum creatinine greater than normal limits of 90 mg/dl in females or 100 mg/dl in males). As CyA may cause liver dysfunction or hypercholesterolemia, serum transaminases, bilirubin and serum cholesterol had to be within normal range. All patients underwent urodynamic studies to rule out detrusor overactivity. If the urodynamic study was done within the last 2 years and no change in clinical symptoms occurred suggestive of other disease than IC, it was not obligatory to redo it. The study protocol was approved by the Ethical Committee of Helsinki University Hospital.

All patients gave written informed consent. No other treatments for IC were accepted during the study. If the patients were using nonsteroidal anti-inflammatory drugs or other painkillers or medication for insomnia when entering the study, they were allowed to continue the treatment. Randomization was centralized. Closed envelopes were divided into 2 identical blocks, and a nurse not otherwise involved in the study opened the envelopes containing the name of the drug.

Baseline voiding symptoms were recorded in 2-day voiding diaries, visual analogue scale (VAS) for worst pain, and O'Leary-Sant symptom and problem indexes for IC.[7] Control visits were at 1, 3 and 6 months. At the visits patients returned 2-day voiding diaries, marked the VAS score, filled out symptom and problem questionnaires, and gave the global response assessment (GRA). GRA was defined as 1—worse, 2—no change, 3—slightly better, 4—moderately better, 5—much better and 6—completely cured. Participants who reported categories 4 to 6 were considered treatment responders.

Due to possible nephrotoxicity and development of hypertension in CyA group, serum creatinine and blood pressure were controlled monthly. If blood pressure or serum creatinine exceeded the normal limits, the CyA dose was reduced to half. Also, in case of subjective intolerable side effects, it was possible to reduce the CyA dose. In all visits urinalysis was performed to rule out bacterial infection.

The primary end point of the study was micturition frequency in 24 hours. Secondary end points were maximal bladder capacity, mean voided volume, number of nocturia episodes, O'Leary-Sant symptom and problem scores, VAS score, and GRA. A sample size of 64 patients was selected to detect a difference in response rates of 70% and 35%. Our hypothesis was that in 70% of patients with IC, micturition frequency in 24 hours is reduced to half when on CyA treatment, and the same effect would be seen in 35% of patients on PPS. Power of 80% at a 2-sided significance level of 5% was used. Loss of 10% of patients in both groups was estimated. Baseline factors were compared with the t test and the Mann-Whitney rank sum test, and differences between treatment outcomes were calculated with the Mann-Whitney rank sum test. Proportions of responders were calculated with the Fisher exact test with $p < 0.05$ considered significant. The Wilcoxon signed rank test was used in calculating differences in blood pressure changes during CyA treatment. Statistical analysis was performed with Jandel SigmaStat® statistical software.

RESULTS

The recruitment of patients was effective and the planned number of patients was achieved in a reasonable time. Each center enrolled between 1 and 21 patients. Baseline patient characteristics are presented in table 1. The patients did not differ in any of the baseline parameters.

Hunner's ulcer was seen on cystoscopy in 15 of 64 patients, with 5 patients with Hunner's ulcer in the CyA group and 10 in the PPS group. Median bladder capacity in all patients under anesthesia was 500 ml (range 250 to 1,330). Previous treatments for IC were as usual in both groups. In both groups 12 patients had had repeated hydrodistention. There were 18 patients in the CyA group and 17 patients in the PPS group in whom at least 3 different treatments had previously failed. In the CyA group 16 patients had received intravesical dimethyl sulfoxide, 8 had received intravesical hyaluronate and 5 had intravesical bacillus Calmette-Guerin previously. In the PPS group 15 patients had received intravesical dimethyl sulfoxide, 10 had intravesical hyaluronate and 6 had intravesical bacillus Calmette-Guerin. In individual cases hydroxyzine, cimetidine, oxychloroquine, antipsychotics, α-blockers, transcutaneous neurostimulation and urethral Hegar dilations had also been tried. In both groups 8 patients had been on antimuscarinics. There were 5 patients in the CyA group and 4 patients in the PPS group who had received tramadol (50 to 250 mg) as a painkiller when entering the study. None received strong opioids.

TABLE 1. *Baseline patient characteristics by treatment group*

	Mean ± SD	
	Cyclosporine A	Pentosan Polysulfate Sodium
Pt age	56.2 ± 14.7	59.7 ± 13.0
Yrs symptoms	7.8 ± 7.0	8.9 ± 6.7
Cystometric capacity (ml)	232 ± 99	201 ± 99
Frequency in 24 hrs	16.7 ± 4.4	19.1 ± 8.4
Nocturia episodes	3.9 ± 2.2	4.2 ± 3.3
Max bladder capacity awake (ml)	230 ± 81	189 ± 78
Mean voided vol (ml)	122 ± 39	106 ± 46
O'Leary-Sant symptom score (range 0–36)	29.4 ± 4.8	30.2 ± 3.7
IC symptom index (0–20)	15.7 ± 2.8	16.6 ± 2.0
IC problem index (0–16)	14.0 ± 1.7	14.0 ± 1.8
Visual analogue scale VAS (0–10 cm)	6.8 ± 2.0	7.0 ± 2.1

There were no statistically significant differences in baseline parameters between the 2 groups.

A total of 29 patients completed the study in both groups. In the PPS arm the reason for withdrawal was gross hematuria in 1 patient after 2 months, while 2 other patients discontinued the study at 1 and 3 months as they did not benefit from treatment. In the CyA arm all 3 withdrawals occurred within 1 month. The reasons for discontinuation were multiple adverse events in 1 patient (headache, paresthesia in palms of the hands and gingival hyperplasia), gastrointestinal pain and gingival hyperplasia in another, while the third patient dropped out due to emesis after just 5 days of treatment.

The primary end point of this study was the reduction by half of micturition frequency in 24 hours. This effect was seen in 11 patients (34%) in the CyA group and in no patients (0%) in PPS group ($p < 0.001$). CyA was also significantly more effective than PPS in all other objective and subjective parameters measured. Number of nocturia episodes, O'Leary-Sant symptom score, IC symptom index and problem index, as well as VAS score decreased while maximal bladder capacity and mean voided volume increased significantly more in patients treated with CyA (table 2).

The proportion of responders (GRA category 4 to 6) in the CyA group increased at every visit while in the PPS group it remained the same, so that CyA was significantly superior to PPS from the 3-month visit (table 3). In the CyA group the number of responders at 6 months was significantly higher

TABLE 2. *Changes in parameters after 6 months treatment*

	Mean ± SD		
	Cyclosporine A	Pentosan Polysulfate Sodium	p Value
Frequency in 24 hrs	−6.7 ± 4.7	−2.0 ± 5.1	<0.001
Max bladder capacity awake (ml)	81 ± 94	2.8 ± 60	0.003
Mean voided vol (ml)	59 ± 57	1 ± 31	<0.001
Nocturia episodes	−2.2 ± 1.6	−0.2 ± 2.1	<0.001
O'Leary-Sant symptom score sum	−15.0 ± 9.4	−3.1 ± 4.3	<0.001
IC symptom index	−7.9 ± 4.6	−2.0 ± 2.6	<0.001
IC problem index	−7.1 ± 4.4	−1.5 ± 1.8	<0.001
VAS (cm)	−4.7 ± 3.5	−1.6 ± 3.3	<0.001