CHAPTER 6

A PLACEBO-CONTROLLED STUDY ON INTRAVESICAL PENTOSANPOLYSULFATE FOR THE TREATMENT OF INTERSTITIAL CYSTITIS

BADE JJ, LASEUR M, NIEUWENBURG A, WEELE L van der, MENSINK HJA

Submitted

Read at:
Abstract:

Objective. To evaluate the therapeutic efficacy of intravesical pentosanpolysulfate (PPS) in interstitial cystitis (IC) patients.

Patients and Methods. After a preliminary pilot-study 20 IC patients participated in a double-blind placebo-controlled study with intravesical PPS, applied twice a week, for a period of 3 months. All patients fulfilled the diagnostic NIH-NIADK criteria for IC.

Results. Nineteen patients were evaluable. In the group of patients treated with PPS, 40% experienced symptomatic relief versus 20% in the placebo-group. Only urodynamic bladder capacity showed a statistically significant increase in patients treated with PPS (p=0.047). Following the blinded, controlled period of three months eleven (55%) patients continued PPS instillations. From the group of patients (n=8) who continued with PPS after 3-months-placebo six (75%) reported symptomatic improvement.

Conclusions. We concluded the efficacy of intravesical PPS to be slight superior to oral PPS. In addition, self-catheterisation enabled long-term treatment and facilitated the ’self-help’ capacity of IC patients.
INTRODUCTION

Interstitial Cystitis (IC) includes a large group of patients with bladder pain, irritative voiding symptoms (urgency, frequency, nocturia and dysuria) and sterile urine. With little certain about its pathology and etiology a committee convened by the National Institutes of Health has arbitrarily proposed a set of characteristics to define the disease\textsuperscript{1}. Despite the exponential growth in clinical and basic research, no effective standard treatment is available. Small series have reported favourable results with a large variety of drugs, but placebo-controlled studies are rare.

Surface glycosaminoglycans, the 'mucus' lining of the bladder, have been identified as the defence mechanism coating and protecting the transitional cell surface\textsuperscript{2,3}. A current etiologic hypothesis of IC is a defect in the epithelial barrier of the bladder, which allows normal or abnormal substances in the urine to gain inappropriate access to the deeper layers of the bladder wall, initiating a circle of irritation and recruitment of immune cells and immune-mediated responses. Experimentally sodium pentosanpolysulfate (PPS), a heparin analogue, has been shown to reinforce the glycosaminoglycans and reduce transitional cell injury\textsuperscript{4}. These results and theories formed the rationale to use PPS for the treatment of interstitial cystitis. Different success rates were reported with oral PPS\textsuperscript{4-9}. In a preliminary pilot study at our centre, pentosanpolysulfate was applied intravesically (300 mg in 50 ml saline 0.9%, twice in a week) instead of orally. Long-term symptomatic and objective remission was observed in four out of the six patients, and tolerance was excellent\textsuperscript{10}.

Based on these results, a placebo-controlled prospective, double-blind study was designed to evaluate the therapeutic efficacy of intravesical pentosanpolysulfate compared to placebo in IC patients.

PATIENTS AND METHODS

This study was conducted in a double-blind manner, and a placebo control group was used as a comparison. The study was unicentered and approved by the Human Investigation Committee at our hospital. Patients were informed verbally and in written, and informed consent was obtained from each of them. The requested number of patients for each protocol was estimated before the trial on the basis of the results of the preliminary pilot-study; the outcome was 10. The treatment period in both protocols was 3 months.

Patients were recruited from the northern part of the Netherlands, with an estimated population of $1.7 \times 10^6$; our university hospital serving as a primary and referral hospital.
treatment, clinical evaluation comprised routine laboratory examinations, urine culture, urine cytology, a cystometrogram awake (20 cc fill rate per minute) and cystoscopy under anesthesia with coldcup biopsies and capacity measurement (1 minute at 80 cm H2O pressure). Patients were selected for enrollment in the study on the basis of inclusion and exclusion criteria as established by the N.H.I. of the U.S.A.\textsuperscript{1}. Patients were assigned at random to receive pentosanpolysulfate or placebo in accordance with a random code providing two parallel groups for comparison: a PPS-group and a placebo-group. After receiving treatment for three months the code was broken. All the patients were offered to continue with PPS instillations. Patients who decided to continue received intravesical PPS for at least an additional 3 months. Positive responders were offered to continue arbitrarily up to one year, or to participate in another study evaluating the effect of a change in frequency and composition of the PPS instillations.

\textit{Pentosanpolysulfate} was ordered commercially (Bayer a.g., München-Germany) as injection fluid vials (100 mg/ml). The hospital pharmacy converted them into sterile bladder instillations of 300 mg pentosanpolysulfate in 50 cc Urotainer (0.9% sodium chloride). The solution was colourless, without odour and remained stable for a minimum of 6 weeks, stored in a refrigerator. All the patients applied twice weekly intravesical pentosanpolysulfate. The first instillations took place at the hospital and treatment was continued at home by self-catheterisation, after instructions, or with the help of a district nurse. Instillations were collected every 3 weeks at the hospital.

\textit{Efficacy evaluation} was based on subjective and objective parameters. An overall impression of the symptom-status was recorded at the end of three months. The subjective improvement was evaluated using a visual analogue scale scoring 1 to 5 points. Treatment was considered to be successful if there was a 1-point or greater reduction on the severity scale.

Objective parameters. The 24-hour frequency, the average voiding volume, the maximum volume voided and the nocturia were recorded from a 48-hour voiding chart completed by the patient before treatment started and at 6-weekly intervals. A cystometrogram was performed before installment of therapy and after 3 months, using a flow rate of 20 ml/min. Urodynamic capacity was defined as the voided volume after maximum filling increased with the residual bladder volume. In this way, differences in diuresis during the filling phase were eliminated. Normal desire volume was defined as the feeling that leads the patient to pass urine at the next convenient moment.

\textit{Data analysis}. Parameters were analysed between the two groups with the Student t-test for independant samples for quantitative variables. Between pre- and posttreatment within the two
groups the Student t-test for matched samples was used. Qualitative variables, improvement or not, were tested with Fisher’s exact test. Testing was performed one-sided because greater improvement was expected with PPS than with placebo; \( p<0.05 \) was considered to be statistically significant.

RESULTS
A total of 20 consecutively diagnosed IC patients were enrolled in the study from May ’94 to December ’94. All the patients not only met but exceeded the NIH criteria. Despite severe symptoms, only one patient refused to participate in the placebo-controlled study. One patient did not complete 3 months of treatment and was excluded from further analysis. Nine patients received PPS and 10 received placebo. All the patients were women, with an average age of 53.8 years (range 24 - 75 years) in the PPS group versus 52.8 years (range 24 - 79) years in the placebo group. The average duration of the disease was 5.4 years (range 1-18 years) in the PPS group and 4.1 years (range 2-9 years) in the placebo group. Mean bladder capacity under anesthesia (1 minute at 80 cm/H₂O) was 305 ml in the PPS group, versus a mean of 243 ml in the placebo group. The bladder biopsies of all the patients showed features associated with interstitial cystitis syndrome, such as transitional-cell erosion, mononuclear infiltrates and mast cells. A moderate to high density of mast cells was observed in seven patients from the PPS group, and in eight from the placebo group.

Subjective and objective parameters in the two groups were comparable at the start of the study.

Patients retained the pentosanpolysulfate intravesically for as long as urge and pain made it possible. Retention varied from 30 to almost 180 minutes, without irritative side-effects. Nineteen of the patients managed with self-catheterisation, while one was assisted by a district nurse. Urine cultures remained negative. The main expected side-effect, hematuria, attributed to the heparin-like qualities of the drug, was reported incidentally after instillation. The hematuria always disappeared spontaneously within 2 days, never necessitating a medical consult.

After three months of treatment, an overall subjective improvement in symptoms was reported by four patients (44%) in the PPS group (n=9), by two (20%) in the placebo group (n=10). This difference was not statistically significant. All other patients reported unchanged symptoms. Table 1 shows the mean values of the objective parameters. Except for the urodynamic capacity other, marginal, differences were not statistically significant. A decrease was noted in the average voiding volume in the PPS-after-placebo group caused by a dramatic decrease in one patient who remained symptomatically unchanged. A statistically significant increase (\( p=0.047 \), Student t-test, one-tail probe) in the urodynamic capacity was recorded after 3 months of PPS treatment compared to the
pre-trial volume. The increase (from 208 to 229 ml) in the patients receiving PPS after placebo was not statistically significant.

Following the placebo-controlled period of three months eleven (55%) patients continued PPS instillations. Four patients did not continue because they judged their symptoms acceptable while five patients preferred other conservative options. From the group of patients (n=8) who continued with PPS after 3-months-placebo six (75%) reported symptomatic improvement and mean objective parameters improved although, not statistically significant (Table 1).

Table 1.
Mean objective parameters pre and post-treatment, determined by micturational profiles and cystometrogram.

<table>
<thead>
<tr>
<th></th>
<th>PENTOSAN (n=9)</th>
<th></th>
<th>PLACEBO (n=10)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Start</td>
<td>3m</td>
<td>Start</td>
<td>3m</td>
</tr>
<tr>
<td>Frequency/24-hrs</td>
<td>18x</td>
<td>18x</td>
<td>22x</td>
<td>24x</td>
</tr>
<tr>
<td>Nocturia/24-hrs</td>
<td>4.0x</td>
<td>2.8x</td>
<td>5.0x</td>
<td>5.0x</td>
</tr>
<tr>
<td>Average volume/24-hrs</td>
<td>116 ml</td>
<td>125 ml</td>
<td>91 ml</td>
<td>107 ml</td>
</tr>
<tr>
<td>Urodynamic capacity</td>
<td>226 ml</td>
<td>265 ml**</td>
<td>202 ml</td>
<td>208 ml</td>
</tr>
<tr>
<td>First desire volume</td>
<td>73 ml</td>
<td>74 ml</td>
<td>101 ml</td>
<td>102 ml</td>
</tr>
</tbody>
</table>

* = Patients receiving intravesical PPS during 3 months following initial treatment with placebo instillations (n=8).
** = statistically significant increase, p = 0.047

From the 3 patients who continued, following 3-months PPS instillations, 2 reported further impro-
ovement and one sustained relief of symptoms. Comparison of short-term and long-term results of PPS instillations was prohibited due to a change in frequency (3 times per week) and composition of the instillations in most of the patients. At one and a half year from the start of the study 8 (40%) of the patients were still receiving PPS instillations; surgical treatment had been applied to 4 (20%) patients, twice after failure of continued PPS instillations and twice after exhausting other conservative options (prolonged hydrodistension under anesthesia, corticosteroids).

**DISCUSSION**

The primary subjective measurement used to determine effectiveness was the patient evaluation of overall improvement. In the group of patients treated with PPS, 44% experienced symptomatic relief versus 20% of the patients treated with placebo. This difference was not statistically significant. Differences between objective parameters were marginal, only functional bladder capacity showed a statistically significant increase in patients treated with PPS. Eleven (55%) patients continued PPS instillations after completion of the study protocol. One and a half year from the start of the study eight (40%) patients are still on treatment.

The treatment of IC is largely empiric because of the unknown cause of the disease. A wide variety of oral and intravesical agents are currently employed. Employment of pentosanpolysulfate in the treatment of IC is based on the pathogenetic theories referred to previously. The pharmacological effect of PPS is affinity for mucosal membranes, which results in coating of the surface, particularly where the normal sulfonated glycosaminoglycan layer is missing. Furthermore, PPS inhibits inflammatory processes involving lysosomal proteases and inflammatory mediators. Because pentosanpolysulfate orally is absorbed only marginally (3-5%) from the gastro-intestinal tract, we hoped to improve its therapeutic efficacy by intravesical application. The dose we applied was similar to the daily oral prescription (300 mg) and arbitrarily instilled twice a week for a period of 3 months. The double-blind design of the study offered the option of cross-over. However, it was considered inhumane to ask patients with persistent symptoms and pain to risk another three months of only placebo treatment. Reports on oral pentosanpolysulfate have shown moderate to substantial relief of symptoms in 50% up to 80%. However, these were un-controlled studies. The main results and characteristics of four placebo-controlled oral PPS studies and our intravesical placebo-controlled PPS trial are shown in Table 2.

---

Table 2.
Placebo-controlled studies on pentosanpolysulfate for IC.

<table>
<thead>
<tr>
<th>Application</th>
<th>Year</th>
<th>Pts</th>
<th>Drop-outs</th>
<th>age</th>
<th>Relief of Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PPS</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td>Parsons et al.; USA⁶</td>
<td>oral</td>
<td>1987</td>
<td>n=75</td>
<td>17%</td>
<td>40%</td>
</tr>
<tr>
<td>Holm-Bentzen et al.; Europe⁷</td>
<td>oral</td>
<td>1987</td>
<td>n=43</td>
<td>9%</td>
<td>63 yrs</td>
</tr>
<tr>
<td>Mulholland et al.; USA⁸</td>
<td>oral</td>
<td>1990</td>
<td>n=110</td>
<td>11%</td>
<td>44 yrs</td>
</tr>
<tr>
<td>Parsons et al.; USA⁹</td>
<td>oral</td>
<td>1993</td>
<td>n=148</td>
<td>12%</td>
<td>43 yrs</td>
</tr>
<tr>
<td>Bade et al.; Europe</td>
<td>intravesical</td>
<td>1995</td>
<td>n=20</td>
<td>5%</td>
<td>53 yrs</td>
</tr>
</tbody>
</table>

S = Statistically significant difference (p<0.05)
NS = Not statistically significant difference

The oral studies are well compatible in respect of the number of included patients, drop-out percentage and methodology. All of them employed visual analogue scales to evaluate improvement, either subdivided in points (0-5)⁷ or in percentages (0-25%-50%-75%-100% improvement)⁹ and all studies included patients who failed to respond to prior conservative treatment. However, compared to the placebo-controlled studies from the USA, the European studies lack statistically significance. Our recent epidemiologic study in The Netherlands revealed that general and specific (mast cells) pathological features of bladder biopsies are the mainstays of diagnosis for Dutch urologists¹². The study of Holm-Bentzen et al. included, in the IC group, only patients with pathologically anatomically verified IC (28 or more mast cells per mm²). In contrast, the USA studies used
the clinical and endoscopic based NIH criteria to diagnose interstitial cystitis. In addition, one may speculate about a difference in awareness concerning the diagnosis of interstitial cystitis. This suspected transatlantic difference in definition and awareness of IC might well explain for the higher average age and the smaller number of included patients in European studies. Compared to the study of Holm-Bentzen et al. our study demonstrated a similar placebo effect; however, the efficacy of intravesical PPS was higher than with oral PPS.

Three additional observations were made on the use of intravesical PPS. One (1): All but one of the patients were successfully instructed in self-catheterisation by experienced nurses at the Urology Diagnostic Centre. Self-catheterisation enabled patients to contribute and participate in their own treatment which certainly influenced the psychological impact of the treatment. This is reflected in the low drop-out percentage (5%) compared to oral PPS studies. Two (2): No side-effects were recorded. The duration of medication retention was always determined by the slow exacerbation of symptoms, never by side-effects. This is an advantage of PPS instillations compared to DMSO applications. The garlic halitus of DMSO is well known and irritative symptoms or complications do occur. A controlled study of DMSO in IC (n=30) reported 5 patients with complications from the instillation and in two of them treatment was discontinued\textsuperscript{13}. The third (3) and probably most encouraging observation refers to the eleven (55%) patients who decided to continue PPS treatment after termination of the first 3-months-period of the study. At one and a half year from the start of the study eight (40%) patients were still using intravesical PPS. However, in four (20%) patients urinary diversion had been inevitable. This percentage is relatively high and might reflect the severity of symptoms and high number of ‘end-stage IC’ in the included IC patients. Even more appreciable is the percentage (40%) of patients still benefitting of intravesical PPS one and a half year from the start of the study. In a study on intravesical heparin (n=48) Parsons et al. reported a long-term remission with continued treatment in 31% of the patients\textsuperscript{14}. However, this was an uncontrolled study. The importance of placebo-controlled studies has well been demonstrated in the studies on oral PPS, and was confirmed by our observation of symptomatic improvement (75%) in the patients who received intravesical PPS after termination of the placebo- and blinded period of the study. Placebo-controlled studies are essential to determine the value of new treatment modalities.

CONCLUSIONS

We concluded the efficacy of intravesical PPS to be slight superior to oral PPS. In addition, self-
catheterisation enabled long-term treatment and facilitated the ‘self-help’ capacity of IC patients. Whether a longer, more intense course of intravesical PPS or a combination with other agents will produce better results is currently under investigation.

REFERENCES

12. Bade JJ, Rijken B, Mensink HJA: Interstitial cystitis in the Netherlands: prevalence, diagnos-
