Efficacy of pentosan polysulfate in the treatment of interstitial cystitis: a meta-analysis

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Authors' objectives
To determine the efficacy of pentosan polysulfate (Elmiron) compared to placebo in the treatment of interstitial cystitis.

Searching
The following databases were searched: MEDLINE (Jan 1966 to June 1994), Excerpta Medica (Jan 1988 to June 1994) and the International Pharmaceutical Abstracts (IPA) Database (Jan 1973 to June 1994). MEDLINE was searching using the MeSH term 'pentosan polysulfate', and the following keywords were used to search Excerpta Medica and IPA: 'pentosan polysulfate', 'pentosan' and 'pentosan polysulfate sodium'. Bibliographies of original and review articles obtained from the literature search were examined to ensure all potential references had been identified and the manufacturers of PPS were contacted for additional information. The searches were limited to English language articles.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled trials of a minimum of 8 weeks' duration were included.

Specific interventions included in the review
Pentosan polysulfate (PPS; minimum daily dose of 300mg orally).

Participants included in the review
Adults (n=413 female, n=30 male, n=5 not specified) presenting with one or more symptoms of interstitial cystitis including pain, urgency, frequency, and nocturia, a symptom history of at least 12 months, normal urinalysis and negative findings for urine culture and cytology. Patients with the following disease states were excluded: haemorrhagic cystitis; drug-, microbial-, or radiation-induced cystitis; carcinoma in situ; and other influencing diseases such as diabetic nephropathy.

Outcomes assessed in the review
The outcome of success was determined for the symptom variables of pain, urgency, frequency, and nocturia. Success was defined as a decrease in a symptom by 50% or more.

How were decisions on the relevance of primary studies made?
Using only the selection criteria to avoid selection bias, two blinded investigators determined study eligibility. The methods section of each articles was photocopied, all identifying statements and titles (ie names of investigators, journals, geographical locations, dates) were removed and an identification number generated by a hand calculator was randomly assigned. If there was disagreement between the investigators, consensus was reached on the eligibility of the study.

Assessment of study quality
Validity was assessed using a modification of the scale of Chalmers et al. (See Other Publications of Related Interest). The studies were evaluated based on the following criteria: basic descriptive material; the study protocol; blinding procedures; testing procedures; statistical analysis; and presentation of results. The maximum number of points was 100, and a quality score index was determined from the total number of points earned from each study. Four investigators assessed study validity and the inter-rater reliability was determined using Rosenthal's method for effective reliability (see Other Publications of Related Interest). A coefficient of 0.80 or more was considered adequate evidence of reliability of scores.
Data extraction
Two investigators extracted the data in a blinded manner similar to that discussed for study selection, using photocopies of the results sections with all identifiers removed. The number of participants reporting success for each variable was independently extracted. Study withdrawals were included in the analyses and were treated as failures. Any disagreements between the investigators on the outcome values were resolved through discussion.

Methods of synthesis

How were the studies combined?
For each of the four outcome variables (pain, urgency, frequency and nocturia) the percent difference between success rates of PPS and placebo (with 95% confidence intervals) and the corresponding number need to treat (NNT) were determined. The data were then combined using the method described by DerSimonian and Laird (see Other Publications of Related Interest). Data were re-analysed, weighted by quality to determine if the outcomes were influenced by study quality.

How were differences between studies investigated?
A chi-squared test was performed to assess the combinability of results.

Results of the review
Four randomised controlled trials including 448 participants were included.

Only one study examined the effects of pentosan on nocturia. The chi-squared analyses showed that studies assessing pain (chi=2.33, 3df, P=0.507), urgency (chi=0.45, 2df, P=0.799) and frequency (chi=0.17, 1df, P=0.680) were homogeneous. Overall success rates for pentosan were 37% for pain, 28% for urgency, 54% for frequency and 48% for nocturia. The results were significantly higher than placebo for pain (16.6%, 95% CI: 8.0, 25.2, NNT=7), urgency (12.9%, 95% CI: 1.0, 25, NNT=8) and frequency (16.7%, 95% CI: 2.3, 31.1, NNT=6), but not for nocturia (-1.0%, 95% CI: -19.8, 21.8, NNT=not applicable). The mean quality index scores ranged from 48.1% to 65.6% and the average inter-rater correlation of 0.867 produced an effective inter-rater reliability of 0.96 (P<0.05). Re-analysis of the outcome data weighted according to quality did not produce any significantly different results. The authors also reported that 12 studies on urgency and 81 studies on pain with zero difference would be required to significantly change the results (P=0.05).

Authors’ conclusions
Pentosan polysulfate is more efficacious than placebo in the treatment of pain, urgency, and frequency associated with interstitial cystitis. Pentosan polysulphate is not significantly different from placebo in treating nocturia associated with interstitial cystitis.

CRD commentary
This was a clearly presented review with well-defined methods and inclusion criteria. The authors performed an adequate search of the literature and although they did not specifically search for unpublished data they did contact the manufacturer. The authors also stated that publication bias was a possibility but unlikely considering that interstitial cystitis is not a common disease and calculations suggest that 12-81 unpublished studies would be required to overturn the findings. They may however have missed relevant data by only including English language publications. A quality assessment and an assessment of study heterogeneity were performed before the studies were combined and the statistical methods used to combine the data appear to be reasonable. It would however have been interesting to know, in the interests of completeness, the drug dose regimens for each individual study. However, it would appear that the evidence presented supports the authors’ conclusions.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.
Research: The authors state 'we recommend that future studies stratify results according to disease severity. This stratification will allow a more precise definition of the patient groups who will receive the most benefit from PPS. In addition, an extended follow-up would provide insight into the long-term effectiveness of the drug'; 'non-significant results were found for nocturia' and 'a clinical trial is warranted to settle the issue'.

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