

DECREASING SYMPTOMS IN INTERSTITIAL CYSTITIS PATIENTS: PENTOSAN
POLYSULFATE VS. SACRAL NEUROMODULATION.

A Research Project by

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We hereby recommend that the research project prepared under our supervision by Katy D. Price entitled "Decreasing symptoms in interstitial cystitis patients: pentosan polysulfate vs. sacral neuromodulation" be accepted as partial fulfillment for the degree of Master of Physician Assistant.

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ABSTRACT

Objectives: Oral pentosan polysulfate (PPS) is the only FDA-approved drug for interstitial cystitis (IC). Several studies have been conducted that show PPS will reduce IC symptoms. Sacral neuromodulation is a newer therapy for IC that has been FDA-approved in incontinent patients. Studies conducted in IC patients have shown that sacral neuromodulation reduces IC symptoms. Both therapies have documents reduction in IC symptoms, but no studies have compared these therapies to see which is more effective.

Methods: An evidence-based systematic literature review was conducted using Pubmed, Medline, and Proquest nursing journals. Inclusion criteria for the studies were a peer-reviewed article, publish date of 1990 or later, level 1 or 2 evidence, were diagnosed with IC, and were only treated with either oral PPS or sacral neuromodulation during the study. Patients were excluded if they were on multiple therapies for IC or a non-IC diagnosis. **Results:** Three PPS studies fit all inclusion criteria. With successful treatment being defined as a 50% overall improvement in symptoms, studies had a success rate of 26-32%. Four studies fit the criteria for sacral neuromodulation. In these studies 40-94% of the patients had a 50% improvement in one or more of the presenting symptoms of IC. **Conclusions:** PPS and sacral neuromodulation have both been shown to reduce IC symptoms. Sacral neuromodulation has been shown to have a higher rate of symptom relief in IC patients. Based on level 2 evidence, a Grade B recommendation can be made for sacral neuromodulation. This evidence is limited by sacral neuromodulation studies having only a level 2 evidence, while PPS has level 1 evidence studies. More studies are needed for each of these therapies.

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CHAPTER 1

INTRODUCTION

1.1 **Diagnosis of Interstitial Cystitis**

Interstitial Cystitis (IC) is a clinical syndrome of unknown etiology, which has led to much debate over its diagnosis criteria and treatment regimens. Patients with IC present with urinary frequency and urgency, burning sensations while voiding, and pelvic pain. There are many conditions that present with the same symptoms, which have led to inaccurate diagnosis, treatment, and symptom resolution. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) have developed diagnostic criteria to help aid in diagnosis. The NIDDK states that the patient must present with the above symptoms and upon examination, patients with IC have a negative urinalysis, have no signs of genitourinary infections, bladder cancer, or prostatitis, and have no history of radiation or tuberculosis cystitis. The definitive sign of an IC diagnosis is the presence of glomerulations or ulcers on the bladder wall found during a cystoscopic examination.¹

There are two different forms of IC. The non-ulcerative type is the most prevalent at 90% and patients have mild symptoms. The second type is characterized by Hunner's ulcers and makes up the other 10% of IC diagnoses. Hunner's ulcers are found upon cystoscopic examination and involve all layers of the bladder. Patients with Hunner's ulcers present with the most severe and debilitating symptoms.²

1.2 **Etiology**

The etiology of IC is still being debated, but has generally been narrowed down to two theories. The epithelium of the bladder contains a glycosaminoglycan layer. This layer is hydrophilic so it forms a protective barrier from urine and its irritative

components.² It is believed that in patients with IC this layer is degraded. This degradation allows urine to irritate the lining of the bladder. This process is what leads to symptoms of IC. In some patients with IC glycosaminoglycans are found in their urine.³

The second theory behind the etiology of IC involves the activation of mast cells in the bladder wall. It is believed that these cells release certain hormones as they are exposed to irritative substances. These hormones then lead to changes in the smooth muscle and increased inflammation.² It is also believed that the cause of IC is possibly linked to both of these theories.⁴ This hypothesis adds to the complexity of diagnosis and the severity of the disease.

1.3 Treatment

Due to the lack of a definitive cause of IC the treatment for this condition is usually multi-modal. There is no definite cure for IC and the goal of treatment is to decrease the severity and frequency of the symptoms. Oral treatments such as pentosan polysulfate, antihistamines, and tricyclic antidepressants have been used to try and reverse the proposed causes of the disease and reduce the painful symptoms. Intravesicular treatments have been used to attempt to coat and protect the lining of the bladder.⁴ A more invasive therapy, which has been studied, is sacral neuromodulation in which a device stimulates sacral nerve roots in an effort to reduce symptoms. Non-pharmacological treatments, like behavioral therapy, have been used to try and reduce the control that the symptoms have over IC patients. Diet changes have also been helpful in some patients as a reduction in acidic and arylalkylaminic foods, such as bananas, cheese, chocolate, nuts, raisins, and beer, have been found to reduce symptoms.⁵

This study will compare treatment of IC with oral pentosan polysulfate (PPS) versus sacral neuromodulation to see which treatment is more effective in reducing symptoms. Pentosan polysulfate is one of two drugs that have been FDA-approved for the treatment of IC and the only oral treatment approved. One caveat of this treatment is that it may take 3 months before an improvement in symptoms is seen.⁵ Hwang et al conducted a meta-analysis and found that pentosan polysulfate was more effective than placebo at reducing pain, urgency and frequency. Sacral neuromodulation is a more invasive treatment which requires a surgical procedure to place a stimulus generator.⁶ One study found that sacral neuromodulation caused statistically significant improvements in frequency, pain, average voided volume, and maximum voided volume.⁷

IC patients experience a variety of symptoms ranging from mild to severe. Many of these symptoms cause alterations in daily activities and a decrease in quality of life. The objective of this study is to compare pentosan polysulfate versus sacral neuromodulation in reducing symptoms in patients with IC. The outcome of this study will help to determine which treatment is the most effective in reducing symptoms of IC.

CHAPTER 2

METHODOLOGY

2.1 Research Methods

The method of research is an evidence-based systematic literature review. The databases used in the review were PubMed, Medline, Proquest nursing journals and First Search from 1990 to present. The year 1990 was chosen to include only the most recent data. The search terms used in this review were interstitial cystitis, polyuria, dysuria, treatments, pentosan polysulfate, and sacral neuromodulation. Selected articles for review were based on level of evidence, journal type, and relevance to the topic. Inclusion criteria for the articles were a peer-reviewed article, a publish date of 1990 or later, level 1 or 2 evidence, subjects with a diagnosis of interstitial cystitis, and were only treated with either oral pentosan polysulfate or sacral neuromodulation therapy during the study. Studies were excluded if subjects were treated with multiple therapies during the study or were not diagnosed with interstitial cystitis. Studies also had to meet the criteria of level 1 or level 2 evidence, which were defined using the Oxford Centre for EBM levels of evidence.⁸ These are defined in Figure 1, Appendix A.

CHAPTER 3

LITERATURE REVIEW

3.1 Introduction

IC affects the lives of approximately 700,000 women in the U.S.⁹ Men and children can also be affected by this disease, but the incidence is lower. The onset of this disease can occur at any age, but is more common in the middle ages.² The symptoms of IC can range from mild to severe, where quality of life can be impaired. With these numbers and symptoms finding an appropriate treatment could significantly improve the lives of IC patients.

The cause of IC has not yet been confirmed. This makes treatment of the disease itself almost impossible and treatment of the symptoms the goal. In this systematic review two treatment options were examined to determine which method is the most effective in reducing the symptom complex associated with IC.

3.2 Pentosan Polysulfate

Pentosan polysulfate is the FDA-approved oral drug therapy for IC. This drug primarily targets the theory of degradation of the glycosaminoglycan layer. PPS is a pharmacological agent which acts like glycosaminoglycans to help rebuild this layer.¹⁰ Initially, this treatment has no effects on symptoms. PPS must be used for at least 3 months before a reduction in symptoms can be seen.⁵ Because of the delayed onset of relief treatment compliance is an issue.

In a study by Mulholland et al. it was found that there was a significant overall improvement in IC symptoms after the use of PPS for three months. This double-blinded, placebo-controlled study, examined the effects of 300mg/day oral PPS on 110

subjects. All subjects had symptoms of urinary urgency, frequency, nocturia and pelvic pain for at least a year. They also had negative urinary cultures and either petechial hemorrhages or ulcers were found on cystoscopic exam. Subjects had no history or signs of pelvic irradiation, urinary tuberculosis, or bladder cancer. The subjects were then randomly assigned to placebo and experimental groups using a computer generated code. Subjects had a baseline evaluation that consisted of symptom evaluation and lab testing. They then followed-up in 3 months using a questionnaire that asked about overall improvement, urgency, and pain.

In this study, the measure of the overall improvement of each patient's condition was emphasized as individual symptoms of IC very widely from patient to patient. The results focused on both the investigator's and patients' reports. It was found that at 3 months 28 percent of the PPS patients found that their overall condition had more that slightly improved as compared to the 13 percent of the placebo patients. The investigator's evaluation confirmed this significant finding as they found that 26 percent of the PPS patients had significant overall improvement as compared to 11 percent in the placebo patients.¹⁰

Parsons et al. conducted a double-blinded, placebo-controlled study which examined overall symptom reduction, pain, urgency, and voiding volumes in patients with IC. The study enrolled 148 patients who had a diagnosis of IC for one year and a minimum number of daily voids, bladder capacities, and episodes of nocturia. One hundred and thirty patients completed the 3 month study. Control and experimental groups were randomly assigned through a computer generated code. Labs and symptoms were assessed at baseline and after 3 months. A follow-up questionnaire, voiding

volumes and pain ratings were also recorded at the end of the study. It was found that 32% of the PPS group and 16% of the control group reported an overall improvement of 50% or greater. Pain was improved by 50% or more in 38% of the PPS group and 18% of the control group. Voiding volumes increased by at least 20 cc's in 40% of the PPS group and 24% of the control. Sexual frequency was increase in 31% of the PPS patients and 18% of the control. The investigators' evaluation found that 36% of the PPS group and 15% of the control had experienced an overall improvement.¹¹

In a study by Jepsen et al. PPS was shown to be less effective than previously thought in studies. This prospective cohort study looked at 97 patients who presented with irritative voiding symptoms, consistent with IC, who had negative urine cultures and a negative cystoscopic exam to rule other causes. Patients were given 300 mg/day oral PPS. They were given a baseline symptom questionnaire at the initiation of therapy and then at 3 month follow-up intervals.

This study also examined the long-term effects of PPS therapy. After 18 months there were only 11 patients still taking PPS. No significant correlations were found between PPS therapy and IC symptoms. The only statistically significant correlation was a weak negative correlation between baseline constant pain and duration of PPS therapy. It was also found that on a long-term basis only 6.2%-18.75% benefit from the use of PPS.¹²

In a randomized, double-blinded study by Nickel et al. dose-ranging of PPS was examined. They compared the recommended dose of 300mg daily to 600mg and 900mg doses. There were 380 patients with IC enrolled initially, with 230 completing the 32 week study. Patients had to be diagnosed with IC and have had symptoms for at least six

months. Patients were given the Patient's Overall Rating of Symptom Index and the O'Leary-Saint Interstitial Cystitis Symptom Index at baseline and at 32 weeks.¹³ The mean scores for symptom indexes significantly improved during the 32 weeks for all dosages. These improvements were not found to be dose dependent.¹⁴

A meta-analysis by Hwang et al. examined four prospective, randomly controlled trial studies, on the effectiveness of PPS in IC patient populations. Three of the studies were published prior to 1990 as a result the meta-analysis was excluded. The fourth study was published in 1990 by Mulholland and has been included.¹⁵

A retrospective study by Waters et al. examined the effects of PPS by a chart review and follow-up patient survey. This study focused on the PPS in the clinical setting. Patients in both experimental and control groups continued other oral medications for IC and were required to participate in the study. This study was excluded from the analyzed data due to patients being on multiple treatments, but included important information on how PPS works with other IC treatments.¹⁶

A third study examining PPS therapy was excluded due to the publish date of 1987. Parsons et al conducted a randomized, controlled crossover that found that patients on PPS had a greater improvement in symptoms than placebo in all symptom categories. The average voided volumes were significantly improves on drug therapy.¹⁷

3.3 Sacral Neuromodulation

Sacral neuromodulation is a procedure that has been used for years to treat many bladder symptoms. Many studies have been done to test this procedure in patients with IC who have complex bladder symptoms. Sacral neuromodulation is done by first doing a test procedure, or percutaneous nerve evaluation (PNE), where a cable is inserted in the

sacral foramina at the level of S3. A test shock is delivered to ensure adequate placement. Then the patient is sent home with an external impulse generator to use for the next 7-14 days. Patients are asked to keep a voiding diary and other records to see if the treatment is effective. If sacral neuromodulation is found to be effective, they are defined as a positive responder, and the patient then receives a permanent implant.⁷

In a small cohort study by Maher et al favorable results were found with the use of sacral neuromodulation in women with interstitial cystitis. The study looked at 15 patients who had met NIDDK criteria for interstitial cystitis and had failed to respond to other traditional treatments. Before receiving the procedure patients recorded pain scores, volumes voided, daytime frequency, nocturia, and urgency. These variables were then recorded during stimulation. Quality of life questionnaires were also given before and after the stimulation. Patients only received a PNE and no permanent placements were studied.

It was found that 73% responded favorably to PNE with significant improvements in pelvic pain, daytime frequency, nocturia, and urgency. These patients requested to have permanent sacral nerve root implantation. Quality of life variables, which were significantly improved, were general health, social health, and bodily pain. There was also a 50% decrease in bladder pain in 87% of the patients. A 50% decrease in 24 hour voiding was seen in 47% of patients.¹⁸

In a slightly larger study, Whitmore et al examined 33 patients who had IC symptoms, had NIDDK findings on cystoscopic exam, and had failed previous therapies. They used a traditional testing method for the placement of a unipolar electrode. A baseline voiding diary that included urinary frequency, urgency, and bladder pain was

kept and recordings were continued for three days after placement. Average and maximum voiding volumes were also recorded for the same period.

The study found that there were statistically significant differences between bladder pain, urinary frequency, and average and maximum voiding volumes. No significant difference was found for nocturia. As a result, 51.5% of the patients requested a permanent placement.⁷

Two studies examined the differences in symptom reduction when two different techniques were used to place the lead. Traditionally, when sacral neuromodulation is first tested patients receive a unipolar lead placed in the S3 foramen. This lead is secured to the skin with dressings. If stimulation is effective, then the lead is replaced with a permanent lead and an internal impulse generator is placed.¹⁹

More recently, a new technique has been using a more permanent method called stage testing. In this procedure a permanent quadpolar lead is placed into the patient as in the same location as the traditional testing. This lead is anchored to the fascia to prevent slippage. If the stimulation is effective this lead stays and a permanent impulse generator is placed.¹⁹

Peters et al compared traditional testing to staged testing in 37 patients. All patients had IC symptoms, met the NIDDK criteria, and failed an average of 6 other treatments for IC. Voiding diaries and pain scores were kept at baseline and during stimulation. Patients were given the option of having a permanent placement after the testing period. Patients qualified for this if they experienced a 50% decrease in urinary frequency or a 50% improvement in IC symptoms.

The study found that staged testing is superior to traditional testing. Of the 16 patients who had received staged testing 94% were positive responders as compared to 67% of the 21 patients who had received traditional testing. Permanent placement was done in 94 percent of the positive responders in the staged testing group. Only 52% of the positive responders in the traditional testing group chose permanent placement.¹⁹

After permanent placement, investigators found that there was a 51% decrease in 24 hour voiding. Significant improvements were found in both daytime voids (47%) and nocturia (60%). At least sixty percent of all patients saw a moderate improvement in urinary frequency and urgency, pelvic pain and pressure, quality of life, incontinence, and vaginal pain. Of the patients who had received permanent placement, 96% said they would receive the implant again.¹⁹

In a second study examining outcomes based on technique, Comiter found similar results. This study included 25 patients who had met the IC criteria for NIDDK and had failed other treatments. Patients in group 1 received temporary placement through traditional testing, while group 2 received placement through staged testing. Patients in both groups kept a voiding log and recorded pain for 7 days prior and 9 days after placement. If a patient experience a 50% decrease in symptoms they were eligible for a permanent placement. In the individuals who chose permanent placement, they followed-up with a voiding log, pain diary, and an interstitial cystitis problem and symptom index at 2 months and then every 3-6 months.

The study found that after temporary placement, 40% of patients in group 1 had a satisfactory response as compared to 87% of the patients in group 2 who had a satisfactory response. After permanent placement a statistically significant improvement

was found in pelvic pain, voiding symptoms, validated symptom scores, and quality of life.²⁰

A study by Peters et al. examined the effects of sacral neuromodulation on narcotic requirements. Twenty-one IC patients were selected for this prospective cohort study based on the criteria that they had been experiencing urgency, frequency, and pelvic pain, and had failed six previous IC treatments. A baseline chart review was done to examine the use of narcotics before operation. Post-operation pain scores and a narcotic use questionnaire were then given to the patients. This study found a 36% decrease in narcotic use from 81.6 mg/day to 52.0 mg/day.²¹

A study by Elihalai et al. examined the long-term efficacy of sacral neuromodulation. This study demonstrated mixed results between patient groups. It was excluded due to only 2 of the 41 patients having an actual diagnosis of IC.⁶

CHAPTER 4

RESULTS

4.1 Results

The systematic literature review found 3 studies examining PPS therapy that fit all inclusion criteria. Two of these studies were a 1b level of evidence and the third study was a 2b level of evidence. Table 1 describes the evidence rating guidelines used in this literature review. Two studies found that the use of PPS in IC patients resulted in a reduction in IC symptoms. The third study only found a very weak relationship in the use of PPS and reduction of IC symptoms in patients. In this study only one IC symptom was reduced with PPS use. The studies included a combined total of 355 subjects. Successful treatment was defined as a 50% overall improvement in symptoms. Two PPS studies with a positive correlation, had a success rate of 26-32% in the subjects.

Four studies fit the inclusion criteria for sacral neuromodulation. These studies' participants were all diagnosed with IC, had used previous IC therapies without improvement, and patients were not taking other medications for IC during sacral neuromodulation. All studies were 2b level of evidence. All studies found that sacral neuromodulation caused a reduction IC symptoms. The studies included a combined total of 110 patients. Successful treatment was defined as 50% improvement in one of more presenting IC symptoms, which is the criteria for permanent implantation, rates were found to be between 40-94% of the subjects. Comparison of the successful treatment percentages can be seen in Figure 2. Maximum relief is defined as the highest percent of patients experiencing treatment success in a single study. Minimum relief is

the lowest percent of patients experiencing treatment success in a single study. Figure 3 shows summation of the articles examined during the literature review.

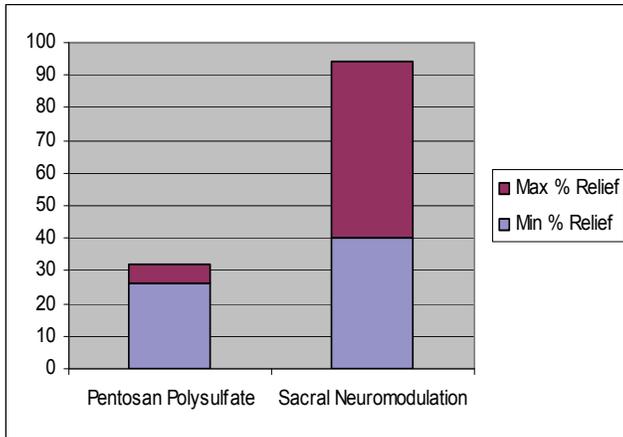


Figure 2. Overall IC treatment success.

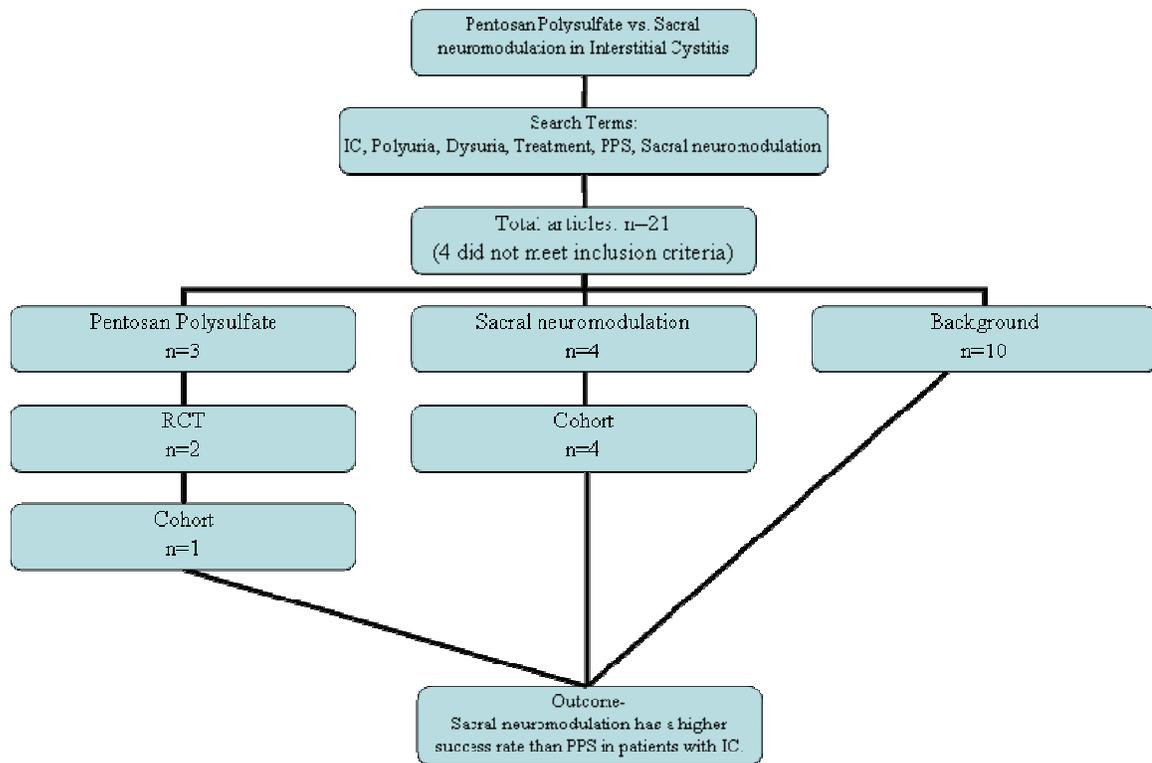


Figure 3. Summation of literature review.

CHAPTER 5

DISCUSSION

5.1 Pentosan Polysulfate

Interstitial cystitis is a debilitating illness for many of its sufferers. The IC symptom-complex has been difficult to treat and control due to the lack of a definite etiology. In this systematic literature review two treatments for IC were examined to find which has a greater effect on decreasing symptoms in IC patients.

Pentosan polysulfate has been the only oral treatment FDA approved for the treatment of IC. In this systematic literature review it was found that PPS does play a role in IC symptom reduction. Studies in this review found overall success rates from 26 to 32 percent.

One limitation of PPS therapy is the amount of time it takes for symptom relief. PPS takes up to 8 weeks to start experiencing symptom reduction. Many patients experience compliance issues, as many have relapses during the first weeks of treatment. This prolonged onset of action limits the findings in PPS studies. If a patient relapses during a study they will be more likely to withdraw, which will increase failure rates.

The use of 300 mg of PPS daily was an inclusion criterion for PPS studies in this systematic literature review. Nickel et al. studied dose-ranging in IC patients. The study examined 300 mg, 600mg, and 900mg daily doses of PPS. This study showed that increasing the daily dose of PPS did not significantly reduce IC symptoms. Patients in all groups found symptom relief, but it was not dose-dependent.

In a retrospective study by Waters et al. subjects were included in the study if they had been on other oral medications while on PPS. By including these patients instead of

excluding them Waters demonstrated the efficacy of PPS in a true clinical setting where IC patients are on multiple therapies. All patients were taking at least one or more oral medications for IC. The control group had not been treated with PPS, while the experimental group had been. The study found statistically significant differences in the PPS group for urinary frequency, urgency, pain, and overall change. Symptoms did improve in both groups, but were only statistically significant in the PPS group.

5.2 Sacral Neuromodulation

Sacral neuromodulation also demonstrated effective IC symptom reduction in this review. Studies have shown that this treatment, even though more invasive, has a very high response rate in IC patients. While this treatment requires a surgical procedure, it is important to note the amount of time it takes for relief afterwards. Sacral neuromodulation provides almost instant relief in patients who are positive responders. PPS takes at least 8 weeks before patients will possibly experience relief. In patients who prefer not to wait for relief or have compliance issues, sacral neuromodulation will most likely benefit them.

Sacral neuromodulation could decrease the use of concurrent therapies in IC patients. Peters et al. found that patients who had an impulse generator placed decreased their use of narcotics by 36%. Since most IC patients are on multi-modal therapy this finding could lead to decreased treatment costs and easier management of medications. More studies are needed see what effects sacral neuromodulation has on other IC therapies.

It has also been found that the technique used to initially test nerve root stimulation in patients is an important factor in their outcome. Two studies included in

this review both found that staged testing was superior to traditional testing. Peters et al. found that staged testing produced a 94% positive responder rate, while only 67% of patients with traditional testing were positive responders. Comiter found similar results with 87% being positive responders in the staged testing group and only 40% were positive responders with traditional testing. Figure 4 shows the positive responder percentages when comparing traditional versus staged test in sacral neuromodulation. Maximum success is defined as the highest percent of positive responders in single study. Minimum success is defined as the lowest percent of positive responders in a single study.

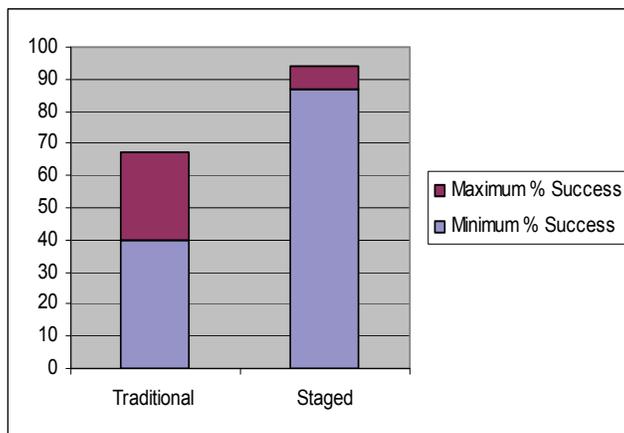


Figure 4. Outcomes of success based on technique in sacral neuromodulation.

This systematic literature review had several limitations. There is an overall lack of high level of evidence studies using PPS and sacral neuromodulation in IC patients. In this literature review a total of seven studies fit the inclusion criteria. There is also a limitation in that a medication was compared with a procedure. This limited the level of evidence regarding sacroneuromodulation because of the difficulty of conducting a

randomized-controlled trial. Due to this all studies are level 2 evidence. Many PPS studies are randomized-controlled trials, giving them a higher level of evidence.

CHAPTER 6

CONCLUSION

Pentosan polysulfate and sacral neuromodulation have both been shown to reduce IC symptoms. PPS has a lower rate of symptom relief in IC patients. Due to slow onset of action patients on PPS experience compliance issues and relapse of symptoms during treatment initiation. Sacral neuromodulation has been shown to have a higher rate of symptom relief in IC patients and demonstrates immediate symptom relief in positive responders. Within sacral neuromodulation, staged testing is superior to traditional testing during PNE and produces a higher rate of positive responders. Upon review of the literature, a level 2b recommendation can be made for sacral neuromodulation in the reduction of symptoms in IC patients. Grades of recommendation were defined by the Oxford Centre for EBM levels of evidence found in Figure 1, Appendix A. Sacral neuromodulation studies are limited by being a lower level of evidence than PPS studies. More studies are needed to further examine the effectiveness of these therapies in IC patients.

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APPENDIX

APPENDIX A

OXFORD CENTRE EBM LEVELS OF EVIDENCE

Levels of Evidence	
1	Systematic Reviews, RCTs
2	Systematic Reviews of cohort
3	SR of case-control studies
4	Case series
5	Expert opinion without explicit critical appraisal
Grades of Recommendation	
A	Consistent Level 1 studies
B	Consistent Level 2 or 3 studies or extrapolations from Level 1 studies
C	Level 4 studies of extrapolations from Level 2 or 3 studies
D	Level 5 evidence or inconsistent or inconclusive studies at any level

APPENDIX B

PPS 1a

Article: (Title, Journal, author, year)	Efficacy of pentosan polysulfate in the treatment of Interstitial cystitis: a meta-analysis. Hwang P, Auclair B, Beechinor D, Diment M, Emanson T Urology 50: 39-43, 1997.		
Study Question (Issue)	Determine the efficacy of PPS to placebo in the treatment of IC.		
Independent Variable (Issue)	Oral Pentosan Polysulfate		
Dependent Variable (Issue)	Symptoms of IC (pain, urgency, frequency, nocturia)		
Methodological Design (How was it done, sampling, etc.)	<ul style="list-style-type: none"> -Meta-analysis of prospective, randomized clinical trials -Inclusion: Prospective RCT, >8 weeks duration, English language, PPS minimum 300 mg daily, >1 symptom of IC, Normal UA, Neg. culture -Exclusion: hemorrhagic cystitis, drug-, microbial-, or radiation- induces cystitis, carcinoma in situ -Selection: methods section photocopied and selected by 2 investigators. -Study withdrawals included and considered failures -Success defined as a decrease in symptoms by 50% or more. 		
Findings	<ul style="list-style-type: none"> -37% decrease in pain -28% decrease in urgency -54% decrease in frequency -48% decrease in nocturia (not statistically significant) 		
What's Missing?	-severity of symptoms in IC patients		
Critical Analysis (Synthesis)	<ul style="list-style-type: none"> -had significant findings for PPS in decreasing symptoms -will be excluded due to one study having publish date prior to 1990 		

PPS 1b

Article: (Title, Journal, author, year)	<p>Pentosan polysulfate sodium for the therapy of interstitial cystitis: a double-blind placebo-controlled clinical study Mulholland S, Hanno P, Parsons C, Sant G, Staskin D Urology 35 (6) June 1990</p>		
Study Question (Issue)	<p>Effects of PPS on IC symptoms</p>		
Independent Variable (Issue)	<p>Oral PPS</p>		
Dependent Variable (Issue)	<p>Overall symptom reduction in IC patients</p>		
Methodological Design (How was it done, sampling, etc.)	<ul style="list-style-type: none"> -Double-blind, placebo-controlled, 110 patients, 3 months, 300 mg oral PPS daily -Categorized in terms of severity of disease -Inclusion: moderate urgency, frequency, nocturia, and pain; symptoms .1 year, failed previous therapy, neg. culture, pos. cystoscopic exam -Exclusion: Chronic narcotics, signs of bacteriuria, pelvic irradiation, cancer, tuberculosis, schistosomiasis -Groups were randomly assigned with computer generated code -Evaluated at baseline and at 3 months with questionnaire 		
Findings	<p>Investigator's overall evaluation: 26% of PPS evaluated as significantly improved compared to 11%</p>		
What's Missing?			
Critical Analysis (Synthesis)	<p>-had significant findings for the use of PPS in IC patients</p>		

PPS 1b

Article: (Title, Journal, author, year)	A quantitatively controlled method to study prospectively interstitial cystitis and demonstrate the efficacy of pentsan polysulfate. Parsons C, Benson G, Childs S, Hanno P, Sant G, Webster G Journal of Urology 150: 845-8, Sept. 1993		
Study Question (Issue)	Evaluating the efficacy of PPS in IC		
Independent Variable (Issue)	Oral PPS		
Dependent Variable (Issue)	Overall symptom reduction, pain, urgency, and voiding volumes		
Methodological Design (How was it done, sampling, etc.)	<ul style="list-style-type: none"> -Double-blind, placebo-controlled- 148 patients (18 drop-outs), 3 months, 300 mg PPS daily -multi-center -Inclusion: diagnosis of IC for 1 year, bladder capacity 350-1000cc, >8 voids per day, average voided (50-200cc), and nocturia Exclusion: <18 years old, pregnancy or lactation, active bleed PUD, bleeding diathesis, use of anticoagulant, chronic narcotic use, allergy to PPS, artificial sweetener use, history of Elmiron within 4 weeks of the study. -randomly assigned, computer generated code -Lab and symptoms checked at baseline and after 3 months -At 3 month follow-up questionnaire and looked at recorded voiding volumes and pain ratings 		
Findings	<ul style="list-style-type: none"> -50% overall improved -32% PPS, 16% placebo -Reduced pain (50% improved)- 38%, 18% -Improved pressure to void- 30%, 18% -Sex (increase in frequency)- 31%, 18% Investigator's evaluation of overall improvement- 36%, 15% -Voiding volumes increased by 20cc or more- 40%, 24% 		
What's Missing?			
Critical Analysis (Synthesis)	-had significant findings for the use of PPS in IC patients		

PPS 1b

Article: (Title, Journal, author, year)	Successful therapy of interstitial cystitis with pentosan polysulfate Parsons C, Mulholland S Journal of Urology v.138, September 1987		
Study Question (Issue)	Efficacy of PPS on IC		
Independent Variable (Issue)	Oral PPS		
Dependent Variable (Issue)	IC symptoms		
Methodological Design (How was it done, sampling, etc.)	<ul style="list-style-type: none"> -Randomized, controlled, crossover, 62 patients -Patients given symptom questionnaire before and during treatment, voiding volumes recorded Inclusion: Symptoms for 1 year, negative culture, cystoscopic exam 		
Findings	<ul style="list-style-type: none"> -Drug did better than placebo in all categories -Average voiding volumes were significantly improved on drug therapy 		
What's Missing?			
Critical Analysis (Synthesis)	<ul style="list-style-type: none"> -had significant findings for the use of PPS in IC patients -excluded due to a publish date prior to 1990 		

PPS 1b

Article: (Title, Journal, author, year)	Randomized, double-, dose-ranging study of pentosan polysulfate for interstitial cystitis. Nickel j, Barkin J, Forrest J, Mosbaugh P, Hernandez-Graulau J, Kaufman D, Lloyd K, Evans R, Parsons C, Atkinson L Urology 65(4) : 654-8, April 2005		
Study Question (Issue)	To compare current recommended dose of PPS with doses 2-3 times higher.		
Independent Variable (Issue)	PPS dosage		
Dependent Variable (Issue)	IC symptom reduction		
Methodological Design (How was it done, sampling, etc.)	<p>-randomized, double-blind, multicenter, 32 week study</p> <p>-380 patients enrolled, 230 patients completed study</p> <p>-Inclusion: Diagnosis of IC and with symptoms for at least 6 months, neg. UA, could speak understand and write English</p> <p>-Exclusion: if on other IC therapy, pregnant or lactating, hepatic disease or abnormal liver function tests, were on anticoagulants, had aneurysms, thrombocytopenia, hemophilia, GI ulcers, polyps or diverticula; pos. occult blood, hypersensitivity to PPS, history of bacterial cystitis, neurogenic bladder, pelvic irradiation, chemical cystitis, carcinoma, tuberculous cystitis, schistosomiasis, obstructive BPH, using schedule II opioids, active genital herpes</p> <p>-Used the Patient's Overall Rating of Symptom Index and the O'Leary-Saint Interstitial Cystitis Symptom Index to evaluate symptoms</p> <p>Doses: 300mg, 600mg, 900mg daily</p>		
Findings	Mean scores significantly improved during 32 weeks for all dosages, but response to treatment was not dose dependent		
What's Missing?	Lack of a placebo group.		
Critical Analysis (Synthesis)	-Symptom relief with PPS is not dose-dependent		

PPS 2b

Article: (Title, Journal, author, year)	Interstitial Cystitis: a retrospective analysis of treatment with pentosan polysulfate and a follow-up patient survey. Waters M, Sulesky J, Finkelstein L, Van Overbeke M, Zizza V, Stommel M JAOA 100(3): S13-S18, March 2000		
Study Question (Issue)	Evaluate the efficacy and safety of PPS in relieving symptoms of IC.		
Independent Variable (Issue)	Oral PPS		
Dependent Variable (Issue)	IC symptoms		
Methodological Design (How was it done, sampling, etc.)	Retrospective chart review w/ follow-up questionnaire, 260 charts reviewed- 27 patients taking PPS, 27 control IC patients not taking PPS -Control and PPS treatment groups were eligible if had IC for at least one year and persistent symptoms of IC, had at least one cystoscopy/hydrodistention procedure, and negative urine cultures. -PPS treated group had to be on PPS therapy for at least 8 weeks. -Control patients had to be taking at least one oral med as treatment for IC -Exclusion: <18 years old, PPS therapy for less than 8 weeks, IC diagnosed for less than 1 year, no previous cystoscopy/hydrodistention, inability to complete the questionnaire.		
Findings	-Statically significant differences were seen in the PPS group for urinary frequency, urgency, pain, and overall change		
What's Missing?			
Critical Analysis (Synthesis)	-had significant findings for use of PPS in IC patients -excluded due to use of multiple drugs for IC during study period		

PPS 2b

Article: (Title, Journal, author, year)	Long-term experience with pentosan polysulfate in interstitial cystitis. Jepsen J, Sall M, Rhodes P, Schimdt D, Messing E, Bruskewitz R Urology 51: 381-387, 1998.		
Study Question (Issue)	Long-term effects of PPS in IC		
Independent Variable (Issue)	Long-term oral PPS		
Dependent Variable (Issue)	Symptoms of IC (pain present, pain constant, voiding pain, bladder pain, pelvic pain, urgency, pain score)		
Methodological Design (How was it done, sampling, etc.)	-Prospective cohort study of 97 patients -Inclusion: irritable voiding symptoms, negative culture, negative endoscopy -Dosage 100mg TID -Questionnaire at baseline and every 3 months -Routine UA and culture, CBC with differential, liver and kidney function tests		
Findings	Very weak statistically significant association between less constant pain at baseline and long-term treatment with PPS		
What's Missing?			
Critical Analysis (Synthesis)	-found no significant correlation between PPS and IC symptoms		

SNM 2b

Article: (Title, Journal, author, year)	Sacral neuromodulation: long-term experience of one center. Elihali M, Khaled S, Kashiwabara T, Elzayat E, Corcos J Urology 65: 1114-1117, 2005		
Study Question (Issue)	To evaluate the long-term efficacy of sacral neuromodulation.		
Independent Variable (Issue)	Sacral neuromodulation (traditional testing)		
Dependent Variable (Issue)	Urinary symptoms		
Methodological Design (How was it done, sampling, etc.)	Retrospective cohort, 41 patients- 2 with IC -Patients with voiding dysfunction who had PNE and 50% improvement in symptoms in 3 days received permanent implants. -Patients kept 3-7 day voiding diary -Follow-up every 6 months		
Findings	-of 17 patients, 45% reported improvement in their symptoms -2 patient with IC showed no improvement		
What's Missing?	-No mention of pain scales, diaries, etc. used at follow-up to determine long-term effectiveness.		
Critical Analysis (Synthesis)	-excluded due to only 2 patients having diagnosis of IC		

SNM 2b

Article: (Title, Journal, author, year)	Sacral neuromodulation for the treatment of refractory interstitial cystitis: outcomes based on technique. Peters K, Carey J, Konstandt D International Urogynecological Association 14: 223-8, 2003		
Study Question (Issue)	Assess the efficacy of sacral nerve modulation in treating IC refractory to standard therapy.		
Independent Variable (Issue)	Sacral neuromodulation (Traditional test, Staged test)		
Dependent Variable (Issue)	Reduction in IC symptoms (day voids, Nocturia, 24-h voids)		
Methodological Design (How was it done, sampling, etc.)	<p>Prospective cohort (Traditional Vs. Staged testing)</p> <ul style="list-style-type: none"> -Inclusion: Symptom complex, met NIDDK criteria, failed avg. of 6 other therapies -Voiding diaries and pain scores at baseline and during stimulation period -Eligible for permanent implant: 50% improvement in urinary frequency or 50% improvement in IC symptom complex 		
Findings	<p>Staged testing is superior to traditional testing</p> <ul style="list-style-type: none"> -94% were positive responders as compared to 67% <p>Sacral neuromodulator permanently implanted: 24 hours voids decreased by 51%, significant improvements in daytime voids (47%) and nocturia (60%)</p>		
What's Missing?	<ul style="list-style-type: none"> -How long study lasted -Any concurrent use with oral/intravesicular meds 		
Critical Analysis (Synthesis)	-Found staged technique superior to traditional testing in sacral neuromodulation		

SNM 2b

Article: (Title, Journal, author, year)	Sacral neuromodulation for the symptomatic treatment of refractory interstitial cystitis: a prospective study. Comiter, C Journal of Urology 169: 1369-1373, April 2003		
Study Question (Issue)	Efficacy of sacral neuromodulation for the treatment of symptoms in patients with refractory IC.		
Independent Variable (Issue)	Sacral neuromodulation (traditional and staged testing)		
Dependent Variable (Issue)	IC symptoms		
Methodological Design (How was it done, sampling, etc.)	Prospective cohort, 25 patients Inclusion: Diagnosis of IC by NIDDK, failed other therapies -Group 1: traditional testing, Group 2: staged testing -measured by voiding diary and pain diary -Patients given permanent SN followed up with voiding log, pain diary, and IC problem and symptom index and 2 months and then every 3-6 months		
Findings	-40% responded with in unipolar group, 87% in quadpolar group -Statistically significant improvement in pelvic pain, voiding symptoms, validated symptom scores, and quality of life measures.		
What's Missing?	-group selection		
Critical Analysis (Synthesis)	-Found staged testing was superior to traditional testing in sacral neuromodulation		

SNM 2b

Article: (Title, Journal, author, year)	Sacral neuromodulation in patients with interstitial cystitis: a multi-center clinical trial. Whitmore K, Payne C, Diokno A, Lukban J International Urogynecological Journal 14: 305-9, 2003		
Study Question (Issue)	Evaluate efficacy of sacral neuromodulation in the alleviation of symptoms in patients with severe IC who would have been candidates for major surgical intervention.		
Independent Variable (Issue)	Sacral Neuromodulation (Traditional testing)		
Dependent Variable (Issue)	IC Symptoms		
Methodological Design (How was it done, sampling, etc.)	Prospective Cohort, 33 patients -All had tried previous therapies -Inclusion: Symptoms, cystoscopic NIADDK findings -Exclusion: Pregnancy, UTI, stress incontinence -Baseline and 3 days voiding diary (frequency, urgency, bladder pain), Average and max voiding volumes		
Findings	-Statistically significant differences between frequency, bladder pain, and average and max voiding volumes. -No significant difference for nocturia -51.5% permanent implant rate		
What's Missing?			
Critical Analysis (Synthesis)	-had significant findings for symptoms relief in IC patients for sacral neuromodulation		

SNM 2b

Article: (Title, Journal, author, year)	Sacral neuromodulation decrease narcotic requirements in refractory interstitial cystitis. Peters k, Konstandt D British Journal of Urology International 93: 777-9, 2003		
Study Question (Issue)	Efficacy of sacral neuromodulation in reducing IC symptoms.		
Independent Variable (Issue)	Permanent sacral neuromodulation		
Dependent Variable (Issue)	IC symptoms		
Methodological Design (How was it done, sampling, etc.)	Prospective Cohort, 21 patients Inclusion: urgency, frequency and pelvic pain; six previous treatments had failed -baseline narcotic by chart review -Post-op pain scores and narcotic use by questionnaires		
Findings	-Found a decrease by 36% in narcotic use: from 81.6mg/day to 52.0 mg/day		
What's Missing?	-No info on how temporary test was done		
Critical Analysis (Synthesis)	-Sacral neuromodulation shown to decrease pain and narcotic usage in IC patients		

SNM 2b

Article: (Title, Journal, author, year)	Percutaneous sacral nerve root neuromodulation for intractable interstitial cystitis. Maher C, Carey M, Dwyer P, Schluter P Journal of Urology 165: 884-6, March 2001		
Study Question (Issue)	Efficacy of Percutaneous sacral nerve root neuromodulation in women with refractory IC.		
Independent Variable (Issue)	Sacral neuromodulation (Traditional testing)- PNE only		
Dependent Variable (Issue)	IC symptoms and quality of life		
Methodological Design (How was it done, sampling, etc.)	Prospective cohort, 15 patients -women met NIDDK criteria, failed to respond to other therapies -1 week before and during stimulation pain scores, mean volume voided, day time frequency, nocturia, and urgency were recorded. -QOL questionnaires were completed before and after PNE		
Findings	-73% responded favorably to PNE-significant improvement in pelvic pain, daytime frequency, nocturia, urgency, and average volume voided -QOL variables significantly improved -50% decrease in bladder pain in 87% of cases -50% decrease in 24 hour voiding in 47%		
What's Missing?			
Critical Analysis (Synthesis)	-had significant findings for sacral neuromodulation in patients with IC		

