The efficacy of chondroitin sulfate 0.2% in treating interstitial cystitis

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Objective: *An open label study of chondroitin sulfate was undertaken to determine the response of patients with interstitial cystitis and positive potassium test results to this agent.*

Method: *Eighteen patients with classic features of interstitial cystitis were enrolled in the study. Patients received 40 mL chondroitin sulfate, 0.2% instilled intravesically once a week for four weeks and then once a month for 12 months. At the same times, Quality of Life Improvement scores, voiding diaries, and pain and voiding indices were reviewed.*

Results: *Thirteen of 18 patients were followed for the entire 13-month study. Twelve of these patients responded to treatment within 3 to 12 weeks, on average. A total of 6/13 (46.2%) showed a good response, 2/13 (15.4%) had a fair response, and 4/13 (30.8%) had a partial response and 1/13 (7.7%) showed no response.*

Conclusion: *Intravesical chondroitin sulfate seems to demonstrate some beneficial effects in treatment of interstitial cystitis patients who have positive potassium stimulation test results.*

Key Words: potassium stimulation, chondroitin sulfate

Introduction

Interstitial cystitis (IC) is an inflammatory disease of the bladder wall that is characterized by frequency, urgency, suprapubic pain, and pressure. Although IC has no confirmed single etiology, evidence suggests that several etiologies may be implicated in this syndrome. This may explain why effective, predictable treatment modalities have been elusive. Recently, it has been shown that approximately 70% of IC patients have damaged or defective glycosaminoglycan (GAG) layers,[1,2,3] a mucus lining made of GAGs such as chondroitin, heparin, dermatin and hyaluronate. This damage causes epithelial leals, which allows urinary solutes to gain access to subepithelial tissues, and induces an inflammatory response. Knowledge that many IC patents have damaged GAG layers has lead to treating these patients by replenishing the mucus lining with GAG products such as heparin, hyaluronate and pentosan polysulfate,[4,5,6] but treatment success has been variable.

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Intravesical instillation of potassium has been used to objectively detect abnormal epithelial permeability of the bladder.[7] In this study, intravesical potassium distinguished normal patients with intact epithelial function from those with IC. This agent may provide a diagnostic test for IC patients with damaged bladder GAGs that allows leakage.

We hypothesized that patients with GAG leakage demonstrated using the potassium stimulation test and who had potassium-induced symptoms neutralized by chondroitin sulfate (a GAG component) would have a greater likelihood of being successfully treated with this agent.

Background

In 1987, Dr Hurst et al[1] elaborated on the role of glycosaminoglycans and proteoglycans focusing on their structure, function and pathology in the urinary tract. He presented evidence suggesting that a dense layer of glycosaminoglycans on the urothelial surface is important to maintaining urothelial impermeability, preventing bacterial adherence and that permeability of this layer was an etiological factor in interstitial cystitis. He demonstrated that GAG damaged by an acid wash caused high levels of chondroitin sulfate and heparin sulfate to migrate from the bladder.

Sodium heparin injection USP has been used as a GAG replenishment treatment, but this treatment has shown inconsistent effects possibly due to variations in composition and strength. Commercially available heparin injections are made of unfractionated heterogeneous polysaccharide mixtures in saline solution, and vary lot by lot in both composition and amount.

Sterile chondroitin sulfate 0.2% (Uracyst®-S, Stellar International Inc.) has become recently available in Canada. The sterile sodium chondroitin sulfate 0.2% used in the current study was a highly purified, non-pyrogenic, chondroitin sulfate with an average molecular weight of 10,000 – 40,000 Daltons.

This acidic natural polysaccharide linear polymer has a more uniform composition and sulfation compared with heparin sodium. Chondroitin sulfate is one of the most abundant GAGs forming the epithelial layer of the bladder. The GAG layer is impermeable to urine solutes.

Chondroitin sulfate has a repeating disaccharide unit made of glucuronic acid and a galactosamine with one sulfate group in b (1-3') linkage. This agent is non-toxic when taken orally. It is often a part of a daily dietary intake, as it is naturally present in animal tissues that contain cartilage or mucus membrane. Oral intake of chondroitin sulfate as a sodium salt for the treatment of osteoarthritis at daily doses of 1 to 10 grams daily for a period of 10 years did not reveal any significant adverse reactions. Unlike pentosan polysulfate, heparan sulfate, or modified heparin sulfates, chondroitin is devoid of any significant anticoagulant effect.

In 1994, Parsons devised a simple method to detect epithelial permeability by using a potassium chloride solution. When a solution of potassium chloride was instilled in bladders of patients with impaired epithelium, the potassium diffused across the transitional cells to stimulate sensory nerves and cause pain or urgency. Patients with normal epithelium usually did not experience symptoms of pain and urgency when the solution is instilled.

Since the most prevalent bladder GAG is chondroitin sulfate, we hypothesized that this agent would neutralize the symptoms of potassium chloride irritation experienced by patients with impaired bladder epithelium, would repair the GAG layer, and would provide a more consistent continuous treatment response.

Objective

The study objective was two-fold. First, we aimed to demonstrate the diagnostic ability of the chondroitin sulfate solution to identify a permeable bladder that could be treated by exogenous chondroitin sulfate instillation. Second, we aimed to investigate the symptomatic relief of IC patients treated with chondroitin sulfate, which replenished the bladder GAG layer.

Diagnostic objective

The first objective of this study was to demonstrate that chondroitin sulfate solution neutralized the irritations induced by sterile potassium chloride solution 3.0% (Solution™ K, Stellar International Inc). This diagnostic test is to identify a leaky bladder or deficient GAG layer that may be treated by instillation of exogenous chondroitin sulfate solution for replacement or replenishment of the bladder GAG layer.

Treatment objective

We aimed to investigate response of IC patients who had permeable bladder GAGs who received instillation of exogenous chondroitin sulfate solution.

Method

The study received approval from the Research Review and Ethical Approval Committee, Capital

Health Region, and each patient signed an informed consent form prior to commencing the treatment. Pretreatment urodynamic investigation was not routinely ordered on all patients. Most patients were newly diagnosed with IC and had not received previous treatment for this condition. All patients tested positive to the potassium stimulation test. The initial evaluation included medical history, physical examination and urine culture. The 24-hour measured voiding diary with pain and urgency severity indices was completed by the patient prior to the initial visit and was reviewed to confirm eligibility for the study. All patients completed the Quality of Life Questionnaire at their initial visit and final visit. Each patient received 40 mL of sterile sodium chondroitin sulfate 0.2% via bladder catheter weekly for 4 weeks and then monthly for 1 year. Data collected at each visit included pain and urgency severity as recorded in a 24-hour voiding diary, and responses to a Quality of Life questionnaire. Patients were also questioned on adverse events and changes in medication.

The potassium stimulation test was always done before hydrodistention of the bladder, as we found hydrodistention affects the patient's response to the potassium test, possibly by desensitizing the bladder wall.

Patient selection

Patients 16 years of age and over demonstrating a positive potassium stimulation test and subsequent neutralization by sterile sodium chondroitin sulfate 0.2% were included. Informed consent was obtained for patients who were enrolled in the study.

Patients with a negative potassium stimulation test were excluded as were those who failed to have their potassium- induced symptoms neutralized with intravesical chondroitin sulfate. (There were no patients in this study who had positive responses to the potassium stimulation test who failed to have their potassium- induced symptoms neutralized by intravesical chondroitin sulfate).

Patients with known sensitivity to chondroitin sulfate or other polysulfated GAGs were also excluded as were those not deemed suitable for intravesical instillation.

Baseline symptoms

Patients were determined to have IC based on National Institutes of Health (NIH) symptom criteria. All patients were confirmed positive IC; all had diffuse glomerulations by cystoscopy and hydrodistention of bladder. Two of the 18 patients were diagnosed with Hunner's Ulcer. Five of the 18 patients had incidental voiding volumes over 350 mL per 24 hour as recorded in their voiding diaries (i.e. functional bladder capacity of over 350 mL) but they were included in the study on the basis of all other criteria.

Potassium stimulation test

Two solutions were instilled into a bladder for 3 minutes. Solution 1 was sterile water for injection, USP (WFI) and Solution 2 was 40 Ml of potassium chloride solution 3.0%.

After instilling solution 1 for 2 - 3 minutes, patients were asked to rate their symptoms on a scale of 1 to 5. Solution 1 was removed and solution 2 was instilled for 2 to 3 minutes, and again, patients were asked to rate their symptoms on a scale of 1 to 5. Patients who stated that potassium chloride was causing their symptoms to increase (a rating of 2 or higher) were considered to have a positive test result. No response implied that the patient did not have GAG deficiencies and might not respond to GAG replacement therapies.

Neutralization of positive potassium stimulation test by chondroitin sulfate

Patients with a positive potassium stimulation test had any residual test (Solution 2) removed and 40 mL solution of sterile sodium chondroitin sulfate 0.2% was instilled. Patients were then asked to rate their symptoms using the same scale of 1 to 5. Symptom reduction of 2 or better was considered a positive response, and these patients were eligible for the study.

Treatment procedure and frequency of instillations

Single- dose 40- mL vials of sterile sodium chondroitin sulfate 0.2% were administered via bladder catheter weekly for 4 weeks and then monthly for 1 year.

Treatment monitoring tools

Patients were asked to complete their voiding diary and Quality of Life Index at home prior to their visits. Unfortunately, many forgot their forms or only partially completed them making these measurement tools of little value in measuring response to therapy. The Quality of Life Questionnaire was not specific to the bladder, and was deemed to be of little value as a monitoring tool for this study. The O'LearySant Interstitial Cystitis Symptom and Problem (ICSP) index is specific to IC patients and was therefore used as the measurement tool in this study.

Results

Of the 18 patients (1 man, 17 women) enrolled in the study, 5 withdrew: 2 patients diagnosed with Hunner's

TABLE 1. **O'Leary, Sant, Interstitial Cystitis Symptom and Problem (ICSP) index scores***

	Baseline		Month 13		Change	
Patient	Symptom	Problem	Symptom	Problem	Symptom	Problem
1	11	7	11	3	0	-4
2	14	13	15	12	1	-1
3	10	8	1	1	-9	-7
4	12	12	3	2	-9	-7
5	15	12	3	2	-12	-10
6	9	9	6	4	-3	-5
7	11	8	10	10	-1	2
8	18	16	16	13	-2	-3
9	13	14	0	0	-13	-14
10	14	13	4	2	-10	-11
11	14	10	6	5	-8	-5
12	17	13	17**	13**	0	0
13	11	9	10	9	-1	0

*12 months only; no end-point measured

ulcers withdrew due to increased pain, 1 patient withdrew because of an unexpected pregnancy, and 2 patients withdrew for nonmedical reasons. Thirteen patients completed the study (although one patient did not return for end-point measurement), and their results have been included in this report. Table 1 summarizes the O'Leary, Sant, Interstitial Cystitis Symptom and Problem (ICSP) index scores. Table 2 shows response to treatment, based on these scores. Of the 18 patients enrolled in the study, 6/18 (33.3%) showed good response, 2/18 (11.1%) showed fair response, 4/18 (22.2%) showed partial response, and 6/18 (33.3%) either showed no response (1 patient), or withdrew from the study due to increased pain after 1 month (2 patients), or due to pregnancy (1 patient) or due to nonmedical reasons (2 patients).

Discussion

Diagnosis and treatment of IC continues to pose a challenge to physicians. To date, research efforts to find an effective therapy for all patients with IC have been unsuccessful. Currently available research tools do not provide adequate symptom measurement data for an increasing number of patients with IC who have unusual symptoms

Our rationale for using patients with demonstrated epithelial permeability may prove to be a useful way to identify IC patients who are most likely to be helped with intravesical GAG replenishment therapy. The patients who withdrew from this trial may have benefited from an increased dosage of chondroitin and/or increase in the frequency of treatments. Starting more than two years ago, we began treating IC patients by instilling chondroitin sulfate (and have also used dosages of 4 times the normal dose to treat chemical and radiation induced cystitis) and it has proven to be well tolerated with no adverse events related to its use. Modifying a patient's treatment regime and dosing regimen according to individual symptoms and response may prove to be even more effective.

In this study, all patients who completed the 13-month study tolerated the chondroitin solution well

TABLE 2. **Response to treatment***

Number	Response type	Improvement in score from baseline to 13 months
6/13 (46.2%)	good	8 to 13 points for symptom scores and 5 to 14 points for problem scores
2/13 (15.4%)	fair	- 2 to 3 points for symptom scores and 3 to 5 points for problem scores
4/13 (30.8%)	partial	1 point for symptom score or 1 to 4 points for problem scores
1/13 (7.7%)	none	none

*The average time to respond to treatment was 3 to 12 weeks

A number of patients experienced minor discomfort from the catheterization. Three of 18 patients experienced increased discomfort post catheterization for up to 48 hours.

Although it is difficult to measure, the urology nurse undoubtedly had an impact on patients' treatment. It has been reported in other studies that a trusting relationship between IC patients and caregivers can facilitate the management of this disease. All patients in the study were treated and managed by an experienced, caring urology nurse who provided individual attention and support regarding self-care techniques, stress reduction, and modifications to diet. This interaction may have introduced a significant placebo effect. A larger, double-blind placebo-controlled study is planned.

We used a variety of measurement tools in an attempt to capture reliable data, but only the O'Leary, Sant, Interstitial Cystitis Symptom and Problem Index results were used for data analysis. The data illustrates that 12 out of 13 patients (92.3%) responded at least partially to treatment, and 8 of 13 (61.5%) had a good- to- fair response. Some patients demonstrated significant improvement in their problem index scores, although their symptom index scores did not decrease correspondingly. This may be due to the pain scores not being able to differentiate between levels of pain/discomfort.

One patient who showed good response agreed to undergo a second potassium challenge test which turned out negative. It would be interesting to look at this type of response more extensively in more patients who are receiving GAG therapies.

Conclusion

These results imply that testing IC patients for increased epithelial permeability appears to identify those who will be more apt to respond to GAG replenishment therapy. Other GAG treatments have not been studied using this type of protocol, nor have different agents been compared in the same trial, so it becomes difficult to compare efficacy with these other therapies. Future studies that address these issues will help to shed more light on treating patients with IC. □

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