Research Article
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Oral pentosan sulfate/intra-vesicle chondroitin sulfate treatment for interstitial cystitis

Abstract

Purpose: Chronic pelvic pain and recurrent cystitis are the most prevalent conditions among the pelvic ailments in the gynecologist's office. The major cause of chronic pelvic pain is either interstitial cystitis or the endometriosis among women. The study has aimed to compare treatment responses of two approved treatment modalities, which include the oral pentosan sulfate (Elmiron) and the intra-vesicle chondroitin sulfate (uracyst) in terms of symptoms and to measure improvement in quality of life.

Material and methods: This research is a retrospective cohort study with total 248patients included. Around 168patients were excluded because of negative diagnostic cystoscopy findings for interstital cystitis. One had cancer, and 23% could not afford treatment. And only the patients who had irritative LUTS history and positive cystoscopy findings for IC with cystoscopy hydrodistention were included.

Results: It was found that the oral pentosan sulfate is highly beneficial and brings symptom relieve faster than the intravesicle chondroitin sulfate.

Conclusion: Interstitial Cystitis is a multifactorial disease that causes severe pain in the pelvic, particularly in bladder. The study compared two treatments modalities determine their efficacy over each other by applying them to patients diagnosied and pretreated with cystoscopy hydrodistention. The handling of this syndrome with oral pentosane sulfate/intra-vesical chondroitin sulfate recovers the signs score; bother score, entire Pelvic Urgency and Frequency score. Both treatment modalities have equal efficacy in reliving the symptoms in 6months time. The oral treatment showed earlier respond in compare to intra-vesical instillation at 3months time.

Keywords: chondroitin, cystitis, interstitial, oral pentosan sulfate, symptom

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Abbreviations: BPS, bladder pain syndrome; FDA, food and drug administration; GAG, glycos amino glycan; HD, hydro distention; IC, interstitial cystitis; LUTS, lower urinary tract symptoms; NIDDK, national institute of diabetes and digestive and kidney diseases; PBS, painful bladder syndrome; PUF, pelvic urgency, and frequency; PPS, pentosan polysulfate

Introduction

Interstitial cystitis (IC) is referred as the bladder syndrome characterized by the symptoms of urinary urgency, frequency, nocturia, and the suprapubic/pelvic pain.[1] IC is more common among women as compared to men and mainly among young women. However, it may also impact children and men, but with a lesser frequency.[2] In the U.S, it affects 501 persons in every 100,000 i.e. 0.5% people.[3] Bladder pain syndrome (BPS)/IC is related to the symptoms of the sensory lower urinary tract. Unfortunately, several of the obtainable oral treatments are unsuccessful in most patients with BPS/IC, which is the drive for increasing therapeutic approaches and new drugs.[4] The BPS/IC has been designated as the mystery in medical science. This is because the correct etiology and causes of this disease are unknown. There have been no clear descriptions for the reasons of the concurrence of the disease. The possible etiology that has been associated with the IC disease includes mast cell activation due to inflammation, neurogenic inflammation, toxins and stress, post-infection auto-immune effects, and the urothelial dysfunctioning. The frail or leaky bladder epithelium caused due to defects in the glycosaminoglycan (GAG) bladder layer. In BPS/IC, chondroitin sulfate is one of the major components of urothelial musingly. Therefore, the chondroitin sulfate is considered as an element in a deteriorating state in the bladder and the solutions of chondroitin sulfate are used for intravesical treatments for the replenishment of the GAG layer and to relieve the symptoms of IC. The pentosan sulfate is a drug, which is also intended to ameliorate the damages caused in GAG mucous lining of the bladder. A three to six months treatment is required for symptom relief. The treatment may also incorporate some side effects including a headache, hair loss, and the gastrointestinal issues.[2]

Like many other chronic pelvic pain syndromes, the IC is also a bewildering syndrome that proves difficult to be managed efficiently by the gynecologists. The vague pathogenesis of disease has made it difficult for the gynecologists to manage the symptoms effectively through systematic treatments.[5] IC continues to worsen periodically, and the aggravation of symptoms is triggered by the physical and psychosocial stress. In 75% women, sexual intercourse has been reported to exacerbate the symptoms. Some evidences are also pertinent that links IC with the panic disorder showing their genetic associations.[6] In light of this evidence, IC has been regarded as the neuroimmune endocrine condition.[1] The intravesical treatments have long been adopted as the first mode of therapeutic interventions among which the hydrodistention (HD) of the bladder is consistently performed and widely recommended as the most preferred method.[7] The HD of the bladder is a process to diagnose IC among patients. The procedure is followed by the distention of bladder by filling water, saline, or the glycine solution. The water or solutions are instilled into the bladder at the higher pressure up to 80-100cm H_2O. The filling of

a bladder is performed by a cystoscopy. The pressure-filled water is allowed to release from the bladder; it leaves small bleeding points under the surface of a bladder in patients with IC. These bleeding points on the surface of the urinary bladder are referred as the glomerulations which are considered as the active predictors of IC among patients.

The process of HD is highly discomforting and despite the fact that it is performed under the general or spinal anesthesia, the process induces severe pain and restlessness among the patients.[1] The fact that intravesical treatments require catheterization makes it unsuitable for patients with higher pain symptoms. The catheterization is itself painful that may induce certain complexities and risks in treating patients with IC.[8] It has been hypothesized that symptom relief after oral pentosan sulfate (Elmiron), and the intra-vesicle chondroitin sulfate (Uracyst) helps in treating the IC patients, but pentosan sulfate (Elmiron) is more effective than Intra-Vesicle Chondroitin Sulfate. A pilot study was conducted to gather information on the differences between inactive vehicle control and intravesical chondroitin sulfate for the treatment of painful bladder syndrome (PBS)/IC. This was a randomized, double-blind, prospective, randomized, 12-week study, which was followed by six weeks follow-up period in patients with PBS/IC. Patients with 2.0% sodium chondroitin sulfate were randomized to weekly intravesical vehicle control. The primary efficiency of analysis was the responders that markedly or moderately improved according to the 7-point global response assessment. The quality of life and the secondary input and questionnaire focused on symptoms were included in secondary endpoints. This study was underpowered, and the difference in treatment effect was not statistically significant. Although the patients were reported a clinical benefit with intravesical chondroitin sulfate treatment as compared to other vehicle control treatment.[9] The aim was to compare the two important modalities: the oral pentosan sulfate (Elmiron) and the chondroitin sulfate (Uracyst). Elmiron is an oral administration method whereas the uracyst includes precise intra-vesicle bladder instillation.

Materials and methods

This study was a retrospective cohort study. Approximately, 248patients were recruited who had cystoscopic HD for irritative lower urinary tract symptoms (LUTS). Out of total 248patients, 168patients were excluded due to the following reasons: 1patient diagnosed with bladder cancer, 99patients had negative cystoscopic findings for interstitial cystitis, 56patients had no treatment due to cost, 6patients were lost to follow-up or had incomplete data on the Pelvic Urgency, and Frequency (PUF) Scale and 6 patients received alternative treatments (Figure 1).

Data collection

Elmiron is an oral treatment, and it needs at least 6months treatment course to treat this condition whereas uracyst is administrated intravesically on a weekly basis and particularly required 4-6weeks then monthly to complete 6months treatment course. Two groups were compared: 51patients used oral pentosan sulfate treatment and 29 patients received intra-vesicle chondroitin sulfate treatment. PUF scores were collected prospectively before and at 6weeks following cystoscopic HD, and then subsequently at 3 and 6months after initiating the treatment course in each of the two groups. The PUF scores were collected from hospital and urodynamic charts, in addition to the electronic demographic data. The t-test has been applied to evaluate the significance of the variables. The data was then analyzed by SPSS software.

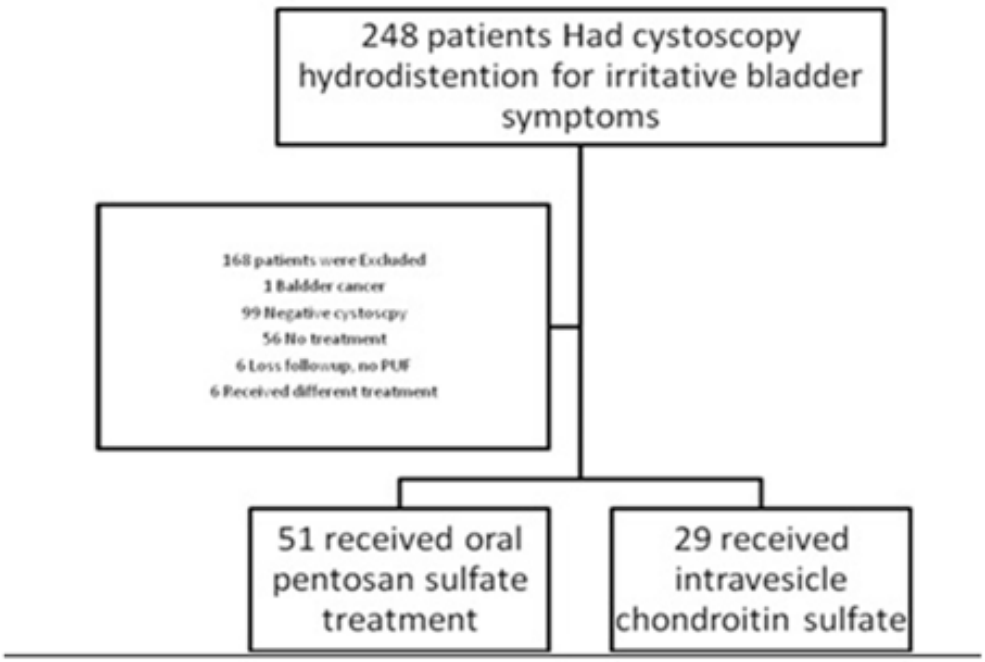

Figure 1 Flowchart.

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Data analysis

The mean symptom score, the bother score, and total score were calculated in each of the two treatment groups through SPSS. Symptom score included day and night time frequency, dyspareunia, severity, type of pelvic pain, severity, and type of urinary urgency. Bother score included the degree of bothersome symptoms with nighttime frequency, dyspareunia, pelvic pain and urinary urgency. The total score included the combination of symptom and bother scores.

Ethical consent

This study was ethically approved by the University of Western Ontario Ethics committee, collected and conducted in Canada, Royal Victoria and St Joseph hospitals.

Results and discussion

Out of 80patients, 51patients had oral pentosan sulfate treatment and 29patients received intra-vesicle chondroitin sulfate for 6 months treatment course. All study patients had a history of irritative LUTS and completed the PUF score before undergoing cystoscopic HD for diagnostic and therapeutic value. The PUF results were separately analyzed as symptom score, bother score, and total score in each treatment group. 62.5% of the study population underwent multi-channel urodynamics assessment. There were no differences in the demographic characteristics or multi-channel urodynamic findings between the two treatment groups. Both groups of women were associated with a smaller bladder capacity with a mean less than 300ml (Table 1). Both oral pentosan sulfate and intra-vesicle chondroitin sulfate treatments significantly improved the symptom score, bother score, and total PUF score compared to baseline scores before treatment and six months after treatment (Table 2). It has been found that the symptom score, bother score, and a total score were significantly improved after three months with the use of oral pentosan sulfate treatment as compared to intra-vesicle chondroitin sulfate treatment, P-value of 0.027, 0.035 and 0.026 respectively. No differences were found after six months of treatment between the two treatment groups (Table 3).

Table 1 Showing the demographic characteristics

	Oral pentosan sulfate(n=51)	Intravesicle chondroitin sulfate(n=29)	P value
Age-Mean(sd)	53.1(14.2)	54.0(17.3)	0.785
Age-Median	49.0	51.0	
BMI-Mean(sd)	27.0(5.9)	26.3(4.9)	0.593
Menopausal Status-Post	25(49.0%)	15(51.7%)	0.816
Gravida-Mean(sd)	3.16(2.43)	2.62(1.90)	0.39
Gravida-Median	3.0	2.0	
Living Children-Mean(sd)	2.35(1.82)	2.10(1.21)	0.988
HD Fluid Volume-Mean(sd)	822.4(214.7)	808.6(279.7)	0.806
UDS findings 1st Urge-[n] mean(sd)	[32] 156.3(76.0)	[18] 144.8(85.2)	0.626
Max bladder capacity-[n] mean(sd)	[32] 273.6(115.2)	[18] 248.4(139.8)	0.497
Pdet at capacity-[n] mean(sd)	[32] 13.4(13.2)	[18] 9.4(10.8)	0.289
UI/evidence of OAB	11/31(35.5%)	4/18(22.2%)	0.332
PVR capacity-[n] mean(sd)	19.6(16.9)	30.1(29.6)	0.117

Table 2 Prevalence of PUF score

	Oral pentosan sulfate				Intravesicle chondroitin sulfate			
Test	**Before**	**6 months**	**Difference(95% CI)**	**P value**	**Before**	**6 months**	**Difference(95% CI)**	**P value**
Symptoms Score	11 (4.4)	8.4 (4.7)	2.1 (1.0, 3.3)	<.001	12.2 (3.7)	9.2 (4.4)	2.8 (1.1, 4.5)	0.002
Bother Score	5.9 (2.8)	4.3 (2.7)	1.4 (0.5, 2.4)	0.003	6.7 (2.1)	4.7 (2.9)	1.9 (1.1, 2.8)	<0.001
Total Score	16.9 (6.8)	12.6 (7.3)	3.6 (1.7, 5.6)	<.001	18.9 (5.4)	14 (7.0)	4.7 (2.5, 6.9)	<0.001

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Table 3 Demonstrate the treatment results after 6months

		Oral pentosan sulfate(n=51)	Intravesicle chondroitin sulfate(n=29)	P Value
Sexually Active	• Pre HD	32/47(68.1%)	15/29(51.7%)	0.154
	• Post HD	31/46(67.4%)	16/29(55.2%)	0.287
	• 3 Months post treatment	28/40(70.0%)	16/29(55.2%)	0.206
	• 6 Months post treatment	28/41(68.3%)	15/27(55.6%)	0.287
Symptoms Score – [n] Mean(sd)	• Pre HD	[47] 11.0(4.4)	[29] 12.2(3.7)	0.233
	• Post HD	[46] 9.1(3.8)	[29] 11.0(3.4)	0.027
	• 3 Months post treatment	[40] 8.6(3.6)	[29] 10.8(4.4)	0.027
	• 6 Months post treatment	[41] 8.4(4.7)	[27] 9.2(4.4)	0.484
Bother Score- [n] Mean(sd)	• Pre HD	[47] 5.9(2.8)	[29] 6.7(2.1)	0.16
	• Post HD	[46] 4.9(2.2)	[29] 5.5(2.4)	0.235
	• 3 Months post treatment	[40] 4.4(2.2)	[29] 5.7(2.6)	0.035
	• 6 Months post treatment	[41] 4.3(2.7)	[27] 4.7(2.9)	0.564
Total- [n] Mean(sd)	• Pre HD	[47] 16.9(6.8)	[29] 18.9(5.4)	0.176
	• Post HD	[46] 13.9(5.7)	[29] 16.6(5.7)	0.05
	• 3 Months post treatment	[40] 13.0(5.5)	[29] 16.4(6.8)	0.026
	• 6 Months post treatment	[40] 12.6(7.3)	[27] 14.0(7.0)	0.432

Among the oral pharmacologic treatments, pentosan polysulfate (PPS), hydroxyzine, and amitriptyline are the most preferred treatments. However, the pentosan sulfate is the only oral medication legitimately confirmed and permitted by the Food and Drug Administration (FDA) for treating IC. There has been a wide range of successful studies and evidence that confirm the efficacy of oral pentosan sulfate in comparison to other intravesical treatments for providing fast relief with lowest relative risks. It is a sulfated polysaccharide that is believed to alter the permeability of urothelium for meditating the pain symptoms positively. On the contrary, the findings stated in National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) supported trial named as the IC Clinical Trial Group intercepts with the effectiveness of oral pentosan treatment. It fails to provide noticeable evidence supporting the use of oral pentosan for symptom relieves in IC.[10] Nevertheless, the objection for pentosan treatment's effectiveness in IC has been rejected as the study was underpowered.[11] Despite the fact that pentosan sulfate is the only FDA-approved oral treatment for IC, the report by U.S. National Institutes of Health showed that it has no favorable effects in ameliorating symptoms from moderate to severe IC. Also, the study sponsored by the NIH of U.S. showed that oral pentosan has no favorable effects on treating patients with moderate to severe IC.[10]

The pentosan sulfate was first isolated for the use as the oral anticoagulant in the 1950s for the replacement of parenteral heparin. This mucin layer in bladder functions to secure the mucosal binding of proteins and calcium.[12] The pentosan sulfate has proved to be effective in securing the epithelium degradation as it binds with the epithelium and strengthens it to endure the increased pressure of bladder washing during hydrodistention. It also restores the epithelial permeability of bladders that is weakened causing pain due to the depletion of mucin. Fall et al.,[8] have stated that the oral administration of pentosan sulfate is not useful, and the bioavailability of pentosan sulfate greatly decreases when given orally. Therefore, the Pentosan sulfate treatment must be given intravenously as the intravesical procedures maintain the concentrations and provide the full potency of the drug over the infected site. Hence, it has been assessed that the findings of this study contradict with the outcomes of Fall et al.[8] It has been examined that oral pentosan sulfate treatment is better and far efficacious than the intravesical method, as it relieves the symptoms in half the time taken for the intravesical treatment to bring the similar results. The pilot study conducted by Sant et al.,[10] also intercepts with findings made in this study and suggests that the oral pentosan sulfate is not equivalently efficacious for all the 121patients analyzed. The author further stated that the oral pentosan sulfate is effective, but not in the majority of patients. Therefore, it cannot be adopted as the generalized way of treatment for all the patients with IC. The results regarding

the efficacy of oral pentosan sulfate support the retrospective study conducted by Zahrani et al.,[13] study intended to find out the long-term efficacy and tolerability of pentosan sulfate among patients with BPS. The study included 271 individuals with 90% inclusion of women. The results revealed that pentosan sulfate is an effective oral therapy for relieving chronic bladder pain and controlling the symptoms of BPS with long-term efficacy and tolerability. However, the efficacy can be declined if administered among patients with a history smoking or the presence of detrusor overactivity. The results regarding the efficacy of chondroitin sulfate treatment can be confirmed by the meta-analysis conducted by Thakkinstian et al.,[14] which proves that intravesical chondroitin sulfate treatment is an effective therapy. The intravesical chondroitin is a GAG that is proven to be efficacious from two open-labels, non-randomized, and uncontrolled studies.

Steinhoff[15] conducted a study to determine the effectiveness of intravesical chondroitin among patients with IC. The results revealed significant improvements in symptoms in 13patients whereas the remaining patients either left the study or did not show any positive or negative responses. Hence, it was deduced that the intravesical chondroitin is a safe and beneficial treatment for patients with IC. Sorensen[16] conducted a study including 24 refractory women with BPS/IC and all with the history of treatments with any of the one treatments including HD, PPS, and anticholinergic. Firstly, they were treated with a higher dose of chondroitin sulfate with 2.0% instillations twice a week and for two weeks. After the first two weeks, the 2.0% instillation was given once in a week and continued for four weeks. Afterward, the frequency of treatment was reduced to only once in a month and continued for 1year. Around, 20 individuals completed the trial and reported the average symptom improvement of 73.1%. The time length for optimum response was 4-6months which were similar to the results of this study related to intravesical chondroitin sulfate. However, 8patients showed the need of more concentrated 2.0% solutions to maintain the effective results. Thus, the study confirmed the findings made in this study and concluded that the chondroitin sulfate is the beneficent treatment among pre-treated interstitial cystitis patients. Porru et al.,[17] have supported the use of intravesicle chondroitin sulfate but in conjunction with the intravesicle hyaluronic acid. The use of intravesicle chondroitin sulfate may not be effective if administered alone, but its efficacy is enhanced with the functioning of intravesicle hyaluronic acid. The stated evidence and the results deduced from the study indicated for the adoption of a multimodal management approach in patients with IC. The pentosan sulfate must be given as the primary pain relief pharmacologic treatment among patients undergoing HD. The length of trial must be no more than three months as the pentosan sulfate proves to exhibit its efficacy in 3 months. If the oral pentosan sulfates treatment successfully controls the symptoms in the patients, the treatment must be continued further. Conversely, if the oral pentosan fails to bring any pain relief within three months, the treatment must be stopped and a second line treatment must be initiated which is the intravesicle chondroitin treatment with the six months length of the trial. If the treatment succeeds to recover the symptoms in 6months, then the treatment must be continued or if it fails to bring symptom relief, the treatment must be discontinued.

Conclusion

The formulation tested in this study constitutes a new concept in the treatment of IC, that is HD will be more effective, and its effect is "soothed" and improved by application of these agents post treatment. Pentosan sulfate (Elmiron) is administered orally where as chondroitin sulfate (uracyst) through intra-vesicle bladder instillation. Elmiron requires 6months course of action to treat interstitial cystitis while uracyst functions on the weekly basis and particularly require x 4-6weeks to complete 6months treatment course. It contrasts the effectiveness of the two interventions: the oral PPS and the intravesicle chondroitin sulfate. It proposes a multimodality approach of these two treatments and evaluates their efficacy for ameliorating painful symptoms among IC patients previously treated with HD. This study warrants for randomized trials in future studies and provides foundations for extending the research for an efficacy of both the treatments among patients pretreated with treatments other than HD. It also places the need for larger studies in future that must contrast the effectiveness of the two treatments among patients with symptoms of IC perplexed with other chronic pelvic pains. The treatment of BPS/IC with either oral pentosan sulfate or intra-vesicle chondroitin sulfate improves the symptom score, bother score and total PUF score. Although oral pentosan sulfate treatment had an earlier effect at 3months compared to intra-vesicle chondroitin sulfate, there were no differences between the two treatment groups after 6months. Therefore, this study confirmed the efficacy of both the pentosan sulfate and the intravesicle chondroitin sulfate treatment. The results of the study revealed the dominance of effectiveness of oral pentosan sulfate over the intravesicle chondroitin sulfate treatment as it took half the time for relieving symptoms as compared to the chondroitin sulfate treatment. The study recommended the use of oral pentosan sulfate for patients undergoing HD for a more effective and faster relief.

The summary of findings gives us the convincing evidence for using both the oral pentosan sulfate as well as the intravesicle chondroitin treatment. However, there have been no controlled trials directly comparing the efficacy of these two treatments. The study only included patients with interstitial cystitis and excluded patients with symptoms of other pelvic diseases. Also, it has only considered IC patients pretreated with HD. The sample size was restricted to 80patients, potentially relevant variables, they were excluded, and the abilities of study findings were generalized. The present results achieved with the comparison of oral pentosan sulfate and the intravesicle chondroitin sulfate. It constitutes a rationale for using any of the treatments for patients with IC, particularly those pretreated with the HD based on the published scientific evidence to deliver synergistic effects and warrant a randomized trial.

Acknowledegements

None.

Conflict of interest

The author declares no conflict fo interest.

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