PAINFUL BLADDER SYNDROME/INTERSTITIAL CYSTITIS (PBS/IC)- MEDICAL MANAGEMENT OPTIONS

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ABSTRACT

BACKGROUND

PBS/IC is a chronic pain syndrome of unknown aetiology. It represents a spectrum of disorders rather than one single disease. It is a diagnosis of exclusion. Evidence based treatment strategy is impossible, but conservative oral treatment may be effective in some patients.

Limitations- Patients with unremitting frequency, urgency, nocturia, suprapubic pain relieved with voiding were evaluated. Out of 450 patients investigated, 60 patients were selected for the study. Only patients who had fulfilled the NIDDK exclusion and inclusion criteria were included in this present study. Since the study duration was short, we had to limit the sample size for convenience.

Objective/Aim- To study the medical management options of painful bladder syndrome/ interstitial cystitis (PBS/IC)- monotherapy versus multimodality therapy.

MATERIALS AND METHODS

Questionnaire based study was conducted on 450 patients between August 2008 and August 2017. 60 patients were selected for the present study based on National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) inclusion and exclusion criteria for diagnosis of PBS/IC. 54 patients were women and 6 patients were men with a mean age of 44 yrs. and 20% were over 60 yrs. of age. Overall, 48% received pentosan alone and 52% received pentosan plus gabapentin and hydroxyzine. During interview, three questionnaires were administered. One related to pain/ discomfort scores, second overall investigator evaluation after treatment, third efficacy of pentosan alone and in combination with other drugs. Improvement of > 50% was considered as success.

RESULTS

Combined treatment with hydroxyzine, pentosan and gabapentin showed better clinical response 12 patients (40%) compared to monotherapy with pentosan 9 patients (30%).

CONCLUSION

Simultaneous multiple drug initiation can yield better results compared to single drug as PBS/IC is a clinical syndrome of multifactorial aetiology.

KEYWORDS

Painful Bladder Syndrome; Interstitial Cystitis; Pentosan; Hydroxyzine; Gabapentin.

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BACKGROUND

Painful bladder syndrome/ interstitial cystitis (PBS/IC) is a clinical diagnosis. It is a chronic illness based on exclusion of other diseases with similar symptoms.¹

Characterised by urinary frequency, nocturia, urgency and pelvic/ bladder pain of more than 6 weeks' duration, in the absence of proven urinary infection or other obvious pathology.² Interstitial cystitis has no clear aetiology or pathophysiology and diagnostic criteria for the syndrome remain undefined.³ Possible causative factors are defect in glycosaminoglycan (GAG) layer, dysregulated immune or inflammatory signals, neural hypersensitivity and pelvic floor

dysfunction. A commonly accepted theory is that symptoms of PBS/IC may arise due to a defect in the glycosaminoglycan (GAG) layer covering the bladder urothelium.⁴ GAG layer acts as a barrier between toxins and bladder urothelium, and protects it from injury by these toxins. Deficiency in the surface GAG-mucin layer allows toxins to permeate bladder wall, which leads to inflammation and pain. Clinically, interstitial cystitis is often divided into 2 distinct subgroups based on findings at cystoscopy, bladder over distention and histologic features-ulcerative (classic) and non-ulcerative types.⁵ Such differences may have important implications for diagnosis and therapy. In the absence of universally effective treatment, therapy usually consists of various supportive, behavioural and pharmacologic measures. Surgical intervention is rarely indicated.

Currently, there are no specific clinical, urinary marker, radiographic, laboratory or serologic findings available. Biopsy findings are not pathognomonic for interstitial cystitis. The syndrome remains a diagnosis of exclusion. The most promising urinary biomarker for IC/ BPS is anti-proliferative factor (APF).⁶

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Objective

1. To compare the efficacy of single drug (Pentosan polysulphate) versus multiple drug therapy in interstitial cystitis/ painful bladder syndrome.
2. It is a non-randomised controlled study (NRCT) spread over 10 years. As IC/ PBS is a chronic condition and treatment will not result in total cure, but only alleviate the disease condition this protocol is used for IC/ PBS there is no cure.

MATERIALS AND METHODS**Objective**

1. To compare the efficacy of single drug (Pentosan polysulphate) versus multiple drug therapy in interstitial cystitis/ painful bladder syndrome.
2. It is a non-randomised controlled study (NRCT) spread over 10 years, as IC/ PBS is a chronic condition and treatment will not result in total cure, but only alleviate the disease condition. This protocol is used for IC/PBS, there is no cure.
3. Sample size was not predetermined. After NIDDK exclusion criteria, patients were selected. Since the study duration was short, we had to limit the sample size for convenience.
4. A systematic review of the available literature was conducted to identify the various oral treatment modalities available for painful bladder syndrome/interstitial cystitis (PBS/IC).

Statistical Methods

Descriptive statistics. Qualitative variables were analysed using proportions. Quantitative variables were analysed using mean and standard deviation. Chi-square test was applied to note if there is any statistical significance between the single drug regimen and the multidrug therapy. A 'p' value less than 0.05 was considered statistically significant.

It is a non-randomised, controlled study where comparison was made between two medications. Questionnaire based study was conducted on 60 patients between August 2008 to August 2017. 54 patients were women and 6 patients were men with a mean age of 44 yrs. (range 24 - 60) and 20% were over 60 yrs. of age. All patients met the NIDDK definition for PBS/ IC based on the results of laboratory cystoscopy, cytology and biopsy. Screened patients were enrolled for 6 months treatment schedule. Patients who have stopped medication due to poor outcome or side effects are not included in the study. 29 patients were given pentosan sulphate 100 mg three times a day. Gabapentin (methylcobalamin 1500 mcg OD) and hydroxyzine (25 mg OD) were added to pentosan sulphate for 31 patients. Patient's own assessment of bladder pain was the basis of clinical improvement. Improvement of more than 50% was considered as success.

Every Three Months the Patients Rating

Of overall change in pain in comparison to baseline and difference in pain/ discomfort scores were evaluated. At baseline pain/ discomfort scores were severe in 36 patients (60%), moderate in 21 patients (35%) and mild in 3 patients (5%). At three months, 30% (9 patients) in the study had pain scores that improved by pentosan alone compared to

40% (12 patients) with combination therapy. It was found patients responded better with multimodality therapy.

RESULTS

Combined treatment with hydroxyzine, pentosan and gabapentin (methylcobalamin) showed better clinical response (40%) compared to monotherapy with pentosan (30%).

Efficacy Parameter	Pentosan	Combination Therapy
Patient's overall change in pain (recollection of difference between current pain and baseline pain)	N=29 Median=3 Mean=3.44 CI: (3.37, 3.51)	N=31 Median=4 Mean=3.91 CI: (3.83, 3.99)
Patient's satisfaction	09 patients/ (30%)	12 patients (40%)

Table 1. Pain Scores in Reference to Baseline

N= No. of patients six-point scale, 1= worse; 2= no better; 3= slightly improved; 4= moderately improved; 5= greatly improved; 6= symptom gone, CI: 95% confidence interval.

Parameter	Combination Therapy	Pentosan	P-value
Overall investigator evaluation	12 patients (41%)	9 patients (26%)	0.03
Patient assessment			
Overall improved	12 patients (40%)	8 patients (25%)	0.04
Pain questionnaire	12 patients (40%)	9 patients (27%)	0.08

Table 2. Response Assessment after 3 and 6 Months of Treatment (Percentage of Patients Improved) Investigator Evaluation

Efficacy outcomes were based on a follow-up questionnaire completed by the patient after three and six months. Patients were asked if they felt improved overall compared to the beginning of the study, and if they had improved they were asked to rate the improvement as slight (25%), moderate (50%), great (75%) or complete cure (100%). Investigators could rate patients as worse, no change, fair, good, very good or excellent.

Patient-Rated Improvement	Combination Therapy	Pentosan	P-value
Overall	13 patients (42%)	8 patients (26%)	0.01
Pain Questionnaire	15 patients (48%)	8 patients (28%)	0.01
Pain Scale	23 patients (76%)	18 patients (61%)	0.005
Pressure to Urinate	12 patients (40%)	8 patients (28%)	0.04
Urgency Scale	22 patients (71%)	15 patients (53%)	0.01
Improved Sexual Intercourse	13 patients (41%)	8 patients (28%)	0.06

Table 3. Response (Patient-Rated) post 3 and 6 Months Treatment with Pentosan/Combination Therapy (% Improvement)

DISCUSSION

Education, emotional support, behavioural modifications and stress management remains the mainstay of treatment. No long-term therapy has been shown to prevent or delay recurrent episodes. Periodic exacerbations are managed to palliate and alleviate symptoms, because no discrete pathognomonic pathologic criteria exist for assessing and monitoring disease severity. Indications and goals for treatment are based on the degree of patient's symptoms. Assessing patient response to treatment is also complicated because of the subjective nature of symptoms; the waxing and waning nature of symptoms without treatment; and the lack of objective serologic, physical or histopathologic findings. Conservative measures, oral or intravesical treatments are considered first-line treatment. Patients may require trials of multiple therapeutic options including combination therapy. Apart from pain management, pentosan polysulphate, gabapentin, amitriptyline, cimetidine, hydroxyzine and cyclosporine are used.⁷ Pentosan is the only oral drug currently approved by US FDA for the treatment of PBS/ IC.⁸ It promotes restoration of the defective GAG (mucin) layer, thereby preventing further urothelial insult.⁹ Bladder epithelial permeability is reduced with pentosan treatment with reduction in bladder mucosal inflammation.¹⁰ Pentosan also decreases histamine secretion by inhibiting the stimulation of connective tissue and mucosal mast cells.¹¹ The duration of therapy with pentosan appears to be more important in symptom alleviation than the dosage. Dose is 100 mg capsules orally three times daily. The capsules should be taken with water at least 1 hour before or 2 hours after the meals.¹² Side effects are alopecia, diarrhoea, nausea, rash, liver function abnormalities, pruritus and rectal haemorrhage.¹³ Reassessment after 3 months is required for patients receiving pentosan in case no improvement is observed and limiting adverse event are not present. Pentosan may be continued for another 3 months or combination therapy is initiated in patients whose pain is not improved by 6 months of treatment. The clinical value and risks of continued treatment are unknown.

Hydroxyzine (anti-histamine) blocks neuronal activation of mast cells, thus suppressing mast cell degranulation.¹⁴ Dosing starts at 25 mgs given at bed time and may increase to 50 mgs at night and 25 mgs in the morning. Gabapentin (Methylcobalamin is useful for neuropathic pain). Side effects are dizziness, dry mouth, nausea, drowsiness, blurred vision, dry mouth and headache. Opioids and NSAIDs are used for pain management.

Limitations

Since the study duration was short, we had to limit the sample size for convenience.

CONCLUSION

Simultaneous multiple drug initiation can yield better results compared to single drug as PBS/IC is a clinical syndrome of

multifactorial aetiology compared to monotherapy with pentosan (30%). Maximum treatment response can be achieved when patients are treated for 6 months or longer. Currently, pentosan polysulphate is the only approved drug for PBS/IC, because PBS/IC is a chronic condition. Long term treatment would be required. Optimising medication for tolerability is critical to obtaining patient's compliance. Choosing the formulation with the lowest likelihood of adverse events may improve compliance.

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