



Assessment of treatment with Intravesical alkalinized lidocaine and heparin in Painful bladder syndrome /Interstitial cystitis (PBS/IC)

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Abstract

Introduction: Painful bladder syndrome or Interstitial cystitis (IC) is characterized by an unpleasant sensation (pain, pressure, and discomfort) perceived to be related to the urinary bladder and presented as urgency, frequency, nocturia, dysuria of more than 6 weeks duration, in the absence of infection or other identifiable causes. This prospective study done in Patients with symptoms of IC to assess the immediate and sustained relief after a weekly instillation for three weeks of treatment with intravesical alkalinized lidocaine and heparin. by Pelvic pain and Urgency/Frequency Valid scale (PUF)

Method: All included patient were assessed and the PUF score is calculated by the questionnaire. With all aseptic precaution, solution of 40,000 U heparin +10mL, 2% Lidocaine and 10mL, 8.4% sodium bicarbonate was administered intravesically in patients and kept for half an hour then patient is allowed to urinate. the response to treatment was followed after one week and PUF score is calculated and same is repeated for 3 consecutive weeks. The percentage of improvement is calculated by the change in PUF score.

Observation: Total 20 patient (M;F -9:11) with mean PUF score is 23.70 shown significant decrease to 4.85($p < 0.001$) after first instillation. After every instillation, there is constant decrease in PUF score.

Conclusion: It can be concluded that this intravesical therapy has greater symptom relief of painful bladder syndrome who were failing medical therapy by antimuscuranic and alpha blocker for long time.

Keywords: Interstitial cystitis(IC); intravesical; alkalinized lidocaine; heparin.

Introduction

Over Active Bladder (OAB)/ Interstitial cystitis (IC)/ Painful Bladder Syndrome (PBS) is characterized by bladder pain associated with urgency, frequency, nocturia, dysuria and sterile urine. The diagnosis of this disease remains unclear and should be based on exclusion of other diseases. The possible etiologies are (a) Post-

infection autoimmune process (b) Mast cell activation induced by inflammation, toxins or stress (c) Urothelial dysfunction and increased permeability of the urothelium (d) Neurogenic inflammation.⁽¹⁾ Essentially, the diagnosis is usually based on clinical criteria and there are no definite diagnostic tests to confirm it. Validated questionnaires such as the Pelvic pain and

Urgency/Frequency scale (PUF) are often useful for identifying IC.⁽²⁾ There is currently no cure for IC, a chronic disease with relapses and remissions. Because the pathogenesis of IC remains unclear, the current goals of treatment are largely based on symptomatic relief.⁽¹⁾ Physical therapy like walking swimming and aerobics to restore normal pelvic floor muscle tone, may reduce pain. Pharmacological treatment is available as Oral and intravesical therapies. Usually oral medications are utilized first. Oral medication as pentose polysulphate sodium (elmiron), hydroxyzine hydrochloride, antidepressants and urinary analgesics are very useful treatment modalities.

Intravesical therapy offers high local drug concentration, avoids systemic side effects and eliminates the problem of low levels of urinary excretion of oral agents. There are many medicines available but currently, the most often used intravesical treatment is a cocktail of heparin or Elmiron with lidocaine and sodium bicarbonate. This cocktail relieves symptoms in 75 percent of patients with IC.⁽³⁾ Heparin is known to mimic the GAG layer structure, and therefore, it is rational to treat IC/PBS with intravesical heparin with the aim of replenishment of the defective GAG layer in the bladder.⁽³⁾

This study was done on this principal in Indian population to assess the immediate and sustained relief of the symptoms of Overactive bladder/painful bladder syndrome (PBS) by intravesical instillation of alkalized lidocaine and heparin and assessed the patient satisfaction level and acceptance

Method

The prospective study was done in department of surgery, tertiary center in last two year after approval from institute Ethics committee. Patients with symptom of pain in bladder, urgency, frequency and nocturia were taken who were full filling the following criteria. Patients with generalized pelvic pain, Voiding symptoms (frequency, urgency, nocturnal), dysparunia, premenstrual and menstrual exacerbation in

females with duration of more than 3-6 months and sterile urine, were included in study after taking the full informed consent.

Patients with positive urine culture, symptom less than 3 month, symptoms relived by oral medication any other pathology such as malignancy or mass and Prostatic enlargement were excluded from study.

All included patient were assessed for the symptoms. Basic information is taken and symptoms of urgency, frequency and nocturia are noted along with the duration of symptoms. Patient is investigated for the ultra-sonography of KUB area, urine culture and routine microscopy.

The PUF (pelvic pain and urgency frequency valid scale) score is calculated by the questionnaires. The score is noted where the higher scores indicating a greater likelihood of IC, particularly at scores of 8 –10 and above. Patients were informed about the procedure and written consent was taken.

With all aseptic precaution, solution of 40,000 U heparin +10mL, 2% Lidocaine and 10mL, 8.4% sodium bicarbonate was administered intravesically in patients with the help of feeding tube no. 10. Solution is kept intravesically for half an hour then feeding tube was removed and patient is allowed to urinate. Improvement of symptoms, the response to treatment was assessed after one week and PUF score is calculated to compare the improvement in symptoms. Instillations were done on weekly basis for three consecutive weeks. Patients were follow-up weekly and observed for symptoms urgency, frequency, nocturia, and PUF score is calculated every week. The percentage of improvement is calculated by the change in PUF score. Any adverse effect like headache, hematuria, bleeding, allergic symptoms were noted. All data is collected and master-chart is made and data is analyzed statically by Student T test.

Symptom relief was defined as 50% or greater symptom improvement. Failure cases in this study is defined as subjects whose response is less than 50% on PUF scale at the end of 3 instillations.

Observations and Results

20 patients were included in study. 9 patients were Male and 11 were female with maximum patients belong to 40 – 60 years age group. All patients were on some medications like Alpha -blocker and antimuscarinic for long time but not responded to medical therapy. Urgency was present in all patients. 65% patients had 11 – 20 times/day frequency and 5 –10 times/day nocturia. Mean PUF score before procedure was 23.70 which was significantly decreased to 4.85 ($p < 0.001$) after first instillation of intravesical solution. All 20 patient have a significant

improvement in PUF score i.e. 80.10% at first week of instillation. It was observed that after every instillation, there is constant decrease in PUF score, which was maximum after 1st instillation. After 2nd and 3rd instillation, PUF score was decrease to 2.80 and 2.65 respectively. (Table -1)

Urgency and frequency was relieved immediately with 1st instillation and more significantly. Maximum relief of symptoms was seen after 1st dose and after 2nd and 3rd dose still improvement is seen in symptoms.

Table No. 1 PUF Score and P Value

	PUF score [INITIAL]	1st PUFscore	2 week puf score	3 week puf score
Mean	23.70	4.85	2.80	2.65
Std. Deviation	1.34	1.46	0.83	0.93
P value [compared to initial PUF]		<0.001	<0.001	<0.001

Discussion

Interstitial cystitis/PBS has undergone a major conceptual evolution. Previously consider a rare disorder known to be a chronic severely debilitating disease of urinary bladder. This is an important diagnosis which should be kept in mind for all patients presenting with pelvic pain and urinary symptoms.⁽⁴⁾ This condition is a social problem as it affects quality of life of patient affected by it.

Whenever treating a BPS/IC patient, realistic expectations should be kept in mind. Currently, there is no curative treatment, and so the primary goal remains an improvement in the patient's quality of life. Furthermore, even within the available treatment options, valid studies are scarce.⁽⁵⁾

Women make up 90 percent of patients with interstitial cystitis (IC), while men comprise the remaining 10%⁽⁴⁾. It is most prevalent in the fourth and fifth decades of life. The exact prevalence of IC in India is unknown.⁽²⁾ It was found in this study that twelve patients out of 20 were in age group of 40 – 60 years with slight female predominance.

This is a disease of unknown etiology. It involve chronic neurogenic inflammation, primary afferent nerve hyperactivity, and central sensitization, which interact to perpetuate pain. Another common theory behind this disease is a defect in the glycosaminoglycan component of the mucin layer that covers and protects the bladder's urothelium. In the absence of this layer irritative substances in the urine may leak through the urothelium, causing inflammation, tissue irritation and injury, mast cell degranulation and sensory nerve depolarization, which result in the urinary urgency, frequency, and pain of IC. Other factors such as allergy, autoimmunity and infections have also been hypothesized to play a role in the disease process. preemptive application of a GAG analog, GM-0111, provided varying degrees of protection against bladder insult in a mice model, suggesting that GAG molecules might prevent the development of cystitis by blocking apoptosis and the concurrent release of adenosine triphosphate (ATP) from the urothelium.⁽⁶⁾

Heparin is known to mimic the GAG layer structure, and therefore, it is rational to treat IC/PBS with intravesical heparin with the aim of

replenishment of the defective GAG layer in the bladder.⁴

Symptom relief lasted beyond the duration of the local anesthetic activity of lidocaine, suggesting the solution suppresses neurologic upregulation.⁽³⁾

Parsons et al used this principle and instilled 40000 U heparin with 3 ml 8.4% sodium bicarbonate and lidocaine in different concentrations for intravesical treatment three times per week for 2 weeks and found significant immediate symptom relief after a single treatment (75% and 94%). In our study we found 80 % symptoms relief after one week 88% and 89.10% after 2nd (two week) and 3rd instillation (three week) respectively the immediate relief in pain and urgency with In 4 hour with weekly intervals⁽³⁾

Mean PUF score was improved from 23.70 to 4.85 (p value <0.001) after one week in our study. There was a symptom relief of urgency and pain was found nocturia is relieved by 75 %. After 2nd instillation 88.45 % symptoms relief with mean PUF score 2.80 (standard deviation 0.83 p value <0.001) and after third instillation 89.10% improvement in symptom with mean PUF score is 2.65(standard deviation 0.93 p value <0.001).

In our study shows significant improvement in systems which is comparable with previous study. Kuo⁽¹⁾ treated 40 IC patients with intravesical heparin 25000 IU retained for 2 hours, twice per week for 3 months. The symptom scores of 29 (72.5%) patients improved by >50%. Although there is no consensus on the dose, therapeutic frequency or the treatment duration in intravesical heparin therapy, it has been suggested that intravesical heparin therapy should start at a higher frequency in the acute stage, with a reduced frequency in the sub acute stage. Treatment should continue intermittent in the maintenance stage, and should not stop, even in non responders.

In one double blind study,⁽⁷⁾ assessment of the immediate and sustained relief of the symptoms of interstitial cystitis/ painful bladder syndrome after a consecutive 5-day course of treatment with intravesical alkalized lidocaine was done and it

was found that their overall bladder symptoms as moderately or markedly improved and the peak serum lidocaine concentration during the study was <2 microg/ml, and well below the toxic level (>5 microg/ml) establishing the safety of drug.

Raymond Rackley⁽⁸⁾, in his study had used Elmiron, and misoprostol (Cytotec), a synthetic prostaglandin E1 analog instead of heparin and found to be highly successful in otherwise resistant or difficult cases although it required frequent instillations

The difference between those and our study may be due to the environment factor and the dietary habits, age group of the patient .We are using heparin 25000 IU, sodabcarb 8.4% 10 ml and lidocaine 10 ml and Parson used heparin 40000 IU lidocaine with 3 ml of sodabcarb . In our study our frequency of instillation is once a week in their study they are used thrice a week for two week. In KUO study they are used heparin alone 25000IU for thrice a week. The symptom scores of 29 (72.5%) patients improved by >50%. In another study Nickel jcet al⁽⁷⁾ used a consecutive 5-day course of treatment with intravesical alkalized lidocaine.

In our study no serious side effect is there only two patient having a mild headache after the first instillation, which got relieved by simple analgesics. One patient having a hematuria after 1st dose which stopped spontaneously.

Conclusion

Intravesical solution made by combination of heparin 25000IU, lidocaine 8.4% with soda bicarbonate had a very good effect to treat Painful bladder syndrome /Overactive bladder syndrome .It has a significant symptoms relief of 89 % in PBS /OAB patients and it is safe as well . There is both immediate & short term sustained relief of symptoms.

It can be concluded that this intravesical therapy has greater symptom relief of painful bladder syndrome who were failing medical therapy by antimuscuranic and alpha blocker for long time.

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