SUCCESSFUL DOWNREGULATION OF BLADDER SENSORY NERVES WITH COMBINATION OF HEPARIN AND ALKALINIZED LIDOCAINE IN PATIENTS WITH INTERSTITIAL CYSTITIS

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ABSTRACT

Objectives. To test the efficacy of a new intravesical therapeutic solution in relieving urgency/frequency and pain in interstitial cystitis (IC).

Methods. A solution of 40,000 U heparin, 8 mL 1% lidocaine (80 mg; group 1) or 2% lidocaine (160 mg; group 2), and 3 mL 8.4% sodium bicarbonate was administered intravesically in patients with newly diagnosed IC with significant frequency, urgency, and pain. Using the Patient Overall Rating of Improvement of Symptoms, the response to treatment was evaluated within 20 minutes of instillation in all patients, after 24 to 48 hours in group 2, and after three treatments per week for 2 weeks in group 2 patients who elected to receive additional instillations. Significant symptom relief was defined as 50% or greater symptom improvement.

Results. After one instillation, 35 (75%) of 47 patients in group 1 (1% lidocaine) and 33 (94%) of 35 in group 2 (2% lidocaine) reported significant immediate symptom relief. The difference in the response rates was statistically significant (P <0.01). In group 2, 50% of the subjects experienced at least 4 hours of symptom relief from the single instillation, and 16 (80%) of 20 reported significant sustained symptom relief after 2 weeks of treatment.

Conclusions. Intravesical treatment with combined heparin and alkalinized lidocaine immediately reduced the pain and urgency of IC in most patients treated for newly diagnosed IC. Symptom relief lasted beyond the duration of the local anesthetic activity of lidocaine, suggesting the solution suppresses neurologic upregulation. In IC treatment, this new intravesical solution may be helpful in the interval before heparinoid therapy reaches its full effect.

Although heparinoid-based therapy (heparin; the oral agent pentosan polysulfate sodium) is an effective treatment for interstitial cystitis (IC), patients may require several months or more of therapy before they experience relief of pain and urgency/frequency. Heparinoids, which are believed to augment the dysfunctional epithelium that is present in many cases of the disease, take time to reach full effectiveness in reversing the disease process and thereby reducing symptoms. In addition, particularly in severe or long-standing cases of IC, significant upregulation of the sensory nerves in the bladder is present. Heparinoids allow natural downregulation of the nerves over time by gradually restoring the barrier function of the mucus and thus preventing further irritation by urinary constituents such as potassium. No currently available IC therapy achieves immediate symptom relief without destroying the nerve endings or using narcotics. Thus, an IC treatment that offers immediate relief of symptoms and operates directly to downregulate the bladder sensory nerves without any rebound effect continues to be needed.

Intravesical agents have been used for many years as adjuncts to oral treatment regimens or as second-line therapies for IC. One of the most widely used is heparin, which is effective in approximately 50% of patients treated. Heparin is a...
sulfated polysaccharide that is believed to augment the protective effect of the natural bladder surface mucus. Intravesical heparinoid agents alone, however, do not produce immediate and sustained relief of IC symptoms. As with the oral heparinoids, they take several months to produce symptom relief.

We sought to develop an intravesical therapy that would provide immediate symptom relief, as well as offer the potential of long-term relief of IC symptoms. We also wished this therapy to exert a direct effect in downregulating the sensory nerves of the bladder. To do so, we combined heparin with both lidocaine and sodium bicarbonate. Lidocaine, a local anesthetic, has seen limited use as an intravesical agent for short-term pain relief in IC. It has been shown, however, that lidocaine is not well absorbed through a lipid membrane unless it is alkaline-dized into a more lipid-soluble form. For this reason, our solution contained sufficient sodium bicarbonate to achieve a pH of greater than 8.0.

We conducted this study to test the hypothesis that instillation of this therapeutic solution could provide immediate relief of the pain and urinary urgency/frequency of IC. We also wished to determine the duration of relief from one instillation and to test whether sustained symptom relief could be obtained by chronic use of the intravesical therapeutic solution. To do so, we evaluated the effect of a single instillation and of a 2-week course of six instillations of the therapeutic solution on symptoms of pain and urgency in patients with newly diagnosed IC.

**MATERIAL AND METHODS**

The study subjects were University of California, San Diego, Medical Center Urology Clinic patients who were newly diagnosed with IC and had significant urgency, frequency, and pain associated with their bladder. The diagnosis of IC was established using the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases criteria, excepting the requirements for cystoscopy and urodynamic evaluation. All patients were required to have a score of at least 12 on the Pelvic Pain and Urgency/Frequency Patient Symptom Scale. The enrolled patients had received no IC therapy for at least 3 months before the study and had received no therapy other than the intravesical instillations during the study.

At the start of the study, each patient underwent intravesical instillation of a therapeutic solution composed of 40,000 U heparin, 8 mL of 1% lidocaine (80 mg; group 1), and 3 mL 8.4% sodium bicarbonate suspended in a volume of 15 mL total fluid. After 47 patients had been treated with one instillation of this solution, and no adverse events or side effects had developed, we decided to increase the amount of lidocaine in the solution. Subsequently, all subjects received this modified solution, which was identical to the original solution, except that it contained 8 mL of 2% lidocaine (160 mg; group 2).

All patients were evaluated for pain and urgency relief within 20 minutes of the single instillation. Group 2 patients had developed, we decided to increase the amount of lidocaine above 8 mL of 2% lidocaine (160 mg; group 2).

**RESULTS**

A total of 82 subjects were evaluated, 47 in group 1 and 35 in group 2. The mean patient age was 35 years (range 22 to 65).

After one instillation, significant immediate relief of both pain and urgency was obtained in 35 (75%) of 47 subjects who received the 1% lidocaine/heparin/sodium bicarbonate solution (group 1) and in 33 (94%) of 35 who received the 2% lidocaine/heparin/sodium bicarbonate solution (group 2). The difference in the response rates between groups 1 and 2 was statistically significant (P < 0.01; chi-square analysis).

Twenty-eight patients in group 2 were available for the evaluation of the duration of relief by telephone follow-up 24 to 48 hours after the single instillation. One half of these patients experienced...
at least 4 hours of symptom relief from the instillation (Fig. 2).

Twenty patients in group 2 agreed to receive a course of three instillations per week for 2 weeks. Of the 20 patients, 16 (80%) reported significant sustained relief of pain and urgency. In all 16 subjects, the symptom relief lasted for at least 48 hours after the last intravesical treatment.

**COMMENT**

The results support our hypothesis that an alkalinized solution of heparin and lidocaine is effective in controlling the acute symptoms of urgency/frequency and pain in patients who have IC. Most patients with IC treated with the intravesical therapeutic solution experienced immediate, dramatic relief of IC pain and urgency that lasted from 1 to 48 hours. A single instillation of the solution produced significant symptom relief in 94% of patients who received 160 mg lidocaine and in 75% of the patients who received 80 mg lidocaine.

As we have stated, the presence of sodium bicarbonate alkalinizes the therapeutic solution and greatly increases the absorption of the lidocaine. The 1% lidocaine solution should be tried first; if it does not produce symptom relief in the patient, the amount can be increased safely to 8 mL of 2% lidocaine.

Our data showed that one half of the patients experienced greater than 4 hours of symptom relief from the alkalinized lidocaine. Because a 4-hour period extends well beyond the duration of the anesthetic action of lidocaine through direct nerve activity, this result suggests that lidocaine does have a capacity to downregulate nerves past the duration of its anesthetic activity. Additional evidence for this downregulation is that after only six treatments, the patients had symptom relief for periods of at least 48 hours. Again, 48 hours is significantly longer than the actual period of anesthetic activity of lidocaine.

As the heparin aids in the restoration of the bladder epithelium, the lidocaine appears to hasten the process of neural downregulation. If this immediate downregulation of sensory nerves is taking place in the bladder, this treatment offers the potential for a faster, more successful remission even in patients who have severe IC. In the past, patients with long-standing disease have been given agents such as Pyridium, anticholinergics, tricyclic antidepressants, alpha-blocking agents, and narcotics to suppress symptoms of neurologic hyperactivity. Oral pentosan polysulfate sodium allows the bladder to heal, but does not directly downregulate the bladder sensory nerves.

The intravesical therapeutic solution appears to offer a way to achieve immediate anesthetic activity and a direct neural downregulating effect without the safety issues and side effects associated with the oral agents. If the alkalinized lidocaine does down-regulate the neural hyperactivity and neuronal “cross-talking,” it appears that a distinct advantage of lidocaine is that it achieves this effect without the rebound effect of the narcotics. Furthermore, unlike neurotoxins, lidocaine does not destroy the nerves. Neurotoxins potentially may afford immediate relief, but the nerves may then regenerate, with a “sprouting” effect that results in an increase in the absolute number of nerve endings and enhances the neural activity when the nerves eventually recover.

In our clinical practice, we now offer this intravesical therapeutic solution routinely to symptomatic patients in whom we suspect the presence of IC and for whom we have ruled out other definable causes of the symptoms. We have also found that administration of the therapeutic solution can be a diagnostic aid, as symptom relief identifies the bladder as the source of the patient’s symptom complex. In our experience, once the diagnosis of IC is established, the intravesical solution provides immediate symptom relief and makes it possible to achieve a good therapeutic outcome within a period of weeks.

This is the first time we have had the capacity to introduce a solution into the bladder that immediately reduces the pain and urgency of IC in most patients presenting to a urologist with new IC. Although other clinicians have reported the use of intravesical “cocktails” using bupivacaine and lidocaine, to our knowledge, this is the first report of the use of a solution of alkalinized lidocaine and a heparinoid compound. The therapeutic solution of alkalinized lidocaine and heparin appears to provide more effective immediate symptom relief than...
narcotics without the safety issues and side effects associated with the latter. Our results indicate this solution may be a helpful adjunct at the start of heparinoid therapy, when these agents have not reached their full therapeutic effect.

CONCLUSIONS

The intravesical therapeutic solution of heparin and alkalinized lidocaine provided both immediate and sustained relief of pain and urgency in our population of patients with newly diagnosed IC. Because it provides symptom relief for hours beyond the period of immediate anesthetic effect of the lidocaine, the solution appears to downregulate bladder sensory nerves past the actual anesthetic period and thus may accelerate the recovery of the bladder. The development of this solution may represent a significant advance both in the treatment of IC and in the understanding of the downregulation of sensory nerves. No other therapy has been shown to downregulate nerves without injuring the nerves or causing rebound or other side effects.

REFERENCES