Alkalinized Lidocaine and Heparin Provide Immediate Relief of Pain and Urgency in Patients with Interstitial Cystitis

C. Lowell Parsons, MD,* Paul Zupkas, PhD,* Jeffrey Proctor, MD,† James Koziol, PhD,‡ Amie Franklin, PhD,§ Dennis Giesing, PhD,§ Edward Davis, MD,§ Charles M. Lakin, MD,* Bruce S. Kahn, MD,** and William J. Garner, MD §

*Division of Urology, University of California San Diego, San Diego, CA, USA; †Georgia Urology, Cartersville, GA, USA; ‡Scripps Clinic and Research Foundation, La Jolla, CA, USA; §Urigen Pharmaceuticals, Walnut Creek, CA, USA; *Citrus Valley Urologic Medical Group, Glendora, CA, USA; **Department of Obstetrics and Gynecology, Scripps Clinic and Research Foundation, La Jolla, CA, USA

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ABSTRACT

Introduction. It has been reported in an open-label study that the combination of alkalinized lidocaine and heparin can immediately relieve the symptoms of urinary urgency, frequency, and pain associated with interstitial cystitis (IC). This combination has also been reported to relieve pain associated with sex in patients with IC.

Aim. The aim of this study was to corroborate these findings in a multicenter setting.

Methods. The study design was a multicenter prospective, double-blind, crossover, placebo-controlled trial. Each participant met all of the clinical National Institute of Diabetes and Digestive and Kidney Diseases criteria (excluding cystoscopy) for IC. Each patient received drug and control, in random order, within 48 hours of enrolling in the study.

Main Outcome Measures. The primary outcome measure was percent change in pain score (11-point analog pain scale) 12 hours after receiving the drug or control. Secondary measures were the global assessment response (GAR) of symptoms and 12-hour average urgency reduction determined from 11-point urgency scales.

Results. Eighteen (18) patients completed the trial. The average reduction of pain over 12 hours was 21% for control and 42% for active drug ($P = 0.0363$). GAR was 13% for control and 50% for drug ($P = 0.0137$). Average urgency reduction was 13% for control and 35% for drug ($P = 0.0328$).


Key Words. Interstitial Cystitis; Lidocaine; Heparin; Urinary Incontinence; Urge; Dyspareunia

Introduction

Current and robust evidence supports the concept that the generation of bladder symptoms in interstitial cystitis (IC) is primarily due to a dysfunction in the transitional epithelium of the bladder [1,2]. The specialized umbrella cell, at the outer layer of its apical membrane, has mucus that is composed of both proteoglycans containing glycosaminoglycans (GAGs) and glycoproteins. Often, this mucus is referred to as the GAG layer. Scientific evidence has shown that in both rodents and humans, this mucus is responsible for regulating the permeability of the epithelium to small molecules and ions [3,4]. When the GAG layer is experimentally injured, solutes leak through it into the bladder wall. This dysfunctional permeability can be partially reversed with brief treatments of
intravesical heparin [3,4]. Patients with IC are reported to have a dysfunctional or leaky bladder mucous layer [2,5]. Subsequently it was shown that potassium is the urinary metabolite primarily responsible for generating bladder symptoms when the epithelium is dysfunctional [6,7]. Potassium levels in urine are high, 30–120 meq/L [8], and will readily diffuse into the bladder interstitium if the mucus is defective. Potassium levels of 8–10 meq/L can depolarize nerves and muscles. As a result, diffusion of potassium into the bladder wall can initiate a cascade of depolarization and generate symptoms of urgency, frequency, pain (resulting in dyspareunia) [9–11], and incontinence. Data confirming the role of potassium in IC are now very robust and are available in more than 35 publications in the global literature [2]. Heparin or heparinoids used intravesically can restore the bladder surface barrier function not only in normal bladders that have been chemically injured, but also bladders of patients with IC [2,6,9,12–20].

Lidocaine in its free base form is not water soluble. It is protonated with hydrochloric acid to yield lidocaine hydrochloride, which is soluble in water at pH less than 7.0. While the soluble molecule will not pass through lipid membranes, the free base form will. By alkalinization, one can partially convert lidocaine hydrochloride to its free base form, which will readily diffuse through the bladder epithelium and anesthetize sensory nerves [18,21]. The rationale for adding heparin to the alkalinized lidocaine was to coat the bladder wall with the heparin and to potentially increase lidocaine efficacy by blocking potassium diffusion into the bladder wall that could provoke bladder sensory nerves [6]. For this reason, an open-label study was conducted with: (i) heparin and 80 mg alkalinized lidocaine; and (ii) heparin and 160 mg alkalinized lidocaine. The higher dose of lidocaine achieved better results: the median duration of symptom relief was 7–9 hours [20], and 94% of patients reported significant improvement with the treatment; this symptom relief is better than that reported for alkalinized lidocaine only [22]. These results suggested that this combination “downregulated” the sensory nerves.

**Aims**

To verify these observations, a multisite, double-blind, placebo-controlled trial was conducted to determine the efficacy of combined alkalinized lidocaine and heparin in relieving the symptoms of IC patients.

**Methods**

**Study Design**

This study was conducted at four sites in the United States and was a randomized, double-blind, placebo-controlled, crossover trial. All subjects received both drug and control (control was the excipient, sodium bicarbonate) in a blinded and random order. The blind was provided by the statistician for all treatments such that no site knew what treatment was being given. The power estimate calculated by the statistician was at the 95% level and was based on results of a pilot study on 30 patients that received both drug and control; the estimated required number of subjects was 40. The study was designed to be a per protocol analysis, and any subject that was a protocol violation or who did not complete the full crossover was not included in the final analysis. Each site obtained investigational review board approval.

**Subjects**

IC patients who enrolled in the study met all of the clinical criteria of the National Institute of Diabetes and Digestive and Kidney Diseases, with the exception that cystoscopy under anesthesia was not required [23]. In addition, they had to have a score of at least 15 on the Pelvic Pain and Urgency/Frequency patient symptom scale [24]. Patients taking tricyclic antidepressants, neurontin or narcotics were excluded. Patients taking any other medications had to have been on them for a minimum of 3 months. All subjects filled out an 11-point analog scale (0–10) for both bladder pain and urgency. On the day of the first treatment, patients were required to have a minimum score of 5/10 for both pain and urgency. For the second treatment, they were required to have a pain and urgency score of at least 4/10 for both pain and urgency within a 48-hour time frame; if they did not meet this criterion they did not receive a second treatment. Before each treatment, urinalysis was performed, and the results had to be negative for red and white blood cells and bacteria. The participants were not allowed any new medications during the trial.

**Study Medications**

Blinded kits containing the medications or control were supplied to each site’s pharmacy. Active drug consisted of a combination of 50,000 units of heparin (Baxter), 200 mg lidocaine hydrochloride (Hospira), and 420 mg sodium bicarbonate in 15 mL of water. Control consisted of 420 mg
sodium bicarbonate in 15 mL of water. For all catheterizations, a hydrophilic LoFric 10 French catheter was used to minimize urethral trauma.

Protocol
After signing a consent form, each subject was screened. Those who met the entry criteria and on the day of the first treatment had a minimum of 5/10 pain and urgency on the analog scales and a negative urine analysis received the first treatment. The solution was instilled into the bladder via catheter. It was left indwelling for 30 minutes and then drained from the bladder. A blood sample was obtained before treatment and 1 hour after to determine lidocaine level, activated partial thromboplastin time (aPTT), and prothrombin time (PT). Every 2 hours, for up to 24 hours, the subject filled out a diary recording their analog scale for pain and urgency. However, the 12-hour end point was selected as the primary outcome measure. At 1 hour, participants filled out a global assessment response (GAR) six-point questionnaire [25] that rated their overall symptoms as: (i) worse; (ii) 0% better; (iii) 25% better; (iv) 50% better; (v) 75% better; or (vi) 100% better. This questionnaire is also known as the patient overall rating of improvement in symptoms (PORIS) scale. A score of 4 (50% better) was considered to indicate improved symptoms. The scale was balanced: three responses were considered negative (worse, 0% better, and 25% better), and three responses were considered positive (50%, 75%, and 100% better). At 24 hours, the subjects were screened again with the analog scales for pain and urgency. If they had scores for both pain and urgency of at least 4/10, they received the second solution; if not, they were terminated from the study.

Statistical Analysis
Paired student’s t-test and Fisher’s exact test were used to compare the control and active drug groups (Table 1).

Main Outcome Measures
The primary outcome measure was the average percent change in pain and the secondary outcome measures were the GAR, the average percent change in urgency, and the average percent change in pain plus urgency.

Results
The study was intended to include 40 subjects, but it had to be terminated early because the Food and Drug Administration (FDA) suddenly and unexpectedly recalled the heparin used in the trial because of possible contamination. Twenty-eight subjects were enrolled in the study. Two, initially receiving placebo, withdrew, one because of an ear infection and the other because of pain associated with the procedure. Three subjects, initially receiving placebo, did not complete the trial. Five subjects who did complete the trial had protocol violations: three initially received placebo and two initially received active drugs. Eighteen subjects completed the trial with no protocol violations. The primary end point of average percentage of pain reduction over 12 hours was 42% for the drug and 21% for control ($P = 0.036$). The global assessment of symptoms also showed significant improvement of symptoms after treatment with drug vs. control: 50% vs. 13% ($P = 0.013$), respec-

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Table 1: Overall efficacy results

<table>
<thead>
<tr>
<th>End point</th>
<th>Treatment</th>
<th>Control arm</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: average percent change in pain (to 12 hours ($\pm$SD))</td>
<td>Active drug arm N = 18 % (SEM) 42 ($\pm/-7$)</td>
<td>Control arm N = 18 % (SEM) 21 ($\pm/-7$)</td>
<td>0.036*</td>
</tr>
<tr>
<td>Secondary</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAR Q3 $\geq$ 50% overall improvement</td>
<td>50%</td>
<td>13%</td>
<td>0.013†</td>
</tr>
<tr>
<td>Average percent change – pain + urge (0–12 hours) (SD)</td>
<td>38 ($\pm/-7$)</td>
<td>17 ($\pm/-7$)</td>
<td>0.0318*</td>
</tr>
<tr>
<td>Average percent change – urge (0–12 hours) (SD)</td>
<td>35 ($\pm/-7$)</td>
<td>13 ($\pm/-7$)</td>
<td>0.0328*</td>
</tr>
</tbody>
</table>

As can be seen when the patients were on active drug, they showed significant improvement vs. when they were on the control for both the primary end point (pain) as well as the secondary end points

*Student’s paired t-test
†Fisher’s exact test
GAR = global assessment response, SEM = standard error of the mean
There were no serious adverse events attributed to drug. Minor events were equal in the control and drug groups at about 30% for both. The most common side effects were headache, dizziness, lightheadedness, and bladder or urethral pain. Bladder pain or burning was 7% and 13% in the control and drug groups, respectively. Only 2 subjects (one during control instillation and one during drug instillation) reported bladder or urethral pain associated with catheterization. This low frequency of discomfort is attributed to using a hydrophilic-coated catheter.

Serum levels of lidocaine ranged from 0.24 to 2.0 mg/mL, with an average of 0.51 mg/mL. Neither the aPTT nor the PT was altered in any subject.

Discussion

Multicenter, double-blind trials for IC have met with limited success. Separation between active drug and a control group has been seen for only two medications [18,25]. Others have not worked or have shown trends that were not statistically significant [17,26]. At least four other clinical multicenter, double-blind studies have been conducted by commercial enterprises or collaborative trial groups. Results have not been published in the literature; however, some have been posted on the U.S. government website for clinical trials. All results posted on the website are negative. The current clinical trial was conducted to corroborate the open-label study that employed heparin and alkalinized lidocaine to treat patients with IC [22]. This study was a prospective, multicenter, double-blind, placebo-controlled clinical trial involving a complete crossover of active drug and control for all subjects. The study met statistically significant separation of drug vs. control for all of the end points. Most clinical trials on IC employ the GAR or PORIS as the primary outcome measure [25]. The six-point GAR used for this trial is the only one in the literature that has been statistically validated for IC [23]. Other seven-point scales have been reported but never validated, but the two are essentially the same in that both require a minimum of 50% overall improvement to be considered a successful outcome. The GAR used in this trial allows for comparison with other trials that also used the GAR. Heparin and alkalinized lidocaine demonstrated the best separation of drug vs. control yet seen in an IC study, with significant improvement in 50% vs. 13% of patients, respectively (P = 0.0137). The primary end point, the average percent change in pain over 12 hours, was 21% for control and 42% for drug (P = 0.036). Results were similar for the secondary end point of average percent change in urgency: 13% for control and 35% for drug (P = 0.0328). This combination of medications can effectively reduce acute pain and urgency from IC. A solitary dose of medication persistently reduced pain over a 12-hour period (Figure 1). This combination has also been reported to relieve dyspareunia for IC patients [9].

There were no significant adverse events in any subject. Minor adverse events were equal for both drug and control. Only two subjects (one receiving the control and one receiving the drug) reported urethral or bladder pain associated with the catheterization process. This low level of discomfort is attributed to using a hydrophilic-coated catheter.

Serum levels of lidocaine ranged from 0.24 to 2.0 μg/mL, with an average of 0.51 μg/mL. Neither the aPTT nor the PT was altered in any subject.

Figure 1

Individual time points from 0–12 hours of percent change in pain. Graph of individual time points that make up the primary end point demonstrates maintenance in improvement in percent change in pain over the 12-hour period. As can be seen when the patients were on drug, they did significantly better than when on the control (P = 0.036). URG101 = drug (Urigen); PLA Ave = placebo.
to anesthetize the bladder nerves. The results of this study support this concept and the notion that this combination of drugs downregulates the bladder sensory nerves for up to 12 hours.

A strength of this study is the crossover design, which allowed each subject to be their own control. A weakness is that the study goal was to complete 40 patients, but unfortunately, it had to be terminated early because of the FDA recall of heparin, including the source of heparin used for this study. The combination of drugs for this study was stable, and the lidocaine did not precipitate. The heparin source is critical because when the three compounds are combined, the solution may not be stable, resulting in the precipitation of the lidocaine. Nonetheless, data for all the end points achieved statistical significance and demonstrated the superior activity of drug over placebo.

There are many caveats for utilizing bladder instillation “cocktails” with anesthetic agents that are publicized with little or no supporting evidence. Placing a medication into the bladder is unlikely to result in its absorption; scientific data need to be obtained to demonstrate this activity. If lidocaine is employed, then it must be alkalinized and not precipitated to absorb into the bladder wall. When the lidocaine precipitates, efficacy is seriously impaired. Consequently, if one prepares one’s own recipe from commercially available medications, the lidocaine stability needs to be determined. These products prepared for intravenous use are usually not compatible. Additionally, if components (e.g., steroid) other than what is reported herein are added, the solution’s effectiveness could be seriously reduced if the pH is not correspondingly adjusted and the lidocaine stability is not known. Both pH and lidocaine stability must always be determined after the components are mixed. Other local anesthetic agents (e.g., marcaine, also known as bupivacaine) poorly absorb through lipid membranes regardless of pH, and cocktails employing them are less effective.

Conclusions

In large part, the study of heparin plus lidocaine was undertaken to develop a medical therapy that could immediately relieve symptoms of IC, because there are such limited options for these patients. The data indicate that these combined medications will effectively and immediately relieve both bladder pain and urgency for up to 12 or more hours and provide significant immediate relief for IC patients.