Heparin and alkalinized lidocaine versus alkalinized lidocaine for treatment of interstitial cystitis symptoms

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Introduction: *Interstitial cystitis (IC), sometimes referred to as IC/bladder pain syndrome, is a substantial health care problem. Once considered a rare, orphan disease, it is now believed to be relatively common. This pilot study was undertaken to determine if the combination of heparin and alkalinized lidocaine (heparin-lidocaine) was more efficacious than alkalinized lidocaine at relieving pain and urgency symptoms associated with IC and also capable of yielding higher lidocaine absorption.*

Materials and methods: *A single blind study was conducted on 14 IC patients with a heparin-lidocaine combination versus alkalinized lidocaine instilled intravesically. In a separate study serum lidocaine levels for heparin-alkalinized lidocaine combination versus USP lidocaine only were determined by high performance liquid chromatography.*

Results: *Alkalinized lidocaine and heparin have been reported to provide relief from pain and urgency symptoms associated with IC. The heparin-lidocaine combination significantly reduced the % of bladder pain (38% versus 13%, p = 0.029) and urgency (42% versus 8% p = 0.003) compared to lidocaine. In addition the GAR was significantly better for the heparin-lidocaine combination at both 1 hr % improved (77% versus 50%, p = 0.04) and 24 hrs (57% versus 23%, p = 0.002) after study drug treatment. Serum lidocaine levels for the heparin-lidocaine combination were significantly higher compared to USP lidocaine (unalkalinized). The mean ± SEM was 0.45 ± 0.09 μg/mL and 0.20 ± 0.05 μg/mL, respectively (p = 0.019).*

Conclusions: *In this pilot study the heparin-lidocaine combination results in significantly better relief of IC symptoms compared to alkalinized lidocaine and the combination yields higher lidocaine absorption than USP lidocaine.*

Key Words: interstitial cystitis, lidocaine, heparin, bladder instillation

Introduction

Interstitial cystitis (IC) is a substantial health care problem, sometimes referred to as IC/bladder pain syndrome, but not all patients with IC have pain.[1] Once considered a rare, orphan disease, it is now believed to be relatively common, with at least 6.5% of women and 4.2% of men afflicted when households were screened for symptoms by the RAND Corporation.[2,3] Prevalence estimates range up to 25% when groups of females are screened for symptoms.[4]

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Bladder epithelium is relatively impermeable to small molecules, primarily due to the mucus on the surface of the umbrella cell,[1] which is composed of proteoglycans containing glycosaminoglycans (GAGs) and glycoproteins, also known as the "GAG layer." Acute chemical injury to this mucus barrier in rodents and humans results in an epithelial leak of urea and potassium from urine into the bladder interstitium that can be reversed with sulfated polysaccharides such as heparin or pentosanpolysulfate (PPS).[1] Bladder symptoms in syndromes such as IC and overactive bladder have been shown to be associated with a urothelial leak that allows urinary potassium to leak into the bladder wall and generate symptoms.[1] Heparin and PPS have been shown clinically in humans to effectively treat the symptoms of IC[5,6] and restore the barrier effect.[7]

Lidocaine is a free base that is not soluble in water. To make it soluble it is protonated with hydrochloric acid to form lidocaine hydrochloride and is available for human use in an aqueous solution with a pH of about 6.1-6.5. At this pH there is some equilibration, but most of the lidocaine exists as the hydrochloride with a minimal amount as the free base. If the pH of the solution is raised above 7.0, more of the free base form exists but if the pH is raised too high then the lidocaine precipitates. The free base form of lidocaine diffuses more readily across lipid membranes such as a nerve ending or the bladder urothelium.[8]

A combination of heparin plus alkalized lidocaine (heparin-lidocaine combination) has been reported to relieve the symptoms of patients with IC in both an open labeled and a multisite double blind study.[9,10] The rationale for combining heparin and alkalinized lidocaine to acutely relieve bladder symptoms is two-fold. First, buffering lidocaine to raise the solution pH above 7.0 to increase its absorption across the bladder epithelium and second, to take advantage of the beneficial effect of heparin in restoring the bladder permeability barrier.[1] The hypothesis was that the absorbed lidocaine would anesthetize the bladder nerves and heparin would coat the bladder epithelial and reduce the ability of potassium to diffuse into the bladder wall, resulting in prolonged activity of both drugs.

The current study was conducted to determine if a heparin-lidocaine combination was superior to alkalinized lidocaine alone at relieving symptoms in patients with IC. A second study was conducted whose purpose was to determine if the serum levels of lidocaine were higher when the combination drug was compared to USP lidocaine (unalkalinized).

Materials and methods

Study design

The study was conducted at two sites in North America, UC San Diego and Georgia Urology. It was a single blind complete crossover study with each subject receiving both study medications in random order on different days. Half of the patients randomly received the heparin/lidocaine first and half received the lidocaine only first. The subjects were blinded to the solutions they received but the attending clinicians were not. An a priori power calculation of the sample size was not applicable as this is a pilot study.

Patients

Patients with IC had normal urine analyses showing no infection, a minimum of 15 on the PUF questionnaire,[11] and a minimum of 1 year of continuous bladder symptoms consisting of frequency (10 or more voids in 24 hrs), urgency, and pelvic pain (not due to a gynecologic cause). They met all of the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases clinical criteria for IC (cystoscopy not required).[12] This study was reviewed and approved by the UC San Diego Human Research Protections Program Institutional Review Board with an informed consent waiver. Before receiving medication, each subject emptied their bladder and 15 mins later filled out 11 point visual analog scales (VAS) for both pain and urgency. If they scored a minimum of 5 on the pain scale they were eligible to receive study medication; no minimum was required for urgency. Patients received no pain medications during the trial period and could not have had any bladder instillations for the past 7 days.

Medications

The heparin-lidocaine combination consisted of a 15 mL solution containing 50,000 units of heparin (Baxter, Deerfield, IL, ISA) and 200 mg of USP lidocaine hydrochloride (Hospira Inc., Lake Forest, IL, USA) buffered to pH 7.2 made from powder forms of both drugs at licensed compounding pharmacies (PJs Prescription Shoppe, San Diego, CA, USA and Innovative Compounding Pharmacy, Atlanta, GA, USA). This medication was tested by the pharmacies for stability through APL Laboratory (Oklahoma City, OK, USA) and verified that both lidocaine and heparin were stable for a minimum of 6 months. The lidocaine solution was 10 mL of USP lidocaine 2% (200 mg) plus 3 mL of USP 8.4% sodium bicarbonate plus 2 mL sterile water (pH 7.2) prepared at the site just prior to drug administration.

Serum lidocaine study

This was a separate study from the efficacy study done on different patients and at another time. It was done primarily to determine if alkalinizing lidocaine increased its absorption.

This study was conducted with 25 mL of a heparin-lidocaine solution containing 50,000 units of heparin and 333 mg of USP lidocaine buffered to a pH of 7.2 (PJ's Prescription Shoppe, San Diego, CA, USA). This solution was tested at APL Laboratory for stability and both heparin and lidocaine were stable for at least 6 months. For the lidocaine a 25 mL of solution containing 333 mg of USP lidocaine hydrochloride (Hospira Inc.) in sterile water, pH approximately 6.5 was prepared at the site just prior to administration of the medication.

Procedure for efficacy of heparin-lidocaine combination

The patients were first asked to empty their bladder and 15 mins later they filled out 11 point VAS for pain (needed a minimum of 5) and urgency. Their bladder urine volumes were determined if < 50 mL they received study drug. A lubricious coated Coloplast Speedi Catheter (8, 10 or 12 Fr) was placed into the empty bladder and the medication was inserted. They were randomly assigned to receive either the heparin-lidocaine combination or alkalinized lidocaine on the first day of treatment. Patients held the study drug for 45 mins and then voided it out. They filled out pain and urgency VAS at 1, 3, 5 and 24 hrs after treatment. At 1 hr and 24 hrs, participants filled out a global assessment response (GAR/PORIS) six-point questionnaire[6] that rated their overall symptoms as: (1) worse; (2) 0% better; (3) 25% better; (4) 50% better; (5) 75% better; or (6) 100% better. 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) and this questionnaire has previously been statistically validated as an outcome measure for IC studies.[6] At 24 to 48 hrs after receiving the first medication they were crossed over to the medication they did not receive and the procedure was performed in the same manner. For the second treatment they were required to also have a minimum pain of 5 on the VAS.

Statistical considerations

The trial design is that of a two-treatment, two-period crossover trial. In the first period, seven patients were randomly assigned to alkalinized lidocaine, the other seven patients to the heparin-lidocaine combination; all patients were then observed for 24 hrs post treatment. After a washout period, the experimental procedure was repeated in period 2, but with a crossover in treatment assignment: the seven patients assigned to alkalinized lidocaine in period 1 received the heparin-lidocaine combination in period 2, and the seven patients assigned to the heparin-lidocaine combination in period 1 received alkalinized lidocaine in period 2.

The primary outcome measure was the relative % pain drop from 0 to 24 hrs using Area Under the Curve (AUC). The AUC was determined on a per patient basis by means of the trapezoid rule, using the baseline time 0 hr followed by 1 hr, 3 hrs, 5 hrs, and 24 hrs pain scores. The AUCs were normalized by baseline pain scores to yield relative pain AUC values. The method of analysis for the primary outcome measure is that of Chow and Liu,[13] this being a standard analysis for 2 x 2 crossover trials. Our principal interest is in a treatment effect (i.e., difference between relative AUC scores on alkalinized lidocaine compared to heparin-lidocaine combination), but we also assess both period and carryover effects. All 14 patients were included in this analysis, under the intent to treat paradigm.

The same analysis was undertaken with the secondary outcome measure, relative % urgency drop from 0 to 24 hrs. Four patients experienced no urgency either at baseline or throughout the study, hence analysis of urgency was based on the experience of 10 patients.

The crossover analyses were undertaken in NCSS Version 7.1.21 (NCSS LLC, Kaysville, UT, USA). In subsequent analyses, the actual % pain and % urgency differences between alkalinized lidocaine and heparin-lidocaine combination for the distinct time points 1 hr, 3 hrs, 5 hrs and 24 hrs after treatment were compared with paired Student's t tests (since there is a natural pairing of patient treatment responses in this crossover trial).

Serum lidocaine determination

Patients with IC using the same criteria as listed above with a minimum score of 5/10 for pain on the visual analog scale 15 mins after voiding had their bladder urine volumes determined. If volume < 50 mL they received study medication via catheterization into the bladder in the same manner as noted above. Blood was drawn for lidocaine levels 45 minutes after drug administration. This was a separate study from the efficacy study conducted at a different time on symptomatic patients.

Lidocaine levels were determined by C_{18} reverse phase high performance liquid chromatography with UV detection as described previously.[14] For quantification, a calibration curve of lidocaine hydrochloride (USP standard, Hospira Inc.) in the range of 0.01-1 µg was used. The means for each group were compared with the Student's t test.

Results

In the heparin- lidocaine combination versus alkalinized lidocaine treatment study there were 3 males and 11 females and all subjects completed the trial, there were no dropouts. The age range was 31 to 68 years with a median age of 48. To assess the primary endpoint, we undertook a standard analysis[13] for 2 x 2 crossover trials. We failed to reject the hypothesis of equal period effects ($t_{12} = 1.03$, $p = 0.33$), and similarly the hypothesis of equal carryover effects ($t_{12} = -1.71$, $p = 0.11$). On the other hand, the two treatment means (heparin-lidocaine combination and alkalinized lidocaine) were significantly different ($t_{12} = 2.48$, $p = 0.029$). The mean ±

TABLE 1. **Relative % pain drop and relative % urgency drop**

Group	n	Relative % pain drop	p value	n*	Relative % urgency drop	p value
Heparin-lidocaine	14	38%	0.029	10	42%	0.003
Alkalinized lidocaine	14	13%		10	8%	

*not all subjects had urgency

SEM hourly pain score relative to baseline with heparin-lidocaine combination was 0.62 ± 0.06 (a 38% drop) compared to 0.87 ± 0.10 (a 13% drop) with alkalinized lidocaine, Table 1.

The secondary endpoint of relative change in urgency over 24 hrs was similarly analyzed. As with pain, we found no evidence of either period or carryover effects ($t_8 = 0.45$, $p = 0.66$ and $t_8 = 0.02$, $p = 0.99$, respectively) but again the two treatment means (heparin-lidocaine combination and alkalinized lidocaine) were significantly different ($t_8 = 4.22$, $p = 0.003$). The mean ± SEM for hourly urgency score relative to baseline with heparin-lidocaine combination was 0.58 ± 0.07 (a 42% drop) compared to alkalinized lidocaine, which was 0.92 ± 0.10 (an 8% drop), Table 1.

The percent relative pain and percent urgency reductions at 1 hr, 3 hrs, 5 hrs and 24 hrs are listed in Table 2. A better response was seen at all times for the % drop in both pain and urgency in the heparin-lidocaine combination group versus alkalinized lidocaine group. The % urgency drop was also significantly better for patients receiving the heparin-lidocaine combination at all time points.

The results of the global assessment response of symptoms of the heparin-lidocaine combination treatment resulted in a significantly better improvement compared to alkalinized lidocaine alone at 1 hr and 24 hrs time point, Table 3.

The serum lidocaine study was conducted on female IC patients with an age range of 34 to 65 years.

TABLE 2. **Relative % pain and urgency reduction**

A

Group	n	% pain drop 1 hr	p value*	% pain drop 3 hrs	p value*	% pain drop 5 hrs	p value*	% pain drop 24 hrs	p value*
Heparin-lidocaine	14	52%	0.06	55%	0.015	40%	0.06	23%	0.01
Alkalinized lidocaine	14	30%		20%		20%		9%	

B

Group	n**	% urg drop 1 hr	p value*	% urg drop 3 hrs	p value*	% urg drop 5 hrs	p value*	% urg drop 24 hrs	p value*
Heparin-lidocaine	10	49%	0.048	46%	0.047	49%	0.005	28%	0.012
Alkalinized lidocaine	10	30%		16%		11%		11%	

*paired Student's t test
**not all subjects had urgency

TABLE 3. **Percent improved in global assessment response**

Group	n	(% improved GAR)* 1 hr	p value**	(% improved GAR)* 24 hrs	p value**
Heparin-lidocaine	14	77%	0.04	57%	0.002
Alkalinized lidocaine	14	50%		23%	

*defined as at least 50% overall improvement
**Chi-square test

TABLE 4. **Heparin-lidocaine combination compared to USP lidocaine**

Group	N	Serum lidocaine level (mean ± SEM)	Range	p value*
Heparin-lidocaine	11	0.45 ± 0.09 µg/mL	0.17-0.84 µg/mL	0.019
USP lidocaine	10	0.20 ± 0.05 µg/mL	0.04-0.51 µg/mL	

*compared two groups using the Student's T test

It showed a significant increase in the serum lidocaine level for the heparin-lidocaine combination compared to USP lidocaine. The mean ± SEM was 0.45 ± 0.09 µg/mL and 0.20 ± 0.05 µg/mL, respectively (p = 0.019, Table 4). The highest lidocaine level achieved was 0.84 µg/mL, well below 6.0 µg/mL associated with symptoms of toxicity.

Discussion

There are two studies on using heparin plus alkalinized lidocaine that report significant efficacy at relieving IC symptoms.[9,10] There were two multicenter double blind trials reported, one that used alkalinized lidocaine alone[15] and another that used a heparin-lidocaine combination.[10] The efficacy was two-fold higher for the combination versus alkalinized lidocaine alone on the reported results of the global assessment response scale but one cannot readily compare the differences between these two separate trials. This study was conducted to determine if the combination of heparin plus alkalinized lidocaine was more effective at relieving symptoms of IC than alkalinized lidocaine alone.

For both the pre-specified primary and secondary outcome measures, AUC for % pain and % urgency respectively, the combination of drugs resulted in a significant improvement over alkalinized lidocaine alone, Table 1. Another secondary outcome measured the global assessment response was also significantly better in those receiving the combination of medications, Table 3. All of the outcomes evaluated in this study were in agreement in that the combination of drugs was better than the solitary one. These data support the rationale for combining the drugs, lidocaine to anesthetize the nerves and heparin to augment the bladder's defective permeability barrier seen in patients with IC. It also appears that the presence of the heparin is important to stabilize lidocaine solubility when it is alkalinized.

To support these results, serum lidocaine levels were measured to determine if a stable solution of heparin-lidocaine combination is better absorbed into the bladder wall than USP lidocaine alone. Serum levels of lidocaine were 2.25-fold higher with the heparin-lidocaine combination, Table 4. These findings are consistent with the data reported herein showing better clinical activity for heparin-lidocaine combination compared to lidocaine alone.

There are potential problems when utilizing bladder instillation "cocktails" with anesthetic agents that are publicized with little or no supporting evidence. Instilling a medication into the bladder does not necessarily result in its absorption; scientific data need to be obtained to demonstrate this activity. If lidocaine is employed, it must be alkalinized and not precipitated to effectively absorb into the bladder wall. When the lidocaine precipitates, efficacy is seriously impaired. Consequently, if one prepares a recipe from commercially available USP heparin and USP lidocaine, the lidocaine stability needs to be determined. These USP products prepared for intravenous use are usually not compatible when alkalinized and the lidocaine will precipitate. 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 be determined after the components are mixed.

To overcome these limitations for this study, the combination medication was made from heparin and lidocaine powder and the buffer carefully added to raise the pH of the solution as noted in the material and methods section.

Conclusions

This was a pilot study conducted to determine if a heparin-lidocaine combination is better than alkalinized lidocaine alone. A weakness of this study is that it was a single-blind, but nonetheless the data support the overall hypothesis of using the combination product for better efficacy. The results are promising, and could be validated and extended in a larger multicenter four arm study using

heparin, lidocaine, placebo and a heparin-lidocaine combination. In summary, a combination of heparin-lidocaine compared to alkalinized lidocaine was shown to give better relief of IC symptoms in patients with IC. The concept that alkalinizing lidocaine yields higher serum lidocaine levels was supported by the finding that the heparin-lidocaine combination resulted in higher serum lidocaine levels compared to USP lidocaine alone. □

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