Headaches are common, affecting approximately 20% of the population at some time in their lives. Seventeen percent of adult women and 6% of adult men experience a migraine headache each year. It is estimated that headache is the chief complaint of 2.7% of all emergency visits. At our institution it was the fourth most common complaint in 1997, surpassed only by chest pain, abdominal pain, and dyspnea. This is similar to national statistics. The majority of headaches seen in the emergency department (ED) are benign, falling into the migraine, tension, or mixed-type category.

Symptom relief is one of the goals of ED headache management. Many medications have been used, and there is no single-agent regimen with an acceptable side-effect profile that consistently prevents headaches or alleviates headache pain. Commonly used medications include opioids, opioid agonists/antagonists, ergot preparations, and antiepileptics either as single agents or in combination. Nonsteroidal and serotonin inhibitors are also frequently used. Prochlorperazine is commonly used as the first-line therapy in many EDs throughout the United States. However, many patients report intolerance to it. Therefore, the search for alternative medication continues.

Previous small studies reported that nasal lidocaine and cocaine decreased cluster and migraine headache symptoms rapidly, with their effects being seen between 15 seconds and 2 minutes. It is hypothesized that the mechanism for these agents is by local anesthesia with the blockage of neural transmission of the vidian nerve, the sphenopalatine ganglion (SPG), or the maxillary division of the trigeminal nerve. The other possible mechanism for cocaine is the sympathomimetic effect.

Kudrow et al. and Maizels et al. each report that approximately half of ambulatory patients with headache had pain relief within 5 minutes of
receiving nasal lidocaine alone.\textsuperscript{15,16} Kudrow et al.’s uncontrolled study selected migraine patients from a headache clinic and therefore may not be generalizable to an ED setting.\textsuperscript{15} Maizel et al.’s study was done in an urgent care setting and was a double-blind placebo-controlled study that included all patients with headache.\textsuperscript{16} Lidocaine produced statistically significant immediate pain relief, but the effect was short-lived, with 28\% of those who had pain relief from lidocaine requiring rescue medication.

This suggests that lidocaine may be effective for immediate pain relief, but that its best use may be in combination with other therapies that provide permanent relief. Prochlorperazine is an effective agent commonly used in EDs for headache management. Its onset of action intravenously is approximately 20 minutes.\textsuperscript{17} We undertook this randomized controlled clinical trial to evaluate the short-term effects of nasal lidocaine in headache in the ED setting. Specifically, we evaluated whether using intranasal lidocaine for initial treatment of headache would reduce pain levels at 5 minutes compared with the use of placebo. Secondarily, we investigated whether the combination of lidocaine and intravenous (IV) prochlorperazine improved patient outcomes over time compared with IV prochlorperazine alone. The rationale for our study was to improve patient outcomes by producing rapid relief of headache at 5 minutes with nasal lidocaine and to maintain relief for 30 minutes using IV prochlorperazine.

\section*{Methods}

\textbf{Study Design.} We performed a randomized, double-blind, placebo-controlled clinical trial. Written informed consent was obtained from all participants. The hospital’s institutional review board approved this study.

\textbf{Study Setting and Population.} Patients were enrolled from July 27, 1997, to November 11, 1997, while being treated in the ED at a two-campus community teaching adult hospital. The combined annual census is approximately 90,000 patients. Patients were enrolled at both campuses.

All patients presenting to the ED with cephalalgia were eligible for the study if they were between 18 and 50 years of age, were given the diagnosis of migraine as defined by the International Headache Society Ad Hoc Committee on Classification of Headaches, and were able to provide informed consent.\textsuperscript{18} Migraine in this classification system is defined as episodic, recurrent headache of a throbbing nature, associated with anorexia and often with nausea and vomiting. It may occur with or without aura. Patients were excluded if this was their first ED visit for headache, if they were pregnant or lactating, or if they had an oxygen saturation of less than 90\%, had trauma or seizure within 24 hours, or had evidence of fever, meningismus, or altered mental status. Patients with immediate use of analgesics (within 2 hours), a history of drug or alcohol abuse, and evidence of current drug or alcohol use were excluded. Patients who reported adverse effects, intolerance, or allergy to lidocaine, other local anesthetics, or phe-nothiazines were also excluded.

\textbf{Study Protocol.} Patients were examined, asked for written, informed consent, and enrolled by emergency medicine residents and faculty after initial evaluation. The hospital pharmacist packaged the active medications and placebos into identical kits following a computer-generated set of random numbers. Once enrolled the patient received the next numbered kit, which contained either pro-
chlorpromazine 10 mg IV and 2 mL of 4% lidocaine topical solution (lidocaine group) for nasal instillation or prochlorperazine 10 mg IV and 2 mL of saline for nasal instillation (placebo group).

Before receiving treatment, each patient was placed in a dimly lit room and had an IV catheter placed in his or her arm and received a normal saline infusion at 150 mL/hr. Demographic and symptomatic information, including gender, duration of headache, laterality, and whether the headache was typical of previous headaches, was obtained. Patients were asked whether this was one headache or separate episodes of the same headache, whether medications had been used within 48 hours, whether they had had previous ED visits for headache, and whether there were associated symptoms.

Attending physicians asked patients to grade their pain on a 10-cm horizontal visual analog scale (VAS). The left end of the scale was used as the zero point for complaints and measurements and had the words “no pain.” The right end of the scale was labeled “worst possible pain.” Patients were instructed to indicate their current pain severity with a single mark through the scale.

Nasal lidocaine or placebo was administered by a physician according to the method of Barre. Simultaneously, 10 mg of prochlorperazine was administered IV over 2 minutes. All physician staff members were trained in the Barre method using a video developed by one of the investigators (MB), and a review of the procedure was included with study packets. In the method of Barre, patients are asked to lie in a supine position with their necks extended 30–45 degrees. Their heads are turned toward the side of the headache. Drops (0.5 mL) were instilled into the nose toward the headache-side eye. Patients then sniffed and were asked to maintain their position for at least 30 seconds. The procedure was repeated at 2 minutes. This dose of nasal lidocaine was previously described.

If the patient reported bilateral headache, drops were placed initially on the side with most severe pain and repeated on the opposite side after 30 seconds. At 2 minutes, a repeat dose was given on the initial side of drug administration and in 30 seconds repeated on the opposite side.

Patients were asked to rate their pain on the VAS at 5, 10, 15, 20, and 30 minutes after the end of the administration of the drops. Blood pressure, pulse, and respirations were recorded every 15 minutes up to 30 minutes after the medication was given. Any patient believed to be experiencing dystonia or akathisia was treated with 25 mg of IV diphenhydramine. Akathisia was defined as perceived agitation or restlessness by the patient or by the treating physician. Thirty minutes after the patient received medication, the study ended and the treating physician was notified. The treating physician then assessed the patient and, if necessary, prescribed rescue medication. Use of rescue medication, side effects, and use of diphenhydramine were recorded. Investigators reviewed ED logs to track patients’ return to the ED within 24 hours and the number of missed patients. No follow-up was done at surrounding institutions.

Measurements. Our main outcome measure was pain relief at 5 minutes. A decrease of 50% or more of the initial pain score or an absolute pain score of 2.5 cm or less at 5 minutes was considered a successful outcome. This is the same endpoint used by Coppola et al.

Data Analysis. Descriptive information is presented as means and categorical data are presented as percentages, both with 95% confidence intervals. Statistical significance was assessed by using chi-square or Fisher’s exact test for categorical variables and Student’s t-test for continuous variables. All tests were two-tailed. Changes over time in VAS scores were compared using a repeated-measures analysis of variance. Data analysis was performed using BMDP statistical software (version 7, Berkeley, CA).

This study was designed expecting that 50% of patients in the lidocaine group would have successful pain relief at 5 minutes compared with 10% in the placebo group. This decrease in pain is similar to those of other headache studies reported in the literature. Forty-eight patients (24/group) were needed to demonstrate a statistically significant difference in pain scores (alpha = 0.05, power = 0.8).

RESULTS

Figure 1 shows the study’s trial profile. Three hundred sixty-three potentially eligible patients presented to the ED. Of the 180 who were screened, 109 (61%) were excluded for the following reasons: Seventy-one of 254 (28%) potentially eligible patients were approached and 49 (69%) patients gave informed consent and were enrolled in the study. Twenty-seven were randomly assigned to the lidocaine group and 22 to the placebo group. Included in the intention-to-treat analyses were two patients, one with questionable malfunction of the IV and drug administration and one who withdrew from the study after the 5-minute outcome (both from the placebo group).

The characteristics of the groups are shown in Table 1. There was no significant difference between the groups in regard to demographics, headache history, and symptoms. However, the patients in the lidocaine group were more likely to have...
TABLE 1. Characteristics of Headache Patients

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 22)</th>
<th>Lidocaine (n = 27)</th>
<th>% Difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex—male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 (13.6%)</td>
<td>4 (14.8%)</td>
<td>−1.2%</td>
<td>−20.8 to 18.4</td>
</tr>
<tr>
<td>Duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;4 hours</td>
<td>2 (9%)</td>
<td>5 (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 to &lt;12 hours</td>
<td>10 (45.4%)</td>
<td>8 (29.6%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 to 23 hours</td>
<td>4 (18.1%)</td>
<td>9 (33%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥24 hours</td>
<td>6 (27.2%)</td>
<td>5 (18.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unilateral pain</td>
<td>9 (40.9%)</td>
<td>14 (51.8%)</td>
<td>−10.9%</td>
<td>−38.8 to 16.9</td>
</tr>
<tr>
<td>Typical of previous headache</td>
<td>18 (81.8%)</td>
<td>23 (85.1%)</td>
<td>−3.4%</td>
<td>4.3 to 17.6</td>
</tr>
<tr>
<td>One episode</td>
<td>20 (90.9%)</td>
<td>20 (74.0%)</td>
<td>12.9%</td>
<td>−8.6 to 34.4</td>
</tr>
<tr>
<td>Associated symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>18 (81.8%)</td>
<td>22 (81.4%)</td>
<td>0.3%</td>
<td>−21.4 to 22.1</td>
</tr>
<tr>
<td>Photophobia</td>
<td>17 (77.2%)</td>
<td>22 (81.4%)</td>
<td>−4.2%</td>
<td>−27.0 to 18.6</td>
</tr>
<tr>
<td>Phonophobia</td>
<td>12 (54.5%)</td>
<td>14 (51.8%)</td>
<td>2.7%</td>
<td>−25.4 to 30.8</td>
</tr>
<tr>
<td>Previous ED visits</td>
<td>11 (50%)</td>
<td>18 (66.6%)</td>
<td>16.7%</td>
<td>−44.1 to 10.8</td>
</tr>
</tbody>
</table>

headaches that were unilateral, of shorter duration, and single rather than multiple episodes of the same headache.

Pain scores prior to medication were 8.4 (95% CI = 7.8 to 9.0) in the lidocaine group and 8.6 (95% CI = 8.0 to 9.2) in the placebo group (p = 0.75). At 5 minutes, two of 27 (7.4%; 95% CI = 0.8 to 24.3) of the lidocaine group and three of 22 (13.6%; 95% CI 2.8 to 3.49) of the placebo group had a successful outcome (Fisher’s exact p = 0.65). The absolute difference between groups showed a 6.2% (95% CI = −11.2 to 23.6) advantage for placebo. The average pain score at 5 minutes was 6.9 (95% CI = 5.9 to 7.8) in the lidocaine group and 7.0 (95% CI = 5.8 to 8.2) in the placebo group (p = 0.83). The decreases in pain intensity scores were similar for the two groups over 30 minutes (Fig. 2).

Fifteen people required rescue medications after 30 minutes, nine of 27 (33%, 95% CI = 16.5 to 54.0) from the lidocaine group and six of 22 (27%, 95% CI = 10.7 to 50.2) from the placebo group. Rescue medication was administered at the discretion of the attending physician and reflected the wide range of available choices.

There was no adverse reaction to the administration of nasal lidocaine. Physicians did administer diphenhydramine for akathisia in ten of 49 (20.4%, 95% CI = 10.2 to 34.3) patients, six of 27 (22.2%, 95% CI = 8.6 to 42.3) from the lidocaine group and four of 22 (18.2%, 95% CI = 5.1 to 40.3) from the placebo group cases (Fisher’s exact p = 0.10). No dystonic events were recorded.

Forty-five patients were asked whether they would be willing to use this method at home and 33 of the 45 (73.3%, 95% CI = 58.1 to 85.4) reported affirmative, 15 of 24 (62.5%, 95% CI = 40.6 to 81.2) in the lidocaine group and 18 of 21 (85.7%, 95% CI = 63.7 to 97.0) in the placebo group (p = 0.08). No patient (upper 95% CI = 9.4%) made a return visit to either campus for headache within 24 hours following the study.

**DISCUSSION**

Pain is a complex interaction between the central nervous system nerve endings and various neurotransmitters. Substances such as substance P, serotonin, bradykinin, histamine, and prostaglandins are all hypothesized to play a role in producing the pain stimulus. The exact pathogenesis of migraine headaches is unknown. Initially vascular changes were believed to be the cause of migraine headaches, but studies have not found blood flow velocities consistently correlate to headache symptoms or relief. More recently, others have explored other mechanisms for headaches. Neuronal changes may occur due to changes in ion homeostasis. For example, platelet hyperactivity and the release of nitric oxide can occur. Nitric oxide is released from platelets, endothelial cells, neurons, and macrophages. It diffuses across the cell membrane and activates intracellular guanylate cyclase, which is a catalyst for cyclic guanosine 3’,5’-monophosphate (cGMP) synthesis. This activated system then causes smooth muscle relaxation and vasodilation. Dopamine sensitivity has also been suggested as a mechanism for the cause of migraines and inhibition of its uptake and release has been identified as a possible mechanism for treatment.
Medications to relieve pain work at different receptors. Nonsteroids exert their analgesic effect by blocking the synthesis of prostaglandin and interfering with the pain-producing effects of bradykinin. Opiates work in the central nervous system at a specific receptor through an uncertain mechanism. They increase pain tolerance and decrease perception of pain. They may also have a sedating effect that enhances the decreased pain perception. The 5-hydroxytryptamine agonists block the specific receptor on intracranial blood vessels, causing cranial vessel constriction and inhibition of proinflammatory neuropeptide release. Calcium channel blockers may inhibit dopamine synthesis and uptake and therefore prevent headache.\textsuperscript{23,24}

Lidocaine provides its anesthetic effect as a sodium pump inhibitor. Used intranasally, lidocaine has been shown to provide various degrees of relief for migraine headache in certain specific populations.\textsuperscript{12-16} Most of the previous studies have been done on patients seen at headache clinics and are not randomized controlled trials. In 1996 a randomized controlled trial on ambulatory patients at an urgent care center reported a 49% successful treatment rate at 5 minutes using intranasal lidocaine.\textsuperscript{16}

Intranasal lidocaine has great appeal due to its ease of administration and lack of side effects. Its action occurs at the SPG/pterygopalatine ganglion, which resides just posterior and immediately above the posterior tip of the middle turbinate, beneath the nasal mucosa at a depth of 1 to 9 mm. This ganglion along with the internal carotid and cavernous sinus ganglion provide parasympathetic innervation of cerebral blood vessels. It also releases neuropeptides, which can induce headache. The rapid onset of intranasal lidocaine suggests interruption or blockage of nerves or neurons.

Our study’s goal was to improve patient outcome by producing rapid relief of headache at 5 minutes with nasal lidocaine, and then maintain pain relief using IV prochlorperazine, which has an onset of approximately 20 minutes.\textsuperscript{17} We did not observe success in immediate pain reduction. Prochlorperazine’s effect, as expected, was observed between 15 and 20 minutes after administration. The akathisia rates were similar in the two groups and consistent to those reported in other studies.\textsuperscript{8,9} The combination of lidocaine and IV prochlorperazine showed no benefit in improving patient outcomes over time compared with IV prochlorperazine alone.

We found that 7% of the patients receiving lidocaine and 14% receiving placebo reported successful pain reduction at 5 minutes. This differed markedly from the findings of Maizels and colleagues, who reported that 49% of patients receiving lidocaine and 25% of those receiving placebo had a successful outcome at 5 minutes. This discrepancy may be due to differences in headache severity. Our average scores at time zero were higher than Maizels et al.’s, as were the scores at 5 minutes. It may be that patients who had more severe pain were less likely to respond. Other differences could be due to the differences in a midwest population seen in an ED department compared with patients seen in a western health maintenance organization (HMO) urgent care sample. Our sample size was not large enough to test for the effect of pain severity. It also may be that HMO urgent care physicians’ access to medical records allowed them to be better able to select patients with pure migraine for whom lidocaine was effective in the short term.

Of interest, Maizels and colleagues’ placebo group had more than twice as much success as did our total patient group. This suggests that something other than differences in headache type and severity may explain the discrepancy between the study results. One logical explanation is the interaction between patients and clinicians or researchers, such as the possibility that presentation of the study or explanation of the study and its benefits may influence patients’ expectations of success. It is also possible that differences in the socioeconomic characteristics of the two populations from which the samples were drawn may affect responses to pain scales.

**LIMITATIONS AND FUTURE QUESTIONS**

There are some limitations to our study. Our inclusion criteria attempted to select patients with known migraine history as opposed to all patients with benign (tension or mixed-type) headache. It may be that these etiologies were represented despite our attempt to exclude them. Our analysis of
the original data from the National Hospital Ambulatory Medical Care Survey reported by McCaig showed that of the more than 2 million headache visits in EDs, approximately 42% were migraine. If we had had a “pure” migraine population, we may have had different results. This distinction of headache types is not always achievable in an ED setting. It should be noted that the patients in the lidocaine group were more likely to be shorter-duration, unilateral, and single episodes of headache. This characterizes patients with typical migraines who theoretically would be more likely to respond. Still, we observed no benefit.

We realize that physicians in a busy ED were not able to approach all patients. The patient characteristics and baseline pain scores suggest those randomized were representative of primary headache patients presenting to an ED. There was no report of patients returning with alternative diagnosis.

We did not question physicians about which intranasal treatment they thought they administered. The drugs were packaged in identical containers and were visibly indistinguishable.

Prochlorperazine may have modified lidocaine’s effect. However, it was administered to both groups. Its onset of action is reported to be 15–20 minutes. We did observe a small decrease in pain scores in both groups at 5 minutes. This decrease may be due to regression to the mean or an early effect of prochlorperazine. However, as both placebo and lidocaine groups had the same decrease in pain, it does appear that an independent effect of lidocaine was masked.

Future studies may want to look at the isolated effect of lidocaine in the ED setting; however, this study does not suggest that a favorable response would be found.

CONCLUSIONS

Previous work has suggested intranasal lidocaine to be beneficial for the treatment of migraine in established headache populations. We did not find this benefit. Our results do not support a recommendation for using intranasal lidocaine in the ED for immediate relief of headache.

References