Randomized Trial of Intravenous Lidocaine Versus Hydromorphone for Acute Abdominal Pain in the Emergency Department

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Study objective: We compare the efficacy and safety of intravenous lidocaine with that of hydromorphone for the treatment of acute abdominal pain in the emergency department (ED).

Methods: This was a randomized, double-blind, clinical trial conducted in 2 EDs in the Bronx, NY. Adults weighing 60 to 120 kg were randomized to receive 120 mg of intravenous lidocaine or 1 mg of intravenous hydromorphone. Thirty minutes after administration of the first dose of the study drug, participants were asked whether they needed a second dose of the investigational medication to which they were randomized. Patients were also stratified according to clinical suspicion of nephrolithiasis. The primary outcome was improvement in pain scores of 0 to 10 between baseline and 90 minutes. An important secondary outcome was need for "off-protocol" parenteral analgesics, including opioids and nonsteroidal anti-inflammatory drugs.

Results: We enrolled 154 patients, of whom 77 received lidocaine and 77 received hydromorphone. By 90 minutes, patients randomized to lidocaine improved by a mean of 3.8 points on the 0-to-10 scale, whereas those randomized to hydromorphone improved by a mean of 5.0 points (mean difference 1.2; 95% confidence interval 0.3 to 2.2). Need for off-protocol "rescue" analgesics occurred for 39 of 77 lidocaine patients (51%) and 20 of 77 hydromorphone patients (26%) (difference 25%; 95% confidence interval 10% to 40%). Adverse events were comparable between groups. Among the subset of 22 patients with nephrolithiasis, lidocaine patients reported a mean improvement of 3.4 points on the pain scale, whereas hydromorphone patients reported a mean improvement of 6.4 points (mean difference 3.0; 95% confidence interval 0.5 to 5.5).

Conclusion: Intravenous hydromorphone was superior to intravenous lidocaine both for general abdominal pain and a subset of patients with nephrolithiasis. A majority of patients randomly allocated to lidocaine required additional analgesics. [Ann Emerg Med. 2019;74:233-240.]

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INTRODUCTION

Background

Nearly 12 million patient visits to US emergency departments (EDs) annually are due to abdominal pain.[1] Although ED providers have a variety of pharmacologic agents at their disposal to treat this pain, severe undifferentiated abdominal pain often requires intravenous opioids to achieve adequate analgesia. When used in the ED for acute pain, parenteral opioids are generally effective, safe, and well tolerated, although they may cause adverse effects such as nausea, vomiting, drowsiness, dizziness, pruritis, and, uncommonly, respiratory depression.[2-6]

Intravenous lidocaine has emerged as a possible therapeutic alternative for management of acute severe pain in the ED.[7] It has been used for acute pain for more than half of a century.[8] Accumulated data indicate that it is superior to placebo and as effective as morphine for neuropathic pain.[9] Perioperative intravenous lidocaine may also improve postsurgical pain outcomes.[10,11] Published data suggest that intravenous lidocaine in the ED may be efficacious for nephrolithiasis,[12] acute limb ischemia,[13] long bone fractures,[14] and undifferentiated severe pain.[15]

Importance

Acute pain is a very common chief complaint in the ED. There is a continuing need for medications that relieve pain rapidly, effectively, and durably with minimal adverse effects. It is still unclear whether lidocaine can replace

Editor's Capsule Summary

What is already known on this topic

Intravenous lidocaine has known analgesic effects, but they have not been shown to rival those of opioid analgesics.

What question this study addressed

Can intravenous lidocaine provide analgesia comparable to that of intravenous hydromorphone for emergency department patients with acute abdominal pain?

What this study adds to our knowledge

In this randomized study of 154 patients, fixed-dose lidocaine at 120 mg intravenously was less effective than fixed-dose hydromorphone at 1 mg intravenously and was associated with a greater need for rescue analgesics. Serious adverse events were uncommon with both agents.

How this is relevant to clinical practice

Lidocaine at 120 mg intravenously has some analgesic effect, but cannot replace hydromorphone as a first-line agent for acute abdominal pain. Additional research is needed to determine its safety and efficacy in clinical use.

opioid regimens as primary parenteral treatment of severe pain in the ED.

Goals of This Investigation

In this study, we tested the hypothesis that among ED patients with acute abdominal pain, intravenous lidocaine would provide superior analgesia compared with intravenous hydromorphone, as determined by improvement on a 0-to-10 pain scale between baseline and 90 minutes later.

MATERIALS AND METHODS

Study Design and Setting

This was a randomized, double-blind, comparative effectiveness trial conducted in 2 EDs of Montefiore Medical Center, an urban teaching institution in the Bronx, NY, with an annual visit volume exceeding 170,000. Bilingual (Spanish and English) salaried research associates collected data 24 hours per day, 7 days per week. We assessed outcomes throughout the ED stay and by telephone 7 days later. The Montefiore Medical Center institutional review board reviewed and approved this protocol.

Selection of Participants

Eligible patients were aged 18 to 64 years, weighed between 60 and 120 kg, and presented to one of our EDs for treatment of acute, severe abdominal pain. *Acute* was defined as pain for no more than 7 days. *Severe* was defined as warranting the use of intravenous opioids, as determined by the attending physician. Patients were excluded from participation for cardiac conduction system impairment, known renal or liver disease, hemodynamic instability (as determined by the attending physician), pregnancy, breastfeeding, or allergy to either medication. Patients were also excluded if they self-reported use of prescription or illicit opioids within the previous week, or if they had a chronic pain disorder, defined as use of any analgesic medication on more days than not during the month preceding the acute episode of pain. Patients who received off-protocol medication in the ED before enrollment were eligible for enrollment if greater than 1 hour had elapsed since off-protocol medication administration and the patient still met inclusion criteria (pain warranting intravenous opioids).

Interventions

Patients were randomized in a 1:1 ratio to 120 mg of intravenous lidocaine or 1 mg of intravenous hydromorphone. Each of these medications was administered as an intravenous drip over 10 minutes. If patients reported insufficient pain relief when specifically queried at 30 minutes, they could receive a second dose of the medication to which they were randomized. Patients who required additional medication beyond 90 minutes were administered parenteral analgesics at the discretion of the attending emergency physician.

Hydromorphone, dosed with a 1-mg titration strategy every 30 to 60 minutes, has been shown to be a safe and effective analgesic for management of acute severe pain in the ED.[2,5] The optimal dose of intravenous lidocaine for acute pain is unknown. For this study, we chose a dose that was most likely to be efficacious while minimizing potential for adverse events. In the perioperative setting, intravenous lidocaine boluses ranged from 1 to 3 mg/kg.[10] ED-based studies have used lower doses of 1 to 2 mg/kg (Table E1, available online at http://www.annemergmed.com). With weight boundaries of 60 and 120 kg as criteria for study entry, all participants assigned to the lidocaine arm received intravenous lidocaine at at least 1 mg/kg; if they opted for a second dose of medication, they recieved lidocaine at up to 4 mg/kg during 1 hour.

Randomization occurred in blocks of 4 based on a random-number generator. Allocation was concealed. Research subjects, clinicians, and research personnel were blinded. The research pharmacist presented research personnel with identical vials containing a clear solution of either lidocaine or hydromorphone, labeled as an

investigational medication. The clinical nurse removed the solution from the vial, inserted it into a 50- or 100-mL bag containing normal saline solution, and administered the medication as a 10-minute intravenous drip. The same mechanism was used for the optional second dose of investigational medication. Subjects were stratified by study site and diagnosis (presumptive diagnosis of nephrolithiasis versus other causes of pain). The rationale for stratification based on presumptive diagnosis of kidney stones was 2-fold: kidney stones represent a large subset of abdominal pain diagnoses, and they may be more likely to respond to intravenous lidocaine than other causes of abdominal pain.[12]

Methods of Measurement

Baseline variables of interest included age, sex, weight, pain severity, and pain duration. Diagnosis was determined by querying the treating attending physician at ED discharge. Pain intensity was measured with a verbal numeric scale on which 0 represented no pain and 10 represented the worst pain imaginable. Satisfaction with a specific medication is a highly patient-centered outcome, in which individuals determine for themselves the benefit of a particular drug versus the adverse effects experienced. We included in this study a measure that has been used in multiple ED-based pain trials: "The next time you come to the ED for treatment of pain, do you want to receive the same medication?"[16] Patients were asked to choose among the following responses: yes, no, or not sure.

We determined the presence of medication-induced adverse effects by asking the following question: "Did you have any new symptoms that began only after you got the study medication?" An affirmative response was followed by an open-ended question eliciting details. Seven days after the ED visit, we called all discharged patients to determine whether they revisited an ED after the initial ED discharge.

Outcome Measures

The primary efficacy outcome for this study was improvement in 0-to-10 pain scores between medication administration (time 0 minutes) and 90 minutes later. We chose 90 minutes because we believed that would be sufficient time for patients to receive 2 doses of the investigational medication if a second dose were requested. An important secondary outcome was need for additional "off-protocol" analgesia, defined as parenteral opioids or nonsteroidal anti-inflammatory drugs administered subsequently during the ED stay. Exploratory outcomes included patient satisfaction with the medication to which they were randomly allocated. We also recorded pain scores at 15, 30, 45, 60, 90, 120, and 180 minutes after investigational medication administration and report these, as well as the frequency with which patients experienced a greater than 50% improvement in pain between baseline and 90 minutes. Safety endpoints included development of any new symptom after administration of the investigational medication, need for naloxone, change in the disposition of the patient that was attributable to investigational medication, and unplanned return to any ED within 7 days of the index visit. During each patient's ED course, we assessed for the development of adverse effects every hour for 3 hours.

Primary Data Analysis

Baseline characteristics are reported as mean (SD), median (interquartile range), or n/N (%), as appropriate. The primary outcome is reported as the between-group difference in the mean improvement on the 0-to-10 pain score at 90 minutes. Results were considered statistically significantly different if the 95% confidence interval (CI) did not include the null point of 0. All dichotomous values are reported as percentages with 95% CIs.

We performed an intention-to-treat analysis. Once the investigational medication was initiated, the patient was included in the analysis regardless of whether he or she completed the medication infusion or received additional analgesic medication. We also repeated the primary outcome analysis for an a priori predetermined subgroup of patients with the clinical diagnosis of nephrolithiasis.

When 0-to-10 pain score data were missing at an intermediary point, we averaged the adjacent pain scores. When missing data occurred at final measurements, we carried forward the last available pain score.

We based our sample size calculation on previous work. We anticipated a mean improvement in 0-to-10 pain score of 4.9 and an SD of 2.8. Using a between-group difference of 1.3 as a minimum clinically significant difference, with α=.05 and β=.20, we determined the need for 73 patients in each group. We enrolled 105% of this N in anticipation of protocol violations and missing data, thus leaving us with a sample size of 154 patients, 77 in each group.

RESULTS

Enrollment commenced in January 2018 and concluded 7 months later. During this time, we screened 812 patients for eligibility, 154 of whom met criteria and consented to participate (Figure 1). Seventy-seven patients were randomized to each group.

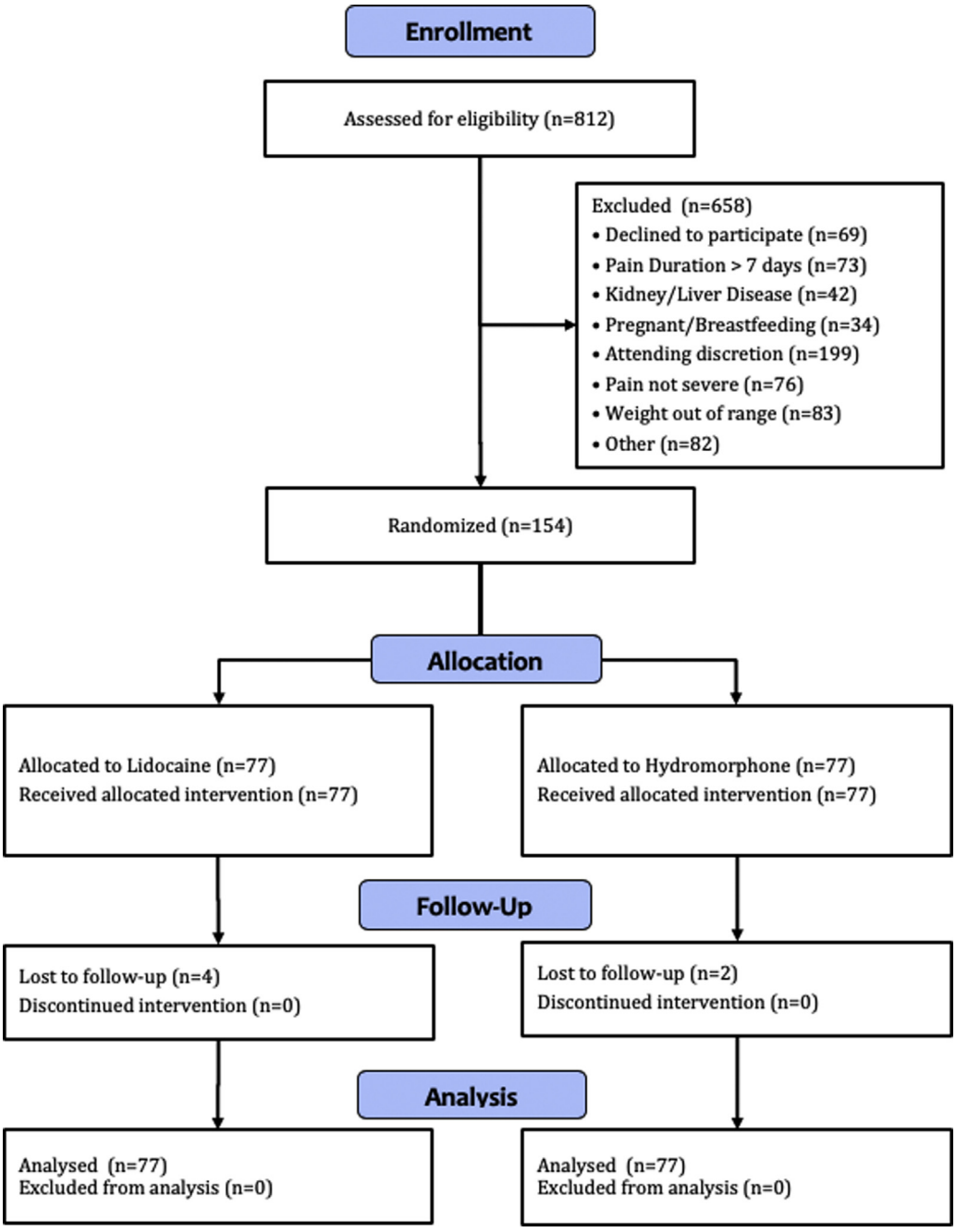

Figure 1. Consolidated Standards of Reporting Trials flow diagram. *Other: Use of opioids before ED presentation (26), lacked capacity to consent (20), chronic pain syndrome (9), hemodynamically unstable (8), not predominantly abdominal pain (7), abnormal ECG result (7), and allergic to investigational medication (5).

Baseline characteristics were similar in the 2 study arms (Table 1), although the lidocaine group was randomly allocated more women than men. Nonspecific abdominal pain was the single most common diagnosis. Twenty-two patients (14%), 11 in each group, received a diagnosis of nephrolithiasis. The mean initial dose of lidocaine received by the 77 patients who received intravenous lidocaine was 1.5 mg/kg (SD 0.3); the mean total dose received was 2.1 mg/kg (SD 0.8).

At the 90-minute assessment, patients randomized to lidocaine improved by an average of 3.8 points on the 0-to-10 pain scale, whereas those randomized to hydromorphone improved by an average of 5.0 points (mean difference 1.2; 95% CI 0.3 to 2.2)

Table 1. Baseline characteristics.

Variable	Lidocaine (n=77)	Hydromorphone (n=77)
Age, mean (SD), y	42 (12)	40 (13)
Sex		
Women	54 (70)	44 (57)
Men	23 (30)	33 (43)
Weight, mean (SD), kg	80 (15)	82 (15)
Pain duration, median (IQR), days	2 (1–4)	2 (1–3)
Clinical diagnosis*		
Nonspecific abdominal pain	27 (35)	22 (29)
Nephrolithiasis	11 (14)	11 (14)
Colitis/diverticular disease	12 (16)	8 (10)
Biliary pathology	6 (8)	12 (16)
Esophageal/gastric/duodenal pathology	5 (6)	8 (10)
Pelvic pain	7 (9)	5 (6)
Appendicitis	4 (5)	4 (5)
Small bowel obstruction/ileus/hernia	2 (3)	2 (3)
Urinary tract infection	2 (3)	2 (3)
Pancreatitis	1 (1)	1 (1)
Other	0	2 (3)

IQR, Interquartile range.
Data are presented as No. (%) unless otherwise indicated.
*Based on attending physician's clinical impression at discharge.

(Figure E1, available online at http://www.annemergmed.com). Pain scores were lower in the hydromorphone arm than the lidocaine arm at all points except baseline (Table 2, Figure 2). At 90 minutes, more hydromorphone patients (47/77; 61%) than lidocaine patients (30/77; 39%) reported a greater than 50% improvement in their pain (difference 22%; 95% CI 7% to 37%).

Need for off-protocol "rescue" analgesics occurred for 39 of 77 lidocaine patients (51%) and 20 of 77 hydromorphone patients (26%) (difference 25%; 95% CI 10% to 40%) (Table 3, Figure 3). Similarly, more hydromorphone patients (64/71; 90%) than lidocaine patients (47/73; 64%) said they would want to receive the study medication again (difference 26%; 95% CI 13% to 39%).

Table 2. Pain scores 0 to 10 throughout the study period, reported as mean (SD).

Time, Minutes	Lidocaine (n=77)	Hydromorphone (n=77)	Difference (95% CI)
Baseline	9.0 (1.3)	9.0 (1.2)	0.0 (–0.4 to 0.4)
15	6.6 (2.4)	5.6 (2.6)	1.0 (0.2 to 1.8)
30	6.1 (2.8)	4.6 (2.8)	1.5 (0.6 to 2.4)
45	5.6 (3.0)	4.1 (2.7)	1.5 (0.6 to 2.4)
60	5.4 (3.0)	3.9 (2.8)	1.5 (0.5 to 2.4)
90	5.2 (3.1)	4.0 (2.9)	1.2 (0.3 to 2.2)
120	5.1 (3.2)	3.7 (2.8)	1.4 (0.4 to 2.3)
180	4.8 (2.8)	3.8 (2.9)	1.0 (0.1 to 2.0)

Medication-associated symptomatology was comparable between the 2 study arms (Table 4). The most commonly reported symptoms were dizziness, drowsiness, headache, nausea, and pruritis. No other symptom was reported by more than one patient. There were no serious adverse events in the study. No patient required administration of naloxone.

Among the 22 patients with a diagnosis of clinical nephrolithiasis (based on the attending physician's discharge impression), those who received lidocaine reported an improvement of 3.4 points on the 0-to-10 pain scale, whereas those who received hydromorphone reported an improvement of 6.4 points (mean difference 3.0; 95% CI 0.5 to 5.5).

We performed a post hoc analysis in which we compared weight-based dose of lidocaine with the primary outcome. There was a clinically important inverse association between patient weight and improvement in pain score. This is detailed in Appendix E1, available online at http://www.annemergmed.com. Patients who weighed 73 kg or less reported a mean improvement in pain scores that was substantially better than that of patients who weighed 85 kg or more (mean difference 1.9; 95% CI 0.5 to 3.4). Patients who weighed no more than 73 kg reported mean improvement in 0-to-10 pain scores of 5.0 (95% CI 3.8 to 6.2).

LIMITATIONS

First, the primary limitation of this trial was that we may have underdosed the initial bolus of intravenous lidocaine. Post hoc data presented in Appendix E1 (available online at http://www.annemergmed.com) demonstrate that initial doses of intravenous lidocaine approaching 2 mg/kg were more effective than lower weight-based doses and as effective as intravenous hydromorphone. When designing this study, we did not identify dose-finding studies of intravenous lidocaine for acute pain (Table E1, available online at http://www.annemergmed.com). We anticipated that our 1- or 2-dose titration scheme would deliver an appropriate dose to each patient, maximizing efficacy while minimizing adverse events. This strategy may have been less effective because of delays, sometimes substantial, in administering the second dose of investigational medication. We did not use weight-based dosing in this

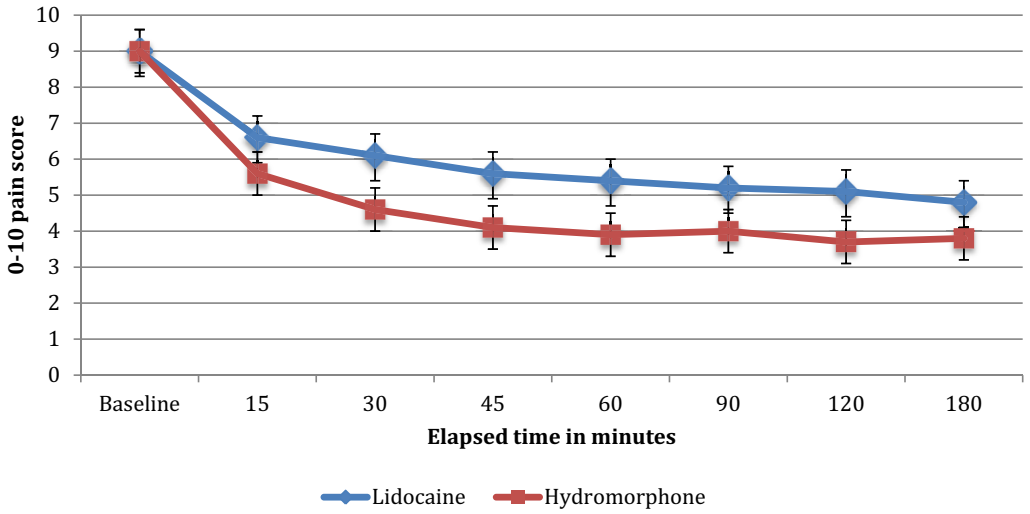

Figure 2. Pain scores from 0 to 10. Error bars depict 95% CI.

study because we did not have research pharmacy resources available 24 hours a day.

Second, because of constraints inherent in conducting clinical research in an active ED, we had some difficulty delivering the second dose of study medication in a timely manner to all patients. As demonstrated in Appendix E2 (available online at http://www.annemergmed.com), the elapsed time to the second dose of medication in some cases was so long that the efficacy was not captured in our primary outcome at 90 minutes. However, as demonstrated in Table 2, our conclusions would not have changed even if our primary outcome had been delayed until 120 minutes.

Third, our mechanism of blinding may have been inadequate. Patients administered hydromorphone were more likely to suspect that they received hydromorphone, whereas research associates were more likely to guess correctly that lidocaine patients received lidocaine (Appendix E5, available online at http://www.annemergmed.com). The reason for this and its significance are not clear. If patients suspected that they received hydromorphone, this may have caused them to overstate its efficacy. Alternatively, if it was the pain relief itself that allowed patients to surmise which medication they received, then the effect on the stated pain scores may have been minimal.

Fourth, we did not use a pain score cutoff for medication redosing. We merely asked patients whether they would want another dose of the medication. Therefore, a between-group difference in pain tolerance may have affected total dose of medication received, and thereby the primary outcome.

Fifth, this study took place in 2 urban academic EDs in the Bronx, NY, caring for an underserved inner-city population. It is uncertain whether these data can be generalized to other settings.

Table 3. Exploratory outcomes.

Outcome	Lidocaine (n=77)	Hydromorphone (n=77)	Difference (95% CI)
Requested additional dose of investigational medication			
Yes	30 (39)	15 (19)	20% (5% to 34%)
No	47 (61)	62 (81)	
Would want the same medication again			
Yes	47 (64)	64 (90)	26% (13% to 39%)
No	19 (26)	5 (7)	
Not sure	7 (10)	2 (3)	
Missing data	4	6	

Data are presented as No. (%), unless otherwise specified.

DISCUSSION

In this ED-based, randomized, comparative effectiveness trial, intravenous hydromorphone was substantially more efficacious than intravenous lidocaine for acute abdominal pain. Hydromorphone was also superior to lidocaine in a subset of patients with nephrolithiasis. Although generally well tolerated, intravenous lidocaine, on all measures, was substantially less efficacious for acute pain.

Hydromorphone, a standard of care for treatment of acute, new-onset, severe pain in the ED, has been shown repeatedly to be safe, effective, and well tolerated.[2-6] It is

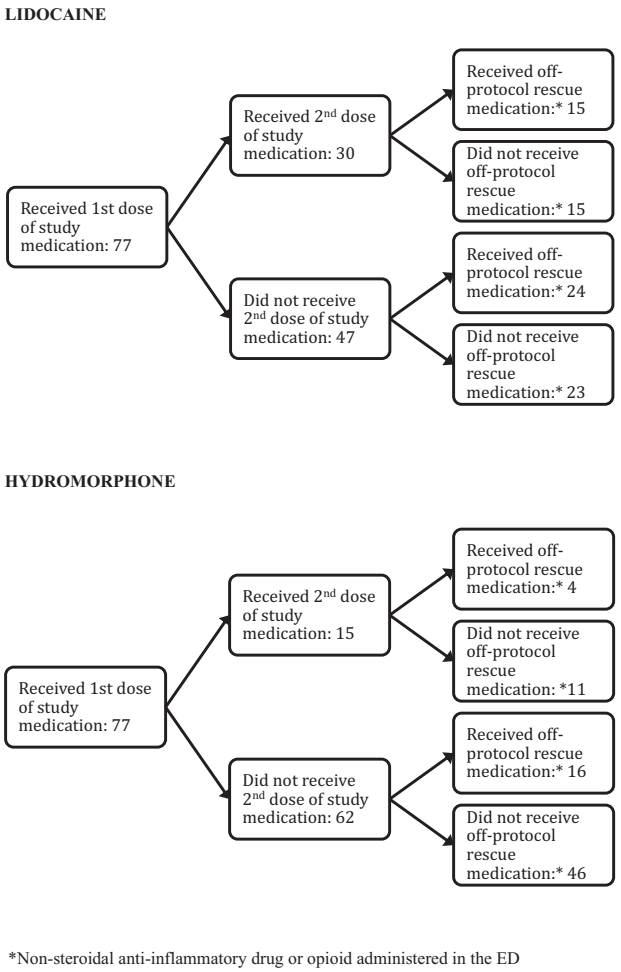

Figure 3. Flowchart of medication administered to study participants.

Table 4. Adverse events.

Adverse Event	Lidocaine	Hydromorphone	Difference (95% CI)
Any patient-reported symptom			
Yes	23 (30)	28 (36)	6% (−8% to 21%)
No	54 (70)	49 (64)	
Specific symptoms reported by patients			
Dizziness	4 (5)	14 (18)	
Drowsiness	6 (8)	4 (5)	
Headache	6 (8)	3 (4)	
Nausea	9 (12)	13 (17)	
Pruritis	1 (1)	2 (3)	
Change in management because of investigational medication			
Yes	0	0	
No	77 (100)	77 (100)	0
Unplanned return visit to ED within 1 wk			
Yes	2 (3)	0	3% (−1% to 6%)
No	71 (97)	75 (100)	
Missing	4	2	
Required naloxone			
Yes	0	0	
No	77 (100)	77 (100)	0

Data are presented as No. (%), unless otherwise specified.

easily titratable and reversible, with a widely available antidote, and there are no compelling, evidence-based reasons not to administer intravenous hydromorphone for severe abdominal pain in a monitored setting such as the ED. It was a highly effective analgesic in this study too, although approximately one third of hydromorphone patients reported medication-related adverse effects, and approximately one third did not achieve a 50% improvement in pain by 90 minutes. These results are generally in keeping with published data, which have demonstrated that 1-mg doses of intravenous hydromorphone, administered repeatedly every 30 to 60 minutes during the first 2 hours of an ED course, are an effective way to achieve high levels of patient satisfaction with analgesic treatment.[5]

Our data do not support the use of a 120-mg dose of intravenous lidocaine as a first-line analgesic for severe abdominal pain. Pain scores among patients who received lidocaine were higher throughout the study period, need for additional analgesia occurred much more frequently among patients randomized to lidocaine versus hydromorphone, and, on average, patients who received lidocaine reported less than a 50% reduction in pain. Our data do not provide any compelling reasons to choose intravenous lidocaine as a first-line analgesic over hydromorphone for abdominal pain. Placebo-controlled studies are needed to determine whether intravenous lidocaine should play any role in the management of ED patients with pain.

In other randomized, ED-based studies of visceral pain, pain scores after administration of intravenous lidocaine improved 45% by 60 minutes in a general pain study[15] and 88% by 30 minutes in a study of kidney stones.[12] Although the former results are generally consistent with the 40% improvement our lidocaine patients experienced at 60 minutes, the latter are substantially different, and may be related to dosing of the medication or differences in the patient populations.

Intravenous lidocaine can cause serious adverse events such as hypotension, cardiac dysrhythmias, and seizures, although these are generally not observed at doses up to 5 mg/kg.[7] At doses less than 2 mg/kg, adverse effects are generally minor and transient (Table E1, available online at http://www.annemergmed.com). As demonstrated in our exploratory analysis in Appendix E1 and in Table E1 (available online at http://www.annemergmed.com), initial doses of 2 mg/kg may have more efficacy than lower doses of intravenous lidocaine. The dose of 2 mg/kg thus may be a reasonable starting point in future investigations of intravenous lidocaine and for patients who have contraindications to intravenous opioids.

In conclusion, intravenous hydromorphone was more efficacious than 120-mg doses of intravenous lidocaine both for general abdominal pain and a subset of nephrolithiasis patients. According to these data, lidocaine should not replace hydromorphone as a first-line analgesic.

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Author contributions: EC, BWF, EI, MPJ, AW, and EJG conceived the study and designed the trial. BWF, EI, FA, EZ, MPJ, SP, and AC supervised the conduct of the trial and data collection. EC, BWF, FN, EI, and AC managed the data, including quality control. EC and BWF analyzed the data. EC, BWF, FN, and AW performed the literature review. EC and BWF drafted the article, and all authors contributed substantially to its revision. EC takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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