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Intravenous Lidocaine for Acute Pain: A Systematic Review

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This systematic review evaluates the safety and efficacy of intravenous (IV) lidocaine for the treatment of acute pain in adult patients. The PubMed database was searched for randomized controlled trials, retrospective cohort studies, case series, and case reports evaluating the use of IV lidocaine for the treatment of acute pain in adult patients, published between January 1970 and January 2018. The primary outcome was pain reduction via the Visual Analog Scale, Verbal Rating Scale, or Numeric Rating Scale among patients treated with IV lidocaine and placebo or active controls. Safety outcomes included both nonserious and serious adverse events. A total of 347 titles and abstracts were screened, and after full-text review, 13 studies met the inclusion criteria involving 512 patients. The four active controls studied were IV morphine, IV ketorolac, IV dihydroergotamine (DHE), and IV chlorpromazine (CPZ). The dosing of IV lidocaine varied among studies between a weight-based dose of a 1- to 2-mg/kg bolus, a fixed-bolus dose of 50–100 mg, and a 1-mg/kg/hour continuous infusion. Monitoring of serum lidocaine concentrations was not done routinely. Intravenous lidocaine had superior efficacy to morphine for renal colic and critical limb ischemia, superior efficacy to DHE for acute migraine, and equivalent efficacy to ketorolac for acute radicular lower back pain. However, lidocaine was less effective than CPZ for the treatment of acute migraine. The most common adverse event reported among all studies were neurologic effects such as altered mental status and slurred speech. Due to the inconsistency in dosing, length of administration, and lack of serum monitoring, the absolute safety of IV lidocaine for acute pain is unknown. Larger, prospective studies are needed before the routine use of IV lidocaine can be recommended for all types of acute pain.

KEY WORDS intravenous lidocaine, acute pain, analgesia, adiposis dolorosa, renal colic, critical limb ischemia, acute migraine.

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Acute pain serves as a warning of disease or threat to the body. It can be caused by a variety of stimuli including injury, surgery, illness, trauma, or painful medical procedures.[1] Pain is a common reason to seek medical care, accounting for 45–75% of emergency department (ED) visits.[2] Treatment modalities to relieve acute pain include both nonpharmacologic (e.g., acupuncture) and pharmacologic strategies, such as nonopioid analgesics and opioids. Opioids agonize μ receptors to provide analgesia, but patients may also develop tolerance and physical dependence with chronic use.[3] Since the 1990s, the overall rate of opioid prescribing has significantly increased to the point where the sales of opioid analgesics to hospitals, pharmacies, and practitioners quadrupled between 1999 and 2010.[4] The misuse and abuse of opioid prescription pain medication has resulted in an opioid crisis, with more than 100 Americans dying from an opioid overdose every day.[5] Due to the ongoing opioid crisis, health care providers are encouraged to explore alternative approaches to pain management. Nonopioid alternatives include nonsteroidal antiinflammatory drugs

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Table 1. Lidocaine Pharmacokinetics[9, 11]

Dosing for analgesia	0.1–0.3 mg/kg bolus, followed by a continuous infusion of 0.5–3 mg/kg/hr
Onset of action	45–90 sec
Terminal half-life	1.5–2 hrs[a]
Active metabolites	Monoethylglycinexylidide (MEGX): may cause toxicity in heart failure patients Glycinexylidide (GX): may accumulate in patients with renal failure
Therapeutic plasma concentrations	1.5–5 μg/ml at steady state
Adverse reactions	Dizziness, tinnitus, QRS prolongation, sinus slowing, hypotension, dysrhythmias

[a]Half-life may be prolonged in patients with heart failure, liver dysfunction, or renal dysfunction.

(NSAIDs), regional anesthesia, topical lidocaine patches, and intravenous (IV) lidocaine.[6]

Historically, lidocaine was used as a local anesthetic and in the treatment of ventricular arrhythmias.[7, 8] Lidocaine is an amino-amide anesthetic that alters neuron signal conduction by modulation of the voltage-gated sodium channels.[9, 10] Table 1 summarizes the dosing and pharmacokinetics. The analgesic properties of lidocaine are thought to be a result of an anti-inflammatory process, through the reduction of circulating inflammatory cytokines (i.e., interleukin [IL]-6, IL-1β, and tumor necrosis factor).[12] Intravenous lidocaine was used in the treatment of chronic neuropathic pain syndromes, such as trigeminal neuralgia and peripheral nerve injury, and showed positive outcomes.[13] Therefore, IV lidocaine may be an effective measure in the treatment of acute pain in adult patients due to its analgesic and antiinflammatory properties. The objective of this systematic review was to evaluate the safety and efficacy of IV lidocaine for the treatment of acute pain in adult patients.

Methods

Study Design

All recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement were followed.[14] The study was registered with PROSPERO, the international prospective register of systematic reviews. The investigators searched the PubMed database for randomized controlled trials (RCTs), retrospective cohort studies, case series, and case reports published between January 1970 and January 2018. Each study was required to be in English and retrievable to allow for full review.

Eligibility Criteria

Adult patients (18 yrs or older) who received at least one dose of IV lidocaine for acute or acute on chronic pain were included. Studies were excluded if lidocaine was not administered systemically or if it was used for local anesthesia, general anesthesia, periprocedural/procedural pain, or chronic pain defined as pain lasting for 12 weeks or longer.[15] Phase I and II clinical trials were also excluded.

Outcome Measures

The primary outcome was defined as pain reduction via any pain scale using the Visual Analog Scale (VAS), Verbal Rating Scale (VRS), and/or Numeric Rating Scale (NRS) among patients treated with IV lidocaine compared with placebo or active controls. Secondary outcomes included average time to pain resolution and time to rescue analgesia. Both nonserious and serious adverse events were collected as safety outcomes. Nonserious adverse events were gastrointestinal, defined as nausea, vomiting, or dyspepsia. Serious adverse events were stratified into three categories: cardiovascular, hepatic, or neurologic. Serious cardiovascular adverse events were defined as new arrhythmias, cardiac arrest, or hypotension. Serious neurologic adverse events were defined as dizziness, altered mental status, seizure, loss of consciousness, or slurred speech. Serious hepatic adverse events were defined as liver dysfunction, in which aspartate aminotransferase and alanine aminotransferase were more than 5 times the upper limit of normal.

Study Selection

Two investigators (D.M. and E.L.) conducted a PubMed search using the search phrase lidocaine AND intravenous AND pain NOT perioperative NOT postoperative NOT epidural NOT anesthesia NOT intraoperative NOT topical NOT intranasal NOT propofol. The two investigators then independently screened all titles and abstracts for eligibility. The senior author (M.A.R.) resolved any disagreements on study eligibility. Interobserver reliability was measured

using Cohen's κ coefficient. Abstracts selected for screening were then retrieved in full text by the initial two investigators and independently assessed for eligibility. Articles were excluded if they were not fully retrievable.

Data Collection

These data were extracted: study design, study size, patient demographics, patient comorbidities, cause of pain, concomitant analgesic medications, pain reduction via any pain scale (VAS, VRS, or NRS), average time to pain resolution, lidocaine dose, lidocaine administration frequency, lidocaine serum concentration/level, pain perception questionnaire, total opioid consumption, time to rescue analgesia, and incidence of adverse drug reactions. The risk of bias was assessed using the Cochrane Collaboration's tool[16] for randomized trials and the Newcastle-Ottawa Scale[17] for observational studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology[18] was used to determine the level of evidence for each included study (Table 2).

Results

A total of 347 titles and abstracts were screened, and 34 studies were identified for full-text review. Thirteen studies met the inclusion criteria (Figure 1). Common reasons for exclusion were lidocaine use for chronic pain, irretrievable articles, and phase I and II study designs. Twenty non-English published articles were excluded. Although the extent and effects of language bias may be diminished due to the shift toward publication of studies in English, it is difficult to predict in which cases this exclusion may bias a systematic review. Therefore, all 20 excluded studies were reviewed, and all non-English studies remained excluded. Excellent interobserver agreement was observed with a κ coefficient of 0.95 (95% confidence interval [CI] 0.84–0.99).

The 13 studies included a total of 512 patients, of which 289 received IV lidocaine and 223 received a comparison agent (active control or placebo) for treatment of acute pain in a variety of acute pain syndromes. The four active controls studied were IV morphine, IV ketorolac, IV dihydroergotamine (DHE), and IV chlorpromazine (CPZ). The etiology of pain ranged from neuropathic to opioid-refractory to obstructive acute pain (e.g., ureteral).

Case Reports and Case Series

Four case reports and three case series described the use of IV lidocaine across a broad range of acute pain etiologies (Table 3).[25–31] Long-standing pain relief (up to 4 mo) was obtained from a single lidocaine infusion for Dercum disease.[27, 28] Unspecified duration of pain reduction was reported with lidocaine used in the case series for trigeminal neuralgia[25]; "near termination of pain" was achieved with IV lidocaine for a large bowel obstruction[29]; and resolution of pain was reported with IV lidocaine treatment for proctalgia fugax,[30] the case report for trigeminal neuralgia,[31] and short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) syndrome.[26] These cases describe IV lidocaine

Table 2. Summary of Findings Using the GRADE Methodology

Outcome	Effect	No. of studies	Certainty in evidence[a]
Reduction in pain scores	Three trials found significant pain reduction	Two RCTs[19, 20] and one retrospective study[21]	Very low ΘOOO (due to methodological limitations, imprecision, and inconsistency)
Need for rescue analgesia	One study used fentanyl as rescue analgesia but did not indicate amount used. Other studies did not describe in detail the rescue agent used after intravenous lidocaine because it was at the prescriber's discretion	Three RCTs[19, 22, 23] and one retrospective study[24]	Very low ΘOOO (due to methodological limitations, imprecision, and inconsistency)
Incidence of adverse events	Overall, 44 adverse events reported across the studies, 8 nonserious and 36 serious adverse events	Two RCTs,[19, 21] two case series,[25, 26] and one retrospective study[24]	Very low ΘOOO (due to methodological limitations, imprecision, and inconsistency)

GRADE = Grading of Recommendations Assessment, Development and Evaluation; RCT = randomized controlled trial.
[a]Commonly used symbols to describe certainty in evidence in evidence profiles: high certainty ΘΘΘΘ, moderate certainty ΘΘΘO, low certainty ΘΘOO, and very low certainty ΘOOO.

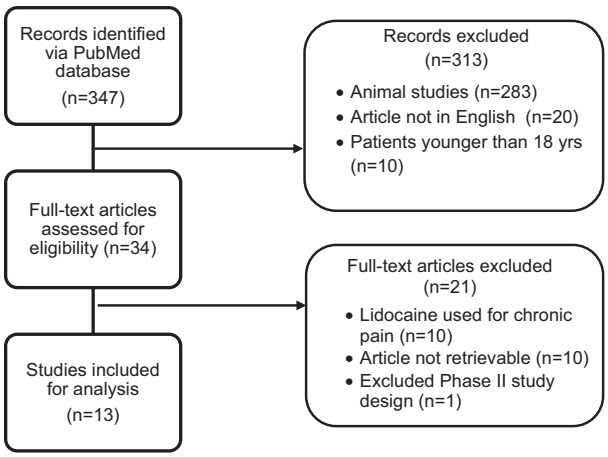

Figure 1. Inclusion and exclusion criteria.

used for a broad range of pain etiologies and differ in dosing and clinical effects. Of note, "near termination of pain" to "complete termination of pain" was documented in the case reports and case series, yet validated pain scales were not used routinely. No safety events were mentioned in any of the case reports. Reported adverse reactions in the case series included dizziness, nausea, vomiting, depression, and paranoia. In the case series evaluating pain management in SUNCT, cessation of IV lidocaine was required in two patients for depressive thoughts and paranoia.[26] No serious adverse reactions were reported in any of the subsequent case series.

Observational Studies and Randomized Controlled Trials

Six clinical studies, two retrospective observational studies and four prospective RCTs, have described the use of IV lidocaine for treatment of pain. Table 4 summarizes each trial, and a summary of the confidence in the evidence using the GRADE methodology is shown in Table 2.

Renal Colic

A prospective double-blind trial randomized 240 patients who presented to the ED with renal colic to receive either lidocaine 1.5 mg/kg IV or morphine 0.1 mg/kg IV as a single dose for acute pain control.[19] The VAS scores were reported at 0, 5, 10, 15, and 30 minutes after each intervention. The mean reduction in VAS at 30 minutes was 8.5 (VAS reduced from a score of 9.6 to 1.1) in the lidocaine group compared with 7.5 (VAS reduced from a score of 9.7

Table 3. Use of Intravenous Lidocaine in Case Reports and Case Series

Study design	Cause of pain	Intervention	Result
Case report[27]	Dercum disease (adiposis dolorosa)	Lidocaine 200 mg IV over 30 min for 4 infusions, then lidocaine 300 mg IV over 30 min for 6 infusions, then lidocaine 300 mg over 90 min	A total of 15 total infusions administered over the course of 10 yrs Each lidocaine infusion provided up to 4 mo of subjective pain relief
Case report[30]	Proctalgia fugax	Lidocaine 1 mg/kg IV in saline solution over 30 min	NRS 7/10 pain while having attacks and reported complete resolution after one treatment
Case report[31]	Trigeminal neuralgia	Lidocaine 1 mg/kg/hr IV for 4 hrs, then 2 mg/kg/hr for 48 hrs, then tapered and discontinued after 72 hrs	NRS 10/10 pain on admission but had resolution upon discharge, 1/10 at 1- and 6-mo follow-up
Case report[29]	Abdominal pain/Large bowel obstruction	Lidocaine 100 mg over 15 min	"Near termination of pain" Pain recurred after 100 min
Case series[28]	Adiposis dolorosa	Lidocaine 5 mg/kg IV for 30 min	N=2 Both patients obtained pain relief for 2–12 mo
Case series[26]	SUNCT syndrome	Loading (optional): Lidocaine 1 mg/kg IV over 15 min if the clinical state indicates the need for rapid resolution of symptoms Treatment: Lidocaine 1–4 mg/min Total treatment period: maximum of 7 consecutive days	N=4 Pain relief obtained
Case series[25]	Trigeminal neuralgia	Lidocaine 100 mg IV with magnesium 1.2 g for 1 hr once/week for 3 wks	N=9 Pain reduction in all 9 cases

IV = intravenous; NRS = Numeric Rating Scale; SUNCT = short-lasting unilateral neuralgiform headache with conjunctival injection and tearing.

to 2.2 in the morphine group; p=0.0001). No major adverse outcomes occurred, although the lidocaine group experienced more transient dizziness (8.3% vs 4.2%) and perioral numbness (2.5% vs 0%) with less nausea and vomiting (0% vs 9.1%) compared with the morphine group, respectively. However, statistical significance was not determined for adverse events. "Trial accomplishment" was considered achieved when the VAS pain score was lower than 3 for 30 minutes after the last analgesic dose or the entire 10 ml of solution in the syringe was administered for each treatment group. There was no discussion of how many patients achieved VAS lower than 3 and how many received the entire 10-ml syringe. Patients with a history of renal disease, liver disease, and heart disease were also excluded.

Adjunctive Analgesia

A multicenter retrospective study evaluated the safety and effectiveness of IV lidocaine as an adjunctive analgesic for the treatment of unspecified acute pain in intensive care unit (ICU) patients.[24] Most patients were admitted to the ICU due to respiratory failure after abdominal surgery. A total of 21 adults received an average lidocaine dose of 0.93 mg/kg as a continuous infusion for a mean duration of 48 hours. The mean time to a more than a 20% reduction in patient self-reported pain scores or adult nonverbal pain scores from the start of IV lidocaine was 3.3 hours that may have been due to the lack of a loading dose.[24] Furthermore, the median morphine dose equivalents required during 6, 12, and 24 hours pre-IV lidocaine were significantly higher compared with the same time periods after IV lidocaine (18.3 mg vs 10 mg at 6 hrs, p=0.002; 41.8 mg vs 18.3 mg at 12 hrs, p=0.002; 93.5 mg vs 30.5 mg at 24 hrs, p=0.037), respectively. During the IV lidocaine infusion, seven patients (33%) experienced an increase in serum creatinine more than or equal to 1.5 times baseline, yet the authors did not comment on the matter. Notably, three patients also received IV ketorolac as an adjunct in addition to lidocaine that may have contributed to the rise in serum creatinine. All other adverse events (listed in Table 5) were reversed upon discontinuation of IV lidocaine. This study suggests that IV lidocaine may be used as an adjunctive agent in the treatment of ICU patients with refractory acute pain after abdominal surgery. However, caution must be used in the critically ill patient population due to the potential risks of lidocaine accumulation with multiorgan dysfunction.

A second retrospective cohort study evaluated IV lidocaine for acute on chronic pain in 82 hospice patients requiring an inpatient admission.[21] Patients received lidocaine 1–2 mg/kg over 15–20 minutes followed by a continuous infusion of 1 mg/kg/hour for an unspecified duration. Pain response was assessed 30 minutes after initiation and stratified into three categories: major pain response (decrease in NRS scores by 3 points or more), partial benefit (decrease in NRS by 1 or 2 scores), and no benefit (no change in NRS scores). As a result, 50 patients (82%) had major pain relief, 5 patients (8%) had a partial benefit, and 6 patients (10%) showed no benefit, with a mean decrease in NRS scores of 6.8 points among all groups. Serum lidocaine concentrations were obtained at steady state in approximately half of the patients, with a mean reported concentration of 5.1 mg/L and standard deviation of 2.9. A higher lidocaine serum concentration was not associated with an increased number of adverse reactions. In terms of safety, 30% of patients experienced adverse reactions, with 3% of patients requiring cessation of IV lidocaine. The reason for discontinuation of IV lidocaine was not specified. Of the adverse events experienced, lethargy or somnolence was reported in 78% of all cases.

In both studies evaluating lidocaine for adjunctive analgesia, IV lidocaine was initiated at the discretion of the physician and "pain refractory to opioids" was not defined. Moreover, although both studies were limited in study design, lacked a comparator group, and had small sample sizes, IV lidocaine was demonstrated to have a broad analgesic effect because most patients experienced major pain relief with minimal adverse events. It is reasonable to consider the use of IV lidocaine when multimodal pain management is required in patients without organ dysfunction or when patients are at risk for opioid-induced respiratory depression.

Critical Limb Ischemia

A prospective double-blind trial randomized ED patients with critical limb ischemia to receive either a single dose of IV lidocaine (20 patients; mean dose 2 mg/kg) or IV morphine (20 patients; mean dose 0.1 mg/kg) administered over 5 minutes.[22] After 30 minutes, the mean decrease in VAS scores was significantly more in

Table 4. Use of Intravenous Lidocaine in Observational Studies and RCTs

Study design	Cause of pain	Intervention	Comparator	Results
Retrospective[21]	Acute on chronic pain of inpatient hospice	Lidocaine 1–2 mg/kg IV over 15–20 min followed by 1 mg/kg/hr continuous infusion	None	N=82 82% with major pain relief (NRS decrease ≥ 3 points) 8% with partial pain relief (NRS decrease 1–2 points) No benefit in 10%
Retrospective[24]	Adjunct pain in ICU patients	Average infusion of lidocaine 0.93 mg/kg/hr over mean duration of 48 hrs	None, but authors reported morphine dose equivalents required before and after lidocaine	N=21 Mean time to > 20% reduction in NRS or VRS was 3.3 hrs Morphine dose equivalents required during 6, 12, and 24 hrs pre-lidocaine were significantly higher compared with same time periods after lidocaine (18.3 mg vs 10 mg, p=0.002; 41.8 mg vs 18.3 mg, p=0.002; 93.5 mg vs 30.5 mg, p=0.037), respectively
RCT[20]	Acute migraine headache	Lidocaine 50 mg IV at 20-min intervals (maximum total dose 150 mg)	DHE 1 mg IV at 20-min intervals (maximum dose 2 mg), or CPZ 12.5 mg IV at 20-min intervals (maximum dose 37.5 mg)	N=76 Lidocaine headache intensity NRS score reduced from 8 to 4 (50%) DHE headache intensity NRS score reduced from 7.5 to 5.75 (36.7%) CPZ headache intensity NRS score reduced from 8.5 to 1.75 (79.5%), p<0.005
RCT[23]	Acute radicular low back pain	Lidocaine 100 mg IV over 2 min as single dose	Ketorolac 30 mg IV over 2 min as single dose	N=41 Lidocaine VAS decreased from 8.3 to 0.8 (95% CI 0–23, p=0.003) Ketorolac VAS decreased from 7.4 to 1.4 (CI 0–28, p=0.007) No difference in degree of reduction between groups (p=0.835)
RCT[19]	Renal colic	Lidocaine 1.5 mg/kg IV as single dose	Morphine 0.1 mg/kg IV as single dose	N=240 Lidocaine VAS reduced from 9.6 to 1.1; morphine VAS reduced from 9.7 to 2.2 (p=0.0001) 90% of lidocaine group responded successfully compared with 70% in the morphine group (p=0.0001)
RCT[22]	Critical limb ischemia	Lidocaine 2 mg/kg IV over 5 min as single dose	Morphine 0.1 mg/kg IV over 5 min as single dose	N=40 Lidocaine VAS was 7.5 at 0 min, 5.75 at 15 min, and 4.25 at 30 min Morphine VAS was 7.65 at 0 min, 7 at 15 min, and 6.5 at 30 min (95% CI 1.218–3.282)

CI = confidence interval; CPZ = chlorpromazine; DHE = dihydroergotamine; ICU = intensive care unit; IV, intravenous; NRS = Numeric Rating Scale; RCT = randomized controlled trial; VAS = Visual Analog Scale; VRS = Verbal Rating Scale.

Table 5. Adverse Events Associated with Intravenous Lidocaine Administration

Study design[a]	Cardiovascular[b]	Neurologic[c]	Gastrointestinal[d]	Hepatic[e]
Case series[28]	0	0	0	0
RCT[20]	0	0	0	0
Case series[26]	0	1/4 (25%)	3/4 (75%)	0
Retrospective[21]	1/82 (1%)	19/82 (23%)	5/82 (6%)	0
RCT[19]	0	10/120 (8%)	0	0
Case series[25]	0	2/9 (22%)	0	0
RCT[23]	0	0	0	0
RCT[22]	0	0	0	0
Retrospective[24]	0	3/21 (14%)	0	0

[a]Safety data were not reported in the four case reports.[27,29,30,31]
[b]Cardiovascular adverse events: new arrhythmias, cardiac arrest, or hypotension.
[c]Neurologic adverse events: dizziness, altered mental status, seizure, loss of consciousness, or slurred speech.
[d]Gastrointestinal adverse events: nausea, vomiting, or dyspepsia.
[e]Hepatic adverse events: liver dysfunction (aspartate aminotransferase and alanine aminotransferase ≥ 5 times the upper limit of normal).

the lidocaine group compared with the morphine group (−3.25 vs −1.15, 95% CI 1.22–3.28), respectively. Four patients in the morphine group required rescue analgesia with fentanyl compared with no patients in the lidocaine group. No patients reported adverse effects. This study showed that IV lidocaine appears safe and effective in alleviating acute pain within 30 minutes due to critical limb ischemia. However, the short follow-up period of 30 minutes and the small sample size may not have been sufficient to detect adverse events.

Acute Radicular Lower Back Pain

A prospective double-blind study randomized 41 patients who presented to the ED with acute radicular back pain to receive either IV lidocaine at a fixed-dose of 100 mg (21 patients) or IV ketorolac 30 mg (20 patients) over 2 minutes as a single dose.[23] The mean weight of patients in each group was 195 kg. Median VAS scores from baseline to 60 minutes were significantly reduced in both groups (8.3–0.8 in the lidocaine group [p=0.003] vs 7.9–1.4 in the ketorolac group [0.007]), yet no significant difference was observed in the degree of reduction between the two groups (p=0.84). A nonsignificant increase in the need for rescue analgesia was observed in the IV lidocaine group compared with the ketorolac group (67% vs 50%, p=0.35), respectively. No adverse effects were reported in either group. This study was limited by its small sample size, short follow-up period, and fixed-dosing strategy. The average weight-based lidocaine dose was 0.5 mg/kg, potentially leading to suboptimal analgesia and a lower incidence of adverse events because other studies administered a dose of 1–2 mg/kg. However, this is the only study that compared IV lidocaine with an NSAID and concluded similar efficacy. Intravenous lidocaine may be a reasonable alternative to ketorolac in patients with acute pain who are not candidates for NSAID administration.

Acute Migraine

A prospective randomized single-blind trial enrolled 76 ED patients with acute migraine to receive one of three study medications: IV lidocaine 50-mg bolus (26 patients), IV CPZ 12.5-mg bolus (24 patients), and IV DHE 1-mg bolus (26 patients).[20] Each medication dose could be repeated twice at 20-minute intervals. Numeric Rating Scale scores 60 minutes after administration decreased from 8 to 4 (50%) in the lidocaine group, from 7.5 to 4.75 (36.7%) in the DHE group, and from 8.5 to 1.75 (79.5%) in the CPZ group (p<0.005). Although patients in the CPZ group had the best analgesic response, widespread CPZ use was limited due to its known neurologic adverse reactions such as seizures and dystonic reactions. Eleven patients (57.9%) in the DHE group developed severe gastrointestinal adverse effects; four patients (22.2%) in the CPZ group developed minor gastrointestinal adverse effects. The authors did not describe what constituted a severe versus minor gastrointestinal adverse effect. No adverse effects were documented in the lidocaine group, aside from five patients (29.4%) who reported that therapy was ineffective. This study was limited by its small sample size and lack of reporting on total study drug doses. Also, lidocaine resulted

in a 50% reduction in pain scores that may be acceptable in most cases. More research is warranted using an adequate weight-based lidocaine dose because this may have influenced outcomes.

Discussion

This systematic review identified and reviewed the literature supporting the use of IV lidocaine for acute pain. Although a variety of indications were studied (renal colic, intestinal obstruction, trigeminal neuralgia, proctalgia fugax, adiposis dolorosa, SUNCT syndrome, adjunctive analgesia in the ICU, opioid-refractory pain, critical limb ischemia, acute radicular lower back pain, and acute migraine), the GRADE methodology summarized in Table 2 reflects that the certainty in the evidence is very low. In retrospective cohort and prospective studies, IV lidocaine consistently demonstrated a significant decrease in pain scores for a variety of indications compared with both placebo and active comparators, with limited adverse events. It is notable that almost all studies in this review had a limited sample size. The lidocaine dose and dosing regimen (e.g., slow IV push vs continuous infusion) varied among all studies. In the case reports and case series, a validated pain scale was not used. Finally, the absolute safety of IV lidocaine for acute pain cannot be assessed because most of the studies did not monitor serum lidocaine concentrations. Three studies only administered a single dose of lidocaine, and the practice of obtaining serum levels after a single dose of lidocaine is controversial.

The mainstay of therapy for the treatment of acute pain has traditionally included opioids such as morphine, hydrocodone, and oxycodone. However, the incidence of prescription opioid misuse progressing to opioid overdose continues to rise in the United States.[32] A 2002 study demonstrated that acute pain accounts for more than 50% of ED visits, making these health care providers the front line of preventing opioid abuse.[33] Due to the increased vigilance about the potential long-term risks of opioids, the search for alternative evidence-based medications to manage various types of acute pain is essential. Recent literature evaluated the analgesic effects of opioid alternatives such as antidepressants,[34] ketamine,[35] and nitrous oxide.[36] However, lidocaine remains an attractive option due to its analgesic and antiinflammatory properties.

The studies in this systematic review demonstrated the analgesic and opioid-sparing benefit of IV lidocaine for acute pain, yet the quality of the evidence was very low. Although the optimal dosing regimen for analgesia has yet to be determined, IV lidocaine administration was shown to be safe for up to 48 hours. Dosing ranges for IV lidocaine used for analgesia varied and included a 1- to 2-mg/kg bolus dose,[19, 21, 22, 30] a fixed 50- to 100-mg bolus dose,[20, 23, 29, 37] and a 1-mg/kg/hour continuous infusion.[24, 31, 33] Because lidocaine dosing is weight based for all indications approved by the U.S. Food and Drug Administration, a reasonable dose of lidocaine for acute pain is a bolus between 1 and 2 mg/kg. If a continuous infusion is initiated, 1 mg/kg/hour would be the recommended dose. However, when lidocaine was used as a continuous infusion for acute pain, most studies did not specify the duration of the infusion, and serum concentrations were not monitored routinely.

Although the quality of evidence was very low, lidocaine was efficacious as an analgesic for a variety of acute pain indications. When lidocaine was studied against an active comparator, it showed a greater reduction in VAS and higher response rate as compared with morphine for both critical limb ischemia and renal colic.[19, 22] In addition, lidocaine showed no difference in efficacy compared with ketorolac for the treatment of acute radicular low back pain, possibly a result of lidocaine's antiinflammatory properties.[23] The study that compared lidocaine with an NSAID was conducted in 2014,[23] whereas opioid prescribing rates peaked in 2012. Therefore, providers may have been more aware of opioid overuse at the time of the study and avoided opioids for the treatment of acute radicular low back pain. Finally, lidocaine administration resulted in a 50% reduction in pain scores when used for acute migraine headache but showed inferior efficacy when compared with CPZ.[20] It is notable that widespread CPZ use is limited due to its neurologic and hematologic adverse reactions, and the 50% reduction in pain scores from lidocaine may be acceptable in many patients with acute migraine. The median time to initial pain relief was 30–60 minutes with IV lidocaine. However, the dosing strategies among trials varied. Further studies for the treatment of acute pain with IV lidocaine should be addressed in general abdominal pain, pancreatitis, and acute fracture or dislocation. Studies should also examine the analgesic impact of repeat lidocaine dosing.

The most prevalent adverse event reported throughout all of the studies included neurologic symptoms such as dizziness and altered mental status. Remarkably, the incidence of cardiovascular and hepatic adverse events was low, yet patients with cardiovascular disease and hepatic disease were included in most of the trials. Only one trial excluded patients with a history of renal disease, liver disease, and cardiac disease.[19] In all studies, liver function tests were routinely monitored at least once/day. Patients in the cited studies had baseline characteristics notable for a cardiac history (26%),[21] an arrhythmia history (10%),[24] and a history of hypertension (25%).[22] There were no reports of any new arrhythmias associated with lidocaine use; however, one patient in hospice care died suddenly.[21] Because no death could be characterized as unexpected in the hospice study population, the authors attributed this sudden death as secondary to cardiac in nature. The patient had a confirmed deep vein thrombosis that was capable of progressing to a massive pulmonary embolism leading to death. However, because lidocaine has the potential for cardiac toxicity, it was also considered a possible contributing factor to the patient's death. In studies where a continuous lidocaine infusion was used for cardiac patients with ventricular arrhythmias, accumulation and slower clearance was seen in patients who received lidocaine for longer than 36 hours with a higher incidence of hypotension.[13, 37] When lidocaine is administered as a bolus dose, the literature defines a lower incidence of accumulation and adverse events. Overall, the absolute safety of IV lidocaine for the management of acute pain cannot be assessed because most of the studies did not monitor serum lidocaine concentrations, and the short follow-up periods may have resulted in inadequate detection of adverse events.

This review is limited by the heterogeneous nature of each study and lack of consistent reporting of outcomes. Although systematic and random error was minimized due to the development of a protocol and an independent review of each study for inclusion by two separate authors, investigator bias may still be an underlying limitation. Tables 6 and 7 summarize the risk of bias in both randomized and nonrandomized trials that were included in this systematic review.

In conclusion, IV lidocaine is currently not considered the standard of care for acute pain management due to a lack of adequate literature supporting its safe and effective use. Case reports, case series, retrospective cohort studies,

Table 6. Cochrane Collaboration's Tool for Assessment of Risk of Bias in RCTs

Selection bias		Performance bias	Detection bias	Attribution bias	Reporting bias	Other bias	
Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecified	Low on risk of bias
Low risk[22]	Unclear risk	Low risk	Low risk	Low risk	Low risk	Unclear risk	5/7
Low risk[23]	Low risk	Low risk	Low risk	Low risk	Unclear risk	Unclear risk	5/7
Low risk[19]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Unclear risk	5/7
Unclear risk[20]	Unclear risk	High risk	High risk	Low risk	High risk	Unclear risk	1/7

Table 7. Modified Newcastle-Ottawa Scale for Assessing Quality of Nonrandomized Studies[a]

Representative of exposed cases	Ascertainment of exposure (intravenous lidocaine, time, dosing)	Demonstration that outcome of interest was not present at start of study	Assessment of outcome	For case series: consecutive selection of patients
Truly representative[24]	Structured interview	Yes	Self-report	NA
Truly representative[21]	Secure record	Yes	Record linkage	NA
Truly representative[25]	Secure record	Yes	Record linkage	Unclear
Truly representative[26]	Structured interview	Yes	Self-report	Unclear
Somewhat representative[28]	Structured interview	Yes	Self-report	Unclear

NA = not available.
[a]The criteria "selection of nonexposed cohort" and "comparability of cohorts" were not applicable because all included observational and retrospective studies had no control or comparison groups.

and RCTs have demonstrated the analgesic efficacy of IV lidocaine with an acceptable safety profile across a broad range of disease states, but the quality of evidence is very low. It is also unknown whether more adverse events would be prominent with larger sample sizes, longer follow-up periods, and consistent monitoring of serum lidocaine concentrations. Because each study reported a different dosing strategy, the optimal lidocaine dosing regimen for analgesia is not well defined. Larger, prospective studies are needed before the routine use of IV lidocaine can be recommended for all types of acute pain.

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