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CONTINUOUS LIDOCAINE INFUSION AS ADJUNCTIVE ANALGESIA IN INTENSIVE CARE UNIT PATIENTS

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Abstract

Despite a paucity of data, the role of intravenous lidocaine (IVLI) as adjunctive analgesia in the intensive care unit (ICU) seems promising due to a low potential to contribute to respiratory depression. A retrospective chart review was conducted to evaluate the safety and effectiveness of IVLI for the treatment of pain in ICU patient with varying degrees of organ dysfunction from March 2014 to March 2016. The primary outcomes included the time to a 20 % reduction in pain scores after the initiation of IVLI and the difference in opioid requirements as well as pain scores prior to and during IVLI therapy. Other variables included the presence of IVLI-related adverse events and the dosage and duration of IVLI. A total of 21 ICU patients were included from two different hospitals. The mean time to a 20 % reduction in pain scores from the start of IVLI was 3.3 hours (SD = 2.2). The median morphine dose equivalents required during 6, 12, and 24 hours pre-IVLI were significantly higher compared to the same time periods after IVLI (18.3 vs. 10 mg, $p=0.002$; 41.8 vs. 18.3 mg, $p=0.002$; 93.5 vs. 30.5 mg, $p=0.037$). Neurological adverse

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effects of lidocaine were noted in 3 patients, but the effects were reversed upon IVLI discontinuation. This report suggested that IVLI as an adjunctive agent in the treatment of acute pain may be a potential option in ICU patients who are refractory to opioids or those in whom opioid-induced respiratory depression is a concern.

Keywords

Intravenous lidocaine; opioids; pain; intensive care unit; surgery

Intravenous lidocaine (IVLI) has been commonly used as a local or regional anesthetic as well as an antiarrhythmic agent for the treatment of ventricular arrhythmia.^{1,2} Previous clinical studies and case reports have demonstrated that patients with pain caused by various etiologies have been successfully treated with IVLI therapy.^{1,3,4} Continuous lidocaine infusion has been shown to be effective in treating pain secondary to a terminal illness, severe neuropathic pain, postamputation pain, and postoperative pain, particularly in major abdominal surgeries.^{3,5}

Lidocaine is a sodium channel blocking agent, which results in its antiarrhythmic and local anesthetic properties.^{6,7} The plasma protein binding of lidocaine is approximately 60 to 80 %, primarily to the alpha-1-acid glycoprotein. Lidocaine is extensively metabolized in the liver to two active metabolites, monoethylglycinexylidide (MEGX) and glycinexylidide (GX), which may contribute to lidocaine-induced central nervous system (CNS) toxicity.^{6,7} The initial and terminal half-lives of lidocaine in a healthy adult are 7 to 30 minutes and 1.5 to 2 hours, respectively; however, the half-life can be prolonged in patients with heart failure, liver disease, and severe renal failure.⁷

It has been proposed that lidocaine may exert its analgesic effect by suppressing neuronal action potentials arising from injured nerve fibers and posterior root ganglion cells.^{1,5} Lidocaine has been reported to have an anti-inflammatory property that may lead to positive effects on the recovery of bowel function after abdominal surgery.^{8,9} In a meta-analysis conducted by Marret and colleagues, patients treated with lidocaine infusion during and after abdominal surgery were found to have decreased opioid consumption and postoperative ileus.⁸

Lidocaine, particularly given as continuous IV infusion, can cause several major side effects related to cardiovascular (arrhythmia, hypotension, heart block, etc.) and central nervous (confusion, disorientation, lethargy, etc.) systems.^{1,2,5} However, significant side effects of IVLI as an adjuvant for pain management have rarely been reported. The low incidence of adverse effects could be explained by several reasons. Most published studies and case reports have used IVLI for a short period of time (e.g., < 24 hours) to treat pain. The majority of plasma concentrations of lidocaine in these studies were below the upper limit where toxicity is more likely to occur.^{6,10} Moreover, pharmacologic effects of lidocaine quickly dissipate once IVLI is discontinued due to its short half-life.^{1,3,5,11,12}

Systemic lidocaine infusion is of special interest in intensive care unit (ICU) patients suffering from severe pain not relieved by high-dose opioid therapy. Lidocaine infusion may

mitigate serious complications caused by opioids such as respiratory depression, sedation, and ileus by reducing opioid requirements.³ On the other hand, the use of IVLI in the ICU setting may raise some safety concerns because critically ill patients are more vulnerable to the adverse effects of lidocaine due to fluctuating hemodynamics and organ functions.¹³ Currently, there are very limited data available on the use of IVLI for pain relief in ICU patients. Therefore, this retrospective review focused on the utility of IVLI as an adjunct analgesic agent for pain within the ICU patient population with varying degrees of organ dysfunction. The main objective was to determine the role of IVLI in reducing opioid requirements in ICU patients. As the secondary objective, the safety and tolerability of IVLI in the ICU setting were thoroughly investigated.

Methods

Study design and setting

We conducted a multicenter, retrospective, observational, chart review at two institutions, Mercy Medical Center (MMC, a 300-bed acute care hospital, Springfield, Massachusetts) and University of Florida Health Shands Hospital (UF Health Shands Hospital, a 950-bed tertiary teaching hospital, Gainesville, Florida). The Institutional Review Board (IRB) approval with a waiver of informed consent was obtained from the respective institutions. At MMC, out of a total of 25 patients (22 surgical and 3 medical patients) who received IVLI for pain relief during the study period, 15 patients were eligible for inclusion (Figure 1). A total of 22 patients were treated with IVLI at UF Health Shands Hospital during the same period of time; 6 patients were included in the analysis.

Patients

Patients were eligible for inclusion in this study if they met the following criteria: (1) adults aged 18 years or older, (2) ICU stay of at least 24 hours, and (3) systemic lidocaine infusion for any duration as an adjunct therapy for pain management during ICU stay. Excluded were patients: (1) who received IVLI within 24 hours of admission, (2) who received ketamine infusion in conjunction with IVLI or within 24 hours after IVLI was discontinued, and (3) who were initiated with IVLI as part of comfort care due to their terminal medical conditions. In addition, the data during comfort care were excluded in the analysis when the decision was made to turn to comfort care while patients were receiving IVLI. The eligible patients were identified by querying electronic medical record (EMR) data for any patient who was dispensed IVLI from March 2014 to March 2016.

Outcome measures

At both institutions, pain was assessed every 1 to 4 hours using patient self-report scale, but if patients were unable to self-report pain, the Adult Non-Verbal Pain Score (ANVPS) and the Pain Assessment in Advanced Dementia (PAINAD) scale were used to rate the severity of pain in the ICUs at UF Health Shands Hospital and MMC, respectively. Patients with pain were managed primarily with opioids as well as other agents including nonsteroidal anti-inflammatory drugs (NSAIDs), antiepileptics, and antidepressants per the treating physician. Systemic lidocaine infusion therapy for pain management was initiated at the discretion of

ICU physicians at both institutions. Additionally, initial doses, titrations of IVLI, and ordering serum lidocaine levels were determined at ICU physicians' discretion.

The following patient demographic data were recorded: age, gender, diagnosis, past medical history, type and duration of surgical procedures, home pain medications, reasons for ICU admission, the requirement for mechanical ventilation at the initiation of IVLI, and baseline functions of major organs such as liver, heart, and kidney. The Modified Sequential Organ Failure Assessment (MSOFA) scores were calculated at the start of IVLI for all patients.¹⁴ The MSOFA score, a simplified version of the SOFA score, provides a total score ranging from 0 to 19 based on clinical or laboratory assessments of five organ systems (cardiovascular, respiratory, liver, central nervous system, and renal). In the present study, the MSOFA score, as opposed to the SOFA score, was used to measure the severity of illness because the measurements of arterial oxygenation were not available for all included patients. Changes in major organ functions over the course of IVLI were documented.

The primary outcomes included the time to a 20 % reduction in pain score after IVLI and the difference in opioid requirements as well as pain scores prior to and during treatment with IVLI. The amount of opioids administered and highest pain scores during each 6-hour period over the first 24 hours before lidocaine infusion and after the start of infusion were documented. The total opioid doses during a given period of time were converted into the parenteral morphine dose equivalents (MDEs) using the American Pain Society guidelines.¹⁵

For secondary outcome measures, the investigators evaluated the safety of lidocaine infusion for the treatment of acute pain in ICU patients. The EMR was thoroughly reviewed for the presence of adverse events such as electrocardiogram (ECG) changes, bradycardia, hypotension, seizure, changes in level of consciousness (LOC), muscle tremors and/or twitching, dizziness, tinnitus, visual disturbances, numbness, tingling, and metallic taste during IVLI in all included patients. In an effort to ensure complete collection of adverse events that are likely to be associated with lidocaine therapy, the investigators further probed the cases associated with abrupt discontinuation of lidocaine infusion, decreases in lidocaine infusion rates, or orders for lidocaine levels. Other outcome measures included the doses and duration of IVLI, ICU length of stay (LOS), hospital LOS, and duration of mechanical ventilation (MV) while on IVLI.

Data analysis

Data were summarized using descriptive statistics. A paired Wilcoxon rank-sum test was used to compare opioid requirements between pre- and post-treatment. All statistical analyses were performed using SPSS Statistics software (version 22; SPSS Inc, Chicago, IL). A p-value < 0.05 was considered statistically significant.

Results

Patient demographics

This study included a total of 21 patients (14 males and 6 females) from two different hospitals. The majority (n=20, 95%) were surgical ICU patients who underwent the

following surgeries: gastrointestinal (n=12), vascular (n=3), thoracic (n=3), spinal (n=1), and neuro (n=1) surgeries. The mean age was 66 years (SD = 14 years, range 25 to 90 years). The mean MSOFA score was 4 (SD = 3) with a range of 0 to 11. Of these 21 patients, 4 were taking chronic opioid medications prior to hospitalization. The demographics and clinical characteristics of included patients are summarized in Table 1.

Clinical outcome measures

Twenty-one ICU patients weighing from 60 to 121 kg (mean = 89 kg, SD = 22) received IVLI at an average infusion rate of 0.93 mg/min (SD=0.61) for a mean duration of 48 hours (SD = 33) (Figure 2). None of these patients received a loading dose. The mean time to a 20 % reduction in pain scores from the start of IVLI was 3.3 hours (SD = 2.2). Figure 3 displays MDEs during 24 hours before and after the start of lidocaine therapy in a 6-hour period. The opioid requirements (as median morphine dose equivalents) during 6, 12, and 24 hours pre-IVLI were significantly higher compared to the same time periods after IVLI (18.3 vs. 10 mg, $p = 0.002$; 41.8 vs. 18.3 mg, $p = 0.002$; 93.5 vs. 30.5 mg, $p = 0.037$). Additionally, the changes in median pain scores are shown in Figure 3. Although the median pain scores seemed similar between before and after IVLI treatment, further statistical analysis was not performed due to the differences in pain assessment scales as well as titrating strategies of pain medications at each institution.

The non-narcotic analgesics used before and/or during lidocaine treatment included oral or intravenous acetaminophen, gabapentin, carisoprodol, and intravenous ketorolac (Table 2). Out of 21 included patients, 8 patients required non-narcotic analgesics for 24 hours both before and after IVLI treatment while no other non-narcotic pain medications besides IVLI were given to 9 patients. Furthermore, two patients were started on non-narcotic pain medications after the initiation of IVLI.

Adverse drug events

Of the 21 patients included in the present study, IVLI was discontinued in three patients due to either high serum levels of lidocaine, suspected adverse reactions related to lidocaine or both. One patient with a history of diastolic heart failure and atrial fibrillation was treated with IVLI at 1mg/min, and 26 hours later, she became less responsive with a Riker Sedation-Agitation scale (SAS) of 2 decreased from 5 despite cessation of opioids and sedatives. The lidocaine serum level (8.4 mcg/ml [therapeutic level, 1.5–5 mcg/ml]) was obtained, and lidocaine treatment was discontinued. The patient's laboratory values were significant for serum creatinine (SCr) 1.56 mg/dL (baseline 1mg/dL [normal range, 0.6–1.1 mg/dL]) and blood urea nitrogen (BUN) 40 mg/dL (baseline 18 mg/dL [normal range, 8–25 mg/dL]) with a significantly decreased urine output (0.1–0.2 ml/kg/hr) at the time of lidocaine initiation. The patient had been weaned off norepinephrine infusion before starting IVLI and did not require further vasopressor support during IVLI therapy. After the withdrawal of lidocaine, the patient's mental status improved over the next three days.

The other case involved a 65-year-old female with a history of congestive heart failure who underwent small bowel resection. The patient was transferred postoperatively to the ICU and started on IVLI at 0.5 mg/min. Thereafter, her hospital course was complicated by acute

kidney injury with a peak SCr of 1.51 mg/dL (baseline 0.86 mg/dL) and elevated liver enzymes with aspartate aminotransferase (AST) of 339 IU/L (baseline 24 IU/L) and alanine aminotransferase (ALT) of 523 IU/L (baseline 23 IU/L) as a result of sepsis while receiving IVLI. Two serum lidocaine levels were drawn while IVLI was continued at 0.5 mg/min (3.2 mcg/ml at 19 hours after the start of IVLI; 11.5 mcg/ml at 63 hours after the start of IVLI). Although the patient described the improvement in pain while on IVLI, she complained of brief episodes of dizziness when attempting to stand up. Due to the high lidocaine level and concerns for potential lidocaine-related adverse effects, IVLI was discontinued. After the withdrawal of IVLI, such symptoms were no longer noted.

Lastly, a 62-year-old male with a history of aortic valve replacement was admitted to the ICU after motor vehicle collision-related injuries. The lidocaine infusion was started on ICU day 2 and continued at 2.1 mg/min for 19 hours. His laboratory values at the time of IVLI were remarkable for an elevated serum SCr of 2.58 mg/dL (baseline 1.06 mg/dL). The patient experienced disorientation and confusion during IVLI therapy. The lidocaine infusion was discontinued to rule out all possible causes of altered mental status. No serum lidocaine level was drawn at that time. His mental status gradually improved after cessation of IVLI although its exact etiology remains elusive.

Discussion

Continuous lidocaine IV infusion therapy has been shown to be effective for the management of pain as an adjunct to a traditional opioid-based regimen in a variety of clinical settings.^{3,16,17} The available evidence suggested that IVLI could be a promising adjuvant analgesic to traditional opioids, especially in postoperative patients who require high doses of opioids for adequate pain relief due to its lack of respiratory depression and opioid-sparing effect.^{3,17} This is particularly important in the ICU setting because using high doses of opioids decreases respiratory drive, which may increase mechanical ventilation requirements. Nonetheless, the evidence evaluating the safety and effectiveness of IVLI therapy for acute pain in ICU patients is very limited. In most recent years, several systematic reviews of the use of perioperative IVLI for pain have been published, including a Cochrane review in which 45 randomized controlled trials with a total of 2802 participants were thoroughly analyzed.^{18–20} Among all these trials, however, only a handful of studies included ICU patients and attempted to assess ICU-related outcomes.^{16, 21–24} Furthermore, ICU patients with organ dysfunctions such as decreased cardiac output, kidney dysfunction, or hepatic impairment were not examined in detail in these studies. To the best of authors' knowledge, this study is the first attempt to address the effects of IVLI as an adjunctive analgesic exclusively in ICU patients with a wide range of medical diagnoses and comorbidities.

The present study found that IVLI appeared to reduce opioid requirements in ICU patients. None of the patients experienced serious adverse events during the study period. However, central nervous system adverse events, which led to the discontinuation of lidocaine infusion, were observed in three patients, but all these events were reversed upon the withdrawal of lidocaine therapy. This report did not provide sufficient data to determine predisposing risk factors for lidocaine-related adverse events. However, extra caution should

be taken when treating patients with congestive heart failure, shock, severe renal impairment, or hepatic disease, in a similar manner using IVLI as an antiarrhythmic.¹³

Previous studies have observed a concentration-dependent effect of IVLI on pain scores.^{10,25} Additionally, lidocaine plasma concentrations at which pain relief was achieved were below 3 mcg/ml (1.5–2.5 mcg/ml), which is at the lower end of the therapeutic range for patients treated for ventricular arrhythmias (1.5–5 mcg/ml).¹⁰ In concert with these findings, this report suggested that low-dose IVLI (2 mg/min), as opposed to higher doses, provided adequate pain control to most of our patients. Taken together, periodic monitoring of lidocaine serum levels may be considered in certain ICU patients such as those with predisposing risk factors for drug accumulation outlined above and who require long-term IV lidocaine therapy (>24 hours). It seems prudent to use IVLI at the lowest effective dose in order to minimize potential adverse effects associated with lidocaine therapy.

The following key questions pertaining to the use of lidocaine for pain in the ICU setting should be further explored in future studies. First, given the fact that a wide range of doses of IVLI has been used in the present and previous studies, uncertainty exists regarding optimal dosing for pain control.^{3,8} Additionally, there is a lack of evidence concerning the safety and tolerability of long-term IVLI therapy, particularly in ICU patients. Thus, future studies are warranted to determine the optimal dosing and monitoring regimen for IVLI that appears to be effective and devoid of serious side effects in ICU patients. Second, studies demonstrated that IVLI might not be effective for all types of pain.⁵ It has been suggested that IVLI seems more effective in postoperative abdominal surgery patients than in those who underwent non-abdominal surgery including cardiac, orthopedic, and thoracic surgery.^{3,8,18} At both participating institutions, IVLI has been primarily used for acute pain control in surgical ICU patients. For this reason, the vast majority of the included patients (n = 20; 95%) in this study were treated with IVLI following various types of surgeries, yet abdominal surgeries were performed in more than half of the patients. It should be further investigated whether IVLI also has beneficial effects on acute pain in non-abdominal surgical as well as non-surgical ICU patients.

The retrospective study design with a small sample size and no control groups was one of the major limitations inherent in the study design. Another limitation was that this study was conducted at two institutions that are different concerning the number of hospital beds, teaching status, the types of patients, pain assessment scales, etc. However, the heterogeneity in the enrolled patients across two institutions may be helpful in investigating the analgesic effect and safety of IVLI in more diverse ICU patients as a preliminary study, given that very few data exist on the use of IVLI for pain in ICU patients.

Conclusions

This retrospective study suggested that IVLI could be a safe and effective adjunctive treatment option for selected ICU patients with severe pain, especially those in whom opioid-induced respiratory depression is a concern. However, extra caution may be warranted when using IVLI in critically ill patients with organ dysfunction. The optimal role of IVLI as analgesia in ICU patients should be further investigated in future clinical trials.

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Figure 1.

Flow chart of patient inclusion

A flow chart of patients who were eligible for inclusion in this study at Mercy Medical Center and University of Florida Shands Hospital.

Figure 2.

Mean doses of intravenous lidocaine infusion at each time point. The value at each time point shows the number of patients (out of 21 included patients) who were included in the calculation of the mean doses at that point.

Figure 3.

Pain scores and morphine dose equivalents (MDEs) before (PRE) and after (POST) lidocaine infusion

The amount of opioids administered (as median parenteral morphine dose equivalents) and median pain scores during each 6-hour period over the first 24 hours before lidocaine infusion and after the start of infusion were documented.

Table 1

Patient demographics and clinical characteristics

Demographics and clinical characteristics	Number of patients (n= 21)	
Age, mean, years (SD)	66 (14)	
BMI, mean (SD)	30 (7)	
MSOFA scores, mean (SD)	4 (3)	
ICU LOS, days, mean (SD)	9 (13)	
Hospital LOS, days, mean (SD)	14 (13)	
Sex, n (%)	Male	14 (67)
	Female	7 (33)
Surgery, n (%)	Yes	20 (95)
	Gastrointestinal	12 (57)
	Vascular	3 (14)
	Neuro/spinal	2 (10)
	Thoracic	3 (14)
	No	1 (5)
Mechanical ventilation at the time of IVLI initiation, n (%)	Yes	8 (38)
	No	13 (62)
Reason for ICU admission, n (%)	Sepsis/septic shock	5 (24)
	Hemodynamic instability	11 (52)
	Respiratory failure	6 (29)
	Neurological conditions	3 (14)
	Post-operative complication	1 (5)
Past medical history, n (%)	Heart failure	3 (14)
	Liver disorders	1 (5)
	Arrhythmia	2 (10)
	Psychiatric disorders	3 (14)
	Seizure disorders	1 (5)
	Kidney disorders	6 (29)
	Respiratory disorders	6 (29)
Home opioid use, n (%)	4 (19)	
Baseline SCr, mean, mg/dL (SD)	0.98 (0.95)	
An increase in SCr ≥ 1.5 times baseline during IVLI infusion, n (%)	7 (33)	
Elevated liver enzymes ^a (baseline), n (%)	0(0)	

Demographics and clinical characteristics	Number of patients (n= 21)
An increase in AST and/or ALT $\geq 1.5 \times$ ULN during IVLI infusion, n (%)	3 (14)
Expired during this admission, n (%)	5 (24)

SD = standard deviation; BMI = body mass index; MSOFA = modified sequential organ failure assessment; ICU = intensive care unit; LOS = length of stay; IVLI = intravenous lidocaine; SCr = serum creatinine; AST = aspartate aminotransferase; ALT = alanine aminotransferase

^aAST (normal range, 11–47 IU/L) ≥ 1.5 times the upper limit of normal (ULN) and/or ALT (normal range, 7–53 IU/L) $\geq 1.5 \times$ ULN

Table 2

Non-opioid pain medications given to included patients 24 hours before (PRE) and after (POST) lidocaine infusion.

Patient	PRE-lidocaine infusion	POST-lidocaine infusion
1	APAP po 1650 mg, gabapentin 600 mg	APAP po 1300 mg, gabapentin 600 mg
2	None	None
3	None	None
4	None	None
5	None	APAP iv 4000 mg
6	None	None
7	Ketorolac iv 30mg	None
8	None	None
9	APAP po 1625 mg	APAP iv 3000 mg, ketorolac iv 60 mg
10	APAP po 1000 mg	APAP 1000 mg
11	None	None
12	Carisoprodol 350 mg	Carisoprodol 700 mg
13	None	APAP iv 4000 mg
14	APAP iv 1000 mg, ketorolac iv 30 mg	None
15	APAP iv 2000 mg	APAP iv 2000 mg
16	Gabapentin 3600 mg, nortriptyline 25 mg	Gabapentin 3600 mg, nortriptyline 25 mg
17	APAP iv 1000 mg	Gabapentin 200 mg
18	None	None
19	APAP iv 2000 mg	APAP iv 2000 mg, APAP po 650 mg
20	None	None
21	None	None

APAP = acetaminophen; po = by mouth; iv= intravenous