Safety and Tolerability of Lidocaine Infusions as a Component of Multimodal Postoperative Analgesia in Children

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OBJECTIVES Use of lidocaine as part of a multimodal approach to postoperative pain management has increased in adults; however, limited information is available regarding safety and tolerability in pediatrics. This study's primary objective was to evaluate the incidence of adverse effects related to lidocaine infusions in a sample of pediatric patients.

METHODS A retrospective analysis was conducted in pediatric patients receiving lidocaine infusion for the management of postoperative analgesia at the University of Virginia Health System.

RESULTS A total of 50 patients with 51 infusions were included in the final analysis. The median patient age was 14 years (range, 2–17 years). The most frequent surgeries were spinal fusion (30%), Nuss procedure for pectus excavatum (16%), and nephrectomy (6%). The mean $\pm$ SD starting rate was 13.6 ± 6.5 mcg/kg/min. The mean infusion rate during administration was 15.2 ± 6.3 mcg/kg/min, with 14.4 ± 6.2 mcg/kg/min at discontinuation. The mean length of therapy was 30.6 ± 22 hours. A total of 12 infusions (24%) were associated with adverse effects, primarily neurologic ones, including paresthesias in the upper extremities (10%) and visual disturbances (4%). The average time to onset was 16.2 ± 15.2 hours. Seven infusions were discontinued, whereas the remaining infusions resulted in either dose reduction or continuation without further incident. No patients experienced toxicity requiring treatment with lipid emulsion.

CONCLUSIONS In this sample, lidocaine was a well-tolerated addition to multimodal postoperative pain management in the pediatric population. Although adverse effects were common, they were mild and resolved with either dose reduction or discontinuation.

KEYWORDS lidocaine; pediatrics; postoperative analgesia

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Introduction

Pain management in the postoperative setting is an important concern because it can affect morbidity and mortality, quality of life, and the cost of hospitalization. According to a recent national survey, postoperative pain occurs in approximately 80% of patients.¹ Current standards for the management of postoperative pain focus on multimodal approaches using non-pharmacologic and pharmacologic therapies.² The most common types of pharmacologic treatment employed postoperatively include both opioid and non-opioid therapies. Although effective, opioid therapies have significant and unfavorable side effects, limiting their use. Opioid-induced respiratory depression is potentially life-threatening, requiring close monitoring, whereas the most commonly reported adverse effects include nausea (25%), constipation or postoperative ileus, sedation (20%–60%), and pruritus (2%–10%).^{3,4} In addition to short-term effects, long-term use is associated with the development of tolerance and dependence, which could potentially lead to addiction. As a result, the use

of other non-opioid therapies, such as lidocaine, has increased.²

Lidocaine is an amide-type local anesthetic that has analgesic, antihyperalgesic, and anti-inflammatory actions. Lidocaine works by preventing the generation and conduction of nerve impulses by altering the permeability of the cell membrane to sodium ions. Much of the support for the use of intravenous lidocaine for analgesia has been in the adult population. In 2010, McCarthy et al⁵ conducted a systematic review to evaluate the overall efficacy of lidocaine infusions on postoperative analgesia in patients undergoing a variety of procedures. In patients undergoing abdominal surgery, beneficial effects, including significant reduction in pain scores, were found in patients receiving lidocaine infusions compared with controls. Although information on adverse effects was not provided for all studies, 1 study included in the systematic review included a report of arrhythmias and bradycardia following lidocaine use. A 2015 Cochrane review evaluated 45 randomized controlled studies comparing lidocaine infusions to placebo, standard intravenous analgesics, or epidural

analgesia.⁶ There was a clinically relevant effect on pain scores within 1 to 4 hours following surgery. A update to the 2015 Cochrane review was published in 2018 stating that the effect on pain scores within one to four hours following surgery was no longer seen with the use of lidocaine infusions. Several studies reported adverse effects related to the lidocaine infusion, including lightheadedness, dizziness, visual disturbances, confusion, and perioral numbness/peripheral paresthesia; however, these effects were deemed by the investigators to be clinically insignificant.

Although data in adults are promising, there is little evidence for use of lidocaine infusions in the pediatric population. Gibbons et al⁷ evaluated the use of lidocaine infusions in 4 cancer patients ages 8 to 18 years with opioid-refractory pain. A 1 mg/kg loading dose was administered during 2 to 3 minutes in 10 of 14 lidocaine infusions evaluated, followed by a continuous infusion. The doses for the continuous infusion ranged from 15 to 50 mcg/kg/min and were titrated to maximal pain relief or emergence of intolerable side effects. Pain scores were significantly reduced 4 hours after initiation of the infusion as well as at cessation of the infusion. Adverse events included paresthesias and visual disturbances; however, these symptoms resolved without a change in therapy or with a reduction in the infusion rate.

Based on the positive findings in multiple studies in adults and this small case series, the University of Virginia Children's Hospital introduced a standard protocol for lidocaine infusions in pediatric patients, guided by the Acute Pain Service. The use of lidocaine infusions was restricted to patients with an Acute Pain Service consult. Prior to initiation, the patient had to be evaluated for any contraindications to lidocaine administration, including abnormal liver function, significant heart disease, sensitivity or allergy to lidocaine, or patients receiving lipid infusion for nutrition. During the administration of lidocaine, patients were monitored for blood pressure, heart rate, respiratory rate, oxygen saturations, pain level, and sedation level upon initiation and every 4 hours thereafter. Patients were also assessed for signs and symptoms of lidocaine toxicity every 4 hours. If mild to moderate symptoms of toxicity were suspected, the lidocaine infusion was to be stopped, a lidocaine level obtained, and notification sent to the Acute Pain Service resident physician. Mild to moderate severity was defined as dizziness, headache, tingling of the mouth or tongue, tremors, tinnitus, sedation, dysarthria, or metallic taste. If severe symptoms of toxicity were suspected (defined as seizures, cardiac dysrhythmias, loss of consciousness, or cardiac arrest), the infusion was to be stopped, the pediatric emergency response team contacted, and lipid emulsion rescue started based on the Lipid Rescue protocol.⁸ The purpose of this study was to review the safety and tolerability of patients treated under this protocol for the first 2 years of use.

Materials and Methods

The analysis was a single-center, retrospective cohort study. All patients at the University of Virginia Children's Hospital receiving lidocaine infusions between January 1, 2015, and December 31, 2016, were identified using the electronic medical record. Infants and children younger than 18 years were included in the study if they received a lidocaine infusion for postoperative analgesia. Patients were excluded from the study if they were age 18 years or older, if they received lidocaine for its antiarrhythmic properties or for analgesia not associated with surgery, or if the infusion was initiated more than 72 hours following surgery. This study was approved by the Institutional Review Board for Health Sciences Research at the University of Virginia. The primary objective of this study was to evaluate the incidence of adverse effects related to lidocaine infusions in the pediatric population. Secondary objectives include the range of doses used, time to appearance and resolution of adverse effects, and frequency of discontinuation of lidocaine. Baseline characteristics, including age, sex, height, and weight, were collected. Additional data collected included the preoperative diagnoses and surgical procedures performed, as well as the lidocaine infusion rate at initiation, discontinuation, and maximum rate. Data collection for each adverse effect included time of onset and description of adverse effect as documented by the Acute Pain Service resident physician, as well as any plasma lidocaine concentrations or the need for lipid rescue therapy. Descriptive statistics were used to analyze the data.

Results

A total of 67 patients received lidocaine infusions during the study period, approximately 0.02% of total surgical cases excluding cardiovascular surgery. Of those, 8 patients received lidocaine for reasons other than postoperative pain, including 1 treated for intractable pain and 4 receiving lidocaine as an antiarrhythmic. There were 5 patients older than 18 years, and 4 patients had an order for lidocaine but did not receive it. There were 50 patients receiving a total of 51 courses of lidocaine who met inclusion criteria. All patients received treatment in either the pediatric intensive care or intermediate care units, with continuous telemetry.

The patient population was primarily made up of well-grown adolescents, with a median age of 14 years (range, 2–17 years) and median weight of 48.7 kg (range, 11–130.3 kg). A total of 34 patients (68%) were female. A total of 40 infusions (80%) were started in the operating room, whereas the remaining ones started in the pediatric intensive care or intermediate care units. Table 1 describes the perioperative diagnoses and associated surgical procedures, with the most frequent surgeries being spinal fusion (30%), the Nuss procedure for pectus excavatum (14%), and nephrectomy (6%). None

Table 1. Perioperative Diagnoses and Surgical Procedures Performed

Perioperative Diagnosis (n)	Surgical Procedure Performed	n (%)
Scoliosis (13) Severe spinal cord compression (1) Congenital hemivertebra (1)	Spinal fusion	15 (30)
Pectus excavatum	Nuss procedure	7 (14)
Renal mass	Nephrectomy	3 (6)
Bilateral excessive anteversion/hamstring contractures	Surgical repair	2 (4)
Ureteropelvic junction obstruction	Pyeloplasty	2 (4)
Kidney and liver transplantation	Abdominal wall closure	1 (2)
Low pacemaker battery	Generator/right ventricular wire placement	1 (2)
Urine leak	Surgical washout/repair	1 (2)
Right lower extremity fractures	Surgical repair	1 (2)
Long-bone fracture	Surgical repair	1 (2)
Acquired equinus deformity of left foot	Achilles tendon lengthening, plantar fascia release, midfoot osteotomies	1 (2)
Median arcuate ligament syndrome	Open median arcuate ligament release	1 (2)
Mucopolysaccharidosis type 1	C2–C6 laminectomy; C2–T2 instrumentation	1 (2)
Multiple fractures due to motor vehicle accident	Open reduction with internal fixation	1 (2)
Spondylolisthesis at L5–S1	Spinal decompression and fusion	1 (2)
Pelvic mass	Left salpingo-oophorectomy	1 (2)
Low lumbar myelomeningocele	Bilateral femoral osteotomy	1 (2)
Apparent infectious disease of lungs	Thoracoscopic wedge resection of lung tissue	1 (2)
Right acetabulum dysplasia associated with myelomeningocele	Right hip acetabular osteotomy with allograft	1 (2)
Neurogenic bladder	Bladder augmentation	1 (2)
Jejunal polyp	Small bowel resection	1 (2)
Myelomeningocele	Posterior fossa decompression and fenestration of cervical cyst	1 (2)
Left ureteropelvic junction obstruction	Pyeloplasty	1 (2)
Left lower lobe mass	Left lower lobectomy	1 (2)
Burns on 39.5% body surface area	Excision of left abdomen and chest burns with autografting	1 (2)

C, cervical; L, lumbar; S, sacral

of the patients received a bolus dose prior to initiation of the lidocaine infusion. The mean starting rate of the lidocaine infusions, with SD, was 13.6 ± 6.5 mcg/kg/min. The mean maximum infusion rate during administration was 15.2 (6.3) mcg/kg/min, with a rate of 14.4 ± 6.2 mcg/kg/min at discontinuation. The mean length of therapy was 30.6 ± 22 hours.

A total of 12 infusions in 11 patients (22%) were associated with adverse effects, with an average time to onset of 16.2 ± 15.2 hours. The adverse effects experienced included twitching, tingling, or numbness in hands or feet ($n = 5$); perioral twitching, tingling, numbness, or swelling ($n = 3$); visual disturbances ($n = 2$); tinnitus ($n =$

1); nausea ($n = 1$); hives ($n = 1$); or confusion ($n = 1$; Table 2). One patient experienced oxygen desaturations and hypotension during the lidocaine infusion; however, this was felt likely to be due to receiving the combination of morphine and dexmedetomidine in addition. There were no reports of cardiovascular adverse effects. In 6 patients, the adverse effects resulted in the discontinuation of the lidocaine infusion with resolution of the symptoms. Reinitiation of the lidocaine infusions was not attempted because the patient's pain was well controlled on an oral regimen.

In 1 patient, the lidocaine infusion, running at a rate of 15.9 mcg/kg/min, was held for approximately 15.5

Table 2. Description of Adverse Effects Experienced During 12 Lidocaine Infusions (n = 11) and the Resultant Change in the Lidocaine Infusion

Adverse Effect Experienced	Rate of Lidocaine Infusion at the Time of Adverse Effect, mcg/kg/min	Resultant Change in Lidocaine Infusion
Twitching/tremors in the upper extremities	20.6	Discontinuation
Confusion, tingling in the upper extremities	20.1	Discontinuation
Tinnitus	12.8	Discontinuation
Numbness in the left hand	12.3	Discontinuation
Perioral tingling	15	Discontinuation
Oxygen desaturations and hypotension	15	Discontinuation
Perioral tingling, swelling, and numbness; tingling in lower extremities	8.8	Discontinuation
Mild nausea	20.2	Dose reduction
Tongue twitching	19.2	Dose reduction
Hives	15.9	Reintroduction
Blurry vision	9.6	Reintroduction
Diplopia; numbness in fingertips	25	No change

hours following the emergence of hives. The patient was evaluated by the resident for the Acute Pain Service with documentation of resolution. The lidocaine infusion was resumed at the same rate with no further adverse effects. In the patient who experienced nausea, the lidocaine infusion, running at a rate of 20.2 mcg/kg/min, was reduced by 50% with resolution of symptoms. Another patient received lidocaine infusions following 2 separate surgical procedures separated by 48 hours. During the first infusion, the patient experienced tongue twitching, which resolved after the infusion was held. The patient had no return of symptoms after the infusion was restarted at 9.6 mcg/kg/min, a 50% reduction from the original infusion rate. Following the second procedure, the lidocaine infusion was readministered at 9.6 mcg/kg/min, the previously tolerated rate; however, the patient experienced blurry vision, which resolved after the infusion was held. The infusion was again restarted at the same rate after 24 hours without a return of symptoms. An additional patient was noted to have diplopia and fingertip numbness; however, the patient's symptoms had resolved by the time of evaluation by the Acute Pain Service resident, without a change in the lidocaine infusion. All of the adverse effects were of mild to moderate severity with no severe effects experienced by any patient.

Lidocaine serum concentrations were obtained in only 6 of the 11 patients who experienced adverse effects. Of the 6 patients, 3 had the lidocaine infusions discontinued as a result of the adverse effect, whereas 1 patient had the infusion held then reintroduced. All were below 5 mg/L, the level associated with toxicity.⁴ Two additional patients had lidocaine concentrations obtained because of the inability to assess pain control as a result of ongoing sedation in one patient and non-

verbal status in the other. The concentrations obtained were 6 mg/L and greater than 12 mg/L, respectively. In the patient receiving ongoing sedation, daily lidocaine concentrations were obtained and the infusion was discontinued when the value was greater than 5 mg/L. A value of greater than 12 mg/L was considered an error in obtaining the sample because the repeat concentration was 1.1 mg/L. None of the patients who experienced an adverse effect were believed to have adverse effects significant enough to require lipid rescue therapy.

Discussion

In this small sample of patients gathered from the first 2 years of use at our institution, the administration of intravenous lidocaine for the management of postoperative pain was well tolerated in our study population. Most patients had no complications. A total of 22% of the patients experienced adverse effects, but the symptoms were typically mild and quickly resolved. Only 9 patients required a change in dose or discontinuation of therapy.

The results from our study were similar to those of previous reports. Gibbons et al⁷ found 35% of lidocaine infusions administered for opioid-refractory pain in patients with cancer were associated with adverse effects. As in our study, these adverse effects were primarily neurologic, including paresthesias and visual disturbances. The authors concluded the lidocaine infusion therapy was well tolerated, with the side effects being preferable to the patients than the refractory pain. Mooney and colleagues⁹ found a much higher incidence of adverse effects, with 79% classified as minimal and 21% classified as moderate/severe. The most common symptoms were neurologic, including

numbness and tingling, followed by nausea and vomiting. The authors found these results encouraging and drew conclusions similar to those of our study and the Gibbons et al⁷ study. As a result of the mild severity of the adverse effects and subsequent resolution of symptoms, there were very few plasma lidocaine levels obtained. Similar to other studies, none of the appropriately obtained levels were outside of the therapeutic range, with the exception of one which resulted in discontinuation of the lidocaine infusion without the presence of adverse effects.

This study was limited by the retrospective design and a small sample size. Although lidocaine infusions are being used more commonly at our institution, they are not yet considered a routine part of postoperative care. The evaluation of adverse effects was limited by the subjective assessment performed by the Acute Pain Service resident physician. There was often a delay between the first appearance of symptoms and the evaluation by the resident, and in several cases the symptoms had resolved by the time the patient was seen.

In conclusion, our study suggests that lidocaine infusions appear to be a safe option for a multimodal postoperative pain management in the pediatric population. Although adverse effects occurred in many patients, they were mild and resolved with discontinuation or dose reduction. A prospective study with assessments performed on a scheduled basis using a standardized documentation tool would better assess the clinical significance of the adverse effects seen with lidocaine infusions. Additional prospective, randomized, controlled studies are recommended to assess the clinical efficacy of lidocaine on management of postoperative pain and its effect on use of opioid therapies.

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