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Continuous Lidocaine Infusions to Manage Opioid-Refractory Pain in a Series of Cancer Patients in a Pediatric Hospital

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Background. Research on the safety and efficacy of continuous lidocaine infusions (CLIs) for the treatment of pain in the pediatric setting is limited. This article describes a series of pediatric oncology patients who received lidocaine infusions for refractory, longstanding, cancer-related pain. ***Procedure.*** This is a retrospective review of patients who underwent lidocaine infusions to manage severe, opioid-refractory, cancer-related pain. Four patients ranging in age from 8 to 18 years were admitted to a pediatric hospital for their medical conditions and/or pain management. Structured chart review established demographic and diagnosis information, infusion rates, side effects, and efficacy of infusions in providing pain relief. Lidocaine bolus doses, infusion rates, serum concentrations, and subjective pain scores were analyzed. ***Results.*** Median pain scores prior to lidocaine infusions were 8/10, falling to 2/10 at the infusion termination ($P < 0.003$), and rising to 3/10 in the first 24 hr after lidocaine ($P < 0.029$ compared to preinfusion pain). The infusions were generally well tolerated, with few side effects noted. In most cases, the improvement in pain scores persisted beyond termination of the infusion. ***Conclusions.*** CLIs were a helpful adjuvant in the four cases presented and may be an effective therapy for a more diverse array of refractory cancer pain. The majority of patients experienced pain relief well beyond the metabolic elimination of the lidocaine, corroborating a modulation effect on pain windup. Additional research regarding infusion rates, serum concentrations, side effects, and outpatient follow-up in a larger group of patients will provide additional insight into the role and safety of this therapy in children. Pediatr Blood Cancer 2016;63:1168–1174. © 2016 Wiley Periodicals, Inc.

Key words: cancer; chronic pain; lidocaine; pediatrics

INTRODUCTION

The World Health Organization ladder describes an approach to medical therapies for pain management starting with nonopioid therapies for mild pain, and progressing to opioid medications for moderate to severe pain. However, in cases of severe or refractory pain where the use of first-line and opioid therapies is inadequate, ineffective, or creates untoward side effects, the number of viable alternatives for pain management is limited. Lidocaine is an amide local anesthetic as well as a Class 1B antiarrhythmic agent. It is known to block nerve conduction via sodium channels on sensory neurons and inhibit G protein coupled receptors and NMDA receptors, giving it analgesic, antihyperalgesic, and anti-inflammatory actions. By inhibiting individual sodium channels, the inward sodium current is reduced, thus impeding transmission of pain impulses to the central nervous system (CNS). With rising lidocaine concentrations, neural transmission is increasingly diminished, eventually inhibiting sensory and motor function to the point of surgical analgesia and clinical motor blockade. Local injections, epidural administration, and nerve blocks achieve high regional concentrations while diminishing risks of systemic toxicity and CNS depression. However, systemic administration can also reduce neural transmission in circumstances where regional administration is not practical.[1] In many circumstances, it can be systemically administered at doses that effectively reduce pain and nociceptive sensation without impacting other sensory or motor function. Intravenous lidocaine exhibits a steep dose–response curve such that minimal increases in dose result in large increases in pain relief.[2]

In several reports in the adult literature, lidocaine has proven to be effective in chronic pain management for opioid-refractory pain.[3–6] Lidocaine infusions have also been useful in ameliorating daily and migraine headaches in adult patients.[7] And in adult patients afflicted with various oncologic diagnoses, Sharma et al. demonstrated that intravenous lidocaine was effective in reducing pain scores.[15] Interestingly, Schwartzman et al. reported that a cohort of complex regional pain syndrome patients enjoyed improved pain control for 3 months following a 5-day infusion of lidocaine. This implies that lidocaine may partially "reset" dysregulated pain pathways.[6]

Additional supporting information can be found in the supporting information tab for this article.

Abbreviations: CLI, continuous lidocaine infusion; PICU, Pediatric intensive care unit

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Recently, the use of lidocaine therapy for pain management in the pediatric population has been documented. Lidocaine infusions helped control refractory pain in case reports of pediatric patients with cancer and primary erythromelalgia.[8–10,14] Additionally, lidocaine infusions were effective in managing pain in a series of adolescent and young adult patients suffering from headaches and neuropathic pain states.[9,10]

Since information on lidocaine infusions for refractory pain in pediatrics is underrepresented in the current literature, we aim to describe the effectiveness of continuous lidocaine infusions (CLIs) used in several patients with cancer pain. CLIs in this patient population are an important therapeutic option to consider for pediatric patients suffering from cancer-related pain who have either exhausted all other classes of pain medication, or whose pain therapy is limited by medication side effects.

METHODS

After Institutional Review Board approval was obtained, the electronic medical records of patients who had received lidocaine infusions to manage severe, refractory pain were reviewed. A total of four pediatric patients with diverse oncologic diagnoses resulting in longstanding refractory pain were identified. Pain was considered refractory when dose escalations of opiates did not result in clinical improvement in pain and/or when other adjuvant therapies (e.g., ketamine, gabapentin) failed to achieve pain scores tolerable to patients. Eligibility to receive lidocaine was determined by primary managing clinicians. The four patients received lidocaine infusions between January 2010 and December 2013. During this time period, there were a total of 14 infusions.

Although care was not protocolized, all patients were admitted to the Pediatric Intensive Care Unit (PICU) to initiate the infusions, where cardiorespiratory monitoring and frequent neurological assessments were employed during initial therapy. The institutional standard for bolusing lidocaine nonemergently is over 2–3 minutes. If lidocaine infusion doses were stable and patients were medically stable after initiation in the PICU, infusions could be continued on the general care units. Lidocaine infusions were delivered via an infusion pump with lidocaine infusion concentrations of 8 mg/ml. Infusions were initiated and titrated at the discretion of the pediatric critical care team in consultation with the palliative care and acute pain service teams.

Demographic data including age, sex, and weight were collected by the study members through structured chart abstraction. Additional data collection included the following: diagnosis, length of therapy, continuous infusion rates, loading doses used, serum lidocaine concentrations, subjective pain scores, and side effects potentially related to the lidocaine infusion. Patient-reported pain scores were measured on a 0–10 numeric scale (0 for no pain and 10 for worst pain).

Conventional descriptive and comparative biostatistical analyses were made, including correlation coefficients and Wilcoxen Rank Sum tests using cloud-based statistical software (StatCrunch by Integrated Analytics LLC, distributed by Pearson Education). Unadjusted p values are provided in the comparisons of pain scores before, during, and after CLIs (Fig. 3), and a conservative Bonferroni correction for these six comparisons would establish a significant p value of <0.008.

RESULTS

The four patients, ages 8, 16, 17, and 18 years, received a total of 14 infusions among them. There were two females and two males. All patients suffered from advanced solid tumors (teratoma, osteosarcoma, rhabdomyosarcoma, and neurofibromatosis with malignant transformation into a malignant peripheral nerve sheath tumor). These patients had been previously treated with a multimodal approach to their longstanding pain of weeks to months—with days to weeks of acutely escalating pain severity. They had been prescribed combinations of opioid and nonopioid medications to manage pain without satisfactory relief prior to initiation of lidocaine therapy (Table I), and two of four patients had pain features with stigmata of neuropathic pain that had partly responded to neuropathic pain agents (gabapentin, pregabalin, and duloxetine). All pain medications that patients had been taking prior to lidocaine were continued during CLIs. However, in three of four patients the total opiate dose was reduced by at least 50% during their first CLI, after which re-escalation of these same opiates occurred to doses modestly lower than before CLI therapy.

Details of lidocaine loading doses, infusion rates, duration of infusions, and side effects noted are given in Table I. During the reviewed 4 years, the patients each underwent two to eight infusions with a median duration of infusion of 2.15 days (range 5 hr–17 days). A lidocaine loading dose of 1 mg/kg was administered in 10 of 14 (71.4%) of the infusions. For nonemergent medication boluses prior to infusions, our institution's standard loading procedure is over 2–3 minutes on an infusion pump. The continuous infusion doses ranged from 15 to 50 μg/kg/min. The median initial and maximum infusion rates were 30 and 36 μg/kg/min, respectively. The infusions were titrated to either maximal pain relief or emergence of intolerable side effects.

Three of our patients experienced adverse events that could have resulted from the lidocaine infusions. These side effects included changes in vision, visual hallucinations, and paresthesias. These symptoms occurred in 35% (five of 14 infusions); in all cases, the symptoms resolved either spontaneously or with decreasing the infusion rate. No patients experienced seizures or cardiac complications during their inpatient lidocaine infusions.

Serum concentrations were measured in some of the patients (three of four) during some of the lidocaine infusions (10 of 14) at the discretion of the primary service, palliative care, and acute pain service teams. The serum lidocaine levels ranged from 1.7 to >40.1 μg/mL, the upper limit of quantification by the assay. Lidocaine level data were evaluated for outliers for the purpose of this analysis, and five of 60 levels were excluded for being greater than 28 μg/mL (four of them beyond measurable limits). Exclusions were done with thorough review to ensure (i) the patients' providers believed these to be contaminants, (ii) there was a lack of correlation with changes in clinical status or management, and (iii) timely repeat values were obtained (available in three of five cases).

Lidocaine serum concentrations corresponding with infusion rates for patients B–D are displayed in the left panel of Figure 1. There was a statistically insignificant weak correlation

TABLE I. Patient Demographics, Previous Pain Therapies, and Lidocaine Infusion Details

Patient	Age (years)	Weight (kg)	Gender	Primary diagnosis	Previous pain therapies	Clinical status	No. of infusions	Loading dose (mg/kg)	Length of each infusion (days)	Initial dose for each infusion (μg/kg/min)	Dose range for all infusions (μg/kg/min)	Possible side effects
A	17	59	♀	Metastatic osteosarcoma with primary mandible tumor	Hydromorphone, methadone, ketamine, dexamethasone, diazepam, cannabinoids	Deceased (17 months after initial infusion)	1[a]	0	2	35	35–40	None
B	18	68	♂	Metastatic teratoma of the retroperitoneum	Hydromorphone, methadone, ketamine, diazepam, lorazepam	Deceased (4 months after initial infusion, continued at time of death)	3	1 0 0	3 17 10	15 30 30	15–50	Blurred vision, visual hallucinations (third infusion)
C	16	90	♀	Neurofibromatosis type I with malignant peripheral nerve sheath tumor	Methadone ketamine, pregabalin, duloxetine, ibuprofen	Deceased (19 months after initial infusion)	8	1 1 1 1 1 0 1 1	2 4 0.4 0.2 0.6 1.5 1.6 1.9	15 15 33 33 33 36 25 33	15–38	Paresthesias (first/eighth infusions)
D	8	32	♂	Metastatic rhabdomyosarcoma	Hydromorphone, gabapentin, methadone, ketamine, methylprednisolone, lorazepam, dexmedetomidine	Deceased (3 months after initial infusion, was receiving CLI for pain management at time of death)	2	1 1	10 10	20 20	20–40	Paresthesias (both infusions)

[a] Patient received one additional infusion outside of our institution while in home hospice.

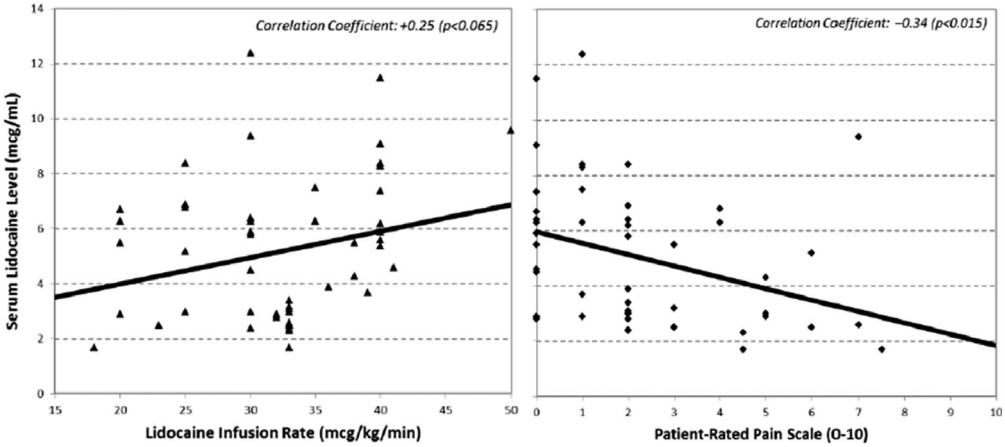

Fig. 1. The left panel shows the scatter plot and best fit trend line of serum lidocaine level versus lidocaine infusion rate (triangles). The right panel shows the scatter plot and best fit trend line of serum lidocaine level versus patient-rated pain scores (diamonds), with a statistically significant, moderately negative correlation coefficient.

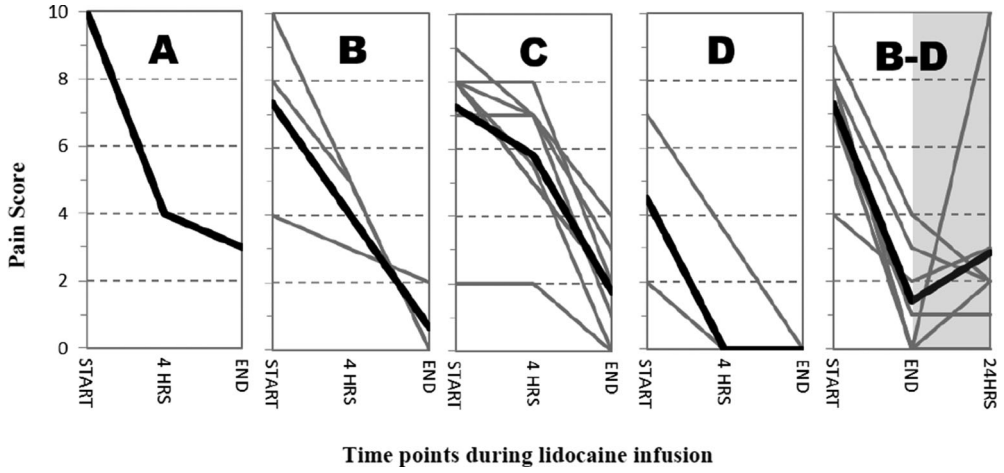

Fig. 2. The four leftmost panels represent the four patients (A–D) with pain ratings during the 14 individual lidocaine infusions (gray lines) and an average of all responses for that patient (heavy black lines). Pain ratings are recorded at initiation (START) of the lidocaine infusion, 4 hr into the infusion (4 HRS), and at the termination (END), although this time point varied between infusions from 6 hr to 17 days. The rightmost panel represents the seven individual lidocaine infusions where documented pain scores were available for the 24 hr after cessation of the lidocaine infusion, and the highest pain score recorded in that 24 hr without lidocaine (gray shaded) is noted (24 HRS).

between increasing infusion rates of lidocaine and serum levels in all patients. The slope of the relationship between infusion rate and serum lidocaine levels varied among patients, with some having higher serum levels at the same infusion rate (data not shown). In addition, patients' pain scores were significantly inversely correlated with their serum lidocaine concentrations, as shown in the right panel of Figure 1, indicating that improved subjective pain scores were associated with increasing serum lidocaine concentrations.

Figure 2 summarizes the four patients' pain scores at key points during and after their infusions. Compared to pain scores at initiation, scores were significantly reduced 4 hr into the infusion and further significantly reduced by the end of the infusion. In the 24 hr after cessation of the lidocaine infusion, pain scores rebounded slightly, but nonsignificantly, and remained significantly lower than pain scores at initiation (Fig. 2). Absolute pain score reduction was greater for severe versus moderate pain states prior to lidocaine therapy, but similar in proportional reduction. Episodes with pain scores of 8–10 at initiation of therapy (n = 9 infusions) showed reductions in average pain score from 8.6 to 1.8, a change of –6.8 (–79%), whereas starting pain scores of 2–7 (n = 5 infusions) showed average pain score reduction from 4.4 to 0.6, a change of –3.8 (–86%). All patients received more than one CLI, with repeat infusions predicated on the clinical impression that they responded favorably to a prior CLI (one in home hospice, not included in this analysis).

The left panel of Figure 3 graphically depicts the four patients' pain scores at the initiation of lidocaine infusion, 4 hr after initiation, and the termination of the infusion for all 14 infusions. The difference in pain scores between the initial pain

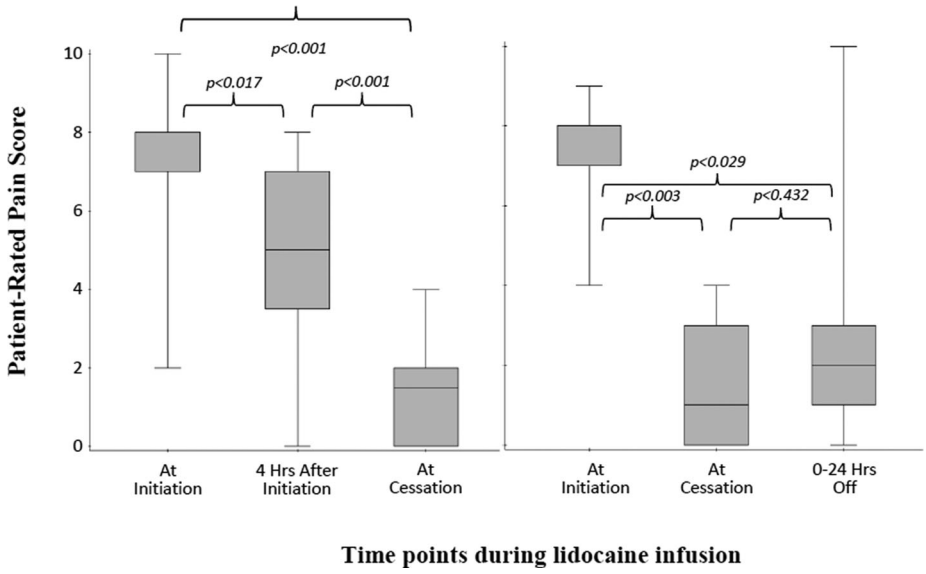

Fig. 3. The left boxplot shows pain ratings during the 14 individual lidocaine infusions for all four patients (A–D). The right boxplot shows pain ratings during and after the seven individual lidocaine infusions in three patients (B–D) where documented pain scores were available for the 24 hr after cessation of the lidocaine infusion (the highest pain score recorded in that period is noted).

TABLE II. Examples of Long-Term Pain Relief Subsequent to Cessation of Lidocaine Infusions

Patient	Pain score prior to lidocaine infusion	Pain score at end of lidocaine infusion	Recorded pain score remote from lidocaine infusion
A	10	3	4 at 4 months
B	4	2	0 at 6 days
C	9	4	2 at 2 weeks
D	7	0	0 at 2 days

score and 4 hr into the infusion, 4 hr into the infusion and termination of infusion, and initiation and termination pain scores are all statistically significant. The right panel of Figure 3 depicts time point including the 24 hr after termination of the infusion, in the patients in whom these data were available. The reported pain scores were largely unchanged in the 24 hr after termination of the infusion. Documentation of pain scores after 24 hr was sparse; however, in one series from each of the four patients, reduced pain scores were identified between 2 days and 4 months off lidocaine (Table II).

DISCUSSION

Opioids are usually the first-line pharmacologic agents for moderate to severe pain, but in some instances neuropathic and oncologic pain can be opioid-refractory and challenging to manage. Our series describes four patients suffering from malignant pain as a result of invasive solid tumors in various anatomic locations who underwent a total of 14 lidocaine infusions. This therapy was well tolerated and markedly reduced pain scores for at least 24 hr after cessation, and occasionally much longer periods.

Data have shown that the analgesic response to intravenous lidocaine is characterized by a precipitous "break in pain" over a narrow dosage and concentration range for a given patient.[2] Prior studies of intravenous lidocaine have also found that symptoms of toxicity develop in a reasonably sequential and predictable manner based on serum lidocaine levels. Serum levels of 4–6 mcg/ml may be associated with lightheadedness, perioral numbness, and dizziness, which may progress to visual/auditory hallucinations and muscle twitching at levels of 8 mcg/ml. Progression to convulsions, coma and respiratory arrest/cardiovascular collapse occur around serum levels of 12, 16, and 20 mcg/ml, respectively.[8] The early expected toxicities (lightheadedness and sensorium disturbances) for a relatively short/finite infusion time were preferable to inadequately controlled pain, so the approach employed was titration of lidocaine infusions either to a pain score of zero or emergence of early, tolerable toxicities. As these patients were managed in an ICU where benzodiazepine therapy was readily available, infusions were titrated to achieve adequate pain control, even in the presence of fairly high serum levels and infusion rates in some cases. This was directed by patient priorities, in an effort to balance pain management and the side effect profile of intravenous lidocaine therapy, which is known to cause seizures at higher serum levels.[8] This approach may not be advisable in patients who either would not prioritize pain management over the emergence of seizures or even more serious side effects, or in patients receiving therapy on the ward or at home, where the treatment of seizures may be difficult. In our series of 14 infusions, there were no seizures noted during lidocaine therapy.

Due to a paucity of information on the safety of this therapy in the pediatric setting, the initial CLI for each patient was started in the PICU where the intensive care, palliative care, and acute pain service teams collaborated. These infusions were initiated for high pain scores reported by patients, which were not responsive to escalating opioids or other treatments, including adjuvant nonopioid agents such as ketamine, gabapentin, and steroids. In all cases, the patients' pain scores were lower

during and immediately after the lidocaine infusion. In some cases, the effect was more dramatic and prolonged than in others, but as became evident with retrospective chart review, the patients' pain scores were not assessed at scheduled intervals, complicating structured analyses, and long-term follow-up. Interestingly, subjective pain scores were more dramatically decreased when the patients reported higher scores prior to therapy. This is consistent with previously published studies that demonstrated that the magnitude of the response to therapy correlated with the degree of pain intensity at the start of therapy.[3,9]

A significant safety concern with systemic lidocaine administration is risk of seizures, relating to both a direct effect and that of the predominant hepatic metabolite monoethylglycinexylidide, which can accumulate in the setting of renal dysfunction. There is also concern regarding the pharmacokinetics of amino amides (e.g., lidocaine and bupivacaine) in neonates and infants, and members of these age groups were not represented in our series. Due to reduced metabolic clearance and protein binding, neonates and infants can develop drug and metabolite accumulation and resultant toxicity during administration of these medications.[12] However, among the 8- to 18-year-old patients we describe, the lidocaine infusion therapy was well tolerated. Side effects observed were primarily paresthesias, blurry vision, and visual hallucinations, but in all cases were preferable to the patients than the uncontrolled pain. Two patients had episodes of paresthesias during therapy. Patient C had paresthesias in the right lower extremity during the first lidocaine infusion, which may have been due to the primary disease process, as the patient was experiencing similar symptoms on admission prior to therapy. During this patient's eighth infusion, tingling was reported when the lidocaine infusion was increased from 32 to 35 μg/kg/min. This symptom resolved when the infusion was reduced to 32 μg/kg/min and maintained at this rate. Patient B reported blurry vision and visual hallucinations during the third infusion; however, this patient was receiving adjuvant analgesic ketamine and high dose dexamethasone at the time, which may have been contributory, as the infusion rate was not changed, and the symptom spontaneously resolved.

Serum lidocaine concentrations were not reliably correlated with infusion rates, and the degree of serum lidocaine concentration increase as a result of infusion rate varied among patients. For example, patient B had concentrations of 6–7 μg/mL when receiving an infusion of 35 μg/kg/min, whereas patient C had concentrations of 2.5–3.5 μg/mL during an infusion of 33 μg/kg/min. It is likely that organ function, drug interactions, and other comorbidities affect the serum concentrations in individual patients. Patient pain scores improved as serum lidocaine concentrations increased, although this inverse correlation was weak. Because of both interindividual variability in metabolism and tolerance, titrating infusion to effect and monitoring serum lidocaine levels to define a particular patient's therapeutic window may be more useful than predefined infusion ranges and toxicity thresholds. In contrast to intravenous lidocaine's use as an antiarrhythmic, the individualized approach used in these children with uncontrolled pain and, ultimately, terminal cancers is consistent with palliative care models—carefully balancing risks and benefits. It should be emphasized that pain management was of utmost priority for these specific patients, and therefore infusions were maintained and adjusted with this as the primary goal. A more conservative approach may be necessary for patients who are not at end of life, or in whom the emergence of side effects is unsettling or undesirable.

As reported in previous literature, several of the study patients' analgesic benefit persisted days to months beyond the termination of the lidocaine infusion.[9,11] This is an interesting phenomenon, given that the half-life of lidocaine is 90–120 minutes. The direct pharmacologic action of lidocaine would have been terminated soon after discontinuing the infusions, suggesting that lidocaine exhibits unconventional pharmacodynamics on longstanding or wound-up pain. Further research may clarify the mechanism of this prolonged clinical benefit observed in some patients. It may relate to interrupting sensitization or intensified pain from positive feedback loops, or alternately by mitigating opiate-induced hyperalgesia. Lidocaine's impact on complement and proinflammatory cytokines may also contribute to pain modulation.[4] Ultimately, some of the effects may not be specific to lidocaine per se, but rather relate to an effective interruption of the physiology leading to wound-up pain states that could be potentially achieved with other agents.

Of note, one of our patients who did not tolerate weaning of the lidocaine infusion (i.e., did not experience the sustained, postinfusion relief) was successfully transitioned to an oral sodium channel blocker, mexiletine, making it feasible to discharge him from the hospital without an ongoing intravenous therapy. Successful transition from lidocaine infusion to oral mexilitine has previously been reported in the adult literature.[13] Thus, this may present a viable outpatient option for patients in whom intravenous lidocaine is effective in providing opiate-refractory analgesia but whose benefits appear to be from the direct mechanism of the sodium channel blockade.

Limitations of this case series analysis include its retrospective design, small sample size, and absence of pediatric patients less than 8 years of age. It is inadequately powered to reliably detect adverse complications, but is consistent with the safety profile of lidocaine reported in other studies. Strengths of this analysis include applicability across a wide range of cancer diagnoses, reproducibility within and among patients, and objective pharmacokinetic data corroborating the subjective patient-reported outcome measure of pain.

Overall, this review indicates that lidocaine infusion therapy was a well-tolerated and useful adjuvant for these pediatric patients with cancer pain refractory to conventional and even other nonconventional, second- and third-tier therapies such as steroids, gabapentin, ketamine, and cannabinoids. This therapy was associated with some side effects that were tolerable, and infusions were able to be transitioned to non-ICU settings. Given the relative inexperience with continuous intravenous lidocaine therapy for this indication in pediatrics, and because of the complex multidisciplinary, multiprofessional care coordination required, our institution subsequently developed a clinical practice guideline (see Supplementary Appendix). This guideline is intended to reduce unnecessary practice variation among providers within our institution and was based on the general approaches successfully used in these patients and described in the published literature. Further clinical studies are warranted to better describe the therapeutic role, safety, and optimal management of intravenous lidocaine infusions for the treatment of opioid-refractory pain in the pediatric population as well as

its potential application in more diverse pain syndromes among children.

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