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Multivariate Analysis of Chronic Pain Patients Undergoing Lidocaine Infusions: Increasing Pain Severity and Advancing Age Predict Likelihood of Clinically Meaningful Analgesia

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Abstract

Objectives—The proportion of chronic pain patients with suspected neuropathic pain who will have clinically meaningful pain relief with intravenous (IV) lidocaine and the clinical characteristics that identify these patients have not been described previously.

Methods—We conducted a cohort study of 99 patients who underwent IV lidocaine infusions for suspected neuropathic pain. An 11-point Numerical Rating Score (NRS) of pain intensity was recorded at the beginning and end of each infusion. A predefined literature-based criteria for “clinically meaningful” reductions in pain score was used to classify patients as responders or nonresponders. Multivariate logistic regression was used to determine clinical variables that predicted an increased likelihood of being a lidocaine responder.

Results—The mean reduction in NRS during lidocaine infusions was 2.34 (95% confidence interval 2.83–1.85, $P < 0.001$). Forty-two percent of patients (95% confidence interval 32.5%–52.8%) had NRS reductions of 30% or greater and met the predefined criteria as lidocaine responders. Univariate and multivariate analyses indicated that advancing age and pain severity significantly increased the odds of being a lidocaine responder. Controlled for all other factors, each decade of advancing age increased the odds of being a lidocaine responder by 36%. Each 1-point increase, on an 11-point scale of baseline pain severity, increased the odds of being a lidocaine responder by 29%.

Discussion—IV lidocaine effectively reduces pain in a minority of patients suspected of having neuropathic pain. Pain severity and patient age can be used to target therapy to those most likely to respond.

Keywords

intravenous lidocaine; systemic lidocaine; lidocaine; neuropathic pain; chronic pain; palliative care; lidocaine infusion; cohort study; logistic regression; aging; prediction

Neuropathic pain, pain caused by an injury to nerves, afflicts an astounding 5.5 million Americans.¹ Patients with neuropathic pain are at high risk of being undertreated. As many as 60% of patients with neuropathic pain do not receive appropriate anticonvulsant, antidepressant, or antiarrhythmic medications for relief of neuropathic pain.^{2,3}

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Lidocaine can be safely and effectively administered intravenously (IV) to treat neuropathic pain.^{4,5} Lidocaine's efficacy has recently been confirmed and reviewed in a meta-analysis by Tremont-Lukats, et al.⁶ Nonetheless, little has been published to clarify the degree of relief which can be expected, and the proportion of patients who will achieve relief. Furthermore, little has been done to identify the patients most likely to benefit from systemic lidocaine. One cohort study of IV lidocaine treatment in peripheral neuropathic pain patients reported that response to lidocaine is predicted by the severity of mechanical allodynia, and the degree of sensory impairment.⁷ Other variables such as age of patients, pain duration, and pain severity did not significantly impact the degree of relief in response to systemic lidocaine.⁷

The same group reported on another cohort of patients with central neuropathic pain treated with IV lidocaine.⁸ They reported that lidocaine significantly reduced ongoing spontaneous pain in patients with central neuropathic pain. This study did not evaluate factors possibly associated with analgesia such as age, sex, pain duration, severity, or the degree to which patients had been refractory to previous treatments.⁸ The power of these studies to identify factors predicting analgesic response was limited by the small number of patients studied. Other studies have similarly been limited by small numbers or by the lack of statistical analysis.^{9,10}

Therefore, there remains a paucity of data on how patients respond to systemic lidocaine and which clinical characteristics determine the degree of analgesic efficacy in patients given IV lidocaine. Our center has previously reported protocols to administer computer-controlled targeted infusions of IV lidocaine as a therapeutic tool.¹¹ We have not previously reported on the efficacy of IV lidocaine within this setting, and to our knowledge others have not reported on similar experience in the literature.

We conducted a retrospective cohort study of chronic pain patients with a clinical suspicion of neuropathic pain, who underwent a lidocaine infusion at our center. On the basis of our clinical experience, we hypothesized that the analgesic response to IV lidocaine would be bimodal with clear responders and clear nonresponders. We also hypothesized that more refractory patients, specifically patients with pain of longer duration and patients who had failed more previous analgesics, would be less likely to respond to IV lidocaine. To test our hypotheses, we identified the distribution of pain relief in our cohort, identified lidocaine responders as those patients with Numerical Rating Score (NRS) reductions of 30% or greater based on literature defined criteria for meaningful reductions in pain scores,^{12–14} and conducted multivariate logistic regression to identify factors associated with increased odds of being a responder to IV lidocaine. Our goals were to clarify what proportion of patients will achieve relief, what degree of relief can be expected, and identify the patients most likely to benefit from systemic lidocaine.

MATERIALS AND METHODS

Design and Setting

We conducted a retrospective cohort study of patients who had undergone IV lidocaine infusions for suspected neuropathic pain at the Stanford Pain Management Center, a tertiary referral-based pain management center.

Study Participants

We screened 635 alphabetically sequential charts of patients currently being treated in our clinic to identify patients who had undergone IV lidocaine infusions. Patients were given lidocaine infusions when neuropathic pain was suspected based on the presence of allodynia,

hyperalgesia, hyperpathia, hyperesthesia, and hypoesthesia. All patient charts with records of IV lidocaine infusions were eligible and included.

Lidocaine Infusions

At the time of infusion, patients had an IV catheter placed. Over approximately 1 hour, patients received a step-wise, computer-controlled, lidocaine infusion to a targeted plasma level of 5 µg/mL using a paradigm previously developed in our institution.¹¹ Specifically, computer-controlled infusion was accomplished using 2% lidocaine injected by a Harvard 200 infusion pump (Harvard Apparatus; Holliston, MA) driven by STAN-PUMP software programmed with patient's weight, height, age, and sex. STANPUMP software is openly available at: <http://anesthesia.stanford.edu/pkpd> at no charge. Patients provided initial and final NRSs of spontaneous pain. The NRS is an 11-point scale (0 to 10) of spontaneous pain intensity. The NRS is a well-accepted scale with high reliability, validity, and correlation with both Visual Analog Scales of pain and patients' perceived global assessment of change. The NRS has advantages over a Visual Analog Scale, including ease of understanding by participants and improved participant data reporting.¹⁵ Blood pressure and pulse oximetry were monitored continuously throughout the infusions.

Data Collection and Independent Variables

Lidocaine infusion records were completed during the infusions and included initial and final NRSs of pain. Independent variables analyzed to predict subsequent lidocaine success were obtained from clinic intake forms filled out by the patients before their infusions at the time of their initial evaluation in the pain clinic. Independent variables examined included the patient's age, sex, duration of pain problem, previous trials of anticonvulsants, tricyclic antidepressants, venlafaxine, duloxetine, antiarrhythmics, opiates, and nonsteroidal anti-inflammatory medications. We had patient recorded information on these variables for 91 patients. For another 8 patients who completed lidocaine infusions, these variables were recorded by the physician.

Statistical Analysis

We defined lidocaine responders as those patients with a decrease in NRS of 30% or more based on studies, suggesting that smaller changes are of limited clinical relevance in patients with chronic pain.^{12–14} Initial analysis examined patient's age, sex, pain severity, pain duration, number of opiates tried, number of antineuropathic medications tried, and number of nonsteroidal anti-inflammatory medications tried, with comparison between lidocaine responders and nonresponders using Student *t* test or χ^2 test as appropriate. All statistical tests were 2-sided. A *P* value less than 0.05 was considered statistically significant. Normality of data was assessed with Kolmogorov-Smirnov test. Logistic regression is preferred to linear regression when the data do not meet normality assumptions and the outcome variable is dichotomous.¹⁶ The logistic regression model was used to adjust for demographic and clinical factors in analysis of variables associated with being a lidocaine responder. Model selection was performed by stepwise reduction from the full model until overall model strength was maximized as assessed by likelihood ratio. Hosmer and Lemeshow test of model fit of logistic model was used to test for lack of fit. Odds ratios with 95% confidence intervals (CIs) were calculated. SAS version 9.1 (SAS Institute, Cary, NC) was used for all analysis.

RESULTS

Patient Identification

Six hundred thirty-five charts were screened. One hundred and four patients had undergone IV lidocaine infusions. Five patients requested discontinuation of lidocaine infusions in mid-infusion owing to unpleasant nausea or dizziness that resolved upon discontinuation of the infusion. These patients did not have final NRS scores recorded and could not have a change in NRS calculated. These 5 patients did not seem to differ significantly from those who completed the infusion, but their small number gave little power to identify such differences. The remaining 99 of 104 completed the infusion and were included in the analysis. There were no serious adverse events or side effects. Patient characteristics are shown in Table 1.

Lidocaine Analgesia

Forty-two percent of patients (95% CI 32.5%–52.8%) had NRS reductions of 30% or greater and met our predefined criteria as lidocaine responders. The mean reduction in NRS during lidocaine infusions was 2.34 (95% CI 2.83–1.85, $P<0.001$). Figure 1 shows the full range of absolute NRS pain score reductions in response to IV lidocaine. This distribution did significantly differ from the normal distribution Kolmogorov-Smirnov $P<0.02$.

Univariate Analysis

In univariate analysis, longer pain duration and failure to respond to previous medications did not predict a lower likelihood of having an analgesic response to IV lidocaine (Table 2). In contrast, age and pain severity were both significantly associated with response to IV lidocaine. Responders were likely to be older and have more severe pain.

Multivariate Analysis

Table 3 shows the results of multivariate logistic regression to examine predictors of lidocaine analgesia. In multivariate analysis, longer pain duration and failure to respond to previous medications did not predict a lower likelihood of having an analgesic response to IV lidocaine. In contrast, age and pain severity significantly predicted the odds of being a lidocaine responder. Controlled for all other factors and multiple comparisons, each decade of advancing age increases the odds of being a lidocaine responder by 36%. Each 1-point increase in baseline pain severity as assessed by NRS increased the odds of being a lidocaine responder by 29%.

All lidocaine effects were temporary and resolved within hours of the termination of the infusion. No patients experienced long-term relief after lidocaine infusion. A subset of this cohort went on to take chronic mexiletine. Their experiences are reported separately (I.R. Carroll, MD, unpublished data, May 2007).

DISCUSSION

This study reports on the largest cohort of patients undergoing lidocaine infusion subjected to statistical analysis to date in the literature. The analgesic response to lidocaine is not normally distributed (Kolmogorov-Smirnov $P<0.02$). However, the distribution of analgesic responses did not demonstrate self-evident “responders” and nonresponders.

We used literature-defined “clinically meaningful pain reductions” to define people as “responders” or “nonresponders.”^{12–14} Forty-two percent of patients (95% CI 32.5%–52.8%) had NRS reductions of 30% or greater and met our predefined criteria as lidocaine responders. The mean absolute reduction in NRS during lidocaine infusions was 2.34 (95% CI 2.83–1.85). Changes of this magnitude have been characterized as representing “a

clinically important difference”¹² and “much better” improvement among patients with chronic pain.¹⁴ Our results contrast with those of other recent work, suggesting that lidocaine reduces mechanical allodynia but not spontaneous pain.¹⁷ The magnitude of pain relief seen in our large cohort is consistent with earlier work, but is larger than that reported in a recent meta-analysis.⁶ The meta-analysis may have included patients with non-neuropathic pain.¹⁸ Lidocaine may not be helpful in other types of pain,¹⁹ and inclusion of patients with non-neuropathic pain in the meta-analysis would reduce mean pain score reductions in response to lidocaine. Alternatively, the smaller magnitude of pain relief seen in that study may reflect methodologic issues specific to meta-analysis.¹⁸

Age and pain severity influenced the likelihood of responding to IV lidocaine. Each decade of advancing age increase the odds of being a lidocaine responder by 36%. Each 1-point increase in baseline pain severity as assessed by NRS increased the odds of being a lidocaine responder by 29%. As such, lidocaine might be particularly useful for older patients with severe neuropathic pain in an inpatient setting such as on the oncology ward, especially because many of these patients often cannot tolerate oral medications. We have considerable experience using lidocaine within this setting. In our hospital, lidocaine is delivered as a continuous infusion starting at 1 mg/kg/h. Lidocaine levels are checked and possibly adjusted every 8 hours and are kept below 4 µg/mL. Within this context, it should be noted that lidocaine has an active metabolite with a significantly longer half-life than lidocaine: monoethylglycinexylidide. Consequently therapy is titrated to the minimal effective dose, and side effects such as tinnitus, perioral numbness, agitation, and dysarthria are carefully sought and used as a basis for reducing the dose.

Our finding that analgesia is predicted by baseline pain severity is consistent with previous studies of IV lidocaine which have suggested that analgesia is predicted by the severity of mechanical allodynia.⁷ Thus, formal testing of mechanical allodynia may not be needed to identify such patients. Simply assessing baseline NRS in patients with neuropathic pain may be sufficient. In contrast to age and pain severity, indexes of pain refractoriness, such as duration of pain and number of failed medications, did not predict response to lidocaine as we had hypothesized. The importance of these findings is highlighted by recent calls for work specifically on sodium channel blockers in patients with chronic pain to better characterize patients most likely to respond and thus identify possible responders.²⁰

Like other cohort studies, an important limitation of this study is the lack of a placebo group. Placebo analgesia no doubt contributes to the pain relief seen in this cohort, but does not detract from the variables predicting analgesia identified by logistic regression. Placebo-controlled trials of lidocaine analgesia have been reported using a paired design with each patient receiving a placebo infusion and a lidocaine infusion, but have had significantly fewer patients.^{7,8} Future work should attempt to include placebo controls with larger groups.

In this study, recall bias was minimized by recovering all data from contemporaneous records. Furthermore, data on predicting variables were recorded *before* lidocaine infusions. Selection bias was minimized by including all patients who underwent lidocaine infusions from a sample randomly selected from patient charts. To minimize the possibility that the effect of age and pain severity on the odds of being a lidocaine responder was due to the confounding influence of a third variable, results from univariate analysis were confirmed with multivariate logistic regression.

Patients were referred for lidocaine infusions when neuropathic pain was suspected based on the presence of allodynia, hyperalgesia, hyperpathia, hypoesthesia, or hyperesthesia. Diagnosis could rarely be determined from initial clinic visit forms, so we did not attempt to analyze diagnosis as a predicting factor among these patients. The inability to examine

patients' diagnosis as a possible predictor of being a lidocaine responder represents an important limitation of this study. The clinical heterogeneity in this cohort may limit generalizability to a specific recognized diagnostic group. However, most patients with neuropathic pain do not fall into a convenient etiology-based diagnosis, such as postherpetic neuralgia.³ The results from our cohort may therefore be more applicable to the more common patient presenting to pain clinics where a neuropathic origin is suspected on clinical grounds but a clear etiology-based diagnosis is lacking.

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FIGURE 1. Distribution of analgesic response to lidocaine infusions. Reduction in pain scores with IV lidocaine; positive numbers indicate pain reduction.

TABLE 1

Patient Characteristics at Baseline (n = 99)

Characteristic	Mean	Range
Age	48.79	16–78
Sex (percent male)	35	
Pain Intensity Score	6.28	3–10
Pain duration (y)	6.48	1–42
Previous antineuropathics	1.33	0–8
Previous opiates	2.88	0–8
Previous NSAIDs	2.11	0–6

Pain scores are verbal NRS report from 0 to 10. Antineuropathics included anticonvulsants, tricyclic antidepressants, venlafaxine, and duloxetine.

NSAIDs indicate nonsteroidal anti-inflammatory medications.

TABLE 2

Characteristics of Lidocaine Responders in Univariate Analysis

Factor	Lidocaine Responders (Mean)	Lidocaine Nonresponders (Mean)	P
Age	52.8	45.8	0.031
Pain duration	7.7	5.6	0.268
Male sex (%)	40.4	31.5	0.360
Pain severity (baseline NRS)	6.7	5.9	0.041
Antineuropathics tried	1.1	1.5	0.236
Opiates tried	2.7	3.0	0.439
NSAIDs tried	1.8	2.3	0.215

Lidocaine responders defined as patients with minimum 30% drop in NRS of pain severity. Antineuropathic pain medications defined as anticonvulsants, tricyclic antidepressants, venlafaxine, and duloxetine. Continuous variables tested with Student *t* test categorical variables tested with χ^2 test.

NSAIDs indicate nonsteroidal anti-inflammatory medications.

TABLE 3**Characteristics of Lidocaine Responders in Multivariate Logistic Regression**

Characteristic	Odds Ratio	95% CI	P
Age	1.364	1.002–1.856	0.048
Pain duration	1.044	0.988–1.104	0.127
Pain severity	1.288	1.002–1.657	0.048
Male sex	1.097	0.405–2.970	0.855
Antineuropathics tried	0.897	0.625–1.286	0.554
Opiates tried	0.943	0.722–1.231	0.666
NSAIDs tried	0.841	0.629–1.124	0.242

Lidocaine responders defined as patients with minimum 30% drop in NRS of pain severity. Odds ratio presented per decade of age, and 1-point change on NRS pain severity score. Antineuropathic pain medications defined as: anticonvulsants, tricyclic antidepressants, venlafaxine, and duloxetine.

NSAIDs indicate nonsteroidal anti-inflammatory medications.