

Effect of Perioperative Intravenous Lidocaine Administration on Pain, Opioid Consumption, and Quality of Life after Complex Spine Surgery

Ehab Farag, M.D., F.R.C.A.,* Michael Ghobrial, M.D.,† Daniel I. Sessler, M.D.,‡ Jarrod E. Dalton, Ph.D.,§ Jinbo Liu, M.D.,|| Jae H. Lee, B.A.,# Sherif Zaky, M.D.,** Edward Benzel, M.D.,†† William Bingaman, M.D.,‡‡ Andrea Kurz, M.D.§§

ABSTRACT

Background: The authors tested the primary hypothesis that perioperative IV lidocaine administration during spine surgery (and in the postanesthesia care unit for no more than 8 h) decreases pain and/or opioid requirements in the initial 48 postoperative hours. Secondary outcomes included major complications, postoperative nausea and vomiting, duration of hospitalization, and quality of life.

Methods: One hundred sixteen adults having complex spine surgery were randomly assigned to perioperative IV lidocaine (2 mg·kg⁻¹·h⁻¹) or placebo during surgery and in the postanesthesia care unit. Pain was evaluated with a verbal response scale. Quality of life at 1 and 3 months was assessed using the Acute Short-form (SF) 12 health survey. The authors initially evaluated multivariable bidirectional non-inferiority on both outcomes; superiority on either outcome was then evaluated only if noninferiority was established.

Results: Lidocaine was significantly superior to placebo on mean verbal response scale pain scores ($P < 0.001$; adjusted

What We Already Know about This Topic

- Perioperative IV lidocaine infusion improves outcome after abdominal surgery
- The utility of lidocaine administration for spine surgery is not known

What This Article Tells Us That Is New

- Lidocaine administration to patients undergoing complex spine operations reduced pain but not opioid requirements early in the postoperative period

mean [95% CI] of 4.4 [4.2–4.7] and 5.3 [5.0–5.5] points, respectively) and significantly noninferior on mean morphine equivalent dosage ($P = 0.011$; 55 [36–84] and 74 [49–111] mg, respectively). Postoperative nausea and vomiting and the duration of hospitalization did not differ significantly. Patients given lidocaine had slightly fewer 30-day complications than patients given placebo (odds ratio [95% CI] of 0.91 [0.84–1.00]; $P = 0.049$). Patients given lidocaine had significantly greater SF-12 physical composite scores than placebo at 1 (38 [31–47] *vs.* 33 [27–42]; $P = 0.002$) and 3 (39 [31–49] *vs.* 34 [28–44]; $P = 0.04$) months, postoperatively.

Conclusion: IV lidocaine significantly improves postoperative pain after complex spine surgery.

MORE than half-million spine surgeries are performed each year in the United States. Extensive spine surgery is painful, and postoperative pain is often difficult to control. Opioids—the most common analgesic approach—in turn, often provoke postoperative nausea and vomiting. Patients with extensive lumbar spine surgery are prone to life-threatening complications, with incidences varying from 2.3% among patients having decompression alone to 5.6% among those having complex fusions.¹ However, the overall complication incidence, including minor and major complications, is up to 16.4% (17.8% in thoracolumbar *vs.* 8.9% in cervical procedures).² Therefore, functional recovery is often prolonged.² A likely common mechanism for many adverse outcomes is the systemic inflammatory response to surgical tissue injury.

Systemic lidocaine is antiinflammatory,³ analgesic,⁴ and antihyperalgesic.^{5,6} The antiinflammatory effects of IV

* Associate Professor, Departments of General Anesthesiology and Outcomes Research, ‡ Michael Cudahy Professor and Chair, † Research Fellow, # Research Coordinator, §§ Professor and Vice Chair, Department of Outcomes Research, § Senior Biostatistician, Departments of Quantitative Health Sciences and Outcomes Research, ** Assistant Professor, Department of General Anesthesiology, †† Professor, Chairman, Department of Neurosurgery, ‡‡ Professor and Vice Chair, Department of Neurological Institute, Cleveland Clinic, Cleveland, Ohio. † Clinical Research Fellow, Department of Outcomes Research, Cleveland Clinic, Cleveland, Ohio. Current affiliation: Internal Medicine Resident, Fairview Hospital, A Cleveland Clinic Hospital, Cleveland, Ohio.

Received from the Department of General Anesthesiology; Department of Outcomes Research; Department of Quantitative Health Sciences; Department of Neurosurgery; and the Neurological Institute, Cleveland Clinic, Cleveland, Ohio. Submitted for publication October 10, 2012. Accepted for publication April 15, 2013. Support was provided solely from institutional and/or departmental sources.

Address correspondence to Dr. Kurz: Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Avenue/P-77, Cleveland, Ohio 44195. ak@or.org. On the World Wide Web: www.OR.org. Information on purchasing reprints may be found at www.anesthesiology.org or on the masthead page at the beginning of this issue. ANESTHESIOLOGY's articles are made freely accessible to all readers, for personal use only, 6 months from the cover date of the issue.

Copyright © 2013, the American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins. Anesthesiology 2013; 119:932–40

lidocaine are mediated by inhibition of *N*-methyl-D-aspartate receptors^{7,8} and leukocyte priming.⁹ Lidocaine stimulates secretion of the antiinflammatory cytokine interleukin-1 receptor antagonist.¹⁰ Therefore, as might be expected, systemic lidocaine has been shown to reduce pain, postoperative nausea and vomiting, and major complications after abdominal surgery.¹¹

Extensive spine surgery, like abdominal surgery, involves substantial tissue injury and provokes a large inflammatory reaction. And like abdominal surgery, systemic lidocaine may be analgesic and improve recovery. We therefore, tested the hypothesis that perioperative IV lidocaine administration decreases pain scores and/or opioid requirements during the initial 48 h after extensive spine surgery. Secondary outcomes included a composite of major 30-day postoperative complications (cardiovascular, gastrointestinal, pulmonary, neurologic, and infectious); the 24-h incidence of postoperative nausea and vomiting; the duration of hospitalization; and postoperative quality of life at 1 and 3 months.

Materials and Methods

With approval of the Cleveland Clinic Institutional Review Board (Cleveland, Ohio) and written informed consent, we enrolled 116 American Society of Anesthesiologists Physical Status I–III patients, between the ages of 18 and 75 yr, who were scheduled for elective multilevel spine surgery with or without instrumentation, with general anesthesia. Patients were enrolled from September 2009 to October 2011 (ClinicalTrials.gov #NCT00840996).

We excluded those with contraindication to lidocaine, such as those with substantial hepatic impairment (alanine aminotransferase or aspartate transaminase more than twice normal), renal impairment (serum creatinine >2 mg/dl), seizure disorder requiring medication within 2 yr, and/or planned epidural anesthesia or analgesia.

Protocol

Patients were assigned to one of two groups using a reproducible set of computer-generated random numbers that were maintained in sequentially numbered opaque envelopes until just before induction of anesthesia: (1) IV lidocaine (2 mg·kg⁻¹·h⁻¹) with maximum of 200 mg/h starting at induction of anesthesia and continuing until discharge from the postanesthesia care unit (PACU) or a maximum of 8 h; or (2) an equal volume of saline placebo. Investigators, clinicians, and patients were all fully blinded to treatment allocation.

General anesthesia was induced with propofol or etomidate and maintained with sevoflurane. Tachycardia was treated with esmolol to keep the heart rate less than 85 beats/min after other causes of tachycardia, like hypovolemia, pain, light depth of anesthesia, had been excluded; atropine or glycopyrrolate was used to keep the heart rate greater than 40 beats/min; and to keep the mean arterial blood pressure within 20%

of the baseline. Anesthetic, fluid, and transfusion management was at the discretion of the attending anesthesiologist.

Postoperatively, pain was treated with patient-controlled analgesia with morphine sulfate at a concentration of 1 mg/ml, with a demand dose of 1 mg and a lockout interval of 10 min. Comparable doses of fentanyl or hydromorphone were used on patients unable to tolerate morphine. Bolus doses of opioid were provided if additional analgesia was required. Patients were transitioned to oral opioids on the first postoperative day (POD) according to the pain management protocol at our institution.

Measurements

Demographic and morphometric measurements, including age, height, and weight, were recorded at baseline. Preoperative laboratory values and historical factors were also recorded, including smoking history, number of alcoholic beverages consumed per week, preoperative hemoglobin, certain coexisting systemic diseases, and medication use (table 1). Routine anesthetic variables were obtained electronically from our anesthesia information management system. Pain was evaluated with verbal response scores (0 = no pain and 10 = worst pain) at 30-min intervals while in the postanesthesia care unit, and every 4–6 h, thereafter. Opioid consumption during the initial 48 postoperative hours was converted to morphine sulfate equivalents.¹²

Postoperative nausea and vomiting were monitored for the first 24 h after anesthesia. Patients were queried about postoperative nausea and vomiting on discharge from the postanesthesia care unit, and on the first postoperative morning and afternoon. Any nausea or vomiting between queries was considered a positive response for that interval.

The decision to discharge a patient from the hospital was made by the attending surgeon, who was unaware of the patients' group assignment. Thus, discharge timing was based on routine surgical considerations, control of infections (if any), adequate healing, and pain control.

We evaluated a collapsed composite of major 30-day pulmonary, cardiovascular, renal, neurologic, gastrointestinal, and infectious complications. We mainly included those complications most likely to be affected by lidocaine administration. Quality of life, 1 and 3 months after surgery, was evaluated with the well-validated Acute Short-form (SF-12) health survey, an abbreviated version of the SF-36, which consists of 12 items. It measures two domains, including mental and physical component summaries (mental component summary and physical composite score, respectively).^{13,14} The survey was administered by phone; use of the SF-12 by phone has been shown to be valid.¹⁴

Statistical Analysis

Analysis of our primary outcome was implemented on an intention-to-treat basis. Postoperative analgesia was characterized using both verbal response scale pain scores and opioid consumption (total IV morphine equivalent doses)

Table 1. Summary of Baseline and Intraoperative Patient Characteristics for the Randomized Groups

Factor	Placebo (N = 58)	Lidocaine (N = 57)
Rank ordering of treatment	58±34	58±33
Age, yr	54±11	58±11
Male sex (vs. female)	60.3	61.4
Body mass index, kg/m ²	30±5	29±5
ASA Physical Status*		
II	58.6	71.9
III/IV	41.4	28.1
White (vs. other)	84.5	91.2
Smoking status		
Never smoked	41.4	40.4
Former smoker	36.2	43.9
Smoker	22.4	15.8
Number of drinks/week	0.2 [0.0, 2.0]	0.0 [0.0, 1.0]
Chronic opioid use†	32.8	15.8
Duration, mo‡	18.8±11.0	14.7±7.4
Daily dosage (mg IV morphine per day)‡	7.5 [5.0, 7.5]	10.0 [7.5, 30.0]
Hemoglobin, g/dl	14.1±1.2	14.2±1.4
Hematocrit, %	42.0±3.0	42.5±3.6
Glucose, mg/dl	88 [82, 98]	92 [85, 101]
BUN, mg/dl	15 [12, 18]	16 [14, 19]
Duration of lidocaine/placebo infusion, h	7.9±2.2	8.5±2.6
Case duration, min	259 [209, 292]	280 [226, 353]
Time-weighted sevo concentration, %	1.3±0.2	1.3±0.4
Crystalloids, l	2.6 [1.7, 3.1]	3.1 [2.1, 3.6]
Colloids, l	0.5 [0, 1]	0.5 [0.5, 1]
Blood transfusion, units	0 [0, 0]	0 [0, 0]
Time-weighted mean arterial pressure, mmHg	84±8	83±7
Time-weighted heart rate, beats/min	71±9	71±9
Superior vertebral region, %		
Cervical	45	50
Thoracic	2	7
Lumbosacral	53	43
Number of levels*	3 [3, 4]	4 [3, 5]
Use of instrumentation*	52.6	66.1
Intraoperative opioids (mg IV morphine equivalent)	31 [25, 55]	36 [23, 60]

All statistics reported as “mean ± SD,” “median [first quartile, third quartile],” or “N (%)”, as appropriate.

* These factors were used for adjustment in our main analysis. † Chronic opioid use defined as daily opioid use lasting >6 months preoperatively. ‡ Results for daily chronic opioid dosage and duration of chronic opioid use are restricted to the subset of patients who are chronic opioid users (N = 19 in the placebo group and N = 9 in the lidocaine group).

ASA = American Society of Anesthesiologists; BUN = blood urea nitrogen; IV = intravenous.

from admission to the PACU through POD 2 (or discharge, if earlier). The first POD was defined as starting at 05:00 AM on the day after surgery. Total IV morphine equivalent doses were calculated from the opioid consumption doses.^{||||} We considered one of the groups to be better than the other on postoperative pain control if: (1) it was superior (*i.e.*, a significantly lower mean) on both pain scores and opioid consumption; (2) it was superior on pain scores and

noninferior on opioid consumption (*i.e.*, a mean mg IV morphine equivalent not more than 30% greater than that of the other group); or (3) it was superior on opioid consumption and noninferior on pain scores (*i.e.*, a mean postoperative mean verbal response score not more than 1 point higher than the other group).¹⁵ Superiority on either outcome, in the presence of noninferiority on both outcomes, was therefore, sufficient to conclude better pain relief overall. Thus, our primary hypothesis was assessed in a joint hypothesis testing framework as described by Mascha and Turan.¹⁵

Our analysis, correspondingly, was a two-step procedure. First, we evaluated noninferiority on both outcomes in both

|||| Opioid Equianalgesic Conversion Chart Aspirus Wausau Hospital December 2004. Available at: <http://www.aspirusmedicalstaff.org/media/pdf/PHARM-033.pdf>. Accessed December 28, 2012.

directions (lidocaine *vs.* control, control *vs.* lidocaine). For a particular treatment direction, we only evaluated superiority on either outcome if noninferiority was established for both outcomes. Using this approach we maintained overall type I error rate at 0.05 for the primary hypothesis. Noninferiority hypotheses were evaluated against a one-sided significance criterion of 0.025 (adjusting for testing in both directions, $0.05/2 = 0.025$) and superiority hypotheses were evaluated against a one-sided significance criterion of 0.0125 (adjusting for testing in both directions and for assessing two outcomes, $0.05/4 = 0.0125$). Overall type I error was maintained at 0.05, even though, both noninferiority and superiority were tested at the overall 0.05 level (with adjustments for multiple comparisons, as explained above in the previous sentence). This is due to the fact that our joint testing procedure only rejected the null hypothesis of no overall impact on postoperative analgesia, if we found noninferiority on both outcomes and superiority on at least one outcome; any other result of the tests would fail to reject the null hypothesis. This is known in the statistical literature as an *intersection-union test*.¹⁶

We evaluated the percent difference in mean IV morphine equivalent dose using a log-linear regression model, adjusting for any baseline variables which were by some chance inadequately balanced between the groups (balance assessed using standard univariable summary statistics, as appropriate). We added 0.1 mg IV morphine equivalents to all patients' outcome, before taking the logarithm to accommodate the two patients who received zero opioids. To evaluate the overall difference in mean pain scores, we used a linear mixed-effects regression model. This model appropriately accounts for correlation exhibited by the repeated pain measurements on a given patient (we used a spatial power correlation structure, which assumes a greater degree of correlation among pain score measurements closer together in time). This model can also be used to adjust for imbalanced baseline variables.

To study the potential time-dependence of the lidocaine effect, we partitioned postoperative time into the following phases: 0–2 h (after PACU admission), 2–4 h, 4–6 h, 6–8 h, overnight (*i.e.*, 8 h after PACU admission, until 05:00 on POD 1), POD 1 (05:00 POD 1 until 05:00 POD 2), and POD 2 (05:00 POD 2 until 05:00 POD 3). Linear mixed-effects regression models were developed for each outcome (pain and opioids), incorporating an interaction term between the randomized group and the postoperative phase. Wald tests were used to test the significance of the interaction terms (*i.e.*, time-dependent treatment effects). Opioid doses were totaled for each phase in this analysis.

Secondary outcomes were analyzed as follows. Binary 30-day complications were summarized as counts and percentages, and the odds of experiencing a composite outcome, comprising any of the 30-day complications was compared between infusion groups using logistic regression (adjusting for the same factors as in the primary analysis). Incidence of

postoperative nausea and vomiting (during recovery and on PODs 1 and 2) were also reported; logistic regression was similarly used to compare these outcomes.

The physical and mental composite scores of the SF-12 health survey (denoted as SF12-physical composite score and SF12-mental component summary) at 1 and 3 months postoperatively, along with question number 5 of the SF-12 which was a Likert scale evaluation of pain's interference with the ability to work, were analyzed using linear regression models. Hospital length-of-stay was also analyzed using linear regression. The type I error rate was set at 5% for each of the secondary hypothesis tests.

Sample size was driven by the analysis of superiority on opioids because this analysis required more patients than the noninferiority analysis and either analysis on pain scores. A minimum clinically meaningful reduction in morphine requirements of 30% was assumed. A preliminary review of data from our Perioperative Health Documentation System registry guided the sample size estimation by establishing references for opioid consumption in our patient population. We were uncertain whether the distribution of postoperative morphine equivalent dosing was sufficiently modeled under a parametric assumption (*e.g.*, normally or log-normally distributed), mainly due to an anticipated disproportionately large group of patients receiving no opioids whatsoever. We thus used a Wilcoxon test for design purposes, estimating that a maximum of $N = 116$ patients (*i.e.*, up to 58 patients randomized to either the lidocaine, or control groups) was sufficient for providing greater than 90% power. This sample size estimate was adjusted in order to incorporate two interim analyses. SAS statistical software version 9.3 (SAS Institute, Cary, NC) and R statistical software version 2.14.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for all statistical analyses.

Results

A CONSORT trial flow diagram is presented in figure 1.¹⁷ Patients randomized to lidocaine had slightly lower American Society of Anesthesiologists Physical Status scores, had spine surgeries on a slightly higher number of vertebral levels, and were slightly more likely to have had instrumentation with their procedure (table 1). Patients using preoperative chronic opioids for more than 6 months were included in the study (table 1). We therefore, adjusted for these factors in our statistical analyses.

We found that patients randomized to lidocaine were significantly noninferior to (not worse than) the placebo on both pain and opioids ($P < 0.001$ and $P = 0.011$, respectively, with a significance criterion of 0.025) (fig. 2). The converse was not true, though: Noninferiority tests of the placebo group relative to the lidocaine group on each outcome were not significant ($P = 0.12$ and $P = 0.54$). Testing for superiority of lidocaine (with significance criterion of 0.0125) revealed significant results for pain ($P < 0.001$) but not for opioids ($P = 0.12$). For our primary hypothesis, we

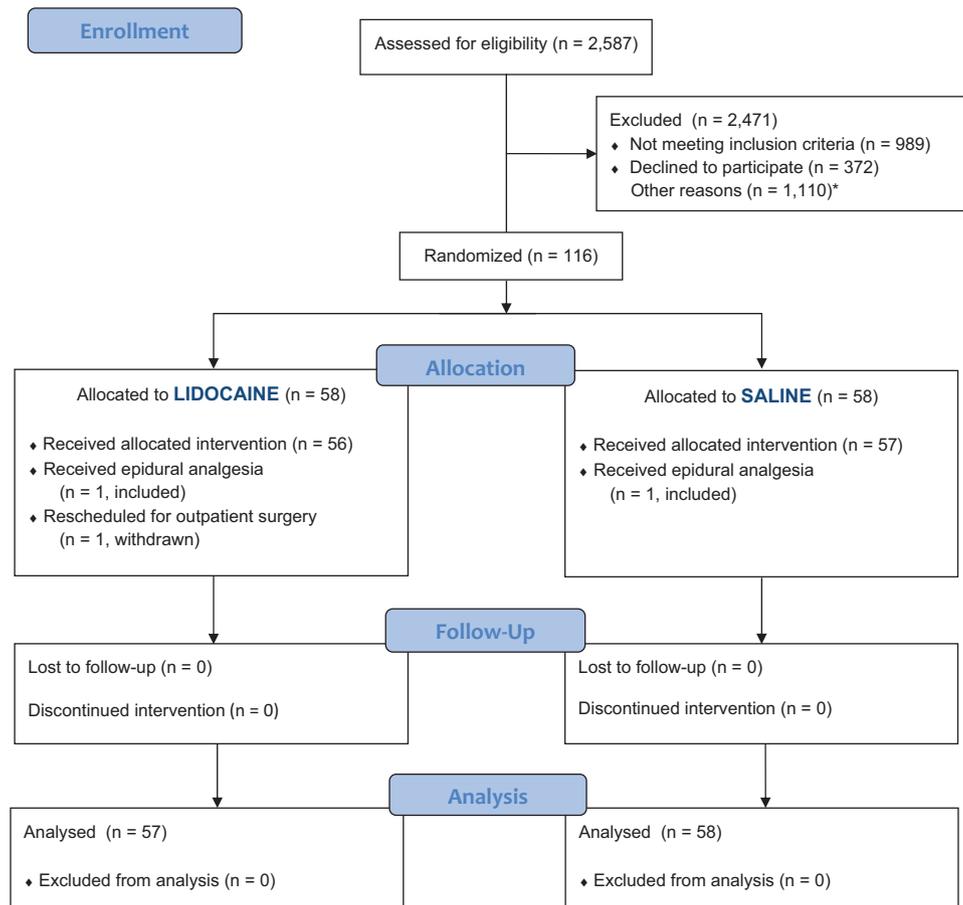


Fig. 1. CONSORT trial flow diagram. *Other reasons include the following: no possibility to consent preoperatively; participation in other research studies. Also, four patients with single-level spine surgery (three lidocaine and one saline) were enrolled early in the study (these were included in the analysis). n = number of patients.

therefore conclude that lidocaine is superior to placebo for postoperative analgesia because superiority was found for at least one of the two outcomes. Adjusted mean (Bonferroni-adjusted 95% CI) pain scores were 5.3 (5.0–5.5) points and 4.4 (4.2–4.7) points on the verbal response scale for the placebo and lidocaine groups, respectively; adjusted mean total IV morphine equivalent doses were 74 (49–111) mg for placebo and 55 (36–84) mg for lidocaine.

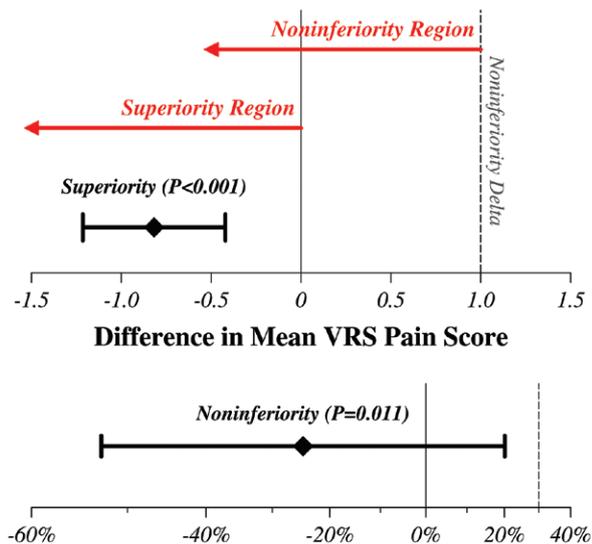
Mean pain scores and opioid consumption estimates as a function of postoperative time for each group are shown in figure 3. We found no significant time-dependence of the treatment effect in our sample (group-time interaction Wald test $P = 0.21$ and $P = 0.56$ for pain and opioids, respectively).

There was no difference between the two groups neither in postoperative nausea and vomiting, nor in antiemetic medication. Duration of hospitalization was also comparable between the groups. Patients given lidocaine had slightly fewer 30-day complications than patients given placebo (odds ratio [95% CI] of 0.91 [0.84–1.00]; $P = 0.049$). Lidocaine patients exhibited a significantly higher SF-12 physical composite score at 1 ($P = 0.002$) and 3 months ($P = 0.04$), postoperatively (table 2).

Discussion

IV lidocaine is analgesic in patients having major abdominal surgery.¹⁸ In contrast, lidocaine has not proven helpful in patients having total hip arthroplasty,¹⁹ gynecological surgery,²⁰ cardiac surgery,²¹ or tonsillectomy.²² The distinction between major abdominal and other types of surgery was recently confirmed in a meta-analysis. The authors postulated that IV lidocaine may be especially helpful for visceral pain, and furthermore, lidocaine may decrease acute pain by reducing ileus and postoperative nausea and vomiting.¹⁸ Lidocaine significantly improved pain scores from 5.5 to 4.4 on an 11-point Likert scale in our patients having major spine surgery. Lidocaine also reduced 48-h opioid requirements by approximately 25%, although the reduction was not statistically significant. However, the analgesia we observed was comparable to that reported for major abdominal surgery, and greater than that reported in previous studies in nonabdominal surgery studies.

Why our results should differ remains unclear. But an alternative to distinguishing on the basis of visceral *vs.* non-visceral pain is to distinguish on the magnitude of surgical tissue injury. Major abdominal surgery obviously involves



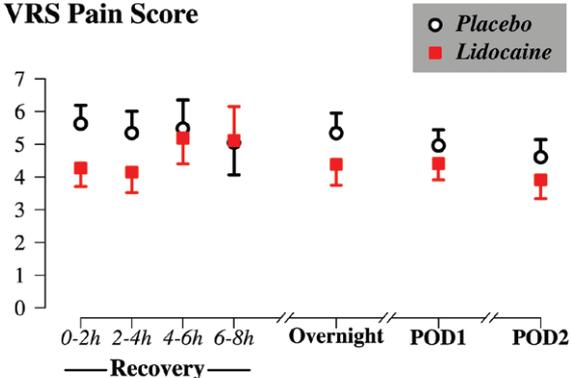
% Difference in Mean IV Morphine Equivalent Dose

Fig. 2. Results of primary analysis. We first assessed noninferiority of the lidocaine group on each outcome, using a one-sided significance criterion of 0.025; such noninferiority is represented by differences in means—lidocaine minus placebo—that are either negative, or not meaningfully positive. Because significant noninferiority was found on both outcomes ($P < 0.001$ and $P = 0.010$ for verbal response scale (VRS) pain score and mg intravenous (IV) morphine equivalent dose, respectively, and graphically indicated by the 95% CIs being entirely within the displayed noninferiority region for each outcome), we proceeded to assess superiority on at least one of the outcomes, using a Bonferroni-adjusted one-sided significance criterion of 0.0125. Superiority on pain was found ($P < 0.001$; 95% CI entirely below a difference of 0 VRS units), whereas, superiority on total 48-h postoperative IV morphine equivalent dose was not found ($P = 0.10$; 95% CI overlaps 0%). Estimates and 95% CIs (confidence level adjusted based on the relevant significance criterion for each outcome) are given in the figure; these estimates were adjusted for American Society of Anesthesiologists Physical Status, number of levels operated, and use of instrumentation.

substantial tissue injury, as does major spine surgery, and lidocaine appears to provide analgesia for both types of surgery. However, the distinction is not entirely consistent in that lidocaine is reportedly ineffective for hip arthroplasty¹⁹ and cardiac surgery,²¹ both operations that also involve substantial tissue disruption. Also, our patient population included patients with moderate to complex spine surgery, and only half of our patients had spine surgery with instrumentation. Thus, we included patients with varying amounts of tissue injury, which makes interpretation of the results with regard to tissue injury more challenging.

Another distinction that might be made is on the basis of lidocaine dose and duration of treatment. In our study, the lidocaine infusion was started at induction of anesthesia and continued up to 8 h in the PACU. Thus, the average duration of lidocaine administration in our study was approximately 8 h. The half-life of IV lidocaine is approximately 1.5 h after bolus injection or infusions

A VRS Pain Score



B IV Morphine Equivalent Dose (mg)

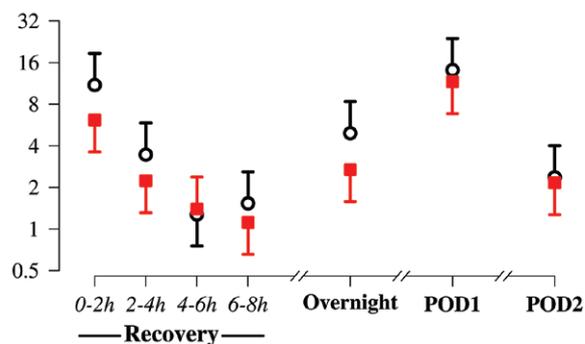


Fig. 3. Estimated mean verbal response scale (VRS), pain score (A), and mean milligram IV morphine equivalent doses (B) for each of the randomized groups as a function of postoperative time. Recovery time expressed as time from postanesthesia care unit admission. “Overnight” refers to the time between 8 h after postanesthesia care unit admission, and 05:00 AM on postoperative day (POD) 1, “POD 1” refers to the time between 05:00 AM on POD 1 and 05:00 AM on POD 2, and “POD 2” refers to the time between 05:00 AM on POD 2 and 05:00 AM on POD 3. Error bars extend to two standard errors of the mean (standard errors estimated *via* respective linear mixed models). No group-time interaction was found for either outcome (Wald test P value of 0.21 and 0.56, respectively). Estimates are adjusted for American Society of Anesthesiologists’ Physical Status, number of levels operated, and use of instrumentation.

lasting up to 12 h.²³ However, prolonged analgesic effects of lidocaine as well as other benefits on postoperative outcomes have been shown repeatedly, even when the lidocaine administration was discontinued at the end of surgery.^{11,24} Most likely, the perioperative administration is sufficient because modulatory action on the initiation of the inflammatory response primarily takes place during surgery. The prolonged analgesic effect of lidocaine, which extends well beyond the infusion time, could potentially also be explained by sustained concentrations of lidocaine in the cerebrospinal fluid.²⁵ In addition, lidocaine metabolites have analgesic effects by inhibiting the glycine transporter 1.²⁶ Inhibition of glycine transport 1 was shown in an animal model of chronic pain, to not only reduce pain but also to improve cognitive function.²⁷ Therefore, it is likely that

Table 2. Results for Secondary Outcomes

Outcome	Placebo N/Total	Lidocaine N/Total	Comparison	Estimate (95% CI)	P Value		
Pneumonia	0/57	0/57	—	—	—		
Respiratory failure	0/57	0/57	—	—	—		
Prolonged use or need for reinsertion of chest tube	0/57	0/57	—	—	—		
Cardiac arrest	0/57	0/57	—	—	—		
Arrhythmia	0/57	0/57	—	—	—		
Congestive heart failure	0/57	0/57	—	—	—		
Stroke	0/57	0/57	—	—	—		
Intravascular coagulopathy	0/57	0/57	—	—	—		
Thromboembolic disease (pulmonary embolism)	0/57	0/57	—	—	—		
Injury to great vessels	0/57	0/57	—	—	—		
Delirium	0/57	0/57	—	—	—		
Monoplegia or paraplegia	1/57	0/57	—	—	—		
Upper gastrointestinal bleeding	0/57	0/57	—	—	—		
Gastrointestinal block	1/42	0/43	—	—	—		
Ureteral obstruction	2/57	0/57	—	—	—		
Syndrome of inappropriate antidiuretic hormone secretion	0/57	0/57	—	—	—		
Wound infection requiring debridement	1/57	0/57	—	—	—		
Sepsis	0/57	0/57	—	—	—		
Readmission	3/57	2/57	—	—	—		
Any of the above 30-day complications*	5/57	2/57	Odds ratio	0.91 (0.84–1.00)	0.049		
Nausea–recovery	7/58	7/57	Odds ratio	1.00 (0.88–1.13)	1.00		
Nausea–POD 1	20/56	18/55	Odds ratio	0.97 (0.81–1.17)	0.74		
Nausea–POD 2	8/36	4/39	Odds ratio	0.91 (0.77–1.09)	0.31		
Vomiting–recovery	0/58	1/55	Odds ratio	1.02 (0.98–1.06)	0.35		
Vomiting–POD 1	10/56	6/55	Odds ratio	0.94 (0.82–1.08)	0.39		
Vomiting–POD 2	1/36	2/39	Odds ratio	1.04 (0.94–1.14)	0.44		
Antiemetics–recovery	6/58	5/57	Odds ratio	0.98 (0.88–1.10)	0.77		
Antiemetics–POD 1	17/56	16/56	Odds ratio	0.98 (0.82–1.16)	0.78		
Antiemetics–POD 2	7/37	5/39	Odds ratio	0.96 (0.81–1.14)	0.64		
Outcome	N	Median [Q1, Q3]	N	Median [Q1, Q3]	Comparison	Estimate (95% CI)	P Value
Hospital length-of-stay, d	55	3 [2, 4]	57	3 [2, 4]	Difference in means	–1.0 (–2.4 to 0.4)	0.15
Fatigue score (VAS)–1 mo	54	4.0 [3.0, 6.0]	54	4.0 [2.0, 5.8]	Difference in means	–0.3 (–1.2 to 0.5)	0.40
Fatigue score (VAS)–3 mo	54	5.0 [3.0, 6.8]	51	5.0 [2.0, 5.0]	Difference in means	–0.6 (–1.5 to 0.3)	0.17
SF-12 physical composite–1 mo	55	33 [27, 42]	54	38 [31, 47]	Difference in means	6.2 (2.3–10.0)	0.002
SF-12 physical composite–3 mo	54	34 [28, 44]	51	39 [31, 49]	Difference in means	4.6 (0.3–8.9)	0.04
SF-12 mental composite–1 mo	55	54 [46, 59]	54	56 [44, 61]	Difference in means	0.7 (–3.5 to 5.0)	0.74
SF-12 mental composite–3 mo	54	54 [43, 60]	51	58 [50, 61]	Difference in means	4.0 (–0.4 to 8.5)	0.08
SF-12 question #5†–1 mo	55	3 [2, 4]	54	3 [1, 4]	Difference in means	–0.5 (–1.0 to 0.0)	0.07
SF-12 question #5†–3 mo	54	3 [2, 4]	51	2 [2, 3]	Difference in means	–0.4 (–0.9 to 0.0)	0.06

For outcomes with statistical comparisons between the two groups, results are reported as lidocaine vs. placebo, adjusted for American Society of Anesthesiologists' Physical Status, number of levels operated and use of instrumentation, using either logistic regression (wherever odds ratios are reported), or linear regression (wherever differences in means are reported).

* Excluding gastrointestinal block, which was unavailable for 29 patients. † During the past week, how much did pain interfere with your normal work (including both work outside the home and housework)? This is a 5-point scale ranging from "not at all" to "extremely."

POD = postoperative day; SF-12 = Short-form-12 health survey; VAS = visual analogue scale.

local anesthetics exert their protective effects beyond their presence in the blood. Whether our lidocaine administration (for up to 8 h which is longer than in most studies previously published) further enhanced its effects, remains unclear. The

fact that most previous studies, in which lidocaine was used intraoperatively only, showed comparable effects on pain and opioid consumption suggests, however, that prolonged administration might not be necessary.

There were no significant differences in postoperative nausea and vomiting or administration of antiemetic drugs, perhaps reflecting the small (nonsignificant) difference in opioid use. This result differs from many previous reports, in which lidocaine did reduce nausea and vomiting, although, most were in abdominal surgery and may have been mediated by a reduction in ileus.²⁴ Similarly, we did not observe any benefit of lidocaine administration on hospital length-of-stay; but again, reduction in hospital length-of-stay has mostly been reported in patients having major abdominal surgery.²⁸

The lidocaine patients had slightly but significantly fewer postoperative complications than those given placebo. Although this result is promising and suggests that lidocaine might improve overall patient outcome, our patients had a low complication rate, with a total of only seven observed among the 116 enrolled patients. More importantly, the incidence of complications was one of four secondary outcomes and was evaluated at an unadjusted alpha level of 0.05. A larger study, well powered for postoperative complications, might better determine whether IV lidocaine in fact reduces the risk of serious complications after major spine surgery.

Patients assigned to lidocaine exhibited significantly greater SF-12 physical composite scores at 1 and 3 months postoperatively. Few previous studies included long-term outcomes of perioperative IV lidocaine administration. Two studies evaluated the effect of lidocaine on neurocognitive functions in patients after cardiac surgery. However, the results of those studies were conflicting. Mitchell *et al.*²⁹ showed better neurocognitive functions 6 months postsurgery in patients who were given lidocaine during cardiac surgery, whereas, Mathew *et al.*³⁰ and also Mitchell *et al.*,³¹ did not confirm these findings. A third study^{19,29} evaluated patients undergoing total hip arthroplasty, but was unable to observe significant differences in hip flexion 3 months postoperatively^{19,29} (interestingly, fatigue scores were comparable, suggesting that other components of recovery dominated patients' experience). Nonetheless, available data now suggest that a brief period of perioperative lidocaine administration may improve long-term outcomes.

Assessed alone, neither pain score nor opioid consumption adequately measures the effect of lidocaine on pain control; for example, pain can be reduced by aggressive opioid use, even if the treatment being evaluated is not analgesic. In our primary hypothesis, we thus jointly assessed both pain and opioid consumption, following methods described by Mascha and Turan.¹⁵ We thus avoided the problem of choosing either outcome as primary and relegating the other as secondary, or analyzing both as primary without clear *a priori* rules for interpretation. Specifically, we decided *a priori* to claim lidocaine more effective than placebo on pain control only if it was superior on at least one of the two outcomes (pain scores or opioid consumption), as long as it was not worse on either outcome. Another option would have been to require superiority on both outcomes, but we felt that would be too restrictive. For example, our conclusion that lidocaine is effective

because it significantly reduces mean pain score and is "no worse" on mean opioid consumption (*a priori* defined as less than 30% higher) seems quite reasonable, particularly because the observed lidocaine effect on opioid consumption was in the direction of superiority.

Although our study is among the largest evaluating perioperative IV lidocaine, it was marginally powered for secondary outcomes, including nausea and vomiting, complications, and quality of life. To the extent that lidocaine improves longer-term outcomes, the drug's antiinflammatory effect is an obvious mechanism, but other mechanisms remain possible. Additional work is thus necessary to confirm longer-term benefits of perioperative IV lidocaine and establish their mechanisms. Especially the effect of perioperative lidocaine administration on chronic neuropathic pain seems worth studying.

One limitation of our study was that we included a variety of spine procedures ranging from moderate to complex including surgeries at all levels of the spine as well as surgeries with and without instrumentation. Unfortunately our sample size was not sufficiently large to evaluate interaction, *i.e.*, whether or not lidocaine's effect differs with different magnitude or types of spine surgeries. Also, the patient population included in our study was probably only representative for our institution's patient population. For example, very few of the patients included in the study were on chronic opioids before surgery, as seems to be the case for many spine patients in other centers (table 1). However, we included patients on chronic opioids in the analysis. Thus generalizability of our results is somewhat limited. Whether the effect of lidocaine differs in patients on chronic opioids remains unknown.

Despite the randomized nature of the study, we had some imbalance in baseline characteristics. Patients randomized to lidocaine had slightly lower American Society of Anesthesiologists Physical Status scores, had spine surgeries on a slightly higher number of vertebral levels, and were slightly more likely to have had instrumentation with their procedure. With the restricted number of patients and wide inclusion criteria such imbalances can happen even in randomized trials. We, therefore, adjusted for these factors in our statistical analyses.

Another limitation of the study is that we did not measure baseline quality of life before surgery. Patients receiving lidocaine in the intraoperative period had significantly higher quality-of-life scores at 1 and 3 months after surgery. However, these results were not adjusted for baseline functional status. Considering the above mentioned imbalances, the lack of baseline functional status makes it difficult to have a definitive assessment of the long-term functional benefits of using lidocaine in patients undergoing spine surgery.

In summary, IV lidocaine improved postoperative pain scores in patients recovering from major spine surgery. Furthermore, patients given lidocaine had significantly higher SF-12 physical composite scores 1 and 3 months after surgery, although, this was not controlled for baseline functional status. Future large studies are needed to address the

effect of lidocaine on functional and/or long-term outcomes after complex spine surgeries.

References

- Deyo RA, Mirza SK, Martin BI, Kreuter W, Goodman DC, Jarvik JG: Trends, major medical complications, and charges associated with surgery for lumbar spinal stenosis in older adults. *JAMA* 2010; 303:1259–65
- Nasser R, Yadla S, Maltenfort MG, Harrop JS, Anderson DG, Vaccaro AR, Sharan AD, Ratliff JK: Complications in spine surgery. *J Neurosurg Spine* 2010; 13:144–57
- Hollmann MW, Durieux ME: Local anesthetics and the inflammatory response: A new therapeutic indication? *ANESTHESIOLOGY* 2000; 93:858–75
- Marret E, Rolin M, Beaussier M, Bonnet F: Meta-analysis of intravenous lidocaine and postoperative recovery after abdominal surgery. *Br J Surg* 2008; 95:1331–8
- Koppert W, Zeck S, Sittl R, Likar R, Knoll R, Schmelz M: Low-dose lidocaine suppresses experimentally induced hyperalgesia in humans. *ANESTHESIOLOGY* 1998; 89:1345–53
- Koppert W, Ostermeier N, Sittl R, Weidner C, Schmelz M: Low-dose lidocaine reduces secondary hyperalgesia by a central mode of action. *Pain* 2000; 85:217–24
- Hahnenkamp K, Durieux ME, Hahnenkamp A, Schauerte SK, Hoenemann CW, Vegh V, Theilmeier G, Hollmann MW: Local anesthetics inhibit signalling of human NMDA receptors recombinantly expressed in *Xenopus laevis* oocytes: Role of protein kinase C. *Br J Anaesth* 2006; 96:77–87
- Watkins LR, Maier SF, Goehler LE: Immune activation: The role of pro-inflammatory cytokines in inflammation, illness responses and pathological pain states. *Pain* 1995; 63:289–302
- Hollmann MW, Gross A, Jelacin N, Durieux ME: Local anesthetic effects on priming and activation of human neutrophils. *ANESTHESIOLOGY* 2001; 95:113–22
- Lahav M, Levite M, Bassani L, Lang A, Fidder H, Tal R, Bar-Meir S, Mayer L, Chowes Y: Lidocaine inhibits secretion of IL-8 and IL-1 β and stimulates secretion of IL-1 receptor antagonist by epithelial cells. *Clin Exp Immunol* 2002; 127:226–33
- Groudine SB, Fisher HA, Kaufman RP Jr, Patel MK, Wilkins LJ, Mehta SA, Lumb PD: Intravenous lidocaine speeds the return of bowel function, decreases postoperative pain, and shortens hospital stay in patients undergoing radical retropubic prostatectomy. *Anesth Analg* 1998; 86:235–9
- Schumacher M, Basbaum A, Way W: Opioid analgesics and antagonists, *Basic and Clinical Pharmacology*, 11th edition. Edited by Katzung B, Masters S, Trevor A. Beijing, The McGraw-Hill, 2009, pp 533
- Gandek B, Ware JE, Aaronson NK, Apolone G, Bjorner JB, Brazier JE, Bullinger M, Kaasa S, Lepage A, Prieto L, Sullivan M: Cross-validation of item selection and scoring for the SF-12 Health Survey in nine countries: Results from the IQOLA Project. *International Quality of Life Assessment. J Clin Epidemiol* 1998; 51:1171–8
- Kim SB, Williams SB, Cheng SC, Sanda MG, Wagner AA: Evaluation of patient-reported quality-of-life outcomes after renal surgery. *Urology* 2012; 79:1268–73
- Mascha EJ, Turan A: Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. *Anesth Analg* 2012; 114:1304–17
- Berger R, Hsu JC: Bioequivalence trials, intersection-union tests and equivalence confidence sets. *Stat Sci* 1996; 11:283–319
- Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, Elbourne D, Gøtzsche PC, Lang T; CONSORT GROUP (Consolidated Standards of Reporting Trials): The revised CONSORT statement for reporting randomized trials: Explanation and elaboration. *Ann Intern Med* 2001; 134:663–94
- Vigneault L, Turgeon AF, Côté D, Lauzier F, Zarychanski R, Moore L, McIntyre LA, Nicole PC, Fergusson DA: Perioperative intravenous lidocaine infusion for postoperative pain control: A meta-analysis of randomized controlled trials. *Can J Anaesth* 2011; 58:22–37
- Martin F, Cherif K, Gentili ME, Enel D, Abe E, Alvarez JC, Mazoit JX, Chauvin M, Bouhassira D, Fletcher D: Lack of impact of intravenous lidocaine on analgesia, functional recovery, and nociceptive pain threshold after total hip arthroplasty. *ANESTHESIOLOGY* 2008; 109:118–23
- Yardeni IZ, Beilin B, Mayburd E, Levinson Y, Bessler H: The effect of perioperative intravenous lidocaine on postoperative pain and immune function. *Anesth Analg* 2009; 109:1464–9
- Insler SR, O'Connor M, Samonte AF, Bazara MG: Lidocaine and the inhibition of postoperative pain in coronary artery bypass patients. *J Cardiothorac Vasc Anesth* 1995; 9:541–6
- Striebel HW, Klettke U: [Is intravenous lidocaine infusion suitable for postoperative pain management?]. *Schmerz* 1992; 6:245–50
- Rowland M, Thomson PD, Guichard A, Melmon KL: Disposition kinetics of lidocaine in normal subjects. *Ann N Y Acad Sci* 1971; 179:383–98
- Herroeder S, Pecher S, Schönherr ME, Kaulitz G, Hahnenkamp K, Friess H, Böttiger BW, Bauer H, Dijkgraaf MG, Dijkgraaf OG, Durieux ME, Hollmann MW: Systemic lidocaine shortens length of hospital stay after colorectal surgery: A double-blinded, randomized, placebo-controlled trial. *Ann Surg* 2007; 246:192–200
- Tsai PS, Buerkle H, Huang LT, Lee TC, Yang LC, Lee JH: Lidocaine concentrations in plasma and cerebrospinal fluid after systemic bolus administration in humans. *Anesth Analg* 1998; 87:601–4
- Werdehausen R, Kremer D, Brandenburger T, Schlösser L, Jadasz J, Küry P, Bauer I, Aragón C, Eulenburg V, Hermanns H: Lidocaine metabolites inhibit glycine transporter 1: A novel mechanism for the analgesic action of systemic lidocaine? *ANESTHESIOLOGY* 2012; 116:147–58
- Tanabe M, Takasu K, Yamaguchi S, Kodama D, Ono H: Glycine transporter inhibitors as a potential therapeutic strategy for chronic pain with memory impairment. *ANESTHESIOLOGY* 2008; 108:929–37
- Swenson BR, Gottschalk A, Wells LT, Rowlingson JC, Thompson PW, Barclay M, Sawyer RG, Friel CM, Foley E, Durieux ME: Intravenous lidocaine is as effective as epidural bupivacaine in reducing ileus duration, hospital stay, and pain after open colon resection: A randomized clinical trial. *Reg Anesth Pain Med* 2010; 35:370–6
- Mitchell SJ, Pellett O, Gorman DF: Cerebral protection by lidocaine during cardiac operations. *Ann Thorac Surg* 1999; 67:1117–24
- Mathew JP, Mackensen GB, Phillips-Bute B, Grocott HP, Glower DD, Laskowitz DT, Blumenthal JA, Newman MF; Neurologic Outcome Research Group (NORG) of the Duke Heart Center: Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery. *Stroke* 2009; 40:880–7
- Mitchell SJ, Merry AF, Frampton C, Davies E, Grieve D, Mills BP, Webster CS, Milsom FP, Willcox TW, Gorman DF: Cerebral protection by lidocaine during cardiac operations: A follow-up study. *Ann Thorac Surg* 2009; 87:820–5