Effect of Intravenous Lidocaine on Postoperative Recovery of Patients Undergoing Mastectomy
A Double-Blind, Placebo-Controlled Randomized Trial

Abdullah S. Terkawi, MD, Marcel E. Durieux, MD, PhD,* Antje Gottschalk, MD,† David Brenin, MD,‡ and Mohamed Tiouririne, MD**

Background: One of the modalities of treatment for breast cancer surgery pain is opioids, and opioids are associated with adverse effects such as itching and postoperative nausea and vomiting (PONV). Intravenous (IV) lidocaine has been shown to reduce opioid consumption and to improve overall postoperative outcomes in abdominal surgery. In this study, we tested the effect of intraoperative IV lidocaine infusion on the quality of postoperative recovery after breast cancer surgery.

Methods: Seventy-one patients undergoing breast cancer surgery were randomly assigned to receive either placebo (group P; n = 34) or IV lidocaine (group L; n = 37, bolus 1.5 mg/kg at induction, then infusion at 2 mg/kg/h, stopped 2 hours after the end of surgery) in a prospective double-blind design. Intraoperative and postoperative morphine consumption was calculated. Postoperative pain scores, PONV, and fatigue were assessed at 2, 24, and 48 hours after surgery. Duration of postoperative hospital stay was recorded.

Results: Demographics were the same between the groups. There was no statistically significant difference in intraoperative or postoperative morphine consumption ($P = 0.188$ and $P = 0.758$) between groups. Overall pain scores either at rest or activity ($P = 0.348$ and $P = 0.810$, respectively), PONV ($P = 0.350$), fatigue ($P = 0.758$), or duration of postoperative hospital stay ($P = 0.218$) were not statistically different.

Conclusions: Our findings did not show a significant effect of IV lidocaine during breast cancer surgery on opioid consumption, pain score, PONV, or fatigue, indicating that the benefit of this approach does not generalize across all types of surgery.

(*Reg Anesth Pain Med* 2014;39: 00–00)

One of the modalities of treatment for breast cancer surgery pain is opioids, but opioids are associated with adverse effects such as itching, nausea and vomiting, constipation, urinary retention, and dizziness.[1] Thoracic paravertebral blocks using local anesthetics have been recommended for breast surgery. It provides good pain control, possibly blunts the surgical stress response, and decreases anesthetic requirements.[2] However, thoracic paravertebral blocks are not widely used due to technical challenges and the inherent risks associated with placement, such as pneumothorax, nerve injury, and bleeding.[3] Alternative approaches for postoperative pain control are needed. Lidocaine infusion has shown promise for perioperative pain management in many procedures. Specifically, it has been shown to reduce opioid consumption and improve overall postoperative outcomes in patients undergoing abdominal surgery.[4]

The aim of this study was to assess the effects of intravenous (IV) lidocaine infusion on the early postoperative recovery profile [opiate consumption, pain scores, fatigue, postoperative nausea and vomiting (PONV), and length of stay] of patients undergoing breast cancer surgery.

METHODS

Enrollment

After institutional review board approval, patients scheduled for mastectomy for cancer at the University of Virginia Health System between January 2009 and June 2013 were approached for enrollment. The study was registered in ClinicalTrials.gov (NCT01204242). Patients aged 18 to 80 years, with American Society of Anesthesiologists Physical Status I, II, or III, were eligible for the study. Allergy to local anesthetics, fentanyl, or morphine; myocardial infarction within 6 months; profoundly decreased left ventricular function (ejection fraction < 40%) or high-grade arrhythmias; severe liver disease (aspartate aminotransferase or alanine transaminase or bilirubin > 2.5 times the upper limit of normal); renal impairment (creatinine clearance < 60 mL/min); pregnancy or breastfeeding; and enrollment in another clinical trial within the last 30 days (except blood draw studies, surgical technique studies, or questionnaire studies) were considered exclusion criteria. We used the Apfel scoring system (1–4) to assess PONV risk.[5]

Randomization

After patients signed the consent and before surgery, all patients had a 12-lead electrocardiogram performed to screen for acute myocardial infarction or abnormal heart rhythm. Subjects were randomized to 1 of 2 study drug arms: lidocaine infusion versus placebo (normal saline) at 1:1 ratio. The anesthesia provider was given a blinded infusion bag that contained lidocaine 8 mg/mL or 0.9% NaCl (normal saline), which was prepared in the pharmacy. Lidocaine was administered as a bolus to all patients before anesthetic induction, at a dose of up to 1.5 mg/kg, with a maximum of 150 mg (ie, patients 100 kg and above received a fixed dose of 150 mg). This was to prevent the possibility of overdose because of changes in body composition in obese patients. This bolus was followed by a lidocaine infusion at 2 mg/kg/h (to an upper limit of 200 mg/h) or equal volume of placebo until 2 hours after arrival in the postanesthesia care unit (PACU), or PACU discharge, whichever was earlier. If the patient left PACU before 2 hours, study drug infusion was terminated and the subject analyzed per intention to treat. We selected to use this duration/regimen as we felt a 2-hour postoperative infusion to be clinically applicable; in addition, duration of postoperative infusion does not result in major differences in recovery benefit.[6] The patient and research team remained blinded until after all data were analyzed.

From the *Department of Anesthesiology, University of Virginia, Charlottesville, VA; †Department of Anesthesiology, Intensive Care and Pain Medicine, University Hospital Muenster, Muenster, Germany; and ‡Department of Surgery, University of Virginia, Charlottesville, VA.

Accepted for publication July 15, 2014.

Address correspondence to: Mohamed Tiouririne, MD, Department of Anesthesiology, University of Virginia, PO Box 800710, Charlottesville, VA 22908 (e-mail: mt9y@virginia.edu).

The authors declare no conflict of interest.

Supported by the Department of Anesthesiology, University of Virginia Health System, Charlottesville, VA.

An abstract was presented at the International Anesthesia Research Society 2014 Annual Meeting and International Science Symposium, Montreal, Canada, May 17–20, 2014.

ISSN: 1098-7339
DOI: 10.1097/AAP.0000000000000140

Anesthesia Standardization and Protocol

All patients received general anesthesia. At the discretion of the attending anesthesiologist were choice of induction drug and the use of premedication and muscle relaxant.

Sevoflurane in air/oxygen was used for maintenance. Intraoperative analgesia was limited to fentanyl IV (5 μg/kg maximum). Antiemetic prophylaxis was given according to Apfel's recommendations.[7] Residual muscle relaxation was reversed with neostigmine and glycopyrrolate. After surgery, all subjects were transported to the PACU and monitored per institutional PACU protocol (including electrocardiogram monitoring). Pain was assessed every 15 minutes, and patients with scores greater than 3 were treated with either fentanyl 50 μg every 10 minutes or morphine 4 mg every 20 minutes as needed. Nausea was assessed at 15-minute intervals and treated using ondansetron 4 mg IV first, followed by doses of promethazine 6.25 mg IV every 20 minutes as needed. Postoperative analgesia was not standardized. We requested the use of morphine patient-controlled analgesia to allow easier comparison between groups, but postoperative analgesia was at the discretion of the surgical team responsible for the patient.

Outcome Measurements

Primary

Opiate consumption and pain scores in the first 48 hours postoperatively were the primary outcomes of interest. Opiate consumption was assessed at the end of surgery (intraoperative consumption), after recovery in the PACU (at 2 hours) and at 24 and 48 hours after PACU discharge. Opioid consumption was converted to morphine sulfate equivalents.[8] Pain was assessed with an 11-point (0–10) numerical rating scale at 2, 24, and 48 hours.

Secondary

Postoperative nausea and vomiting, fatigue, intraoperative opiate consumption, and blood loss, as well as the duration of hospital stay were the secondary outcomes of interest. Severity of nausea and fatigue were also assessed an 11-point (0–10) scale.

Statistical Analysis

A previous study of postoperative pain and morphine requirements in patients after breast cancer surgery under general anesthesia showed that mean 24 hours opioid requirements were 21.7 mg morphine equivalents.[9] Using a 2-sample *t* test to compare 24-hour morphine requirements and assuming an expected 25% reduction in opioid consumption, an estimated standard deviation of 5.5 mg,[9] with an α of 0.05, it was determined that a sample size of 27 patients per group would be required to obtain 90% power (assuming normality and equal variances). Considering the potential for patient withdrawal and incomplete data sets, we expanded the enrollment to include at least 20% more patients in each study group.

Data were first tested for normality of distribution by evaluating the histogram of distribution and using a Shapiro-Wilk test to determine the best comparison tests to use (ie, parametric versus nonparametric). Mean and standard deviation were used for descriptive analysis of normally distributed variables, whereas median and 25th and 75th interquartile range (IQR) were used for nonnormally distributed variables. Two-sample *t* test was used to compare the mean difference between the 2 groups for normally distributed data, whereas Mann-Whitney *U* test was used for nonnormally distributed data. Repeated-measures outcomes (eg, pain scores) were tested with repeated-measures analysis of variance (ANOVA). Categorical variables were compared with χ^2 tests or Fisher exact tests, as appropriate. A *P* value of 0.05 was considered statistically significant. IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp, Armonk, New York) was used for the analysis.

RESULTS

Eighty patients were enrolled, and 71 patients completed the study. A CONSORT trial flow diagram is presented in Figure 1.

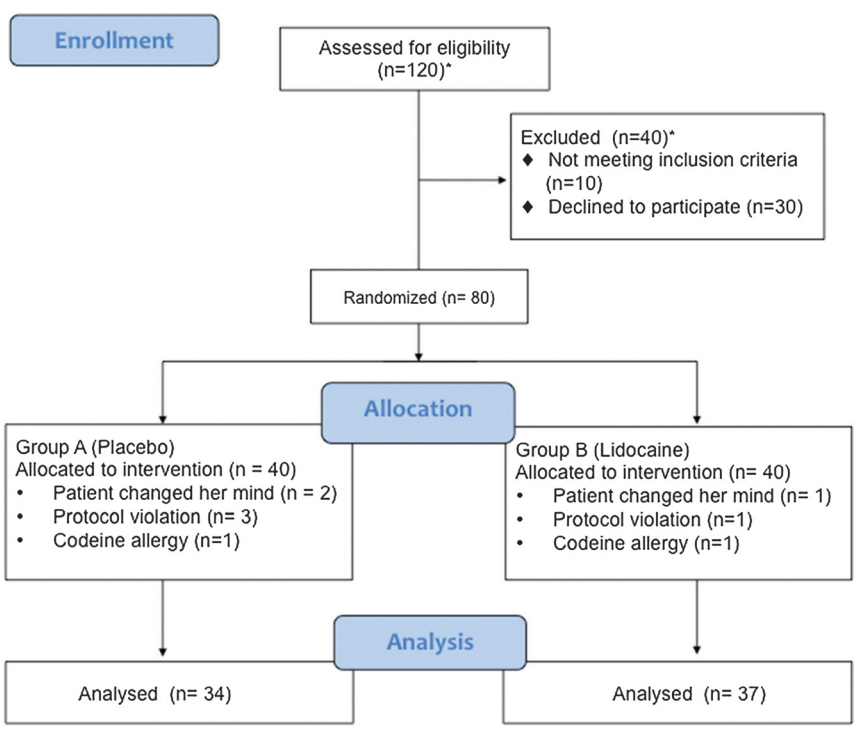

FIGURE 1. CONSORT flow chart. *These are estimated numbers.

The 2 groups were well randomized; there was no statistically significant difference in demographics or in clinical characteristics (Table 1). Twenty-five patients (35%) underwent modified radical mastectomy, and 46 (65%) underwent simple mastectomy. No statistically significant differences were found in the distribution of procedures between the 2 groups (Table 1). The median (minimum, maximum) infusion time in PACU was 75 (57, 120) minutes in the placebo group, whereas it was 85 (45, 120) minutes in the lidocaine group.

Primary Outcomes

The mean postoperative pain scores at rest (Fig. 2A) were 3.88 ± 2.92 at 2 hours, 2.66 ± 2.66 at 24 hours, and 3.09 ± 2.80 at 48 hours in the placebo group, whereas they were 2.94 ± 2.74 at 2 hours, 2.91 ± 2.21 at 24 hours, and 2.72 ± 2.25 at 48 hours in the lidocaine group. Overall pain scores in both groups were similar with no statistical difference by repeated-measures ANOVA test ($P = 0.348$). Mean postoperative pain scores during activity (Fig. 2B) were 4.90 ± 2.90 at 2 hours, 4.12 ± 2.79 at 24 hours, and 4.12 ± 2.95 at 48 hours in the placebo group, whereas they were 4.22 ± 2.69 at 2 hours, 5.40 ± 2.96 at 24 hours, and 4.52 ± 2.92 at 48 hours in the lidocaine group, with no statistically significant difference by repeated-measures ANOVA test ($P = 0.810$).

Mean opioid consumption (morphine sulfate equivalent) (Fig. 3) was 9.69 ± 6.70 mg at 2 hours, 14.43 ± 16.46 mg at 24 hours, and 11.61 ± 19.84 mg at 48 hours in the placebo group, whereas they were 9.35 ± 10.67 mg at 2 hours, 13.00 ± 12.68 mg at 24 hours, and 11.02 ± 8.70 mg at 48 hours in the lidocaine group, with no statistical difference achieved using repeated-measures ANOVA test ($P = 0.758$).

Secondary Outcomes

Mean postoperative nausea severity scores were 1.70 ± 3.09 at 2 hours, 0.96 ± 2.22 at 24 hours, and 0.70 ± 1.89 at 48 hours in the placebo group, whereas they were 0.26 ± 1.23 at 2 hours, 1.14 ± 2.64 at 24 hours, and 0.82 ± 2.19 at 48 hours in the lidocaine group, with no statistical significance between the 2 groups by repeated-measures ANOVA test ($P = 0.350$). Mean postoperative fatigue severity scores were 4.71 ± 3.59 at 2 hours, 3.58 ± 3.77 at 24 hours, and 2.90 ± 3.27 at 48 hours in the placebo group, whereas they were 4.96 ± 3.70 at 2 hours, 4.03 ± 2.98 at 24 hours, and 2.64 ± 2.73 at 48 hours in the lidocaine group, with no statistical significance between the 2 groups, repeated-measures ANOVA test ($P = 0.814$).

Intraoperative morphine equivalent consumption, estimated blood loss, and duration of hospitalization were also evaluated. No statically significant differences between the 2 groups on these variables were identified (Table 2).

Because no toxicity cases were reported in our cohort, we did not measure lidocaine levels in any patients.

DISCUSSION

The data on perioperative lidocaine infusion during abdominal surgery have led to increased awareness of the potential role of lidocaine infusion as an adjunct pain management modality in surgery. In a meta-analysis of 29 studies (17 of various abdominal procedures and 7 of open heart surgery), Vigneault et al found that at 6 hours postoperatively, IV lidocaine infusion reduced pain at rest, during cough, and during movement. It also reduced opioid requirements, time to first flatus, time to first feces, nausea, vomiting, and hospital length of stay. Most of these benefits were observed in the abdominal procedures.[10] More recently, perioperative lidocaine infusion (2 mg/kg per hour) was found to reduce both postoperative pain scores and opioid consumption in complex spine surgery, but it did not affect PONV or the length of hospital stay.[11] Similar benefits were also found in microdiscectomy.[12] On the other hand, lidocaine infusion at a rate 1.5 mg/kg per hour offered no beneficial effect on postoperative analgesia and pain scores after total hip arthroplasty,[13] or in tonsillectomy.[14] Grigoras et al tested the efficacy of a lidocaine infusion at rate of 1.5 mg/kg per hour in 36 patients undergoing breast surgery. They did not find a difference in intraoperative or postoperative opioid consumption but did show a reduction of postoperative pain scores at certain time points; however, the authors did not present an overall performance evaluation of the drug on pain during the whole study period.[15]

Our study, using 2 mg/kg per hour lidocaine, did not find a statistically significant difference in intraoperative or postoperative opioid consumption, postoperative pain, nausea, vomiting, fatigue, or duration of postoperative hospital length of stay. We believe that factors determining the effectiveness of perioperative lidocaine infusion in pain and opioid consumption are concentration (although the optimal concentration has not been determined), and the type of surgery (with higher efficacy in more painful surgeries requiring more opioids, and possibly in operations with a greater inflammatory component, such as abdominal procedures). Our trial used concentrations and infusion durations similar to those of other studies,[6] suggesting

TABLE 1. Demographic and Clinical Characteristics of the Study Population

Characteristic	Placebo Group, n = 34	Lidocaine Group, n = 37	*P*
Age, mean (SD), y	54 (11.13)	53 (13.14)	0.282
Body mass index, mean (SD), kg/m^2	28.29 (7.99)	26.27 (11.74)	0.092
Total amount of drug infused, mean (SD), mg	802 (300.91)	797 (263.71)	0.336
Duration of surgery, min*	161 [122.5, 250]	167 [131, 216]	0.429†
PONV risk score‡			
II	20 (58.82)	21 (56.75)	NA
III	14 (41.17)	16 (43.24)	NA
Modified radical mastectomy‡	11 (32.35)	14 (37.83)	0.918
Simple mastectomy‡	23 (67.64)	23 (62.16)	0.972

P value calculated with χ^2 and Fisher exact test.

*Presented as median and [first quartile, third quartile].

†Using Mann-Whitney *U* test, as they are not normally distributed data.

‡Presented as number (percent).

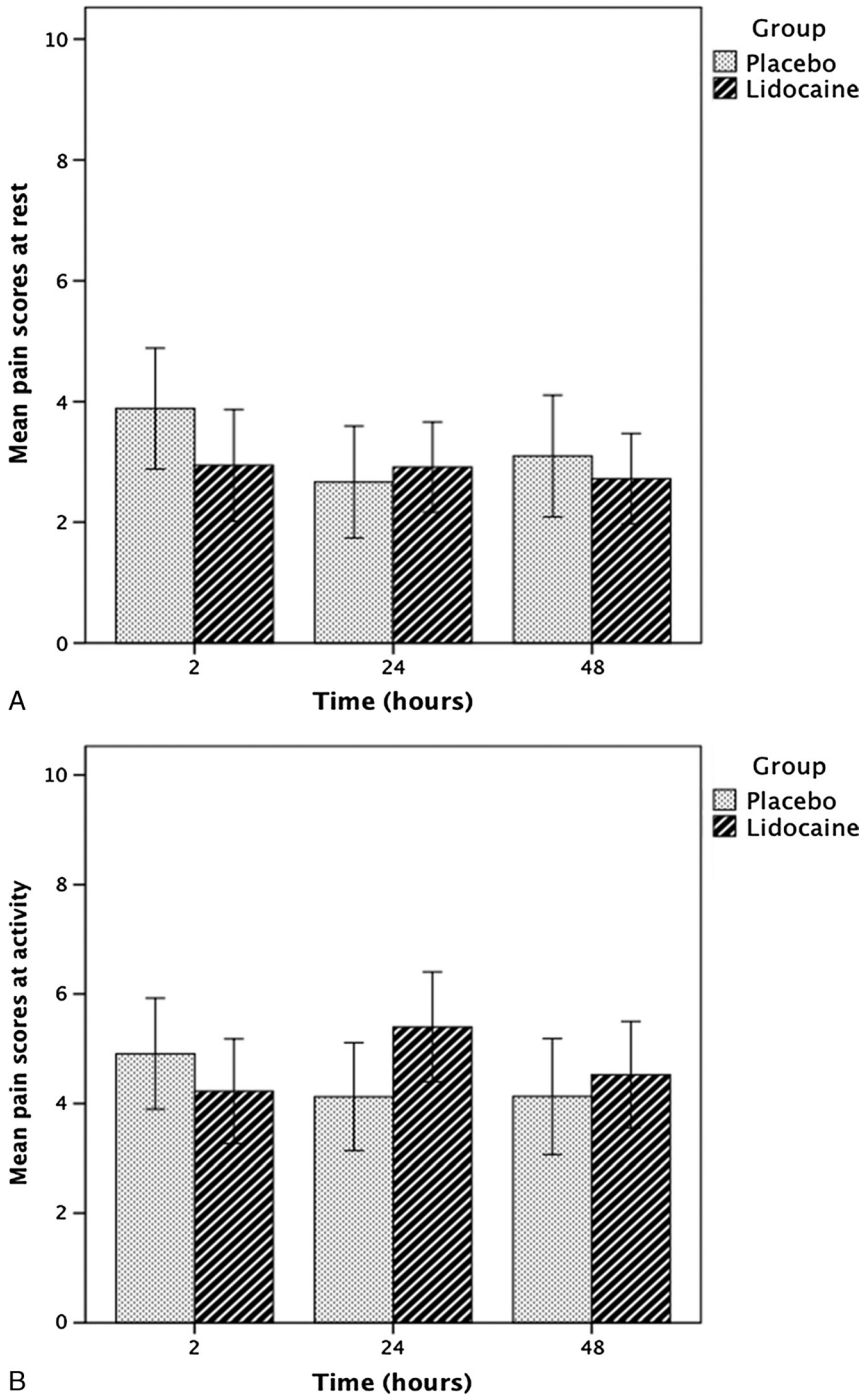

FIGURE 2. Mean and standard error of postoperative pain at rest (A) and at activity (B) in numerical rating scale, at 2, 24, and 48 hours, respectively.

that the lack of observed benefit was related primarily to the type of surgery.

Duration of infusion does not seem to have much effect on postoperative pain. In a meta-analysis of IV lidocaine and postoperative recovery after abdominal surgery, Marret et al[6] evaluated 6 trials that considered different durations of infusion on postoperative pain at 24 hours after surgery, concluding that IV administration of lidocaine during and after abdominal surgery improves patient rehabilitation and shortens hospital stay.

Lidocaine has multiple mechanisms of action. It blocks sodium channels in the neuronal cell membrane that may play a role in the pathogenesis and maintenance of both neuropathic and inflammatory pain.[16] Lidocaine is believed to have analgesic,[17] and antihyperalgesic properties by reducing secondary hyperalgesia through a central mode of action.[18] Systemic administration of lidocaine inhibits the activation of human *N*-methyl-D-aspartate glutamate receptors in a concentration-dependent fashion, which may contribute to reduced hyperalgesia and

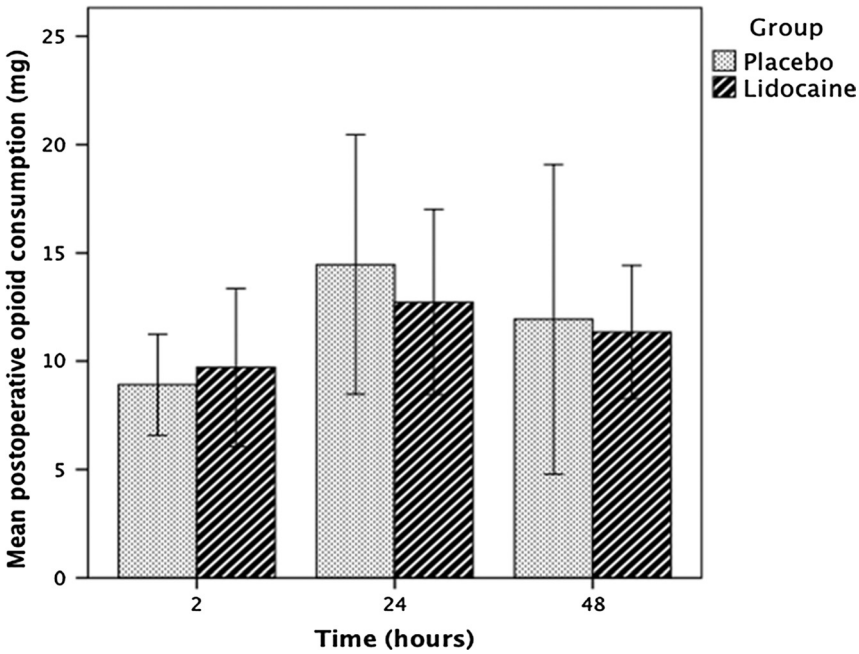

FIGURE 3. Mean and standard error of the postoperative opioid (morphine sulfate equivalent) consumption at 2, 24, and 48 hours, respectively.

opiate tolerance.[19] Lidocaine has also been found to block neutrophil accumulation at the injury site and reduce the release of inflammatory mediators that may account for significant anti-inflammatory properties.[20]

A lidocaine plasma concentration up to 5 μg/mL is believed to be safe. Kaba et al[21] studied perioperative lidocaine administration (bolus injection of 1.5 mg/kg lidocaine at induction of anesthesia, then a continuous infusion of 2 mg/kg per hour intraoperatively followed by 1.33 mg/kg per hour for 24 hours postoperatively) in laparoscopic colectomy patients. Levels were measured at 5 minutes after bolus administration, then 15 minutes, 60 minutes, at the end of surgery, and after 24 hours. No measured level exceeded the therapeutic range. In patients undergoing open colectomy, lidocaine levels were determined at 5 minutes, 2 hours, and 4 hours after initiation of infusion (2 mg/min). In this study of 33 patients, all values were within the therapeutic range, with the exception of a single measurement of 5.8 μg/mL, obtained immediately after lidocaine bolus administration.[22] Studies have used different lidocaine infusion regimens. Hsu et al[23] studied the population pharmacokinetics of lidocaine administered during and after cardiac surgery. Interestingly, they found the concentration in the blood did increase gradually even with a constant rate of infusion. A 2-compartment pharmacokinetic model best described the plasma concentrations of a 48-hour infusion. Thus, they suggested reducing the dose after 24 hours. Despite this variability in approaches, our trial used a well-established dosing scheme, and the lack of effect is unlikely to be due to insufficient dosing.

The half-life of IV lidocaine bolus is approximately 1.5 hours, whereas plasma levels may be measurable as long as 12 hours when the drug is given as infusion.[24] Effects of IV lidocaine, however, may exceed its actual half-life. Two properties of lidocaine have been linked to its extended effects after infusion: the prolonged availability of lidocaine at the spinal dorsal horn level after systemic administrations that suppresses central sensitization within the spinal cord after nerve injury in humans.[25] In addition, lidocaine metabolites (monoethylglycinexylidide and *N*-ethylglycine) were shown to inhibit GlyT1-mediated glycine

TABLE 2. Secondary Outcomes Comparison Between the 2 Groups

Characteristic	Placebo Group, n = 34	Lidocaine Group, n = 37	*P*
Intraoperative morphine equivalent consumption, median [IQR], mg	20.25 [13–25]	16.25 [10–25]	0.202*
Estimated blood loss, median [IQR], mL	100 [50–200]	50 [37.5–100]	0.285*
Duration of hospitalization, median [IQR], h	32 [29–35]	30 [23–35]	0.210*
Patients required antiemetic at 2 h†	5 (14.7)	4 (10.8)	0.734
Patients required antiemetic at 24 h†	9 (26.4)	11 (29.7)	NA
Patients required antiemetic at 48 h†	2 (5.8)	4 (10.8)	0.678

P value calculated with χ^2 and Fisher exact test.

*Using Mann-Whitney *U* test, as they are not normally distributed data.

†Presented as number (percent).

IQR indicates interquartile range [first quartile, third quartile].

uptake by at least 2 different mechanisms, even with a low serum dose, which gives a clue for possible mechanisms for the antinociceptive effect of systemic lidocaine.[26] Furthermore, its effect on blocking neutrophil activation and the subsequent release of inflammatory mediators further contribute to its longer analgesic effects.[20]

The main limitation of our trial is the relatively small sample size. However, as calculated, we should have been able to identify a 25% reduction in opiate consumption with 90% power. Because our data did not show even a clear trend toward benefit, it seems unlikely that our negative results are due to the trial being underpowered.

In conclusion, we did not observe reductions in pain or opiate consumption by intraoperative lidocaine infusion during mastectomy, suggesting that the drug does not produce postoperative benefits for all types of surgery. Results obtained in studies concerning the use of IV lidocaine in one type of surgery should not be extrapolated to another type of surgery. Our findings highlight the need for additional studies of IV lidocaine in specific surgical populations.

ACKNOWLEDGMENTS

The authors thank Fransizka Blum, MD, and Swapna Thammishetti, MD, for the assistance in data collection; and Siny Tsang, MA, and the StatLab at the University of Virginia, Charlottesville, VA, for the help with data analysis.

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