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Randomized Controlled Trial

Intravenous Lidocaine Decreases Pain Scores 24 Hours Post Cardiac Surgery: Substudy of a Randomized Controlled Trial

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Background: Post cardiac surgery pain remains a problem for a significant number of patients. While opioids have long been used for cardiac surgery pain control and hemodynamic stability, methods to improve pain control while also reducing reliance on opioids are desired. Intravenous lidocaine has shown promise for pain and opioid reduction in multiple operative settings, yet its role in cardiac surgery lacks conclusive data.

Objective: To determine the effect of intravenous lidocaine on pain scores and opioid consumption in the first 48 hours post cardiac surgery.

Study Design: Preplanned substudy of a single-center, double-blind, placebo-controlled, randomized controlled trial.

Setting: This study was conducted in a tertiary/quaternary care academic hospital in the United States.

Methods: Following institutional review board approval and informed consent, a total of 449 patients who met the inclusion criteria were enrolled and randomized to receive either a bolus of one mg/kg of lidocaine administered after anesthesia induction followed immediately by a continuous infusion at 48 µg/kg/min for the first hour, 24 µg/kg/min for the second hour, and 10 µg/kg/min for the next 46 hours (lidocaine group) or normal saline (placebo group). Primary outcomes were Visual Analog Scale (VAS) scores and opioid consumption in of morphine milligram equivalents at 24 and 48 hours post surgery. Secondary endpoints included the administration of other nonopiod analgesic medications, postoperative antiemetic medication use, intensive care unit length of stay, hospital length of stay, and time to return of bowel function. Univariable and multivariable regression analyses were performed.

Results: A total of 215 patients who received a placebo and 218 patients who received lidocaine were evaluated. We observed a statistically significant difference in VAS pain score at postoperative 24 hours (adjusted mean difference -0.68; 95%CI, -1.23 to 0.13; $P = 0.016$) between patients treated with lidocaine vs placebo; however, no difference was observed at postoperative 48 hours. The cumulative opioid use in morphine milligram equivalents was not significant, both in univariable and multivariable analysis, at all timepoints between patients receiving lidocaine vs placebo. Among secondary outcomes, the only significant effect was a decrease in odds of acetaminophen use in the first postoperative 48 hours (adj. odds ratio 0.54; 95% CI 0.32 to 0.90, $P = 0.018$).

Limitations: Although pain scores were a preplanned outcome of the parent study, opioid consumption was not. Furthermore, postoperative pain management was not specifically standardized for this study.

Conclusions: We found that intravenous lidocaine resulted in a statistically significant decrease in VAS pain scores at 24 hours post cardiac surgery, with no difference in opioid consumption. While this pain benefit has been noted in other surgical patient populations, our findings are

important since patients undergoing cardiac surgery are unique given the physiologic changes associated with cardiopulmonary bypass graft.

Key words: Cardiac surgery, cardiopulmonary bypass, intravenous lidocaine

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Postoperative pain delays patient recovery, results in morbidity, and leads to psychological dissatisfaction(1). The reported incidence of postoperative pain post cardiac surgery is reported to be highly variable, ranging between 49% – 90% in the acute phase and 21% – 67% in the first 3–12 months post surgery (2–5). Opioids have long been heavily relied upon in the perioperative phase of cardiac surgery for both pain relief and hemodynamic stability.

In line with general trends in global perioperative management, protocols for enhanced recovery after cardiac surgery (ERACS) emphasize a decreased reliance on opioids in favor of multimodal pain management. Data continue to evolve regarding which agents and techniques offer an opioid-sparing benefit. The risks of persistent postoperative opioid use in patients undergoing cardiac surgery is a reported concern (6). An effective opioid-sparing multimodal approach is important as persistent cardiac surgery postoperative pain remains a substantial complication that not only impairs patient quality of life, but also adds significant burdens to health care systems (7). Unlike in abdominal surgery, where the efficacy of multimodal pain management—including the use of intravenous (IV) lidocaine—has been well documented, cardiac surgery presents unique challenges due to the direct and extensive nature of surgical trauma and the high incidence of postoperative pain. Literature specifically addressing the effective management of postoperative pain in cardiac surgery patients is sparse, pointing to a critical gap. This gap underlines the need for stronger data to support adopting opioid-sparing strategies that could mitigate the risks associated with long-term opioid use and enhance recovery by effectively managing acute pain and reducing the incidence of postoperative pain.

Lidocaine is a drug with antiarrhythmic, antinociceptive, and anti-inflammatory properties. It has been used as an IV infusion for postoperative analgesia as well as chronic and neuropathic pain management (8-10). Based on meta-analyses, the intraoperative administration of IV lidocaine has been shown to improve immediate postoperative pain primarily in the first postoperative 24 hours and with the best data in abdominal surgery (11-15). Evidence of its effectiveness and safety specifically in patients undergoing cardiac surgery is limited. This gap is significant because the pathophysiology of pain and the patient's physiological response to cardiac surgery might differ markedly from patients undergoing abdominal procedures. For instance, cardiac surgeries involve cardiopulmonary bypass, which induces a unique inflammatory response that might influence pain perception and analgesic effectiveness (16).

Since the data on lidocaine's effect on cardiac postoperative pain are lacking (17), we aimed to study the effect of IV lidocaine on pain scores and opioid consumption in the first 72 hours post cardiac surgery as a preplanned substudy of a double-blind, placebo-controlled, randomized controlled trial evaluating the effect of IV lidocaine on postoperative cognitive outcomes post cardiac surgery (18). We hypothesized that administering IV lidocaine intraoperatively and postoperatively for a total of 48 hours would reduce postoperative pain scores and opioid consumption in patients undergoing cardiac surgery with cardiopulmonary bypass compared to placebo.

Methods

Study Population

After approval by respective institutional review boards and informed consent, adults at least 50 years old scheduled to undergo coronary artery bypass grafting, valve surgery, or coronary artery bypass grafting plus valve surgery with cardiopulmonary bypass (CPB) were enrolled into this multicenter, prospective, randomized, double-blinded, placebo-controlled, parallel group clinical trial. The enrollment period was from July 2009 through June 2016. For this substudy, we utilized patients enrolled at the Duke University Health System in Durham, North Carolina.

Prospective patients were approached by study staff. Patients were excluded if their scheduled procedure included planned circulatory arrest; a history of diabetes (documented history, elevated fasting blood glucose, or hemoglobin A1c of 6.5% or higher); symptomatic cerebrovascular disease (e.g., prior stroke) with residual deficit; high alcohol consumption (more than 2 drinks

per day); drug abuse (any illicit drug use in the past 3 months); psychiatric illness (any clinical diagnosis requiring therapy); renal failure (serum creatinine more than 2 mg/dL); hepatic insufficiency (liver function tests more than 1.5 times the upper limit of normal); severe pulmonary insufficiency (requiring home oxygen therapy); left ventricular ejection fraction of less than 20%; preoperative intraaortic balloon pump requirement; liver/heart/lung transplant; current pregnancy; and those who were unable to read and thus complete the cognitive testing or who scored less than 24 on the baseline Mini Mental State examination or at least 27 on the baseline Center for Epidemiologic Studies–Depression Scale. Informed consent was obtained by study staff.

Patients were randomized to one of 2 treatment groups: 1) the lidocaine group, who were administered a bolus of 1 mg/kg of lidocaine after anesthesia induction followed immediately by a continuous infusion at 48 μg/kg/min for the first hour, 24 μg/kg/min for the second hour, and 10 μg/kg/min for the next 46 hours or 2) the placebo group, who were administered normal saline as a bolus and an infusion for 48 hours with identical volume and rate changes as the treatment group, such that blinding of both the patient and study/clinical team was preserved.

This weight-based lidocaine infusion regimen is based on previous pharmacokinetics work by our group to determine the optimal infusion strategy to maintain therapeutic lidocaine levels while avoiding potentially toxic levels (19) (more than 5 μg/mL) in patients undergoing CPB. A group assignment schedule was prepared for each site using Nquery software version 7 (STATCON) by the study statistician and stored in consecutively numbered sealed envelopes until allocation by study staff.

As the primary outcomes, pain scores were documented as Visual Analog Scale (VAS) scores at baseline (preoperatively) and at postoperative 24 and 48 hours. In the rare instance that a VAS pain score was not obtained by study personnel, we included nurse-obtained Numeric Rating Scale (NRS-11) pain scores. Opioid consumption in morphine milligram equivalents (MME) was recorded for the first and second 24 hour postoperative periods. Secondary outcomes included the administration of nonopioid analgesic medications as well as postoperative antiemetic medication use in the first postoperative 48 hours, intensive care unit length of stay, hospital length of stay, and time to return of bowel function (time to first bowel movement); these data points were determined via chart review.

Patient Management

Anesthesia was induced with midazolam, fentanyl, and propofol; isoflurane was used for maintenance. All patients underwent nonpulsatile, hypothermic (30°C to 32°C) CPB with a membrane oxygenator and arterial line filter by a centrifugal pump primed with crystalloid using bio-active tubing. Serial hematocrit levels were maintained at 0.21 or greater. Before initiating CPB, heparin (300 to 400 U/kg) was administered to a target activated coagulation time of more than 480 seconds. Perfusion was maintained at flow rates of 2 to 2.4 L/min/m^2 throughout CPB to maintain a mean arterial pressure of 50 mmHg to 80 mmHg. Arterial blood gases were measured every 15 minutes to 30 minutes to maintain the $PaCO_2$ at 35 mmHG to 40 mmHg unadjusted for temperature and the PaO_2 at 150 mmHG to 250 mmHg. We used cell salvage (BRAT, Cobe CV Inc. or Elite, Haemonectics Inc.) for the majority of cases.

Plasma lidocaine levels were sampled at baseline, at the end of CPB, and at post bolus 24 hours and 48 hours. Plasma lidocaine analysis was performed by the Duke University Clinical Laboratories (Durham, NC). Results were only made available by fax to a study team member so that team member could monitor for lidocaine toxicity (plasma levels > 5 μg/mL required discontinuation of the study drug). Blinding of the patient, medical care teams, and study personnel was preserved at all times. If the study drug was discontinued because of high lidocaine levels, the patient and the medical care team were no longer blinded (n = 1).

Postoperative pain management was per unit protocol. Opioid administration was in the form of an IV bolus dosing while the patient was nil per os and converted to oral opioid formulations subsequently. All administered opioids were converted to MME for analysis.

Statistical Analyses

Patient and surgical characteristics were summarized between groups via mean (SD) or median (interquartile [IQR]Q1, Q3) for numeric variables and count (%) for categorical variables, and compared via t test, Wilcoxon rank sum test, χ^2 test, or Fisher's exact test as appropriate. Pain scores at 24 and 48 hours were summarized via median (IQR Q1, Q3) and compared via univariable and multivariable linear regression, adjusting for baseline pain score. Postop medication data were summarized via median (IQR Q1, Q3) for doses or count (%) for administration incidence during the 3 time windows of interest (postsurgical 0–24 hours, 0–48

hours, and 0–72 hours) and compared via univariable and subsequently multivariable linear regression (for doses) and logistic regression (for administration).

Durations of intensive care unit stay, hospital length of stay, and time to first bowel movement were summarized via median (IQR Q1, Q3) and compared with univariable and multivariable Cox proportional hazards models. Multivariable models were adjusted for the following prespecified variables: age, gender, race, surgery type, and years of education. Model assumptions were evaluated via regression diagnostics and fit statistics. As 2 prior interim analyses were conducted, we corrected the α for this final analysis according to the O'Brien-Fleming spending function and set the significance level at 0.045. All tests were 2-sided, and analysis was performed in SAS 9.4 (SAS Institute, Inc.).

Results

From July 6, 2009, through June 2, 2016, a total of 550 patients consented to participate in the study; 478 met all inclusion criteria and were randomized, with 449 of those treated at our institution included (Fig. 1). Of these, 223 were allocated to receive a placebo and 226 were allocated to receive lidocaine treatment. After accounting for patients who met exclusion criteria or withdrew after randomization but prior to surgery, 215 patients who received a placebo and 218 patients who received lidocaine were analyzed. As in the parent study, no demographic factors were found to have a significant difference between the treatment groups (Table 1).

The univariable analysis identified a univariable significant difference in pain score at postoperative 24 hours (mean difference, -0.60; 95% CI, -1.15 to -0.04; *P* = 0.035) and acetaminophen requirement over the first postoperative 48 hours (odds ratio [OR], 0.54; 95% CI, 0.33 to 0.89; *P* = 0.016) (Table 2) between patients treated with lidocaine vs placebo. At postsurgery 48 hours, there was no difference in pain scores between treatment groups (mean difference -0.06; 95% CI,-0.56 to 0.43; *P* = 0.80). While pain scores were unavailable for 15 patients at postoperative 24 hours and for 2 patients at postoperative 48 hours, there was no difference in pain score availability between treatment groups (*P* = 0.591). VAS pain scores were not obtained by study personnel in 34 of the 418 patients (7.9%). For 19 of these patients, nurse-obtained NRS-11 pain scores were utilized. Additionally, 10 patients were not extubated within postoperative 24 hours, but had documented pain scores (either VAS or NRS-11) within the protocol window for the postoperative 24 hour time point and were included in the analysis. Of note, excluding these 10 patients in a sensitivity analysis did not change our outcomes.

A priori we specified multivariable adjustment terms including age, gender, race, surgery type, years of education, and baseline (preoperative) pain score (Table 3). After adjusting the difference in pain scores at postoperative 24 hours between treatment groups (adjusted mean difference -0.68; 95% CI,-1.23 to -0.13; *P* = 0.016) and acetaminophen use over the first postoperative 48 hours (adjusted OR 0.54; 95% CI, 0.32 to 0.90; *P* = 0.018) remained significant.

The cumulative opioid use in MME was not significantly different between treatment groups, both in univariable and multivariable analysis, at all timepoints between patients receiving lidocaine vs placebo (adjusted postoperative 0–24 hours mean difference -1.8; 95% CI, -4.6 to 1.0; *P* = 0.200; 0–48 hours -3.1; 95% CI, -7.7 to 1.6; *P* = 0.194; 0-72 hours, -3.1 95% CI, -9.2 to 3.1; *P* = 0.330). There was also no evidence of a difference in gabapentin administration between treatment groups (adjusted OR, 0.62; 95% CI, 0.31 to 1.21; *P* = 0.158). Postoperative length of stay measured in days, intensive care unit stay measured in hours, and time to first bowel movement measured in days were also similar between treatment groups (Tables 2 and 3).

Discussion

In this preplanned substudy of a larger prospective, placebo-controlled parallel group randomized study of IV lidocaine administration for 48 hours during and post cardiac surgery with CPB, we found that lidocaine treatment resulted in a statistically significant decrease in pain scores at postsurgery 24 hours with no difference in opioid pain medication consumption and with a significantly reduced acetaminophen requirement in the first postsurgery 48 hours.

This result is in line with many studies and reviews noting a significant improvement in pain scores at 24 hours after certain surgeries (most commonly abdominal surgery) in patients treated with IV lidocaine (11,12,14,15,20,21). Consistent with what has been observed in other studies, we failed to detect a benefit in pain scores beyond postoperative 24 hours, even after adjusting for possible cofounding effects. We also did not observe an effect on antiemetic use or time to first bowel movement. This may be due to opioid analgesic use remained the same between patients treated with IV lidocaine vs placebo.

Interestingly, patients receiving lidocaine had a significantly reduced acetaminophen analgesic requirement through the initial postoperative 48 hours. It has previously been reported that IV lidocaine reduces total analgesic consumption in other surgical populations (12), although the mechanism of how IV lidocaine might reduce acetaminophen requirements and not opioid requirements remains unclear.

While the clinical significance of the postoperative 24 hour pain score reduction might have been small, our results are important to add to the current body of literature on using IV lidocaine because there has not been a previously reported positive association between IV lidocaine administration and pain relief post cardiac surgery (17,22). It has been posited by others that the reason that cardiac surgery has failed to show a benefit in pain reduction from IV lidocaine may relate to the effects of cardiopulmonary bypass (23). Based on experimental data, pain produced by the systemic inflammatory response to cardiac surgery and cardiopulmonary bypass should theoretically be targeted by IV lidocaine. Specifically, the lidocaine metabolite N-ethylglycine has been shown to attenuate acute inflammatory hyperalgesia in experimental pain models (24). However, the glycine transporter function, which pumps serum N-ethylglycine into the cerebrospinal fluid where it is posited to affect inflammatory hyperalgesia at the spinal cord level (24,25), may be impaired by the physiologic responses to cardiopulmonary bypass (26,27). Although a modest effect, we did observe a reduction in pain score at 24 hours post cardiac surgery in a sizable cohort of patients who received IV lidocaine.

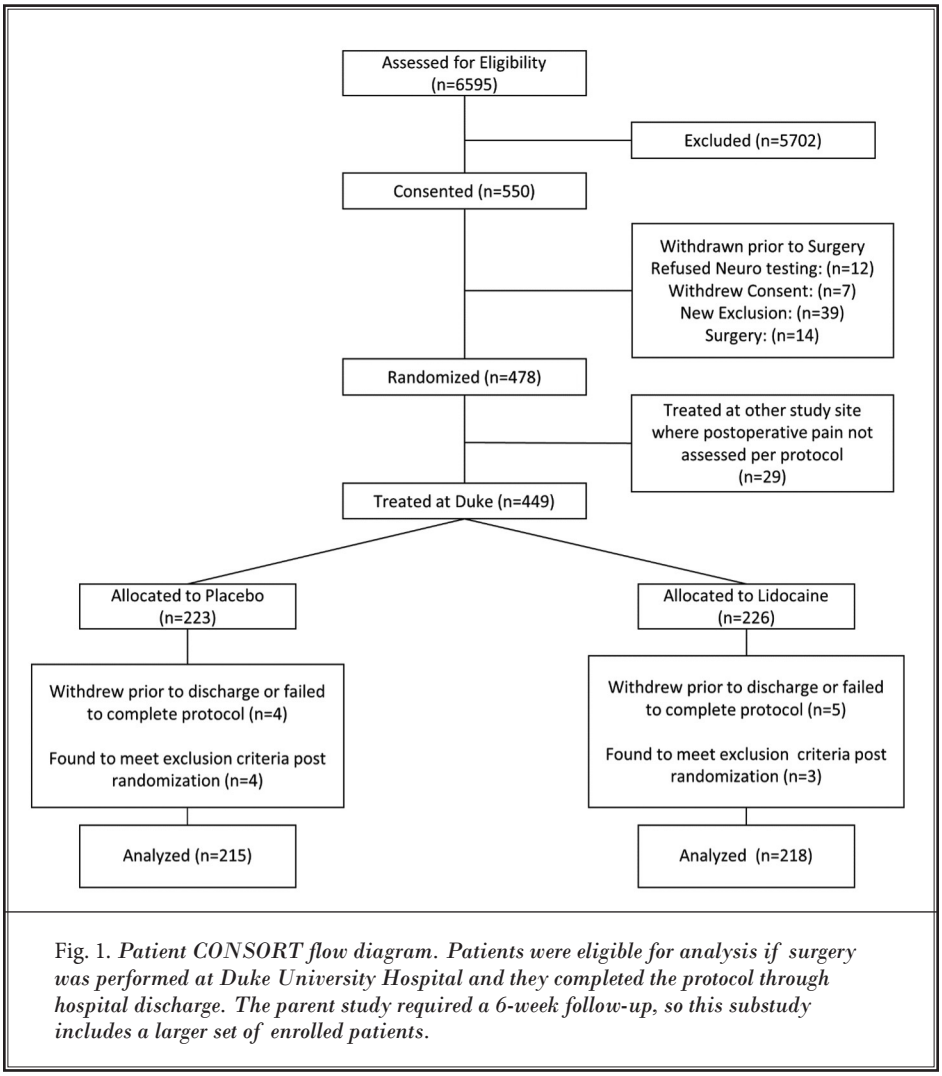


Fig. 1. *Patient CONSORT flow diagram. Patients were eligible for analysis if surgery was performed at Duke University Hospital and they completed the protocol through hospital discharge. The parent study required a 6-week follow-up, so this substudy includes a larger set of enrolled patients.*

Strenghts and Limitations

The strengths of our study include its prospective randomized and placebo-controlled, double-blind design and that pain outcomes were captured as part of the preplanned study design. However, a limitation is that opioid and nonopioid medication use were not initially recorded as part of the prospective data gathering and were rather extracted retrospectively from the medical record via a manual chart review. To attempt to account for this, staff were trained to review the medical records systematically for accurate data extraction. Another limitation is that pain management in the intraoperative and postoperative phases were also not a focus of the primary study nor were they standardized for the study period. Importantly, intraoperative and postoperative management are relatively standardized at our institution and did not change during the study period.

Table 1. *Baseline and surgical characteristics*.

	Lidocaine (n = 218)	Placebo (n = 215)	Total (n = 433)
Baseline Pain*	0 [0,0]	0 [0,0]	0 [0,0]
Gender (% women)	72 (33.03%)	54 (25.12%)	126 (29.10%)
Race (% white)	206 (94.50%)	193 (89.77%)	399 (92.15%)
Age (SD)	67.32 (9.26)	66.91 (9.79)	67.12 (9.51)
Weight, kg (SD)	82.20 (16.37)	82.01 (17.56)	82.10 (16.96)
History of hypertension (%)	131 (60.09%)	128 (59.53%)	259 (59.82%)
Previous MI (%)	32 (14.68%)	40 (18.60%)	72 (16.63%)
Smoking history			
Never	106 (48.6%)	106 (49.3%)	212 (49.0%)
Current	20 (9.2%)	21 (9.8%)	41 (9.5%)
Former	92 (42.2%)	88 (40.9%)	180 (41.6%)
Baseline CES-D Score	9 [3, 13]	6 [3, 13]	7 [3, 13]
Baseline STAI score	35 [28, 45]	36 [26, 45]	35 [27, 45]
Years of education [Q1, Q3]	15 [12, 16]	16 [13, 17]	16 [12, 17]
Preoperative statins (%)	122 (55.96%)	133 (61.86%)	255 (58.89%)
Preoperative platelet inhibitors (%)	153 (70.18%)	155 (72.09%)	308 (71.13%)
Preoperative CNS/psychiatric medication (%)	19 (8.7%)	23 (10.7%)	42 (9.7%)
Preoperative sedative (%)	13 (6.0%)	8 (3.7%)	21 (4.9%)
Preoperative NSAID/COX_2 inhibitor (%)	14 (6.4%)	11 (5.1%)	25 (5.8%)
Preoperative analgesics (%)	2 (0.9%)	7 (3.3%)	9 (2.1%)
Lidocaine level at baseline (SD)**	0.09 (0.31)	0.06 (0.26)	0.07 (0.29)
Isolated valve surgery†	136 (62.39%)	128 (59.53%)	264 (60.97%)
Redo surgery (%)	24 (11.01%)	24 (11.16%)	48 (11.09%)
CPB time, min [Q1, Q3]	159 [127, 203]	169 [133, 218]	165 [128, 211]
Cross clamp time, min [Q1, Q3]	98 [71, 120]	103 [70, 123]	101 [71, 121]
Number of bypass grafts [Q1, Q3] +	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]	3.0 [2.0, 4.0]

*missing for 1 patient
**missing for 6 patients
†Valve includes: Lidocaine--Valve + aneurysm
+ Among those that received grafts
MI, myocardial infarction; CES-D, Center for Epidemiologic Studies Depression Scale; STAI, State Trait Anxiety Inventory; CNS, central nervous system; NSAID, nonsteroidal anti-inflammatory drugs; COX_2, cyclooxygenase-2 inhibitors,

Conclusion

IV lidocaine remains a safe multimodal adjunct; the results of our study suggest a potential benefit in terms of pain reduction in the early postoperative period (24 hours) in patients undergoing cardiac surgery, which is a novel finding. Interestingly, IV lidocaine administration reduced acetaminophen requirements throughout the duration of its administration, further corroborating an analgesic benefit. While other surgical populations have shown a clear and repeatable benefit of IV lidocaine in terms of pain and recovery outcomes, our results should encourage further research into the role of IV lidocaine for patients undergoing nonabdominal surgery.

Author Contributions

Our research was supported by a National Institutes of Health grant, HL096978 to JM. Parent trial ClinicalTrials.gov registration: NCT00938964. The authors confirm contribution to the paper as follows: study conception and design: JM, PG, and RK; data collection: RK; analysis and interpretation of results: RK, MW, AS, JM, PG; draft manuscript preparation: RK, AS, MW. All authors reviewed the results and approved the final manuscript.

Table 2. *Outcome variables summary.*

	Lidocaine (n = 218)	Placebo (n = 215)	Total (N=433)
Postop Medications			
MME postop hours 0-24, mg	19.67 (14.13)	21.73 (15.93)	20.70 (15.07)
MME postop hours 0-48, mg	39.01 (26.36)	42.82 (26.66)	40.90 (26.55)
MME postop hours 0-72, mg	51.21 (36.56)	55.28 (34.72)	53.23 (35.67)
Any acetaminophen dose postop hours 0-24	120 (55.1%)	137 (63.7%)	257 (59.4%)
Any acetaminophen dose postop hours 0-48	169 (77.5%)	186 (86.5%)	355(82.0%)
Any acetaminophen dose postop hours 0-72	200 (91.7%)	203 (94.4%)	403 (93.1%)
Any postop gabapentin dose	16 (7.3%)	24 (11.2%)	40 (9.2%)
Postop Pain			
24h Pain Score*	3.79 (2.74)	4.26 (2.93)	4.02 (2.85)
48h Pain Score**	3.02 (2.59)	3.10 (2.52)	3.06 (2.55)
Postop Durations			
Time to extubation after ICU admission, h	7.5 [5.5, 10.3]	7.2 [5.4, 10.6]	7.2 [5.4, 10.5]
ICU, h	23.45 [20.32, 35.28]	22.73 [19.25, 38.15]	23.05 [19.60, 35.75]
LOS, d	6 [5, 7]	6 [5, 7]	6 [5, 7]
Time to first bowel movement, d***	2.87 [2.33, 3.58]	2.82 [2.09, 3.23]	2.85 [2.16, 3.45]

MME, morphine milligram equivalents; ICU, intenseive care unit; h, hour; d, day; LOS, length of stay
*Pain scores were unavailable for 15 patients at 24 hours.
**Pain scores were unavailable for 2 patients at 48 hours.
***Bowel movements were not charted for 23 patients, so time to first bowel movement is coded as missing

Table 3. *Outcome regression analysis*.

	Univariable		Multivariable	
	Mean Difference (95% CI)[1]	*P* value	Mean Difference (95% CI)[1]	*P* value
MME postop hours 0-24	-2.1 (-4.9 to 0.8)	0.154	-1.8 (-4.6 to 1.0)	0.200
MME postop hours 0-48	-3.8 (-8.8 to 1.2)	0.135	-3.1 (-7.7 to 1.6)	0.194
MME postop hours 0-72	-4.1 (-10.8 to 2.7)	0.236	-3.1 (-9.2 to 3.1)	0.330
	Odds ratio (95% CI)[2]	*P* Value	Odds Ratio (95% CI)[2]	*P* Value
Any acetaminophen dose, postop hours 0-24	0.70 (0.47 to 1.03)	0.067	0.71 (0.48 to 1.06)	0.093
Any acetaminophen dose, postop hours 0-48	0.54 (0.33 to 0.89)	**0.016**	0.54 (0.32 to 0.90)	**0.018**
Any acetaminophen dose, postop hours 0-72	0.66 (0.31 to 1.40)	0.276	0.64 (0.29 to 1.38)	0.254
Any gabapentin dose postop hours 0-72	0.63 (0.33 to 1.22)	0.172	0.62 (0.31 to 1.21)	0.158
	Mean Difference (95% CI)[1]	*P* Value	Mean Difference (95% CI)[1]	*P* Value
24 h Pain Score*	-0.60 (-1.15, -0.04)	**0.035**	-0.68 (-1.23, -0.13)	**0.016**
48 h Pain Score*	-0.06 (-0.56, 0.43)	0.800	-0.14 (-0.62, 0.35)	0.577
	HR (95% CI)[3]	*P* Value	HR (95% CI)[4]	*P* Value
ICU, h	1.04 (0.86, 1.26)	0.662	1.05 (0.87, 1.28)	0.599
LOS, d	1.04 (0.86, 1.25)	0.700	1.05 (0.87, 1.27)	0.625
Time to first bowel movement, d	0.87 (0.71, 1.05)	0.143	0.88 (0.72, 1.08)	0.221

Models used: [1]Linear regression identity link producing mean difference estimates, [2]Logistic regression with logit link producing odds ratio estimates, [3]Cox proportional hazards producing hazard ratio estimates
*For pain score outcomes, baseline pain score was included in the model
Bold numbers were considered statistically significant.
MME, morphine milligram equivalents; ICU , intenseive care unit; h, hour; d, day; LOS, length of stay; HR, hazard ratio

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