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Systemic Lidocaine to Improve Postoperative Quality of Recovery After Ambulatory Laparoscopic Surgery

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BACKGROUND: Perioperative systemic lidocaine has been shown to have beneficial postoperative analgesic effects. The only previous study examining the use of lidocaine in the outpatient setting did not detect an opioid-sparing effect after hospital discharge. More importantly, it is unknown whether systemic lidocaine provides a better postoperative quality of recovery to patients undergoing ambulatory surgery. Our objective in the current study was to examine the effect of systemic lidocaine on postoperative quality of recovery in patients undergoing outpatient laparoscopic surgery.

METHODS: The study was a prospective, randomized, double-blind, placebo-controlled clinical trial. Healthy female subjects were randomized to receive lidocaine (1.5 mg/kg bolus followed by a 2 mg/kg/h infusion until the end of the surgical procedure) or the same volume of saline. The primary outcome was the Quality of Recovery-40 questionnaire at 24 hours after surgery. A 10-point difference represents a clinically relevant improvement in quality of recovery based on previously reported values on the mean and range of the Quality of Recovery-40 score in patients after anesthesia and surgery. Other data collected included opioid consumption, pain scores, and time to meet hospital discharge. Data were compared using group *t* tests and the Wilcoxon exact test. The association between opioid consumption and quality of recovery was evaluated using Spearman ρ. $P < 0.01$ was used to reject the null hypothesis for the primary outcome.

RESULTS: Seventy subjects were recruited and 63 completed the study. There were no baseline differences regarding subject and surgical characteristics between the study groups. Patients in the lidocaine group had better global quality of recovery scores compared with the saline group, median difference of 16 (99% confidence interval [CI], 2–28), $P = 0.002$. Patients in the lidocaine group met hospital discharge criteria faster than the saline group, mean difference of −26 minutes (95% CI, −6 to −46 minutes) ($P = 0.03$). After hospital discharge, subjects in the lidocaine group required less oral opioids, median difference of −10 (95% CI, 0 to −30) (oral milligrams morphine equivalents), than the saline group ($P = 0.01$). There was an inverse association between postoperative opioid consumption and quality of recovery ($\rho = 0.64$, $P < 0.001$).

CONCLUSIONS: Systemic lidocaine improves postoperative quality of recovery in patients undergoing outpatient laparoscopy. Patients who received lidocaine had less opioid consumption, which translated to a better quality of recovery. Lidocaine is a safe, inexpensive, effective strategy to improve quality of recovery after ambulatory surgery. (Anesth Analg 2012;115:262–7)

Postoperative pain can lead to significant morbidity and slow patient recovery after surgical procedures.[1] Postoperative pain after ambulatory surgery has been shown to be poorly managed.[2] The management of postoperative pain after outpatient surgery can be particularly challenging because of the lack of potent analgesics without dose-limiting side effects. Multimodal analgesic strategies have been proposed to improve pain relief and reduce opioid-related side effects of patients undergoing ambulatory procedures.[3]

Systemic lidocaine has been shown to be an effective adjunct strategy to reduce postoperative pain.[4] The only study examining the analgesic effects of lidocaine in the outpatient setting showed a reduction in postoperative pain/opioid consumption in the postanesthesia care unit (PACU) but did not demonstrate a beneficial effect of lidocaine in promoting a faster discharge from the hospital or a reduction in opioid consumption after hospital discharge.[5] A more important question (that has been raised but remains unknown) is, Do the analgesic properties of perioperative systemic lidocaine translate into an improvement of postoperative quality of recovery in patients undergoing ambulatory surgery?[6]

The main objective of the current study was to evaluate the effect of systemic lidocaine on postoperative quality of recovery in patients undergoing ambulatory surgery. We also examined the analgesic properties of systemic lidocaine in the ambulatory surgical setting.

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METHODS

This study was a prospective, randomized, double-blind, placebo-controlled trial. Clinical trial registration for this study can be found at http://clinicaltrials.gov; registration ID: NCT 01250002. Study approval was obtained from the Northwestern University IRB, and written informed consent was obtained from all the study participants. Eligible subjects were healthy females undergoing outpatient gynecological laparoscopy. Patients with a history of allergy to local anesthetics, chronic use of an opioid analgesic, corticosteroid use, and/or pregnant subjects were not enrolled. Reason for exclusion from the study after study drug administration was conversion from a laparoscopic to an open incision. Subjects were randomized using a computer-generated table of random numbers into 2 groups to receive IV lidocaine (1.5 mg/kg bolus followed by a 2 mg/kg/h infusion until the end of the surgical procedure) or the same volume of normal saline. Group assignments were sealed in sequentially numbered opaque envelopes that were opened by a research nurse not involved with the patient care or data collection after the subject provided written informed consent. The same nurse prepared syringes labeled with study drug to blind subjects enrolled in the study, anesthesia providers, and investigators collecting the data.

All subjects were premedicated with 0.04 mg/kg IV midazolam. No preoperative dexamethasone was administered. Propofol 1 to 2 mg/kg was administered for anesthesia induction, remifentanil 0.1 μg/kg/min IV infusion was begun, and rocuronium 0.6 mg/kg IV was administered to induce neuromuscular blockade. Tracheal intubation was initially attempted by an anesthesia resident physician or a certified registered nurse anesthetist under supervision of an attending anesthesiologist. Anesthesia maintenance was achieved using remifentanil, titrated to maintain the mean arterial blood pressure within 20% of baseline, and sevoflurane titrated to a Bispectral Index (Aspect Medical Systems, Inc., Norwood, MA) between 40 and 60. At the end of the procedure with the removal of the laparoscopic instruments, the remifentanil infusion was discontinued and the subjects received IV ketorolac 30 mg and ondansetron 4 mg.

In the PACU, subjects were asked to rate their pain at rest on arrival and at regular intervals on a 0 to 10 pain numeric rating scale (NRS), where 0 means no pain and 10 is the worst pain imaginable. Ramsey sedation score on arrival to the PACU was recorded (1 = anxious/agitated; 2 = cooperative/tranquil; 3 = drowsy/responds to command only; 4 = brisk response to shaking/loud sound; 5 = sluggish response to shaking/loud sound; and 6 = no response). The area under the NRS pain scale versus time curve was calculated using the trapezoidal method as an indicator of pain burden during early recovery (GraphPad Prism version 5.03; GraphPad Software, Inc., La Jolla, CA). Hydromorphone 0.4 mg IV was administered every 5 minutes to maintain an NRS pain score <4 of 10. In cases of postoperative nausea or vomiting, subjects received 10 mg IV metoclopramide, followed by 5 mg IV prochlorperazine if necessary. Discharge readiness was assessed by using the Modified Post-Anesthesia Discharge Scoring System (PADSS)[7] score every 15 minutes until subjects met discharge criteria. The PADSS assesses 5 criteria: vital signs, ambulation, pain, nausea and/or vomiting, and surgical bleed. Each criterion is scored on a 0 to 2 scale with higher scores representing a more acceptable condition. A score of ≥9 is considered ready for discharge. At discharge, subjects were instructed to take ibuprofen 400 mg orally every 6 hours and a combination of hydrocodone 10 mg plus acetaminophen 325 mg for pain >4 of 10. Postoperative opioid consumption (24 hours) was converted to equivalent dose of oral morphine.[8]

Subjects were contacted by telephone 24 hours after the procedure by an investigator unaware of group allocation and were questioned regarding analgesic consumption, pain score was obtained, and the Quality of Recovery-40 (QoR-40) questionnaire was administered.[9] The questionnaire consists of 40 questions that examine 5 domains of patient recovery using a 5-point Likert scale: none of the time, some of the time, usually, most of the time, and all of the time. The 5 domains include physical comfort, pain, physical independence, psychological support, and emotional state. Individualized items of the questionnaire have been previously presented by our group.[10] Other perioperative data collected included subject's age, height, weight, ASA physical status, surgical duration, intraoperative remifentanil use, total IV fluids, and total amount of hydromorphone in the PACU.

The primary outcome was the global QoR-40 score. Global QoR-40 scores range from 40 to 200 representing, respectively, very poor to outstanding quality of recovery. A sample size of 31 subjects per group was estimated to achieve 80% power to detect a 10-point difference in the aggregated QoR-40 score for the 2 study groups to be compared assuming an overall standard deviation of 14, similar to what was observed in a previous investigation.[10] A 10-point difference represents a clinically relevant improvement in quality of recovery based on previously reported values on the mean and range of the QoR-40 score in patients after anesthesia and surgery.[11] The responsiveness of the instrument has been assessed in patients evaluated before and after surgery.[12] To account for dropouts, 70 subjects were recruited and randomized. The sample size calculation was made using PADSS version 8.0.15, release date January 14, 2010 (NCSS, LLC, Kaysville, UT).

The Shapiro-Wilk and Anderson-Darling tests were used to test the assumption of normal distribution ($P > 0.1$). Normally distributed interval data are reported as mean (SD) and were evaluated with 2-group t test with unequal variance assumed. Non-normally distributed interval and ordinal data are reported as median (range or interquartile range [IQR]) and were compared among groups using the Wilcoxon exact test. Categorical data were compared using the Fisher exact test. The criterion for rejection of the null hypothesis for the primary outcome, global QoR-40 and QoR-40 5 subgroup domains, was set at $P < 0.01$and confidence intervals (CIs) of the differences are reported at 99%. The association between 24-hour opioid consumption and the global QoR-40 score was determined using Spearman ρ. PACU and hospital time to discharge were transformed using a log-normal transformation as described by Ledolter et al.[13] and compared using a bootstrap approach as described by Zhou et al.[14] CIs of the log-normal data were calculated using the generalized pivotal approach.[13]

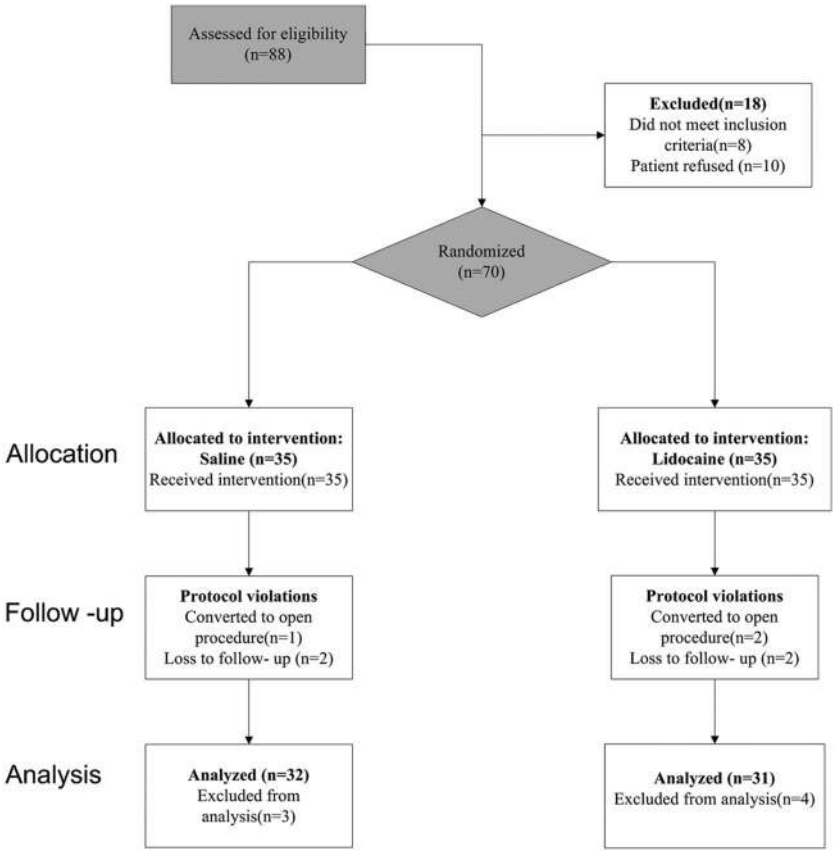

Figure 1. Consort flow study diagram.

Table 1. Baseline Subject and Surgical Procedure Characteristics

	Lidocaine (n = 31)	Saline (n = 32)	Difference (95% CI)	P value
Age (y)	37.2 ± 8.6	39.1 ± 9.3	−1.9 (−6.5 to 2.6)	0.39
Body mass index (kg/m^2)	26.3 ± 4.3	24.7 ± 5.3	1.6 (−0.8 to 4.0)	0.20
ASA physical status				
I	14	14		1.0
II	17	18		
Surgical procedure				
Salpingo-oophorectomy	14	13		
Cystectomy	8	13		0.56
Tubal ligation	2	2		
Diagnostic laparoscopy	7	4		
Surgical duration (min)	105.5 (79–135)	105 (78–124)	0.5 (−24 to 14)	0.52
Remifentanil (μg)	550 (354–714)	553 (386–730)	20 (−157 to 153)	0.94
IV fluid (mL)	1239 ± 456	1291 ± 549	52 (−301 to 198)	0.98

Data are presented as mean ± SD, median (interquartile range), or counts (n).
CI = confidence interval.

The criterion for rejection of the null hypothesis comparisons other than the primary outcome was $P < 0.05$, and CIs for mean and median differences between groups are reported at 95%. All reported P values are 2-tailed.

Statistical analysis was performed using R version 2.14.1, release date December 22, 2011 (The R Foundation for Statistical Computing).

RESULTS

The details of the conduct of the study are shown in Figure 1. Seventy subjects were randomized and 63 completed the study. Patients were enrolled consecutively from November 2010 through September 2011. Patients' baseline characteristics and surgical factors were not different between groups (Table 1).

The median difference (99% CI) in global QoR-40 scores at 24 hours after surgery was 16 (2–28) (P = 0.002) between the lidocaine and the saline groups. Subjects in the lidocaine group also had better scores in the subcomponents of the quality of recovery score that specifically examined pain, physical comfort, and physical independence (Table 2).

Patients in the lidocaine group had lower area under the pain score versus time and less opioid consumption in the

Table 2. Subcomponents of the Quality of Recovery Score by Study Groups

	Lidocaine (n = 31)	Saline (n = 32)	Difference (99% CI)	P value
Physical comfort	54 (50–57)	48 (43.5–53.5)	6 (0–10)	0.003
Physical independence	21 (17–22)	16.5 (14–21)	4.5 (1–6)	0.008
Emotional state	40 (37–42)	36.5 (33.5–40.5)	3.5 (−1 to 6)	0.02
Psychological support	28 (26–29)	26.5 (25–28)	1.5 (−1 to 3)	0.07
Pain	32 (30–33)	29 (26.5–30.5)	3 (0–5)	0.001

Data are presented as median (interquartile range).
CI = confidence interval.

Table 3. Postanesthesia Care Unit Data

	Lidocaine (n = 31)	Saline (n = 32)	Difference (99% CI)	P value
Area under the numeric rating scale for pain versus time curve in postanesthesia care unit (score · min)	210 (120–270)	270 (202–367)	− 60 (0 to − 165)	0.01
Ramsey sedation score	2 (2–3)	2 (2–3)	0 (−1 to 1)	0.76
Opioid (IV morphine equivalents)	6.2 (2.6–8.3)	8.6 (3.8–13.7)	−2.6 (−6.7 to 0)	0.04
Time to opioid requirement (min)	7 (1–27)	1 (1–14)	6 (−1 to 10)	0.06
No. of antiemetics				
0	19	16		
1	7	5		0.15
≥2	5	12		
Time to discharge readiness (min)[a]	58 (45–60)	62 (45–75)	4 (−8 to 12)	0.67

Data are presented as median (interquartile range) or counts (n).
CI = confidence interval.
[a] Mean (25th–75th percentile) of log-normal transformed data.

PACU compared with the saline group (Table 3). The mean (IQR) time to meet hospital discharge readiness based on the log-normal transformed data was 118 minutes (75–161 minutes) in the saline group and 91 minutes (75–107 minutes) in the lidocaine group. The mean difference in time to meet hospital discharge readiness was −26 minutes (95% CI, −6 to −46 minutes) (P = 0.03).

After hospital discharge, subjects in the lidocaine group required less oral opioids, median (IQR) of 20 (0–30) (oral morphine equivalents), than the saline group, 30 (15–35), median difference −10 (95% CI 0 to −20) (P = 0.01). There was an inverse relationship (ρ = −0.64) between the total 24-hour opioid consumption (IV morphine equivalents) and 24-hour postoperative quality of recovery (P < 0.001) (Fig. 2).

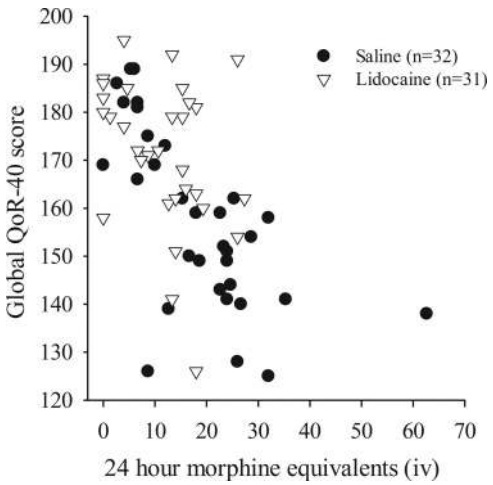

Figure 2. Scatterplot demonstrating inverse relationship between global Quality of Recover-40 (QoR-40) scores and 24-hour cumulative opioid consumption after surgery. Spearman ρ correlation, ρ = −0.64 (P < 0.001); removal of control subject with 24-hour IV morphine equivalent use of 63 mg resulted in correlation of ρ = −0.62.

CONCLUSIONS

The important finding of the current study is the better postoperative quality of recovery provided to patients receiving perioperative systemic lidocaine compared with saline. Besides an improvement in the global quality of recovery score, subjects reported better scores in the physical independence, comfort, and pain subcomponents of the quality of recovery questionnaire. These findings are particularly important in the ambulatory population because these patients do not have the structured support of a hospital staff and are, therefore, expected to have a faster functional recovery. Subjects in the lidocaine group had substantially better postoperative recovery than the saline group with a 23% improvement in global quality of recovery scores. There is evidence that perioperative lidocaine improves postoperative quality of recovery in patients undergoing outpatient surgery.

Another important finding of the current study is the opioid-sparing properties and better analgesia obtained by the lidocaine group compared with saline. These findings are important because the only previous study examining the analgesic effect of systemic lidocaine in outpatient surgery did not detect opioid-sparing effects of lidocaine after hospital discharge.[5] The different surgical procedures concomitantly examined by the previous investigators probably contributed to the inability to demonstrate post-discharge opioid-sparing effects of lidocaine.[15] Also, our subjects received a nonsteroidal antiinflammatory drug on a fixed schedule whereas the subjects in the previous investigation did not.[5] In contrast to the previous study

examining the use of systemic lidocaine in the ambulatory setting, we detected less opioid consumption after hospital discharge in subjects receiving lidocaine. More importantly, we were able to demonstrate that patients who consumed less opioids reported a better postoperative quality of recovery.

Although we observed only a 26-minute benefit in the reduction of time to meet hospital discharge criteria in the lidocaine group compared with saline, this finding has important clinical implications for patients in the ambulatory setting. The sedative properties of systemic lidocaine are a concern for clinical practitioners because of a potential effect in delaying hospital discharge and, therefore, generating negative economic implications.[16] We also did not detect any clinically significant differences in sedation scores between the study groups at arrival in the PACU. It does not seem that the sedative properties of systemic lidocaine present a barrier to its use in the outpatient surgical setting. Systemic lidocaine can be used in ambulatory surgery with the small benefit of speeding hospital discharge.

Other strategies have been used to improve postoperative quality of recovery after ambulatory surgery. Our group has demonstrated that dexamethasone improved quality of recovery in a dose-dependent manner.[10] We also showed that transversus abdominis plane block improves postoperative quality of recovery for ambulatory laparoscopy patients.[17] Lidocaine offers benefits over the previous strategies because it does not have the risk of perioperative infection associated with steroids[18] and it does not require the time and expertise to perform a bilateral transversus abdominis block.[19] Because we did not observe a ceiling effect with any of these strategies, it is possible that an additive or synergistic effect in improving postoperative quality of recovery may result from the combination of 2 or more strategies. It is also plausible that a combination therapeutic strategy to improve postoperative quality of recovery will not be more effective than a single intervention. Future studies examining combination strategies are, therefore, warranted.

We did not observe any potential cardiovascular or neurological side effects associated with the infusion of systemic lidocaine in our investigation. However, subjects were paralyzed under general anesthesia, which limited our ability to detect early signs of neurological toxicity. Nonetheless, the safety of small-dose lidocaine infusion has been demonstrated by others in clinical investigations.[20,21] A meta-analysis examining the use of systemic lidocaine infusion also did not detect any increase in the incidence of potential side effects.[4]

We used a standardized intraoperative remifentanil infusion to obtain strict control of the intraoperative opioid consumption. Remifentanil infusion has been associated with the development of hyperalgesia.[22] This effect has been more pronounced with higher infusion doses of remifentanil than the ones used by our group in the current study.[23] Specifically in patients undergoing outpatient gynecological surgery, Beers et al.[24] did not observe a clinical hyperalgesic effect of intraoperative remifentanil compared with fentanyl. Nevertheless, systemic lidocaine can inhibit remifentanil-induced hyperalgesia, which may have contributed to some of our findings.[25]

There are limitations to our study. We used the QoR-40 instrument to investigate postoperative recovery. Although the QoR-40 instrument has been used to evaluate postoperative recovery after ambulatory surgery by our group and others,[26] validation of the instrument was performed in the inpatient setting, and formal validation for the outpatient setting is still lacking.[11] However, in a systematic review, the QoR-40 was found to be the best instrument to evaluate quality of recovery in ambulatory patients.[12]

In summary, perioperative lidocaine infusion improves postoperative quality of recovery after ambulatory laparoscopy. The preventive opioid-sparing properties of the drug were associated with a better quality of postprocedure recovery. Lidocaine infusion seems to be a safe, low-cost, and highly effective strategy to improve analgesia and quality of recovery after ambulatory surgery.

DISCLOSURES

Name: Gildasio S. De Oliveira, Jr., MD, MSCI.
Contribution: This author helped design the study, conduct the study, analyze the data, and prepare the manuscript.
Attestation: Gildasio S. De Oliveira, Jr. attests to the integrity of the original data and the analysis.
Name: Paul Fitzgerald, MS, RN.
Contribution: This author helped conduct the study and prepare the manuscript.
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Contribution: This author helped conduct the study.
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Name: Robert J. McCarthy, PharmD.
Contribution: This author helped analyze the data and prepare the manuscript.
Attestation: Robert J. McCarthy attests to the integrity of the original data and the analysis.
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