Long-Acting Patient-Controlled Opioids Are Not Associated With More Postoperative Hypoxemia Than Short-Acting Patient-Controlled Opioids After Noncardiac Surgery: A Cohort Analysis

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BACKGROUND: Opioids can contribute to postoperative desaturation. Short-acting opioids, titrated to need, may cause less desaturation than longer-acting opioids. We thus tested the primary hypothesis that long-acting patient-controlled intravenous opioids are associated with more hypoxemia (defined as an integrated area under a postoperative oxyhemoglobin saturation of 95%) than short-acting opioids.

METHODS: This analysis was a substudy of VISION, a prospective cohort study focused on perioperative cardiovascular events (NCT00512109). After excluding for predefined criteria, 191 patients were included in our final analysis, with 75 (39%) patients being given fentanyl (short-acting opioid group) and 116 (61%) patients being given morphine and/or hydromorphone (long-acting opioid group). The difference in the median areas under a postoperative oxyhemoglobin saturation of 95% between short-acting and long-acting opioids was compared using multivariable median quantile regression.

RESULTS: The short-acting opioid median area under a postoperative oxyhemoglobin saturation of 95% per hour was 1.08 (q1, q3: 0.62, 2.26) %-h, whereas the long-acting opioid median was 1.28 (0.50, 2.23) %-h. No significant association was detected between long-acting and short-acting opioids and median area under a postoperative oxyhemoglobin saturation of 95% per hour ($P = .66$) with estimated change in the medians of −0.14 (95% CI, −0.75, 0.47) %-h for the patients given long-acting versus short-acting IV patient-controlled analgesia opioids.

CONCLUSIONS: Long-acting patient-controlled opioids were not associated with the increased hypoxemia during the first 2 postoperative days. (Anesth Analg 2016;XXX:00–00)

Pulmonary complications in the postoperative period are associated with increased morbidity and mortality,[1,2] prolonged hospitalization,[3] and increased cost.[3,4] Postoperative hypoxemia, first recognized nearly 5 decades ago,[5] remains common and—disturbingly—largely unnoticed after surgery.[6] Severe, prolonged episodes of desaturation can result in a multitude of adverse outcomes, including compromised wound healing,[7–9] brain dysfunction,[10,11] arrhythmias,[12] and myocardial ischemia.[13–15] All of these outcomes are considered important measures of hospital quality and safety in the United States.[16]

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Many factors predispose patients to postoperative hypoxemia, including age,[17] type of surgery,[18] type and duration of anesthesia,[19–21] obesity,[19] obstructive sleep apnea,[22] and preexisting pulmonary conditions.[23,24] However, postoperative desaturation has largely been attributed to respiratory depression from postoperative opioid analgesia.[25] Opioids, through effects on the respiratory center, cause a decrease in respiratory rate and alveolar ventilation, resulting in hypercarbia, respiratory acidosis, and hypoxemia.[2,26] Opioid-induced respiratory depression is common, unpredictable, and exacerbated by great variability in individual responses to various opioids.[27] Consequently, individual titration of opioids, along with continuous electronic monitoring, had been advocated by the Anesthesia Patient Safety Foundation.[28] Consistent with the concerns of the foundation, a recent study from the American Society of Anesthesiologists (ASA) Anesthesia Closed Claims database showed that about half of the cases of serious brain damage and death were receiving continuous opioid infusions. The vast majority were deemed by expert reviewers to have been potentially preventable with better patient monitoring and/or appropriate responses.[29,30]

Plasma drug concentrations are more stable with longer-acting drugs,[31] whereas peak and trough concentrations may be exaggerated with shorter-acting agents. Nonetheless, analgesic efficacy with intravenous fentanyl (a short-acting opioid) and morphine or methadone (long-acting opioids) is similar when given by patient-controlled analgesia (PCA) IV pump.[32] Postoperative hypoxemia is common in patients

using morphine PCA.[33] In theory, shorter-acting opioids titrated to individual temporal need might reduce periods of excessive drug concentration. Whether use of short-acting opioids actually reduces hypoxemia remains unknown.

We therefore tested the primary a priori hypothesis that long-acting opioids given through IV PCA are associated with more hypoxemia than similarly administered short-acting opioids within the initial 48 h after noncardiac surgery. For the purposes of this study, hypoxemia was defined as an integrated oxygen saturation <95% within 48 h after a noncardiac surgery. Second, we tested the same hypothesis, but with hypoxemia defined by integrated oxygen saturation <90% or <85% within 48 h after a noncardiac surgery.

METHODS

Our analysis was a substudy of the Vascular events In noncardiac Surgery patIents cOhort evaluatioN (VISION), a 40,000-patient prospective cohort study focused on perioperative cardiovascular events (ClinicalTrials.gov, Registration No: NCT00512109, Principal Investigator: Philip J. Devereaux, MD, PhD, August 3, 2007).[34,35] With Cleveland Clinic institutional review board approval and informed consent from study subjects, 1250 patients who were at least 45 years of age and were scheduled for noncardiac inpatient surgery with general and/or regional anesthesia at the Cleveland Clinic Main Campus were enrolled in this study. A deliberate cross-section of surgical patients was selected to reflect a representative sample of the noncardiac surgical population at our institution. We excluded patients who were not expected to stay at least 1 night in the hospital, who received only local or topical anesthesia, or had previously participated in the VISION study. All the patients reported here were included in a previous analysis of hypoxemia patterns and severity in adults recovering from noncardiac surgery. In that publication, we reported that hypoxemia was common on noncardiac surgical floors after surgery, was frequently missed by nursing staff, and lasted for substantial periods of time.[6]

We attempted to record postoperative oxyhemoglobin saturation (Spo_2) continuously for up to 48 h or until hospital discharge (whichever occurred first). Saturation monitoring started on discharge from the postanesthesia care unit. The pulse oximeter (Model Nellcor OxiMax N-600x, Covidien, Dublin, Ireland) was mounted on a wheeled IV pole, along with an uninterruptible power supply and computer.

Importantly, all caregivers involved with these patients were blinded to the study pulse oximeter readings, and the alarms on the study machines were disabled. Study saturation data were thus recorded internally and subsequently transferred to a secure database. Pulse oximeter waveforms were recorded, but data were averaged to 1-min values for this analysis. Patients were encouraged to remain connected continuously but were allowed to disconnect the system when mobilized or attending to personal hygiene. Study personnel visited each patient at least 4 times daily, including nights and weekends, to promote compliance, but patients had the prerogative to discontinue study monitoring at any point.

Among 1250 patients who met the VISION inclusion criteria, we excluded patients who had fewer than 12 h of continuous monitoring, gaps in the saturation monitor records exceeding 4 h, or overall unrecorded time exceeding 30% of total monitoring time. We restricted the analysis to patients who received solely a short-acting opioid (fentanyl) versus solely a long-acting opioid (hydromorphone or morphine) and excluded patients who received both long-acting and short-acting opioids. Total cumulative opioids were recorded and reported, including IV boluses. The standard IV PCA dosing schemes at the Cleveland Clinic are included in Appendix 1. Patients given postoperative epidural or peripheral nerve catheters were also excluded.

The primary outcome was defined as the integrated area under an Spo_2 saturation of 95% per hour. This outcome characterizes both the duration and severity of hypoxemia because both longer duration and lower Spo_2 would result in a larger area under the threshold of 95%, while adjusting for the duration of Spo_2 monitoring. Linear interpolation was used when measurements were missing.

As a part of VISION, patient demographic and morphometric characteristics were recorded in our preanesthetic clinical evaluation. Intraoperatively, our Perioperative Health Documentation System electronically recorded surgical and anesthetic details.

Statistical Analysis

First, we compared the two study groups (ie, the short-acting and long-acting opioid groups) for balance on potentially confounding baseline and surgical characteristics using univariable summary statistics (mean and standard deviation, median and quartiles, or proportions, as appropriate) and absolute standardized difference (ASD) scores. ASDs are defined as the absolute value of the difference between means, mean rankings, or proportions divided by a combined estimate of standard deviation; thus, the ASD roughly represents the number of standard deviations by which the 2 study groups differ. We conservatively considered an ASD >0.20 as indicative of potential confounding and adjusted for such factors directly in the analyses evaluating outcomes comparing 2 groups. In addition to imbalanced potential confounders, we also adjusted for 7 prespecified variables in all analyses (ie, type of surgery, duration of surgery, ASA physical status, home oxygen use, preexisting pulmonary disease, previous congestive heart failure, and intraoperative opioid dose (in IV morphine equivalents).

We used multivariable median quantile regression with bootstrapped standard errors to assess the association between the primary outcome and the use of long-acting PCA opioids. No interactions were considered in the model. We expected the primary outcome to be highly skewed, and thus, we selected quantile regression instead of ordinary least squares linear regression because of the robustness of this technique. We report the confounder-adjusted change in the median outcome for patients who were given long-acting PCA opioids comparing with a patient receiving short-acting PCA opioids along with 95% confidence interval.

Analogously to the primary analysis, we conducted 2 secondary analyses in which the outcomes of areas under an Spo_2 of 90% and 85% were evaluated. In addition, we performed a post hoc analysis to investigate whether the effect of the chosen opioid group (long-acting versus

short-acting PCA opioids) on hypoxemia was influenced by patients' body mass index (BMI). This was done by adding an interaction variable between the choice of long-acting versus short-acting and BMI to the primary quantile regression model. Model-based Wald-test was used for testing. A significant interaction would suggest that the relationship between choice of long-acting versus short-acting and hypoxemia varies as a function of patients' BMI.

The type I error for the primary analysis was kept at 5% level with a significance criterion of $P < .05$. We used the Bonferroni adjustment for multiple analyses to preserve type I error at 5% level for the secondary analyses with the significance criterion of <.025 for each of the secondary outcomes (ie, .05/2).

The sample size of N = 191 provided 89% power at the .05 significance level to detect inferiority of long-acting opioids relative to the short-acting opioid group on hypoxemia with ratio of means of 1.25 for area under an Spo_2 of 95% per hour and a coefficient of variation (CV, SD/mean before log transformation) of .5.

SAS statistical software version 9.3 (SAS Institute, Cary, NC) for 64-bit Microsoft Windows was used for the statistical analyses. R statistical software version 2.15.2 for 64-bit UNIX operating system (The R Foundation for Statistical Computing, Vienna, Austria) was used for the tables.

RESULTS

Among patients who met inclusion criteria, 1250 consented to participate in the VISION study at the Cleveland Clinic. For this substudy, 191 patients were included in our analyses (Figure 1), including 75 patients (39%) who used fentanyl alone and 116 (61%) who used morphine or hydromorphone alone or in combination for postoperative IV PCA during the first 48 h after noncardiac surgery. The most common reason for exclusion was that patients did not exclusively use IV PCA for postoperative analgesia, or they chose to discontinue monitoring.

Approximately 76% of patients receiving the long-acting opioids and 75% of patients receiving the short-acting opioids averaged at least 10 min per hour, with raw Spo_2 values below 95%. Moreover, approximately 57% of patients receiving the long-acting opioids and 56% of patients receiving the short-acting opioids averaged at least 20 min per hour with raw Spo_2 values below 95%. Consistent results were seen with the duration of hypoxemia with cutoffs of Spo_2 of <90% and Spo_2 of <85% (Figure 2). The distribution of Spo_2 as a function of postoperative time for the 2 study groups is displayed in Figure 3. In general, measured Spo_2 values decreased as postoperative time increased, irrespective of the group with long-acting group measures dropping around 30 h after the surgery.

Demographic and perioperative characteristics of the studied groups (N = 191) are provided in Table 1. Assessing balance between the study groups, 11 imbalanced potential confounders were identified and included for adjustment in the multivariable models, along with prespecified potential confounders. Thus, the results were adjusted for prespecified confounders, including type of surgery, duration of surgery, ASA physical status, home oxygen use, preexisting pulmonary disease, previous congestive heart failure,

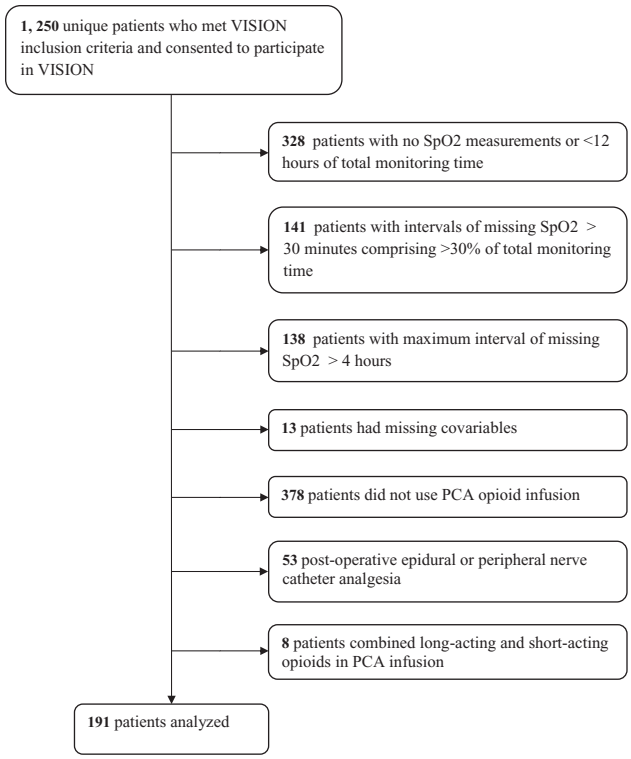

Figure 1. Study flow chart.

intraoperative opioid dose (in IV morphine equivalents), and for the imbalanced variables including patient age, history of aortic stenosis, diabetes, sleep apnea, hypertension, open surgery, and total dose of intraoperative muscle relaxant.

The summary statistics on raw outcomes along with univariable analysis and multivariable results are reported in Table 2. The details on the multivariable median quantile regression model are presented in Appendix 2. The median area under Spo_2 saturation of 95% per hour was 1.08 [q1, q3: .62, 2.26] %-h for the patients given short-acting opioids and 1.28 [0.50, 2.23] %-h for the patients given long-acting opioids. As for the primary hypothesis, no significant association was detected between the long-acting opioid usage and the median area under Spo_2 saturation of 95% per hour ($P = .66$; Figure 4). The estimated difference in the median of area under Spo_2 of 95% was −.14 (95% CI, −.75, .47) %-h, for patients given long-acting PCA opioids compared with similar patients given short-acting PCA opioids.

As for the secondary hypothesis, no significant association was found between the long-acting opioid use and the median of area under Spo_2 of 90% per hour ($P = .69$; Table 2 and Figure 5), with the estimated difference in medians of −0.02 (97.5% CI, −.18, .12) %-h. Again, no association was identified between the long-acting opioid usage and the median of area under Spo_2 of 85% per hour ($P = .54$), with the estimated difference in medians of 0.00 (97.5% CI, −.03, .02) %-h.

Post hoc analysis did not identify a significant interaction between BMI and the effect of long-acting versus short-acting PCA opioids (Wald test, $P = .44$; a significance criterion of .05); that is, the difference in medians of area under Spo_2

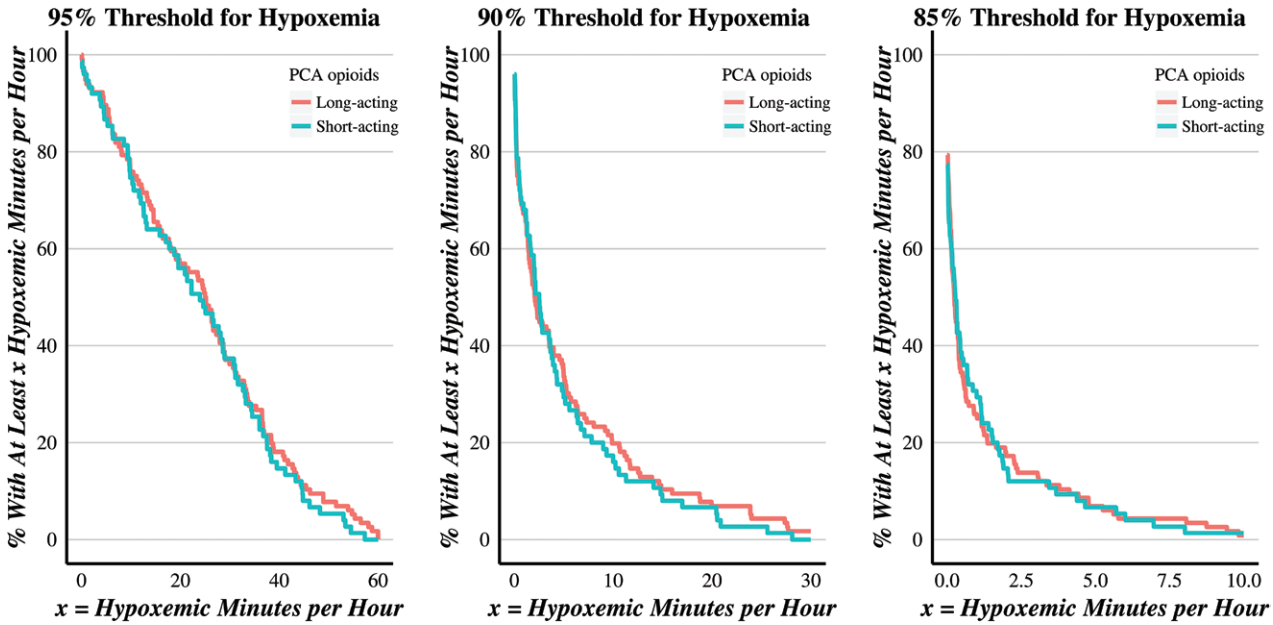

Figure 2. (Raw Spo_2 data) Incidence of patients with an average number of minutes per hour in hypoxemia > X during monitoring. Three thresholds for hypoxemia were considered as 95%, 90%, and 85% of Spo_2. The red line represents patients receiving long-acting PCA opioids, and the green line represents patients receiving short-acting PCA opioids.

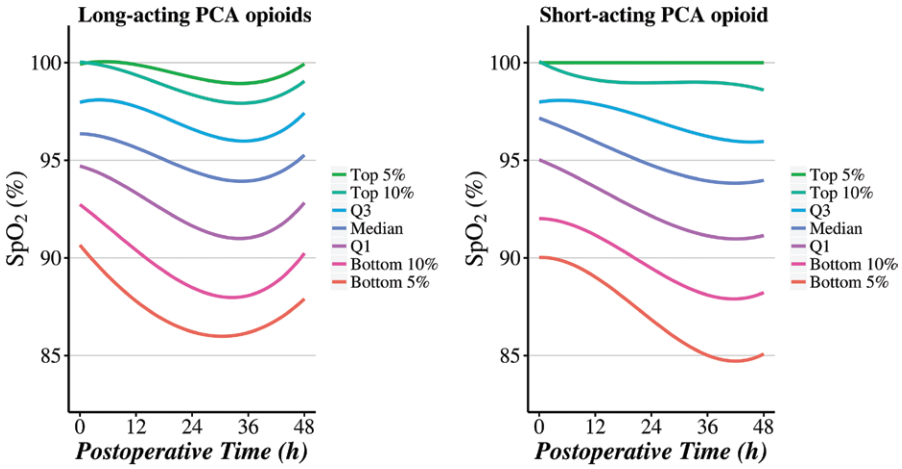

Figure 3. (Raw Spo_2 data) Distribution of Spo_2 over postoperative time for patients receiving long-acting and short-acting PCA opioids. Curves estimated using quantile regression with restricted cubic splines.

Table 1. Demographics and Perioperative Characteristics of 191 Study Patients by Study Groups

Variable	Long-Acting PCA Opioids (n = 116)	Short-Acting PCA Opioid (n = 75)	ASD[a,b]
Age (y)	60.1 ± 8.7	65.9 ± 12.1	0.55[b]
Gender, male, No. (%)	59 (51)	35 (47)	0.08
BMI	29.5 ± 7.7	30.8 ± 10.9	0.14
ASA physical status, No. (%)			0.71[b]
I	1 (1)	0 (0)	
II	43 (37)	11 (15)	
III	67 (58)	48 (64)	
IV	5 (4)	16 (21)	
Preoperative comorbidities, (ie, any history of), No. (%)			
Home oxygen use, No. (%)	2 (2)	2 (3)	.06
Congestive heart failure	3 (3)	6 (8)	.24[b]
Chronic obstructive pulmonary disease	6 (5)	5 (7)	.06
Deep vein thrombosis	11 (9)	11 (15)	.16
Atrial fibrillation	8 (7)	7 (9)	.09
Stroke	4 (3)	3 (4)	.03
Coronary artery disease	10 (9)	11 (15)	.19
Recent catheterization (<12 mo)	5 (4)	5 (7)	.10

(*Continued*)

Table 1. Continued

Variable	Long-Acting PCA Opioids (n = 116)	Short-Acting PCA Opioid (n = 75)	ASD[a,b]
Aortic stenosis	1 (1)	3 (4)	.20[b]
Peripheral vascular disease	5 (4)	6 (8)	.15
Diabetes	17 (15)	22 (29)	.36[b]
Peptic ulcer	4 (3)	5 (7)	.15
Tobacco use	64 (55)	38 (51)	.09
Sleep apnea	17 (15)	22 (29)	.36[b]
Hypertension	65 (56)	50 (67)	.22[b]
Dialysis	1 (1)	1 (1)	.05
Surgical characteristics			
Types of surgery, No. (%)			.61[b]
Peripheral vascular reconstruction surgery	1 (1)	1 (1)	
Complex visceral resection	13 (11)	3 (4)	
Stomach surgery	29 (25)	27 (36)	
Intraabdominal surgery	30 (26)	17 (23)	
Other thoracic surgery	1 (1)	6 (8)	
Visceral resection	6 (5)	5 (7)	
Radical prostatectomy	2 (2)	1 (1)	
Major hip pelvic surgery	3 (3)	0 (0)	
Major spine surgery	22 (19)	8 (11)	
Low-risk surgery	3 (3)	3 (4)	
Others	6 (5)	4 (5)	
Duration of surgery (h)	4.8 ± 1.7	4.0 ± 1.5	.44[b]
Open surgery, No. (%)	81 (70)	38 (51)	.40[b]
Minimally invasive surgery, No. (%)	6 (5)	7 (9)	.16
General anesthesia, No. (%)	116 (100)	75 (100)	
Spinal anesthesia, No. (%)	0 (0)	0 (0)	
Nerve block anesthesia, No. (%)	0 (0)	0 (0)	
Epidural anesthesia, No. (%)	1 (1)	0 (0)	.13
Baseline Spo_2 (%)	98.6 ± 1.5	98.6 ± 1.6	.02
Use of nitrous oxide, No. (%)	14 (12)	5 (7)	.19
Total dose of opioid (IV morphine equivalent; mg)	32 [25, 42]	25 [20, 33]	.01
Total dose of muscle relaxant (rocuronium; mg)	101.5 ± 38.2	86.1 ± 32.7	.43[b]
Supplemental oxygen use in OR, No. (%)			
Nasal cannula	103 (89)	69 (92)	.11
Face mask	24 (21)	19 (25)	.11
Postoperative analgesia characteristics			
Total dose of PCA infusion opioid (IV morphine equivalent; mg[c])	97 [54, 150]	126 [67, 214]	
Total dose of PCA infusion opioid			
Morphine (mg)	43 [25, 76]	N/A	
Hydromorphone (mg)	16 [10, 23]	N/A	
Fentanyl (mcg)	N/A	1262 [672, 2138]	
Use of bolus, No. (%)	78 (67)	46 (61)	
Fentanyl	41 (33)	20 (30)	
Hydrocodone	6 (5)	4 (6)	
Hydromorphone	35 (28)	14 (21)	
Meperidine	0 (0)	1 (1)	
Morphine	6 (5)	3 (5)	
Oxycodone	36 (29)	23 (35)	
Tramadol	0 (0)	1 (1)	
Total dose of bolus opioid (IV morphine equivalent; mg[c])	18 [10, 33]	15 [5, 25]	
Supplemental oxygen use, No. (%)			
POD 1			
Nasal cannula	98 (85)	67 (89)	
Face mask	4 (4)	1 (1)	
POD 2			
Nasal cannula	55 (47)	41 (55)	
Face mask	4 (4)	1 (1)	
Total dose of bolus opioid (IV morphine equivalent; mg[c])	18 [10, 33]	15 [5, 25]	

Summary statistics were presented as mean ± standard deviation, median [lower quartile, upper quartile], or number of patients (%) as appropriate.

Abbreviations: ASA, American Society of Anesthesiologists; ASD, absolute standardized differences; BMI, body mass index; IV, intravenous; PCA, patient-controlled analgesia; POD, postoperative day.

[a]ASD (colloids minus noncolloids): absolute value of the difference in means or proportions divided by pooled standard deviation converted into percentages.

[b]ASD >.20 in absolute value indicates an imbalance in the patients' characteristics, used for adjustment in the analyses.

[c]Opioid conversion doses: 1.5 mg IV Hydromorphone = 10 mg IV morphine; 0.1 mg IV Fentanyl = 10 mg IV morphine; 30 mg oral Hydrocodone = 10 mg IV morphine; 75 mg IV Meperidine = 10 mg IV morphine; 20 mg oral Oxycodone = 10 mg IV morphine; 150 mg oral Tramadol = 10 mg IV morphine.

Table 2. The Summary Statistics on Raw Outcomes by Study Groups and Results for the Primary and Secondary Hypotheses (N = 191)

	Summary Statistics on Raw Data[a]		Univariable Analysis[b]	Multivariable Analysis[c]	
Outcome	Long-Acting PCA Opioids (n = 116)	Short-Acting PCA Opioid (n = 75)	Difference in Medians[b] (95% CI)	Difference in Medians[c] (95% CI)[d]	*P*[d]
Primary analysis					
Area under an Spo_2 of 95% per hour (%-h)	1.28 [0.50, 2.23]	1.08 [0.62, 2.26]	0.18 (−0.40, 0.77)	−0.14 (−0.75, 0.47)	0.66
Secondary analysis					
Area under an Spo_2 of 90% per hour (%-h)	0.11 [0.02, 0.46]	0.11 [0.04, 0.51]	0.00 (−0.13, 0.12)	−0.02 (−0.18, 0.12)	0.69
Area under an Spo_2 of 85% per hour (%-h)	0.01 [0.00, 0.06]	0.01 [0.00, 0.09]	0.00 (−0.02, 0.02)	0.00 (−0.03, 0.02)	0.54

Abbreviations: ASA, American Society of Anesthesiologists; CI, confidence interval; PCA, patient-controlled analgesia; Spo_2, oxyhemoglobin saturation.

[a]Summary statistics are presented as median [q1, q3].

[b]The univariable median quantile regression model with bootstrapped standard errors were used with Spo_2 saturation of 95%, 90%, or 85% per hour as an outcome and type of opioid indicator as a predictor. The difference in medians reflects the change in the outcome for a patient who was given long-acting PCA opioids comparing with patients receiving short-acting PCA opioids.

[c]Association between type of opioid used and area under an Spo_2 saturation of 95%, 90% and 85% per hour were modeled using multivariable median quantile regression with bootstrapped standard errors. Results were adjusted for prespecified potential confounders type of surgery, duration of surgery, ASA physical status, home oxygen use, preexisting pulmonary disease and congestive heart failure, intraoperative opioid dose (in IV morphine equivalents), and for imbalanced variables as patients' age, history of aortic stenosis, diabetes, sleep apnea and hypertension, open surgery and total dose of intraoperative muscle relaxant. The difference in medians reflects the change in the outcome for a patient who was given long-acting PCA opioids comparing with a similar patient receiving short-acting PCA opioids.

[d]The Type I error for the primary outcome was 5% with significance criterion of $P < .05$; we used the Bonferroni adjustment for multiple analyses to preserve Type I error for the secondary analysis at 5% level with the significance criterion of .025 for each secondary outcome (ie, 0.05/2).

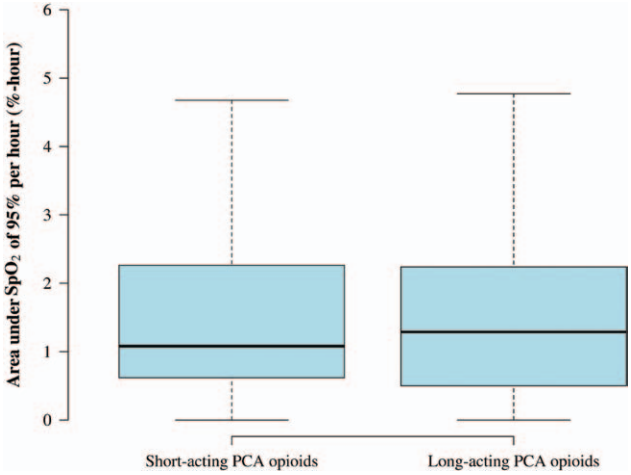

Figure 4. Boxplot of area under Spo_2 of 95% per hour for short-acting and long-acting PCA opioid groups. No significant association was found between the type of opioid use and the median area under Spo_2 of 95% per hour, with the estimated difference in medians of −.14 (95% CI, −.75, .47; $P = .66$) %-h for a unit increase in the score.

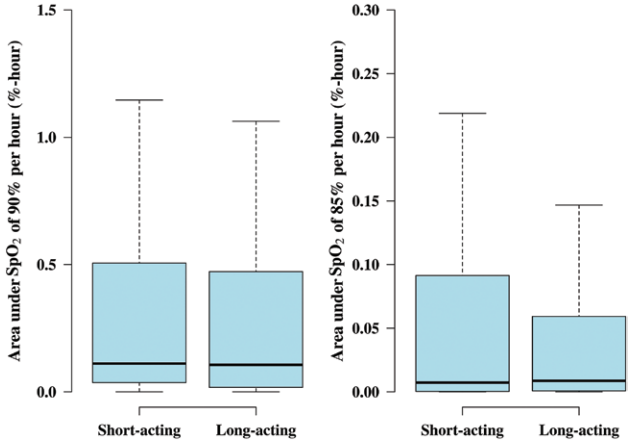

Figure 5. Boxplot of area under Spo_2 of 90% and 85% per hour for short-acting and long-acting PCA opioid groups. No significant associations were found between the type of opioid use and both the median area under Spo_2 of 90% ($P = .69$) and under Spo_2 of 85% ($P = .54$).

of 95% per hour comparing 2 study groups did not differ significantly across the levels of BMI.

DISCUSSION

Many anesthesiologists believe that long-acting opioids provoke more hypoxemia relative to short-acting opioids, which is consistent with the observation that long-acting opioids produce more sedation than short-acting opioids.[32] Nonetheless, we found that the amount of ward hypoxemia was similar for long-acting and short-acting opioids given through IV PCA in adults recovering from noncardiac surgery. Specifically, there were no statistically significant differences in the duration and intensity of hypoxemic episodes using various definitions for hypoxemia in the risk-adjusted analyses comparing long-acting and short-acting opioids.

When dosed according to a fixed schedule, short-acting and long-acting opioids confer similar total systemic opioid concentrations and comparable analgesia.[31] Thus, although there is a theoretical possibility that long-acting patient-controlled opioids might produce high effect-site concentrations that are sustained beyond the time of need (eg, administered during ambulation but persisting to periods of sleep), we saw no evidence of excess hypoxemia, suggesting that long-acting opioids are no more dangerous than short-acting opioids.

Our choice of Spo_2 cutoff of 95% was driven by overall power of the analysis. However, we had consistent

findings across all 3 reported thresholds of 95%, 90%, and 85%.

The fact that the amount of hypoxemia was similar with long-acting and short-acting opioids does not necessarily mean that either was safe. Hypoxemic episodes were common, severe, and prolonged in our current patients, as previously reported in a larger VISION cohort.[6] It is possible that hypoxemia foreshadows avoidable in-hospital cardiac arrests,[13–15] which are more common in nursing wards than in other hospital locations.[36]

Nearly all patients were initially given oxygen, which was then discontinued at some poorly identified postoperative time. The continuous pulse oximeter measurements made for study purposes were not available to the clinical team, and thus would not have been a basis for oxygen administration (few, if any, patients had continuous saturation monitoring for clinical reasons). Of course, clinicians could respond to routine saturation measurements, typically spot checks at 4-h intervals. But we have reported previously that nurses missed 90% of all serious desaturation episodes (<90% Spo_2 maintained for >1 h) in this population.[6] Furthermore, oxygen administration was comparable in patients given short-acting and long-acting opioids (Table 1). Thus, it seems highly unlikely that saturation guided oxygen administration. Moreover, at the Cleveland Clinic, there is no supplemental oxygen policy that is influenced based on whether a patient receives a short-acting or long-acting opioid.

An important strength of our study was that health care providers were blinded to continuously recorded Spo_2 values. Our results thus accurately characterize the natural amounts of hypoxemia with current levels of nursing care. Continuous monitoring differs substantially from the typical 4- to 6-h monitoring intervals on most surgical wards.[37] The difficulty with intermittent measurements is that many patients who breathe adequately while awake do not when asleep. Spo_2 values obtained after awakening patients for intermittent monitoring may poorly reflect values at other times. Moreover, in some cases, nurses respond to poor saturation values by encouraging patients to breathe deeply until a near-normal value is obtained, with that value being the one recorded in the medical record.[38,39] The importance of continuous monitoring was highlighted in our previous report showing that nurses monitoring at 4-h intervals missed 90% of patients who maintained a smoothed oxygen saturation <90% for at least 1 h.[6]

As with all observational studies, our ability to adjust for potential confounding is limited to available data. Although we considered for potential confounding effects of 29 factors, including many that were thought to be associated with postoperative hypoxemia, residual bias attributable to uncontrolled confounding variables may remain, and its magnitude cannot be determined. Our highly selective process of excluding all patients who received a combination of long-acting or short-acting opioids for postoperative pain management resulted in a smaller number of patients included in the analysis. Consequently, we were able to identify the specific and independent effects of short-acting and long-acting opioids on postoperative hypoxemia. Our primary analysis was adequately powered to detect a difference at an oxygen saturation of <95%. However, we recognize that a saturation of 95% is not especially concerning. We thus replicated our analysis with 90% and 85% thresholds. These analyses were less robust because fewer patients demonstrated these degrees of desaturation; nonetheless, there was no evidence of more desaturation with long-acting opioids at either of these more concerning thresholds.

Our nurses generally record the amount of opioid infused by patient-controlled pumps at 6- to 12-h intervals. Consequently, the final nursing recording period may have overlapped 48 postoperative hours. However, relatively little opioid is used so long after surgery, and there is no reason to expect that inaccuracy in our opioid use estimated at 48 h would be unevenly distributed between the long-acting and short-acting opioid groups. More concerning, we had no records of when opioids were requested and administered by patient-controlled pumps. Therefore, it was impossible for us to correlate opioid use and hypoxemia over minutes or hours (eg, by comparing hypoxemia with estimated effect-site concentration based on pharmacokinetic modeling). Finally, we included only the 3 most commonly used opioids in our analysis. Various opioids, regardless of duration of action, exhibit different pharmacodynamics, and it is thus possible, although perhaps unlikely, that results would differ with other combinations of long-acting and short-acting opioids.

In conclusion, there was no association between the use of long-acting versus short-acting postoperative patient-controlled opioids and the amount of postoperative hypoxemia in a representative sample of surgical inpatients. Results were consistent across various definitions of hypoxemia. As reported previously, ward hypoxemia is common, severe, and prolonged in postoperative patients. However, switching from long-acting to short-acting patient-controlled opioids seems unlikely to ameliorate the problem. As also reported previously, STOP-BANG scores (which evaluate risk of obstructive sleep apnea) do not predict hypoxemia risk.[40] Available evidence thus indicates that postoperative hypoxemia can neither be reliably predicted nor be prevented simply by switching from long-acting to short-acting opioids. Routine continuous ward monitoring of oxygen saturation, and perhaps ventilation as well, will likely be necessary to reliably detect hypoxemia, and to potentially prevent serious consequences of inadequate oxygenation.

APPENDIX 1

Standard Intravenous Patient-Controlled Analgesia Dosing Schemes at the Cleveland Clinic Main Campus

Drug	Basal Rate	Demand Bolus	Clinician Dose
Fentanyl	0–20 mcg/hr	20–30 mcg	20 mcg
Hydromorphone	0–.2 mg/hr	.2–.4 mg	.5 mg
Morphine	0–1 mg/hr	1–2 mg	1 mg

The bolus intervals for clinician doses are the same for every drug in the study. The 2 standard intervals at our institution are 6 min, yielding 10 doses per hour or 10 min, yielding 6 doses per hour.

APPENDIX 2

The multivariable median quantile regression model with bootstrapped standard errors to assess the primary hypothesis on association between the area under an Spo_2 saturation of 95% and the use of long-acting PCA opioids (versus short-acting PCA), adjusting for prespecified potential confounders, type of surgery, duration of surgery, American Society of Anesthesiologists Physical Status, home oxygen use, preexisting pulmonary disease and congestive heart failure, intraoperative opioid dose (in IV morphine equivalents), and for imbalanced variables such as patients' age, history of aortic stenosis, diabetes, sleep apnea and hypertension, open surgery, and total dose of intraoperative muscle relaxant

		Coefficient Estimate	Bootstrapped Standard Error	Lower Limit CI	Upper Limit CI	*P*
(Intercept)		1.12	1.27	−1.38	3.61	.38
Study group: long-acting PCA vs short-acting PCA		−.14	.31	−.75	.47	.66
Open surgery		.56	.33	−.09	1.20	.09
Duration of surgery (h)		.15	.12	−.08	.38	.20
ASA status		−.28	.24	−.75	.18	.23
Age (y)		.01	.01	−.02	.04	.42
Preoperative sleep apnea		.26	.33	−.39	.90	.44
Intraoperative total dose of muscle relaxant (rocuronium; mg)		.00	.01	−.01	.01	.70
Preoperative hypertension		.09	.25	−.41	.59	.72
Preoperative COPD		−.18	.59	−1.33	.97	.76
Preoperative aortic stenosis		.39	1.27	−2.11	2.88	.76
Intraoperative opioid dose (IV morphine equivalents; mg)		.00	.00	−.01	.00	.81
Home oxygen use		.21	.93	−1.62	2.03	.83
Preoperative congestive heart failure		−.09	.79	−1.64	1.46	.91
Preoperative diabetes		−.03	.37	−.75	0.70	.94
Type of surgery	Intra-abdominal surgery (vs complex visceral resection)	−.58	.65	−1.86	.71	.38
	Low-risk surgery (vs complex visceral resection)	.11	1.35	−2.54	.76	.94
	Major hip pelvic surgery (vs complex visceral resection)	−1.70	1.11	−3.89	.48	.13
	Major spine surgery (vs complex visceral resection)	−.17	.79	−1.71	1.38	.83
	Other thoracic surgery (vs complex visceral resection)	−.04	.76	−1.54	1.45	.95
	Others (vs complex visceral resection)	−.49	.87	−2.19	1.21	.58
	Peripheral vascular reconstruction surgery (vs complex visceral resection)	1.04	.82	−.57	2.65	.21
	Radical prostatectomy (vs complex visceral resection)	−1.33	.84	−2.98	.31	.11
	Stomach surgery (vs complex visceral resection)	−.66	.69	−2.02	.69	.34
	Visceral resection (vs complex visceral resection)	−1.24	.88	−2.97	.49	.16

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; PCA, patient-controlled analgesia.

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