Isoflurane and postoperative respiratory depression following laparoscopic surgery: A retrospective propensity-matched analysis

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ABSTRACT

Episodes of respiratory depression during the immediate postoperative recovery period (Phase I post-anesthesia recovery) have been associated with respiratory complications during Phase II recovery. Using multivariable analyses in several surgical cohorts, we previously identified potential associations between patient and perioperative factors and increased risk for Phase I respiratory depression. The aim of this study is to use the propensity-matched analysis to specifically assess for a potential association between the use of isoflurane and episodes of Phase I respiratory depression after laparoscopic operations. The electronic medical records of 8567 patients who underwent laparoscopic operations between January 1, 2010 and July 31, 2014, lasting ≥90 minutes, were retrospectively analyzed. Propensity-matched patients anesthetized without isoflurane were identified for 3403 patients anesthetized with isoflurane. Compared to the use of desflurane, sevoflurane or propofol infusion, maintenance of anesthesia with isoflurane was associated with an increased likelihood of Phase I respiratory depression (OR 95% CI, 1.32, 1.15-1.50, $p < 0.001$) and longer Phase I recovery (126 vs. 110 minutes, $p < 0.001$). The use of isoflurane was associated with increased rates of postoperative respiratory depression and postoperative recovery when compared to sevoflurane, desflurane, or propofol infusion.

KEY WORDS: Isoflurane; respiratory depression; laparoscopic surgery; general anesthesia; postoperative recovery
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INTRODUCTION

The immediate postoperative recovery period (Phase I post-anesthesia recovery) is complex, marked by recovery of organ systems affected by operative stress, the need for ongoing resuscitative therapies, and treatment for pain and nausea. Recovery of the respiratory system is crucial and requires recovery of the strength of the respiratory muscles and those needed to maintain the patency of the upper airway as well as a return to normal respiratory drive. During this process, our institution has found that patients who experience episodes of respiratory depression (e.g., apneic episodes) while admitted to the post-anesthesia care unit (PACU) are at much higher risk for the subsequent development of postoperative pulmonary complications [1] and are more likely to have postoperative respiratory emergencies requiring naloxone administration [2]. Our institutional practice is to continuously assess all postoperative patients for respiratory depression during the PACU stay, and if an episode is observed to delay the PACU discharge for at least an hour. Also, patients with repeated episodes are provided with advanced monitoring following discharge [1]. We have published three studies of different surgical cohorts to identify associations between patient and perioperative factors and these early postoperative episodes of respiratory depression [3-5]. Using multivariable regression analyses, all three studies found the use of isoflurane to be associated with increased risk for respiratory depression [3-5]. The use of propensity scores in observational pharmacoepidemiological studies offers several potential advantages over traditional multivariable regression analysis, most importantly a better balance of confounding variables between groups treated and not treated with a specific drug [6]. Using a propensity score method, we were able to describe an association between perioperative use of gabapentin and postoperative respiratory depression [5]. In this report, we analyze the same cohort using the propensity score method to assess

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for a potential association between the use of isoflurane and early postoperative respiratory depression.

MATERIALS AND METHODS

The study was approved by the Mayo Clinic Institutional Review Board (ID#14-008613, study approved on December 2, 2014, administrator Nanette Bateman), and only patients who provided authorization for research use of their medical records (consistent with Minnesota Statute 144.295) were enrolled.

Study design

This study is an analysis of a previously described cohort of 8567 adult patients undergoing index laparoscopic procedures lasting more than 90 minutes and admitted to the PACU between January 1, 2010 and July 31, 2014 [5]. Of these cases, 2258 (26.4%) were performed using a robotic-assisted technique, while the remaining 6309 (73.6%) cases were done via laparoscopic approach without robotic-assistance. No cases were performed via laparotomy. The anesthetic technique for these procedures included the use of muscle relaxation with a neuromuscular blocking drug, which in our institution is routinely monitored with a nerve stimulator and reversed with neostigmine and glycopyrrolate. The typical practice in anesthetic maintenance is to titrate the inhalational agent to achieve an adequate depth of anesthesia based on clinical judgment. During the procedure, fresh gas flows are typically kept low (e.g., 1-2 L/minute) to conserve the volatile agent and preserve patient body temperature. At the end of the procedure, gas flows are increased to 10-15 L per minute to eliminate the volatile agent from the anesthesia circuit. In our practice, nitrous oxide is not used with laparoscopic procedures.

Following surgery, there were 1311 cases of respiratory depression episodes in the recovery room with an incidence of 153 (95% confidence interval [CI] 146-161) per 1000 cases [5]. Isoflurane was used in 3721 cases and the odds ratio of respiratory depression with its use was 1.32 (95% CI 1.17-1.50), $p < 0.001$ [5].

The details of perioperative and PACU management, variables of interest, and data extraction techniques were previously described [5]. Episodes of respiratory depression observed in the PACU were recorded by nurses, and classified and recorded in medical records as four types of respiratory-specific events: hypoventilation, apnea, hypoxemia, and "pain/sedation mismatch" (defined as Richmond agitation-sedation score [RASS] [7] of ≤ -3 and a numeric pain score >5) [1,8]. In addition, respiratory depression was counted when naloxone was administered to treat respiratory depression; when there was a need for unplanned noninvasive positive pressure ventilation devices (in patients not using these devices preoperatively); and in cases notable for a failure to extubate the trachea or that required reintubation during Phase I recovery. The duration of PACU stay was defined as the time when the patient arrived to the PACU to the time that PACU discharge criteria were met [1,8,9]. Other outcomes of Phase I recovery included the highest numeric pain score, lowest RASS score, postoperative opioid analgesic administration (defined as intravenous morphine equivalents [10,11]), and postoperative nausea and vomiting (PONV, defined as nursing documentation of nausea or vomiting or the use of rescue antiemetics). Other postoperative outcomes included myocardial infarction, need for tracheal reintubation, intensive care unit (ICU) admission within 48 hours of surgery, and hospital death.

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median (interquartile range) for continuous variables, and number (percentage) for categorical variables. The primary endpoint was a binary variable indicating respiratory depression during Phase I recovery, but other outcomes of interest were also assessed (e.g., in-hospital mortality and hospital length of stay).

We compared patients with and without respiratory depression using the Student's *t*-test or Wilcoxon rank sum test for continuous variables and the χ^2-test for categorical variables. Multivariable logistic regression analyses were performed to assess for potential associations between isoflurane and outcomes of interest and are summarized using the odds ratio (OR) and 95% CI.

A propensity-matched analysis was performed. Logistic regression was used to calculate propensity scores, utilizing the following potential confounding variables: age, sex, body mass index, Charlson comorbidity index, history or positive screen [12] for obstructive sleep apnea (OSA), preoperative administration of sustained-release opioids, upper vs. lower abdominal surgery, intraoperative morphine equivalents, use of neuraxial opioid, infiltration of the port sites or transverse abdominis plane block(s) with local anesthetic, and perioperative use of midazolam, droperidol, and/or ketamine. Each patient who received isoflurane was then matched with one patient who did not receive isoflurane (1:1 matching), during the same time frame of this study, based on the logit of the propensity score (±0.25 SD). Standardized mean differences after propensity score matching, as well as *p* values from conditional logistic regression using the matched pairs as strata, were obtained for each covariate to ensure balance between patients who

received isoflurane vs. not in the propensity-matched sample. Duration of surgery was then included as an additional covariate in conditional logistic regression, and we assessed whether respiratory depression was associated with the use of isoflurane. Surgery duration was not included in the propensity score model because this variable is not part of the anesthetic plan. A secondary *post hoc* analysis was performed to determine if the rates of respiratory depression and isoflurane use changed during the study timeframe by analyzing results from the first and second halves of the study. Two-tailed $p < 0.05$ was considered statistically significant. Statistical analyses were performed with JMP Pro 9.0.1 and SAS version 9.3. (SAS Institute, Inc.).

RESULTS

During the study timeframe, there were 8567 index cases, of which isoflurane was used in 3721 cases. There were significant differences between patients anesthetized with isoflurane as compared to other agents, as summarized in Table 1. Propensity matches were identified for 3403 patients anesthetized with isoflurane (Table S1). From this analysis, isoflurane was found to be associated with an increased likelihood of respiratory depression [OR 1.32, 95% CI 1.15-1.50, $p < 0.001$] (Table 2). Patients anesthetized with isoflurane also had longer duration of Phase I recovery and were more sedated, but had less maximal pain, received less opioid analgesics, and had less PONV (summarized in Table 2). Following discharge from Phase I recovery; the measured outcomes were similar between the two groups (Table 3).

The *post hoc* analysis that explored whether the rate of respiratory depression changed over the time span of this study found higher rates in the first half (652 of 3330 cases; OR 196, 95% CI 183-210 episodes per 1000 cases) compared to the second half (442 of 3476 cases; OR 127, 95% CI 117-139 episodes per 1000 cases, $p < 0.001$). Similarly, the use of isoflurane also declined from 1903 (57.2%) in the first half of the study to 1500 (43.2%) in the second half, $p < 0.001$.

DISCUSSION

The main finding of this propensity-matched study, that the use of isoflurane was associated with increased risk for respiratory depression during Phase I post-anesthesia recovery, is in agreement with our previous observations [3-5]. It has been well established that less soluble volatile anesthetic agents promote faster time to tracheal extubation than isoflurane [13]. In elective arthroplasty, the use of desflurane compared to isoflurane was associated with 18% lower odds for experiencing respiratory depression in the recovery room [4]. In this cohort, multivariable analysis demonstrated an association between isoflurane and respiratory depression (Table 2) [5]. In our practice, the clinical decision as to the choice of anesthetic maintenance drug depends on individual anesthesiologist preferences based on patient and surgical factors, which can all introduce bias and skew the results. For these reasons, it is reassuring that our prior finding of association between the use of isoflurane and immediate postoperative respiratory depression was confirmed with the propensity-matched analysis. This method allows for better distribution of confounding variables than the traditional multivariable analysis, as it accounts for both measured and unmeasured confounders [6].

Respiratory depression during Phase I recovery has important clinical implications. In one study, 33% of patients who had a positive screen for OSA and experienced respiratory depression in PACU developed later respiratory complications as compared to only 2% of patients who had a positive OSA screen but did not exhibit immediate postoperative respiratory depression [1]. Previously, we found a 5-fold increase in the risk for emergent naloxone administration following PACU discharge, in patients who had respiratory depression during anesthetic recovery [2]. In the same cohort, we described that patients who experienced respiratory depression during Phase I recovery had higher rates of ICU admissions and tracheal reintubation following PACU discharge [5]. Changes in anesthetic management have been associated with a reduction in the rate of respiratory events. For example, a decrease in the use of preoperative gabapentin and sustained-release oxycodone, as part of a multimodal analgesic protocol in our practice, corresponded with a decrease in the rate of postoperative respiratory depression [4]. We previously described that when isoflurane was substituted for desflurane, a reduction of respiratory depression during Phase I recovery occurred [3]. In the present study, the *post hoc* analysis did show a decline in respiratory depression over time with the reduced use of isoflurane. However, the cause-effect remains unclear. More importantly, it remains unknown whether this reduction in respiratory depression would ultimately result in a similar reduction in postoperative respiratory complications.

The duration of Phase I recovery was longer in patients anesthetized with isoflurane. We have previously observed that changing the default anesthetic agent from isoflurane to desflurane shortens Phase I recovery [3]. However, that practice change coincided with other practice changes (i.e., implementation of an aggressive PONV prophylaxis regimen and a reduction in the routine preoperative use of midazolam) which may have also contributed to this observation. At the same time, prospective studies have observed that recovery

TABLE 1. Patient and perioperative characteristics of the total sample by isoflurane versus of other maintenance techniques[a]

Characteristics	Isoflurane		*p*
	Yes N=3721	No[b] N=4846	
Patient			
Age, years	58.2±14.3	57.4±13.7	0.005
Male sex	2077 (55.8)	2515 (51.9)	<0.001
Body mass index, kg/m^2	28.3±6.5	30.0±8.8	<0.001
Charlson comorbidity score	4.07±2.60	3.95±2.45	0.028
Obstructive sleep apnea	680 (18.3)	1336 (27.6)	<0.001
Preoperative medications			
Gabapentin[c]	756 (20.3)	619 (12.8)	<0.001
Sustained-release opioids[d]	297 (8.0)	242 (5.0)	<0.001
Surgery and anesthesia			
Upper abdominal surgery	1946 (47.7)	2112 (43.6)	<0.001
Duration of surgery, minutes	206±76	199±70	<0.001
Neuraxial opioids[e]	411 (11.0)	208 (4.3)	<0.001
Local anesthetic	1905 (51.2)	2449 (50.5)	0.556
Midazolam[f]	2702 (72.6)	2211 (54.4)	<0.001
Ketamine[g]	961 (25.8)	1475 (30.4)	<0.001
Intraoperative opioids, mg IV ME[i]	35.0 [28.3,40.2]	35.0 [28.3,40.0]	0.084

IV ME: Intravenous morphine equivalents. [a]Data are presented as number (%), mean±standard deviation, or median (25^{th,} 75th percentile). [b]Other techniques included 3824 (78.9) desflurane, 492 (10.2) sevoflurane, and 530 (10.9) cases where the anesthetic technique was total intravenous anesthesia or a combined use of sevoflurane and desflurane. [c]The doses of gabapentin were>300 mg (typically 600 mg) in 574 and 447 and≤300 mg (typically 300 mg) in 182 and 172 patients anesthetized with isoflurane or other techniques, respectively, p=0.122. [d]Median dose of sustained-release opioids was 5 [5,5] mg IV ME for both the isoflurane maintenance and other maintenance technique groups, (p=0.138). [e]Median dose of neuraxial opioids was 20 [12,20] vs. 20 [14,20] mg IV ME for both the isoflurane maintenance and other maintenance technique groups, (p=0.421). [f]Median dose of midazolam was 2 [2,2] mg for both the isoflurane maintenance and other maintenance technique groups, (p=0.156). gMedian dose of ketamine was 20 [20,20] mg for both the isoflurane maintenance and other maintenance technique groups, but significantly different (p=0.024), with different ranges between the two groups (10-210 mg [isoflurane] vs. 10-250 mg [other]). iIn total, 3697 (99.4) patients anesthetized with isoflurane and 4806 (99.2) patients anesthetized with other techniques were administered fentanyl (p=0.377), with both groups having the same median dose of 250 [250,250] mcg (p=0.230). Long-acting opioids were used in 3059 (82.2) patients anesthetized with isoflurane and in 4230 (87.3) patients anesthetized with other techniques (p<0.001), with a median dose of 12 [8,15] vs. 12 [7.5,15] mg IV ME (p<0.001). Of the long-acting opioids, hydromorphone was used in 2338 (62.8) and 3349 (69.1), morphine in 5 (0.1) and 13 (0.3), and oxymorphone in 729 (19.6) and 886 (18.3) patients anesthetized with isoflurane or other anesthetic techniques, respectively. Remifentanil was not included in morphine equivalent calculations; it was administered in 2 (<0.1) and 7 (0.1) patients anesthetized with isoflurane or other anesthetic techniques, respectively

TABLE 2. Differences in Phase I recovery between patients anesthetized with isoflurane compared to other agents

Outcome	Multivariable analysis			Propensity-matched analysis		
	Isoflurane		*p*	Isoflurane		*p*
	Yes N=3721	No N=4846		Yes N=3403	No[a] N=3403	
Respiratory depression, n	672 (18.1)	639 (13.2)	<0.001	609 (17.9)	485 (14.3)	<0.001
Phase I, minutes	127 [97,170]	107 [81,144]	<0.001	126 [96,169]	110 [83,148]	<0.001
Maximum Pain Score	4 [0,6]	5 [2,7]	<0.001	4 [0,6]	5 [2,7]	<0.001
Minimum RASS	−2 [−1,−3]	−1 [−1,−2]	<0.001	−2 [−1,−3]	−1 [−1,−2]	<0.001
IV ME, mg	2.5 [0.0,8.0]	4 [0.0,10.0]	<0.001	2.5 [0.0,8.0]	3.3 [0.0,10.0]	<0.001
PONV, n	439 (11.8)	841 (17.4)	<0.001	408 (12.0)	586 (17.2)	<0.001

Data presented as N (%) or median [interquartile range]. RASS: Richmond agitation sedation score, IV ME: Intravenous morphine equivalents, PONV: Postoperative nausea and vomiting (defined as the use of rescue antiemetics or nursing documentation of nausea or vomiting). [a]Other techniques included 2639 (77.6) desflurane, 392 (11.5) sevoflurane, and 372 (10.9) cases where the anesthetic technique was total intravenous anesthesia or a combined use of sevoflurane and desflurane

TABLE 3. Postoperative outcomes between patients anesthetized with isoflurane or other techniques[a]

Outcome	Multivariable analysis				Propensity-matched analysis			
	Isoflurane		OR (95% CI)	*p*	Isoflurane		OR (95% CI)	*p*
	Yes N=3721	No N=4846			Yes N=3403	No N=3403		
Death[a]	15 (0.4)	5 (0.1)	3.83 (1.21,12.10)	0.022	13 (0.4)	4 (0.1)	3.17 (0.91,11.06)	0.071
Myocardial infarction[b]	4 (0.1)	10 (0.2)	0.36 (0.11,1.25)	0.108	4 (0.1)	9 (0.3)	0.33 (0.08,1.36)	0.125
Reintubation[b]	3 (0.1)	7 (0.1)	0.49 (0.12,2.01)	0.325	3 (0.1)	6 (0.2)	0.79 (0.16,3.86)	0.772
ICU admission[b]	269 (7.2)	372 (7.7)	0.92 (0.77,1.11)	0.397	239 (7.0)	262 (7.7)	0.89 (0.74,1.07)	0.204
Hospital LOS≥4 days[c]	891 (24.0)	868 (17.9)	1.14 (1.00,1.30)	0.045	753 (22.1)	682 (20.0)	1.13 (1.00,1.28)	0.055

Data presented as number (%) or odds ratio (95% confidence internal). ICU: Intensive care unit, LOS: Length of stay. [a]During hospitalization. [b]Within 48 hours of surgery. [c]Median hospital length of stay was similar between patient groups assessed by multivariable and propensity-matched analysis, i.e., 2 [1,3] days, but found to be statistically different (p<0.001) by both analyses, with the isoflurane group having longer hospital stays

after the use of isoflurane is longer compared to other anesthetic agents [13]. In this study, it is not clear if Phase I recovery was prolonged because of higher rates of respiratory depression (and our institutional specific practice of extending recovery room stay for these patients), median RASS scores that were lower in the isoflurane group, or other reasons. However, the pain scores and corresponding opioid administration, and the rate of PONV were all lower in the isoflurane group suggesting that these factors can be excluded as explanatory variables for our finding of prolonged Phase I recovery in the isoflurane group.

This study has limitations inherent to all retrospective studies. For example, the rates of respiratory depression and the use of isoflurane declined during the study timeframe. Minor laparoscopic procedures (duration <90 minutes) were excluded from the analysis; so the use of isoflurane in those cases was not assessed. Even though nurse diagnosed respiratory-specific events are based on established criteria, they have inherent elements of subjectivity. However, because this observation extended to all patients, the main reported effect of respiratory depression should remain uniform across different anesthetic agent groups. Another limitation was our inability to extract information regarding fresh gas flows or exact percentages of volatile anesthetics used during surgery. However, these percentages are standard and are set to patients' hemodynamics, and over a large number of cases we had in the study, one may expect little variability. Our institution does not routinely use processed electroencephalogram to monitor the depth of anesthesia, therefore, we cannot comment whether this variable (anesthetic depth) may have impacted our results.

In conclusion, after laparoscopic operations, the rate of respiratory depression in the recovery room was increased in patients anesthetized with isoflurane compared to those who received desflurane, sevoflurane, or propofol infusion. Further studies are needed to evaluate whether the elimination of isoflurane during laparoscopic surgical procedures may result in a reduction of immediate postoperative complications related to respiratory depression.

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DECLARATION OF INTERESTS

Dr. Weingarten currently serves as a consultant to Medtronic in the role as chairman of the Clinical Endpoint Committee for the Prodigy Trial. Dr. Weingarten has received unrestricted investigator-initiated grants from Merck for research unrelated to current study. The other authors declare no conflict of interests.

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SUPPLEMENTAL DATA

TABLE S1. Patient and perioperative characteristics of the propensity-matched sets[a, b]

Characteristics	Isoflurane		Total sample standardized difference	Propensity-matched sets standardized difference
	Yes N=3403	No N=3403		
Patient				
Age, years	58.0±14.2	58.3±13.8	0.061	0.022
Male sex	1874 (55.1)	1840 (54.1)	0.079	0.020
Body mass index, kg/m2	29.6±6.6	29.6±6.9	0.370	0.012
Charlson comorbidity score	4.03±2.56	4.06±2.47	0.048	0.014
Obstructive sleep apnea	657 (19.3)	678 (19.9)	0.222	0.016
Preoperative medications				
Gabapentin	572 (16.8)	538 (15.8)	0.204	0.027
Sustained-release opioids	254 (7.5)	228 (6.7)	0.122	0.030
Surgery and anesthesia				
Upper abdominal surgery	1529 (44.9)	1476 (43.4)	0.083	0.031
Neuraxial opioids	241 (7.1)	207 (6.1)	0.256	0.040
Local Anesthetic	1795 (52.7)	1814 (53.3)	0.013	0.011
Midazolam	2388 (70.2)	2304 (67.7)	0.386	0.053
Ketamine	920 (27.0)	943 (27.7)	0.103	0.015
Intraoperative opioids, mg IV ME	35.0 [29.0,40.0]	35.0 [29.0,40.0]	0.029	0.010

IV ME: Intravenous morphine equivalents