# Multimodal Analgesic Therapy With Gabapentin and Its Association With Postoperative Respiratory Depression

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**BACKGROUND:** Gabapentinoids are widely used in perioperative multimodal analgesic regimens. The primary aim of this study was to determine whether gabapentin was associated with respiratory depression during phase-I postanesthesia recovery after major laparoscopic procedures.

**METHODS:** We retrospectively reviewed the electronic health records of 8567 patients who underwent major laparoscopic procedures (lasting ≥90 minutes) from January 1, 2010, to July 31, 2014. We assessed potential associations among patient and perioperative variables and episodes of respiratory depression during phase-I recovery. Multivariable and propensity score–matched analyses were performed to assess potential associations between preoperative gabapentin use and postoperative respiratory depression.

**RESULTS:** The incidence of respiratory depression was 153 (95% confidence interval [CI], 146–161) episodes per 1000 cases. Multivariable analysis showed that gabapentin was associated with respiratory depression (odds ratio [OR], 1.47 [95% CI, 1.22–1.76]; $P < .001$). These results were confirmed by propensity score–matched analysis among a subset of patients who did not have analgesia supplemented by intrathecal opioids (OR, 1.26 [95% CI, 1.02–1.58]; $P = .04$). Older patients and those who received more intraoperative opioids had increased risk of respiratory depression. Those who had an episode of respiratory depression had a longer phase-I recovery ($P < .001$) and an increased rate of admission to a higher level of care ($P = .03$).

**CONCLUSIONS:** The use of gabapentin is associated with increased rates of respiratory depression among patients undergoing laparoscopic surgery. When gabapentinoids are included in multimodal analgesic regimens, intraoperative opioids must be reduced, and increased vigilance for respiratory depression may be warranted, especially in elderly patients. (Anesth Analg 2017;125:141–6)

Multimodal analgesic therapies for acute postoperative pain have become popular under the premise that combining analgesics with different mechanisms of action improves pain control when mitigating the adverse effects of individual medications.[1–3] Such analgesic therapies have been used to improve patient satisfaction and hasten convalescence. However, to avoid complications, this approach must consider the analgesic and opioid-sparing effects of the individual components, a task made complex by patient-specific drug sensitivities, age, and comorbid conditions. Therefore, precisely accounting for all these interactions is difficult in the clinical practice.

Gabapentinoids (gabapentin and pregabalin) are frequently included in multimodal analgesic regimens. Although recent meta-analyses have demonstrated that their use reduces the need for opioids and improves postoperative pain, they induce sedation.[4,5] When taken in isolation, gabapentinoids do not have respiratory depressive properties,[6,7] but when administered in combination with the ultrashort-acting opioid remifentanil, pregabalin potentiated respiratory depression.[8] Similarly, gabapentin was associated with respiratory depression during postanesthesia recovery in patients undergoing total joint arthroplasty.[9] Given this new evidence, neglect of the interaction between gabapentinoids and opioids may increase the risk of postoperative respiratory depression.

Our institution follows the commonly used postanesthesia care unit (PACU) discharge criteria[10] and additionally assesses patients during phase-I recovery for signs of respiratory depression (termed as respiratory-specific events): (1) hypoventilation; (2) apnea; (3) hypoxemia; and (4) episodes of severe pain, despite moderate to profound sedation (termed as pain-sedation mismatch).[11,12] Surgical patients who experience these events have increased rates of postoperative respiratory complications and require more resources for their care.[9,12,13] Also, at our institution, the decision to include gabapentin in the multimodal analgesic regimen for major laparoscopic procedures varies by surgical specialty.[1,14] These factors provide an opportunity to review a large cohort of patients and allow us to assess the potential associations between preoperative use of gabapentin and respiratory depression.

The primary aim of this study was to test the hypothesis that gabapentin is associated with respiratory depression during phase-I recovery after major laparoscopic procedures. Secondary aims included assessing other patient and perioperative factors to identify potential associations with respiratory depression and to determine whether episodes of respiratory depression were associated with outcomes.

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## METHODS

This study was approved by the Mayo Clinic Institutional Review Board. We included only patients who provided authorization for research use of their health records.

### Study Design and Patient Selection

This study is representative of a high-volume surgical practice within a major tertiary academic institution. We retrospectively searched the Department of Anesthesiology database for the records of adult patients (≥18 years of age) who underwent laparoscopic surgery of ≥90 minutes from January 1, 2010, to July 31, 2014. We excluded patients who bypassed the PACU. For patients who underwent multiple laparoscopic procedures, only the index surgery was included. The 90-minute cutoff was selected a priori to exclude minor surgical procedures with low likelihood of postoperative respiratory depression (eg, straightforward laparoscopic appendectomy).

### Multimodal Analgesic and Anesthetic Management Protocols

Various management protocols were used during the study timeframe.[1,14,15] Analgesic medications included preoperative gabapentin, acetaminophen, celecoxib, and sustained-release opioids and intraoperative ketorolac, low-dose ketamine, and intravenous or neuraxial opioids. The most common agents for anesthesia maintenance were isoflurane and desflurane. The effects of neuromuscular-blocking drugs were routinely monitored with nerve stimulator and reversed with neostigmine with glycopyrrolate.

### Postanesthesia Care Unit Clinical Practice

The medical center has 2 PACUs for each of its hospitals: Saint Marys Hospital and Rochester Methodist Hospital. These PACUs were staffed by registered nurses trained in phase-I recovery, and the Saint Marys Hospital PACU staff also included an anesthesiology resident. The patient:nurse ratio was 2:1, and nurses had visual access to patients. The attending anesthesiologist was available if advanced expertise was required. Discharge from phase-I recovery was determined by widely used criteria.[10] In addition, PACU nurses continuously monitored patients for respiratory depression by screening for 4 respiratory-specific events: (1) hypoventilation (3 episodes of <8 respirations/minute); (2) apnea (episode lasting ≥10 seconds); (3) hypoxemia (3 episodes of oxyhemoglobin desaturations [<90%, with or without nasal cannula], as measured by pulse oximetry); and (4) pain-sedation mismatch (defined as a Richmond Agitation Sedation Score[16] of −3 to −5 and a numeric pain score of ≥5 [from 0, no pain, to 10, worst pain imaginable]).[11,12] Patients with a history of obstructive sleep apnea (OSA) were routinely instructed to bring their noninvasive positive-pressure ventilator (NIPPV; ie, continuous positive airway pressure and bilevel positive airway pressure devices) devices to the hospital on the day of surgery; these were used in the PACU when indicated, and respiratory-specific events that occurred when these devices were being used also were recorded. Discharge goals included a numeric pain score of <5 and controlled nausea.

### Data Abstraction

Medical, surgical, and anesthesia records were electronically abstracted using previously described proprietary software.[17] Presurgical variables included patient age, sex, body mass index, burden of comorbid diseases (as determined by the Charlson Comorbidity Index),[18,19] and a history of OSA or a positive screen for OSA using a standardized screening assessment tool.[20] Anesthesia variables included the preoperative use of gabapentin or pregabalin and sustained-release oral opioids; intraoperative use of intravenous midazolam, ketamine, and droperidol; a cumulative dose of intraoperative opioids; use of local anesthetics for wound infiltration; use of intrathecal opioids to supplement analgesia; and use of the anesthesia maintenance agent (eg, isoflurane versus other techniques). Surgical records were reviewed for surgical site (upper abdominal [eg, laparoscopic bariatric, hepatobiliary, diaphragmatic procedures] versus lower abdominal [eg, robotic prostatectomy, colorectal, gynecologic procedures]) and duration of the operation. Intraoperative opioid administration was converted to IV morphine equivalents using published guidelines.[21,22] The ultrashort-acting opioid remifentanil was not included in the calculations of IV morphine equivalents. Records of the phase-I recovery period were reviewed for (1) the occurrence of respiratory-specific events[11,12]; (2) naloxone administration for treating respiratory depression or excessive sedation; (3) failure to extubate or the need to reintubate the trachea; and (4) the use of NIPPV devices in the PACU in patients who did not have these devices prescribed. We recorded disposition from the PACU to the intensive care unit (ICU), a standard surgical ward, or an outpatient unit. We reviewed whether patients needed activation of the emergency response team, emergency tracheal intubation, naloxone administration, or subsequent admission to the ICU within 48 hours of PACU discharge. Finally, we recorded the incidence of myocardial infarction, deep venous thrombosis, or pulmonary embolism within 30 postoperative days.

### Statistical Analysis

Data are presented as mean (SD) or median (interquartile range) for continuous variables and number (percentage) for categorical variables. The primary end point was a binary variable indicating respiratory depression during phase-I recovery. This end point was defined as the occurrence of nurse-diagnosed respiratory-specific events, administration of naloxone to treat respiratory depression, the need for unplanned use of NIPPV devices (for patients not using these devices preoperatively), or cases notable for a failure to extubate trachea or that required reintubation during phase-I recovery. We compared patients with and without these events using the Student *t* test or rank sum test for continuous variables and the $\chi^2$ test for categorical variables. In addition, multivariable logistic regression analyses were performed to assess potential associations between respiratory depression and abstracted variables. For the multivariable logistic regression analyses, the Box-Tidwell test was used to assess the assumption of linearity for continuous variables. Because of the lack of linearity, age was included as a categorical variable for the multivariable model. The results of the multivariable model are summarized with ORs and 95% CIs.

In addition to performing a standard covariate-adjusted analysis, we performed a propensity score–matched analysis. Because of the high use of gabapentin in patients receiving neuraxial opioids,[1] the propensity score–matched analysis was restricted to patients who did not receive neuraxial opioids. Logistic regression was used to calculate propensity scores using the following potential confounding variables: age; sex; body mass index; Charlson Comorbidity Index; history or positive screen for OSA; outpatient use of gabapentinoids; preoperative sustained-release opioid administration; upper versus lower abdominal surgery; intraoperative morphine equivalents; and intraoperative use of the local anesthetics midazolam, droperidol, ketamine, and isoflurane. Each patient who received gabapentin was then matched with 2 patients who did not receive gabapentin (1:2 matching) based on the logit of the propensity score (±0.25 SD). Standardized mean differences before and after propensity-score matching were obtained for each covariate to ensure balance between patients who received gabapentin versus those who did not in the propensity score–matched sample. Conditional logistic regression was then performed to assess whether respiratory depression among patients not receiving neuraxial opioids was associated with the use of gabapentin. Duration of surgery was included as an additional covariate in the conditional logistic regression because it was not included in the propensity score model (that variable was not a part of the anesthetic plan). Two-tailed *P* values <.05 were considered statistically significant. Statistical analyses were performed with JMP Pro 9.0.1 and SAS version 9.3 (SAS Institute Inc, Cary, NC).

## RESULTS

During the study timeframe, 8567 patients underwent 8670 laparoscopic procedures lasting >90 minutes. Of the 8567 index cases, 1311 had episodes of respiratory depression during phase-I recovery (incidence rate, 153 [95% CI, 146–161] per 1000 cases). Of the 1311 cases, respiratory-specific events were documented for 1258; the remainder of events were inferred from the administration of naloxone (n = 45), use of unplanned NIPPV in patients who were not previous users (n = 8), failure to extubate the trachea (n = 25), or the need for tracheal reintubation during the PACU stay (n = 10; indications were respiratory depression [n = 7], pulmonary edema [n = 1], shock [n = 1], and bronchospasm [n = 1]). Twenty-four patients (0.28%) were administered neostigmine in the PACU, of whom 18 were transferred to the PACU for extubation. Of the remaining 6, 3 met our criteria for respiratory depression, and the other 3 were administered neostigmine to treat reports of weakness.

Of those with documented respiratory-specific events, the median number of events per patient was 2 (interquartile range, 1–4). Details of respiratory-specific events are summarized in Table 1. Table 2 compares the clinical, surgical, and anesthesia characteristics of patients who did or did not have respiratory depression. The propensity score–matched analysis, restricted to patients who did not receive neuraxial opioids, included 965 patients who received gabapentin and 1930 propensity score–matched patients who did not. In this analysis, gabapentin was associated with an increased likelihood of respiratory depression (OR, 1.26 [95% CI, 1.02–1.58]; *P* = .04). Table 3 compares clinical, surgical, and anesthesia characteristics of subjects included in the propensity score–matched analysis, stratified by preoperative gabapentin use. Postoperative outcomes are summarized in Table 4.

## DISCUSSION

The main finding of our study is that the use of gabapentin was associated with an increased incidence of respiratory depression during phase-I recovery after laparoscopic surgery. Patients who had episodes of respiratory depression were older, received midazolam, and had a slightly higher intraoperative dose of opioids. To reduce the rate of respiratory depression during multimodal analgesic therapy, especially when gabapentin is used, intraoperative management must consider the patient's age and the opioid-sparing and sedating effects of gabapentin.

We previously observed that preoperative use of gabapentin was associated with respiratory depression after joint arthroplasty under general and spinal anesthesia.[9] Although ingestion of toxic doses of gabapentin and pregabalin in isolation do not cause respiratory arrest,[6,7] including gabapentinoids in multimodal analgesic therapy with opioids may increase the risk of respiratory depression. A recent trial showed that pregabalin potentiates respiratory depression induced by remifentanil in healthy young volunteers.[8] Gabapentin has an opioid-sparing effect of varying clinical importance for different surgical procedures, making its effects difficult to predict.[4] Keeping this in mind, intraoperative use of opioids (and sedatives) should be reduced when gabapentin is used, especially in patients who may be prone to respiratory depression (eg, elderly, morbidly obese, or deconditioned patients).

The overall rate of respiratory depression in the present study (15.3%) was lower than what was previously

**Table 1. Respiratory-Specific Events**

| Respiratory-Specific Event | No. of Patients[a,b] | Additional Respiratory-Specific Events, No. of Patients | | |
|---|---|---|---|---|
| | | Hypoventilation | Apnea | Desaturation |
| Hypoventilation | 811 | … | … | … |
| Apnea | 772 | 554 | … | … |
| Desaturation | 395 | 214 | 193 | … |
| Pain-sedation mismatch | 165 | 64 | 56 | 41 |

[a]Patient numbers exceed the total number of events because most patients had multiple events. During phase-I postanesthesia recovery, 1258 patients (14.7%) had at least 1 respiratory-specific event.

[b]Not included in this table are 53 patients (0.6%) who did not have a nurse-diagnosed respiratory-specific event. However, respiratory depression was inferred from naloxone administration (n = 29), failure to extubate (n = 24), or need for reintubation (n = 9) during phase-I recovery (number of therapies exceed 53 because some patients had >1 intervention, and the full number of patients [those with and without nurse-diagnosed respiratory depression] who received these therapies is provided in the Results section).

**Table 2. Comparison of Patients With and Without Respiratory Events[a]**

| | Univariate | | | Multivariable Model | |
|---|---|---|---|---|---|
| Variable | Respiratory Event (n = 1311) | Event Free (n = 7256) | *P* value | OR (95% CI) | *P* value |
| Patient and surgical factors | | | | | |
| Age (y) | 59.8 ± 12.8 | 57.4 ± 14.2 | <.001 | | <.001 |
| <50 | 259 (19.8) | 1977 (27.2) | | 1.00 | |
| 50–59 | 361 (27.5) | 1922 (26.5) | | 1.41 (1.16, 1.71) | |
| 60–69 | 404 (30.8) | 2109 (29.1) | | 1.43 (1.15, 1.77) | |
| ≥70 | 287 (21.9) | 1248 (17.2) | | 1.86 (1.43, 2.42) | |
| Male sex | 769 (58.7) | 3823 (52.7) | <.001 | 1.11 (0.97, 1.27) | .13 |
| Outpatient gabapentinoid use | 26 (2.0) | 193 (2.7) | .15 | 0.83 (0.54, 1.26) | .38 |
| Charlson comorbidity index | 4 [3, 5] | 4 [2, 5] | <.001 | 0.99 (0.95, 1.02) | .50 |
| Body mass index (kg/m$^2$) | 29.8 ± 7.3 | 31 ± 8.1 | <.001 | 0.99 (0.98, 0.99) | .001 |
| Obstructive sleep apnea | 293 (22.3) | 1723 (23.7) | .29 | 1.09 (0.93, 1.28) | .31 |
| Upper abdominal procedure[b] | 518 (39.5) | 3369 (46.4) | <.001 | 0.70 (0.61, 0.80) | <.001 |
| Surgery duration, minutes | 199 ± 71 | 203 ± 73 | .06 | 0.99 (0.99, 0.99) | <.001 |
| Preoperative medication | | | | | |
| Gabapentin[c] | 230 (17.5) | 1145 (15.8) | .11 | 1.47 (1.22, 1.76) | <.001 |
| Sustained-release opioids[d] | 56 (4.3) | 483 (6.7) | .001 | 0.54 (0.40, 0.72) | <.001 |
| Intraoperative medication | | | | | |
| Neuraxial opioids[e] | 104 (7.9) | 515 (7.1) | .30 | 1.07 (0.82, 1.38) | .64 |
| Local anesthetic | 745 (56.8) | 3609 (49.7) | <.001 | 1.27 (1.12, 1.44) | <.001 |
| Midazolam[f] | 905 (69.0) | 4432 (61.1) | <.001 | 1.34 (1.16, 1.54) | <.001 |
| Droperidol | 564 (43.0) | 4116 (56.7) | <.001 | 0.69 (0.60, 0.79) | <.001 |
| Ketamine[g] | 309 (23.6) | 2127 (29.3) | <.001 | 0.82 (0.71, 0.96) | .011 |
| Isoflurane | 672 (51.3) | 3049 (42.0) | <.001 | 1.22 (1.08, 1.39) | .002 |
| Intraoperative opioids (mg IV ME)[h] | 35.7 [30, 41.7] | 35 [28.3, 40.0] | <.001 | 1.02 (1.01, 1.02) | <.001 |

Abbreviations: CI, confidence interval; IV ME, intravenous morphine equivalents; OR, odds ratio.

[a]Data are presented as number (%), mean ± SD, median [25th percentile, 75th percentile], or OR (95% CI).

[b]Upper abdominal procedures included colectomy or hemicolectomy (n = 869), nephrectomy (n = 596), bariatric surgery (n = 569), cholecystectomy (n = 459), abdominal exploration or small bowel resection (n = 417), Nissen fundoplication (n = 346), major hepatobiliary surgery (n = 331), splenectomy (n = 140), adrenalectomy (n = 129), and gastrectomy (n = 31). Lower abdominal procedures included prostatectomy (n = 2494), hysterectomy (n = 1385), hernia repair (n = 142), sigmoidectomy or abdominoperineal resection or ileal pouch anal anastomosis (n = 137), sacrocolpopexy (n = 136), salpingo-oophorectomy (n = 125), pyeloplasty (n = 57), ileocecal resection (n = 46), uterine myomectomy (n = 43), proctectomy (n = 41), partial cystectomy (n = 32), appendectomy (n = 30), and ileostomy (n = 12).

[c]Patients in the gabapentin group received doses of 300 mg (n = 349 [25.4%]) or 600 mg (n = 1017 [74%]), with few outliers receiving doses below (n = 1; 200 mg), within (n = 4; 400 mg), or above (n = 4; 900–1500 mg) this interval.

[d]Median [25th percentile, 75th percentile] dose of sustained-release opioids was 5 [5, 5] mg IV ME for both the respiratory event and event-free groups (*P* = .47).

[e]Median [25th percentile, 75th percentile] dose of neuraxial opioids was 16 [14, 20] vs 20 [14, 20] mg IV ME for the respiratory event and event-free groups, respectively (*P* = .51).

[f]Median [25th percentile, 75th percentile] dose of midazolam was 2 [2, 2] mg for both the respiratory event and event-free groups (*P* = .39).

[g]Median [25th percentile, 75th percentile] dose of ketamine was 20 [10, 20] vs 20 [20, 20] mg for the respiratory event and event-free groups, respectively (*P* = .16).

[h]In total, 1299 patients with respiratory depression (99.1%) and 7204 patients without respiratory depression (99.3%) were administered fentanyl (*P* = .48), with both groups having the same median [25th percentile, 75th percentile] dose of 250 [250, 250] mcg (*P* = .27). Long-acting opioids were used in 1130 patients with respiratory depression (86.2%) and in 6159 without respiratory depression (84.9%; *P* = .24), with a median [25th percentile, 75th percentile] dose of 12 [7.5, 15] vs 10.5 [6, 15] IV ME (*P* < .001). Of the long-acting opioids, hydromorphone was used in 865 (66.0%) and 4822 (66.5%), morphine in 2 (0.2%) and 16 (0.2%), and oxymorphone in 265 (20.2%) and 1350 (18.6%) patients with and without respiratory depression, respectively. Remifentanil was not included in morphine equivalent calculations; it was administered in 2 (0.2%) and 7 (0.1%) patients with or without respiratory depression, respectively.

observed in our institution after general anesthesia for total joint arthroplasty (31.2%).[9] However, several differences in anesthetic techniques between the 2 studies may explain this discrepancy. Patients undergoing joint arthroplasty[9] were commonly prescribed sustained-release opioids as a part of the multimodal protocol.[2,3] When considering that the mean (SD) observed duration of surgery in the orthopedic cohort was 121 (49) minutes[9] and that plasma levels of oxycodone after administration of a sustained-release formulation peaked at 157 (64) minutes,[23] these patients would typically have peak plasma levels of oxycodone upon arrival to the PACU. Residual depressive respiratory effects of intraoperative opioids, peak plasma levels of oxycodone, and sedative and opioid-sparing effects of gabapentin were all compounded in the immediate postoperative period to create a favorable setting for the respiratory depression. In contrast, sustained-release opioids were rarely administered preoperatively in the present study. A second difference is that in the present patient cohort, isoflurane was used less frequently (43.4% vs 65.4% in the previous study).[9] We previously showed that the use of isoflurane increased the rate of respiratory depression during phase-I recovery.[9,14] We found that after institution of a clinical protocol that reduced midazolam administration and preferentially used desflurane over isoflurane, the rates of respiratory depression declined.[14] The consistency of findings from those previous studies and the current study suggest that the rate of postoperative respiratory depression is influenced by anesthetic management and that protocols designed to avoid residual sedation are more protective.

It is interesting that 2 sedating medications, ketamine and droperidol, were inversely associated with respiratory depression. Droperidol has been shown to have only minimal respiratory depressive effects,[24] and the typical dose used in this

**Table 3. Patient Characteristics, Stratified by Preoperative Gabapentin Use[a]**

| | All Patients Not Receiving Neuraxial Opioids | | | Propensity Score–Matched Sample | | |
|---|---|---|---|---|---|---|
| Variable | Gabapentin (n = 965) | No Gabapentin (n = 6983) | Standardized Difference | Gabapentin (n = 965) | No Gabapentin (n = 1930) | Standardized Difference |
| Patient and surgical factors | | | | | | |
| Age (y) | 52.4 ± 13.3 | 58.7 ± 13.6 | 0.47 | 52.4 ± 13.3 | 52.4 ± 14.8 | 0.01 |
| Male sex | 281 (29.1) | 3981 (57.0) | 0.59 | 281 (29.1) | 581 (30.1) | 0.02 |
| Outpatient gabapentinoid use | 25 (2.6) | 174 (2.5) | 0.01 | 25 (2.6) | 59 (3.1) | 0.03 |
| Charlson comorbidity index | 3 [1, 5] | 4 [2, 5] | 0.39 | 3 [1, 5] | 3 [1, 5] | 0.01 |
| Body mass index (kg/m$^2$) | 30.5 ± 8.7 | 31.2 ± 8.0 | 0.08 | 30.5 ± 8.7 | 30.6 ± 8.1 | 0.01 |
| Obstructive sleep apnea | 157 (16.3) | 1751 (25.1) | 0.22 | 157 (16.3) | 310 (16.1) | 0.01 |
| Upper-abdominal procedure | 425 (44.0) | 2999 (43.0) | 0.02 | 425 (44.0) | 892 (46.2) | 0.04 |
| Preoperative medication | | | | | | |
| Sustained-release opioids | 34 (3.5) | 499 (7.2) | 0.16 | 34 (3.5) | 76 (3.9) | 0.02 |
| Intraoperative medication | | | | | | |
| Local anesthetic | 558 (57.8) | 3695 (52.9) | 0.10 | 558 (57.8) | 1051 (54.5) | 0.07 |
| Midazolam | 636 (65.9) | 4115 (58.9) | 0.14 | 636 (65.9) | 1250 (64.8) | 0.02 |
| Droperidol | 660 (68.4) | 3682 (52.7) | 0.32 | 660 (68.4) | 1281 (66.4) | 0.04 |
| Ketamine | 472 (48.9) | 1809 (25.9) | 0.49 | 472 (48.9) | 897 (46.5) | 0.05 |
| Isoflurane | 470 (48.7) | 2840 (40.7) | 0.16 | 470 (48.7) | 900 (46.6) | 0.04 |
| Intraoperative opioids (mg IV ME) | 32.3 ± 12.6 | 36.0 ± 11.2 | 0.31 | 32.3 ± 12.6 | 32.9 ± 10.6 | 0.05 |

Abbreviation: IV ME, intravenous morphine equivalents.

[a]Data are presented as number (%), mean ± SD, or median (25th percentile, 75th percentile).

**Table 4. Outcomes of Patients With and Without Respiratory Depression[a]**

| Outcomes | Respiratory Depression (n = 1311) | Event Free (n = 7256) | *P* Value |
|---|---|---|---|
| Duration of phase-I recovery (min) | 195 ± 80 | 117 ± 55 | <.001 |
| Intensive care unit admission | 101 (7.7) | 407 (5.6) | .004 |
| First 48 h after PACU discharge | | | |
| Emergency response team intervention | 18 (1.4) | 62 (0.9) | .09 |
| Tracheal reintubation[b] | 4 (0.3) | 6 (0.1) | .05 |
| Intensive care unit admission from ward | 30 (2.3) | 103 (1.4) | .03 |
| 30-day postoperative outcomes | | | |
| Myocardial infarction | 4 (0.3) | 10 (0.1) | .25 |
| Deep venous thrombosis or pulmonary embolism | 2 (0.2) | 10 (0.1) | .71 |
| Death | 5 (0.4) | 15 (0.2) | .22 |

Abbreviation: PACU, postanesthesia care unit.

[a]Data are presented as number (%) or mean ± SD.

[b]Reasons for reintubation among the respiratory depression cohort included pulmonary edema (n = 1), hypercarbic respiratory failure (n = 1), and shock (n = 2); among the respiratory event–free group, reasons for reintubation included hypercarbic respiratory failure (n = 2) and shock or hypotension (n = 4).

study was small (0.625 mg) and probably inconsequential with regard to postoperative sedation. Ketamine often stimulates breathing,[24] and again, the doses typically used in this cohort were small. We previously observed that neither drug was associated with worsening respiratory depression.[9,14] We were surprised that surgical infiltration of local anesthetics was associated with the increased respiratory depression because this route of administration should be devoid of sedating effects.

Interestingly, the rate of respiratory depression in the present cohort was greater than that of our previous report of patients undergoing laparoscopic bariatric surgery (15.3% vs 4.5%), despite the fact that 64.5% of obese patients had OSA.[15] Also, in this study, we observed an inverse relationship between respiratory depression and body mass index. A plausible explanation for this paradox is that the increased concern for postoperative respiratory depression in obese patients precluded the use of gabapentin in the typical anesthesia management practice for bariatric surgery; desflurane is recommended instead.[15] Our findings suggest that when management is tailored to a specific patient type, the rate of respiratory depression may be reduced. The same principle should be applied to patients who receive gabapentin preoperatively; because of the opioid-sparing effect and sedative properties of gabapentin, intraoperative opioid management should be modified.

Patients with respiratory depressive events had prolonged phase-I recovery. These patients also required more postoperative resources, including higher rates of ICU admission, postoperative mechanical ventilation, and unplanned NIPPV use. Further, we noted higher need for postoperative use of rapid response teams and reintubation because of the respiratory failure, although the incidence rates were not significantly different from those of the event-free group. Our institution supplements standard discharge criteria by delaying the discharge from phase-I recovery if patients have episodes of respiratory depression.[11,12] We previously observed that the rates of emergent naloxone administration and the activation of emergent response teams after discharge from the PACU are highest immediately after discharge and that respiratory-specific events during phase-I anesthesia are highly associated with postoperative naloxone administration.[13,25] In this cohort, the additional time for phase-I recovery allotted to patients with respiratory depressive episodes must be of sufficient duration to mitigate the likelihood for respiratory complications after PACU dismissal.

We acknowledge that this study has limitations inherent to all retrospective studies. However, the use of propensity score analysis strengthens the validity of the positive association between preoperative gabapentin use and respiratory depression. Minor laparoscopic procedures (duration of <90 minutes) were excluded from the analysis; we do not know whether gabapentin is associated with respiratory depression after shorter laparoscopic procedures, specifically because opioid use may be lower during these procedures. Another limitation is that the use and reversal of nondepolarizing neuromuscular blocking drugs was guided by qualitative train-of-four peripheral nerve stimulation; thus, there may be a subset of patients with unrecognized residual weakness contributing to postoperative respiratory depression. The use of nurse-diagnosed respiratory-specific events relies on their witnessing and recognizing signs of respiratory depression, and it therefore is a somewhat subjective measure. However, because these factors are extended to all patients, the main reported effect of respiratory depression should remain unchanged across different analgesia management groups. Finally, the retrospective nature of the data limits the precise identification of patients with chronic pain disorders or with analgesic medication tolerance; however, a review of medications did not find a significant difference in home use of opioid or gabapentinoid medications.

In conclusion, the rate of respiratory depressive episodes in the immediate postoperative period after laparoscopic operations was increased in patients who received gabapentin as part of a multimodal analgesic regimen. The opioid-sparing effect of gabapentinoids should be considered when constructing multimodal analgesic regimens, and increased vigilance for respiratory depression is warranted.

## DISCLOSURES

**Name**: Alexandre N. Cavalcante, MD.
**Contribution**: This author helped collect data and prepare the manuscript.
**Name**: Juraj Sprung, MD, PhD.
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