Anesthesia and Postoperative Respiratory Compromise Following Major Lower Extremity Surgery: Implications for Combat Casualties

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ABSTRACT Care of military casualties requires not only assessment of patient, injury, and setting, but also the consequences of care decisions on other organ systems. In contemporary conflicts, pelviperineal and lower extremity trauma are common injuries, yet the optimal perioperative anesthetic and analgesic care remains unclear. Residual anesthesia and opioids can cause respiratory depression, specifically postoperative respiratory depression and opioid-induced respiratory depression. This observational study quantified and compared the incidences of respiratory depression following general anesthesia (GA) and spinal anesthesia (SA) for lower extremity surgery. Respiratory data were collected from 173 patients receiving either GA (n = 43) or SA (n = 130) via a bioimpedance-based respiratory volume monitor. Patients were further subdivided by postoperative opioid administration. The overall incidence of respiratory depression was significantly higher in the SA group (48/130 vs. 6/43, p = 0.004). These findings suggest that, while SA may be considered the safer alternative, it may in fact introduce confounding factors, which increase the risk of respiratory depression. Ensuring adequate respiratory status is particularly critical for the military population, as combat casualties are often monitored in understaffed environments following surgery. Using an SA strategy instead of GA may not prevent postoperative respiratory depression, and respiratory volume monitor monitoring may be useful to optimize care.

INTRODUCTION

Wounding patterns in contemporary warfare have changed, with recent operations resulting in a significant number of military personnel suffering severe perineal injuries, pelvic fractures, and lower extremity amputations.[1–5] Pelviperineal injuries have become the "signature" injury pattern in Afghanistan, and these injuries are commonly sustained as the result of blast mechanisms, particularly from improvised explosive devices.[1,2,6] Although several reports exist regarding the surgical management of these complex injuries,[1,6–8] less is known about how to select the optimal anesthetic technique and how to safely manage these patients throughout the painful perioperative period.

Major orthopedic surgery on the lower extremities has historically involved the use of general anesthesia (GA), in which central nervous system depression is induced via administration of volatile or intravenous anesthetics. With improvements in anesthetic technique and orthopedic surgical procedure over the past 20 years, regional anesthesia has become a viable alternative, typically consisting of a neuraxial blockade, in which drugs are injected into the epidural space (epidural anesthesia) or subarachnoid space (spinal anesthesia [SA]).

This shift toward regional technique has been driven in part by a growing body of research aimed at assessing the comparative effectiveness of general and neuraxial anesthesia in surgical care. In a broad sense, these studies have associated neuraxial anesthesia with improved outcomes and reduced postoperative complications, in both the short term and long term, and across a variety of procedures and patient types.[9–14] Particular focus has been given to anesthesia technique in joint replacement surgery. Large-scale randomized trials and meta-analyses of total hip and knee arthroplasty data report advantages for neuraxial anesthesia in mortality, resource utilization and incidence of major complications such as deep vein thrombosis, pulmonary embolism, and myocardial infarction.[9,11–13] There have also been suggestions of reduced postoperative pain, opioid consumption, and incidence of opioid-related effects, including nausea and respiratory depression.[9,13]

A major variable in evaluating the risk and physiological impact of anesthesia is the administration of opioids for the management of pain, both intraoperatively and postoperatively. In combination with the effects of surgical insult and anesthesia itself, which can lead to postoperative respiratory depression (PORD), opioids are known to independently decrease respiratory drive and alter normal rhythm generation, leading to a variant of PORD described as

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opioid-induced respiratory depression (OIRD).[15] It is estimated that 50% of postoperative respiratory failure events involve administration of opioid analgesia.[16]

Respiratory compromise is a significant patient safety concern in the postanesthesia care unit (PACU), intensive care unit, general hospital floor, and en route aeromedical care environment. OIRD and PORD present a well-recognized threat to respiratory competence after surgery, and can lead to serious adverse events. Management of respiratory status is complicated by the potential manifestation of obstructed breathing and the confounding effects of supplemental oxygen use. When considering military casualties, one must also consider the setting under which surgery is performed and conditions likely postoperatively. Care of military casualties requires not only assessment of patient, injury, and setting, but also of the consequences of care decisions on other organ systems. The optimal perioperative anesthetic and analgesic care remains unclear.

There is a need for adequate, continuous respiratory monitoring in these settings to address these concerns. Current monitoring in nonintubated patients typically consists of pulse oximetry, respiratory rate (RR) monitoring, and, rarely, capnography; however, these offer, at best, late indications of significant respiratory depression.[17–20] Recent data show that a noninvasive respiratory volume monitor (RVM) was able to detect respiratory depression in advance of a pulse oximeter recorded True Desaturation event by 12.8 ± 2.8 minutes from the immediately preceding respiratory depressive event. In many cases, there were repeated respiratory depressive events starting an average of 71.4 ± 16.5 minutes before each true desaturation.

In order to objectively identify and quantify the effects of OIRD and PORD after anesthesia and address the new American Society of Anesthesiologists practice guidelines for monitoring patients receiving neuraxial anesthesia, objective measurement of the depth of ventilation is needed,[21] which can currently be accomplished continuously and objectively only by the aforementioned noninvasive RVM, which provides digital volume traces and accurately reports minute ventilation (MV), tidal volume (TV), and RR in nonintubated patients.[22,23] Continuous MV measurements provide a direct, real-time assessment of respiratory function, allowing for an objective and quantitative analysis of respiratory depression in the PACU and on the general hospital floor.

Using the RVM, the objective in this study was to directly compare incidence of OIRD and/or PORD in the PACU in orthopedic surgery patients receiving general versus neuraxial anesthesia. We hypothesized that the incidence of respiratory depression in the PACU among patients receiving GA would be significantly higher than in those receiving neuraxial anesthesia, given that both groups are treated under the same pain management protocols postoperatively. We also hypothesized that the results from this investigation would have important implications for the prevention of perioperative complications in service members requiring surgery for pelvi-perineal and complex lower limb injuries.

METHODS

Subjects

This study was approved by the Partners Institutional Review Board (Boston, Massachusetts). All subjects provided written informed consent before enrolment. Inclusion criteria were English-speaking males and females 18 to 99 years of age undergoing elective orthopedic surgery at Massachusetts General Hospital. Surgeries performed in positions other than lithotomy or supine were excluded, as well as subjects undergoing hip arthroplasty in a position other than left lateral (electrodes need to be placed on the chest and right side). All pregnant females were excluded, as well as patients with pacemakers or other electronic implantable devices. Medical history and basic demographic data were obtained from all subjects. Vital signs (BP, HR, RR, and O_{-2} saturation) were recorded throughout the study, along with the time, dosage, and route of administered medications.

Primary Protocol

A bioimpedance-based RVM (RVM, ExSpiron, Respiratory Motion, Inc., Waltham, Massachusetts) was used to collect digital respiratory data from 173 patients undergoing elective total hip or total knee arthroplasty/replacement surgery (mean: 67.3, 44–89 years of age; mean body mass index [BMI]: 30, 19–49 kg/m^2). The RVM PadSet electrodes were placed at the sternal notch, xiphoid, and right mid-axillary line. This placement is consistent with implementation protocols, for which strong correlations (0.96 ± 0.16, mean ± 95% confidence interval for regular and erratic breathing) and high accuracy (average MV and TV errors less than 10% and average RR error less than 2%) between RVM and spirometric measurements have been demonstrated.[22]

Data were collected beginning in preoperative holding, continuing throughout surgery and for the length of the PACU stay. MV, TV, and RR measurements were calculated every 5 seconds for the duration of this period from 30-second segments collected in a sliding window. Care providers were blinded to RVM data. Being an observational study, the choice of anesthetic and PACU management were at the sole discretion of the patient, anesthesiology team, and PACU staff. Monitoring was discontinued at PACU discharge.

Intraoperatively, all patients were managed under either GA or neuraxial (spinal) anesthesia (SA), based on patient preference after consultation with clinical staff. Both anesthetic techniques were initiated intraoperatively, immediately before surgery. Patients undergoing GA were given various doses of a paralytic (rocuronium, vecuronium, or cisatracurium), in conjunction with sedatives (midazolam and propofol), and opioids (fentanyl and hydromorphone). Patients undergoing SA almost exclusively received an

TABLE I. Intraoperative Drug Regimens by Anesthesia Protocol in a Cohort of Patients Reporting for Elective Joint Replacement Surgery.

General Anesthesia	43			
Standard Protocol			Mean Dose	Standard Deviation
Paralytic (One):	37	0.86		
Rocuronium	22	0.512	75.0 mg	29.5
Cisatracurium	8	0.186	13.3 mg	5
Vecuronium	7	0.163	10.4 mg	5
LMA Insertion (No Paralytic)	4	0.093		
Paralytic Not Specified	2			
Inhalation Agent (One):	40	0.930		
Sevoflurane	33	0.767		
Isoflurane	7	0.163		
Reversal Agent:	31	0.721		
Neostigmine	31	0.721	3.10 mg	1.15
Femoral Block:	14	0.326	20 mL	0
Ropivacaine 0.2%	12	0.279	20 mL	0
Bupivacaine 0.25%	2	0.047		
Sedatives (One or More):	43	1		
Midazolam	39	0.907	2.23 mg	0.83
Propofol (Total)	43	1.000	289 mg	302
Bolus	43	1.000	212 mg	74.5
Infusion	3	0.070	1098 mg	296
Ketamine	2	0.047		
Opioids (One or More):	43	1		
Fentanyl	43	1	221 mcg	67.3
Hydromorphone	38	0.884	1.29 mg	0.94
Meperidine	1	0.023		
Remifentanil	1	0.023		
Morphine	1	0.023		
Other:				
Haloperidol	20	0.465	1.1 mg	0.3
Succinylcholine	13	0.302	100 mg	30.4
Spinal Anesthesia	130			
Standard Protocol			Mean Dose	Standard Deviation
Spinal:				
Bupivacaine 0.5% (ITHEC)	125	0.962	3.07 mL	1.58
Bupivacaine 0.75% (ITHEC)	2	0.015		
Spinal Dose Not Specified	3			
No Inhalation Agent Used				
No Reversal Agents Used				
Femoral Block:	69	0.531		
Ropivacaine 0.2%	50	0.385	20 mL	0
Bupivacaine 0.25%	19	0.146	19.7 mL	1
Sedatives (One or More):	127	0.977		
Midazolam	123	0.946	2.59 mg	1.37
Propofol (Total)	87	0.669	290 mg	191
Bolus	26	0.2	31.9 mg	29
Infusion	80	0.615	301 mg	183
Ketamine	1	0.008		
Opioids (One or More)	114	0.877		
Fentanyl	113	0.869	98.8 mcg	55
Hydromorphone	11	0.085	0.45 mg	0.1
Meperidine	2	0.015		
Dexmedetomidine	1	0.008		
Other:				
Haloperidol	10	0.077	2.55 mg	3.54
Succinylcholine	0	0		

TABLE II. Definitions of Terms and Their Abbreviations

Abbreviation	Term	Definition
SA	Spinal Anesthesia	Delivery of local anesthetic via fine needle into the subarachnoid space
GA	General Anesthesia	Delivery of anesthetics both intravenously and via inhalation
$MV_{MEASURED}$	Measured Minute Ventilation	The real-time MV reported by the RVM
MV_{PRED}	Predicted Minute Ventilation	Expected MV Under Baseline Conditions of Quiet Respiration in awake, non-intubated patients
% MV_{PRED}	Percent Predicted Minute Ventilation	In percentage, the degree of deviation $MV_{MEASURED}$ is from MV_{PRED}
LMV	Low Minute Ventilation	MV <40% MV_{PRED}
OIRD	Opioid-Induced Respiratory Depression	LMV sustained for at least 2 minutes within the 15 minutes following an initial opioid dose in the PACU
PORD	Post-Operative Respiratory Depression	LMV sustained over 10 minutes at any point in the PACU in patients receiving no post-operative opioids
	Low Minute Ventilation at Discharge	LMV for at least 10 minutes during the last 30 minutes prior to discharge
POA	PostOperative Apnea	More than five apnoeic or hypopnoeic events per hour over their entire PACU stay
	Hypopnea	A period of at least thirty seconds with greater than 50% reduction in TV from the baseline TV observed during ventilator synchronization
	Apnea	A period of at least ten seconds with no detected breaths

intrathecal dose of bupivacaine 0.5% (1–4 mL), typically supplemented with midazolam, propofol, and fentanyl, but in lower dosages than those used during GA. Additional intraoperative opioids-like hydromorphone were rarely used in spinal cases. Patients undergoing knee surgery typically also received a femoral nerve block, consisting of either 20 mL ropivacaine 0.2% or 20 mL bupivacaine 0.25%, administered in preoperative holding. A detailed summary of relevant medications used intraoperatively, with frequency and typical dosage, is reported in Table I.

For the purposes of this study, we established thresholds for marginal MV and defined respiratory depression in the PACU in a patient-specific manner. A standard formula based on the DuBois formula for body surface area[24] was used to calculate a patient's predicted MV (MV_{PRED}), sufficient to maintain blood oxygen, and carbon dioxide levels under baseline conditions. Previous work suggests that MV below 80% of MV_{PRED} places a patient at risk for a negative response to additional opioids, and identifies MV below 40% of MV_{PRED} as low MV (LMV).[25] This is similar to the ARDSnet volume criteria for extubation,[26] and was considered a potential threat to patient safety if sustained. MV, as reported continuously by the RVM ($MV_{MEASURED}$), was calculated as a percentage of the patient's MV_{PRED} ($MV_{MEASURED}/MV_{PRED} \times 100\%$) and used to assess adequacy of ventilation according to this rubric.

To begin to define clinically relevant thresholds for patient evaluation, we examined significant drops in MV below the LMV threshold under a variety of patient situations. Specifically, among patients receiving postoperative opioids, those showing LMV (MV <40% MV_{PRED}) sustained for at least 2 minutes within the 15 minutes following an initial PCA opioid dose were defined as experiencing OIRD.[25] Patients receiving no postoperative opioids but showing LMV sustained over 10 minutes at any point in their PACU stay were considered to be experiencing PORD.[25] Finally, in order to evaluate patient respiratory status at the time of PACU discharge, patients showing LMV for at least 10 minutes during the last 30 minutes before discharge were designated as experiencing a LMV at discharge, regardless of whether opioids were administered.[25] This designation served as an assessment of patient respiratory safety at discharge from the PACU. Patients with LMV at discharge may require RVM or other monitoring as they are transferred to the floor. All terms and their abbreviations are summarized in Table II.

A posthoc analysis examined incidence of postoperative apnea (POA) in the cohort. Apnea was defined as a period of at least 10 seconds with no detected breaths. Hypopnea was defined as a period of at least 30 seconds with greater than 50% reduction in TV from the baseline TV observed during ventilator synchronization. Patients were classified as demonstrating POA if they averaged more than five apneic or hypopneic events per hour over their entire PACU stay.

Statistical analyses

The main goal of this study was to compare incidence of respiratory depression between patients receiving GA (GA, $n = 43$, 25% of the cohort) and those receiving SA (SA, $n = 130$, 75% of the cohort). We hypothesized that the incidence of respiratory depression would be significantly higher among GA patients. Given that opioid use in postoperative pain management has been associated with an increased risk of respiratory depression, it was necessary to account for systematic differences in opioid intake between the GA and SA groups. To accomplish this, patients in both the GA and SA groups were separated according to whether or not they received opioids in the PACU. Analyses were performed in the subgroups (nonopioid and opioid) as well as across the combined cohort.

The incidences of OIRD, PORD, LMV at discharge, and POA across different groups were compared using two-tailed Fisher's Exact Test with the hypothesis that there would be a significant difference in incidence across groups.

The incidences across combined data from multiple groups were also compared with a two-tailed Fisher Exact Test, which was possible given that the groups were independent (nonoverlapping).[27] Multi-factor analysis of variance was used to evaluate the effects of demographics (age, height, weight, BMI, and sex) across groups. All analyses were performed in Matlab 2012b (Mathworks, Natick, Massachusetts) and results were considered significant at $p < 0.05$.

RESULTS

Opioid-Induced Respiratory Depression

Of the 173 patients, 92 received opioids in the PACU (53.2%, Table I). Consistent with previous work,[28,29] a significantly higher fraction of GA patients received opioids in the PACU than SA patients (GA: 30 of 43, 69.8%; SA: 62 of 130, 47.7%, $p < 0.05$, one-tailed Fisher's exact test). Among patients who received PACU opioids, the mean morphine milligram equivalent received in the PACU was significantly higher in GA patients compared to SA patients (GA: 7.68 ± 0.98; SA: 3.80 ± 0.54, $p < 0.001$).

Of the 92 patients receiving opioids in the PACU, 30 demonstrated OIRD (32.6%). These 30 patients comprised 24 of the 62 SA patients receiving opioids ($SA^{+opioid}$) and 6 of the 30 GA patients receiving opioids ($GA^{+opioid}$). Thus, despite lower opioid intake on average, $SA^{+opioid}$ patients showed a slightly higher incidence of OIRD than $GA^{+opioid}$ patients (SA: 38.7%, GA: 20.0%, $p = 0.098$, two-tailed Fisher's Exact Test), as shown in Figure 1A. No significant difference was observed in demographics (age, height, weight, BMI, and sex) between the $SA^{+opioid}$ and $GA^{+opioid}$ subgroups ($p > 0.05$ for all factors).

Postoperative Respiratory Depression

In patients who did not receive opioids, we used sustained LMV to define PORD. Incidence of PORD in patients not receiving opioids resembled that of OIRD in patients receiving opioids in both the collective cohort and in distribution across the GA/SA subgroups. Of 81 patients not receiving opioids in the PACU, 24 demonstrated PORD (29.6%) at some time during their PACU stay. This group comprised 24 of the 68 SA nonopioid patients ($SA^{-opioid}$) and 0 of the 13 GA nonopioid patients ($GA^{-opioid}$). Incidence of PORD in $SA^{-opioid}$ patients was significantly higher than that in $GA^{-opioid}$ patients (SA: 35.3%, GA: 0.0%, $p = 0.008$), as shown in Figure 1A. Once again, there was no significant difference in demographics between the two sub-groups ($p > 0.05$ for all factors).

Combining the 2 independent opioid-stratified subpopulations allowed us to compare the incidence of either form of respiratory depression (OIRD or PORD) in the PACU, regardless of opioid administration. We found that in the combined SA group (i.e., $SA^{+opioid}$ and $SA^{-opioid}$), incidence of respiratory depression was significantly higher than in the combined GA group ($GA^{+opioid}$ and $GA^{-opioid}$), as shown in Figure 1B (SA: 48/130, 36.9%, GA: 6/43, 14.0%, $p = 0.004$).

Assessment of MV at Discharge

Patient ventilation status was assessed at PACU discharge, with patients showing LMV for more than 10 minutes of the 30 minutes before discharge designated as having an LMV discharge. This designation is intended to signify a greater risk for respiratory complications in a subsequent unit that would likely have reduced patient monitoring. Cohorts were initially subdivided according to whether or not opioids were administered postoperatively. Of 92 opioid patients, 13 patients showed LMV at discharge (14.1%). These 13 comprised 5/30 $GA^{+opioid}$ patients and 8/62 $SA^{+opioid}$ patients. Thus, among patients receiving opioids, the frequency of LMV discharge was marginally higher in GA patients (GA: 16.7%, SA: 12.9%, $p = 0.751$), as shown in Figure 2A.

Among nonopioid patients, 11 of 81 patients displayed LMV at discharge (13.6%). All 11 of these were among the 68 $SA^{-opioid}$ patients. None of the 13 $GA^{-opioid}$ patients were found to exhibit LMV at discharge. Thus, among nonopioid patients, the frequency of LMV at discharge was marginally higher in SA patients (GA: 0.0%, SA: 16.2%, $p = 0.197$), as shown in Figure 2A.

As with the respiratory depression analysis, LMV at discharge was also examined across the combined cohort including opioid and nonopioid patients. We found comparable rates of LMV at discharge between the combined SA group (i.e., $SA^{+opioid}$ and $SA^{-opioid}$) and the combined GA group ($GA^{+opioid}$ and $GA^{-opioid}$), with marginally higher rates in SA patients, as shown in Figure 2B (SA: 14.6%, 19/130, GA: 11.6%, 5/43, $p = 0.800$).

Postoperative Apnea

POA was found significantly more frequently in patients receiving opioids, with 25 of 92 patients receiving PACU opioids showing POA versus 12 of 81 nonopioid patients (Figure 3, 27.2% vs 14.8%, $p < 0.05$). This suggests that opioid analgesia may be a risk factor for apnea. Further analysis revealed that the difference in POA incidence was driven primarily by differences in GA patients, and in particular, by an exceptionally high incidence rate among GA patients receiving opioids. Of 30 $GA^{+opioid}$ patients 13 demonstrated POA in the PACU, as compared to 12 of 62 $SA^{+opioid}$ patients (43.3% vs 19.4%, $p = 0.0237$). For comparison 0 of 13 $GA^{-opioid}$ patients showed POA, as compared to 12 of 68 $SA^{-opioid}$ patients (0% vs 17.6%, $p = 0.198$).

DISCUSSION

The distribution of injuries in contemporary warfare has changed compared to that seen in previous conventional conflicts.[3,4,6,8,30] New wounding patterns, including a greater proportion of severe pelvi-perineal and lower extremity

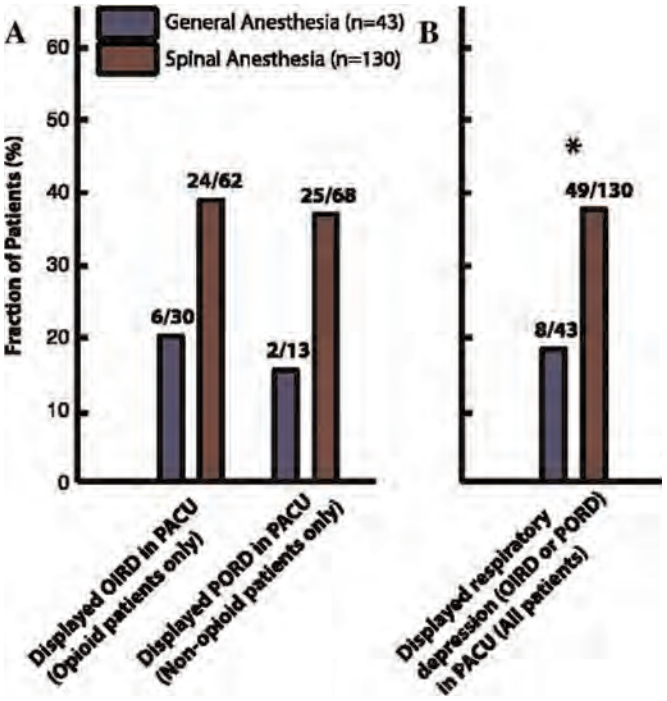

FIGURE 1. Postoperative respiratory compromise in patients receiving joint replacement surgery: general and spinal anesthesia. (A) A novel, bioimpedance-based respiratory volume monitor (RVM) was used to track minute ventilation (MV) during and after surgery in patients presenting for total hip or knee arthroplasty. Patients receiving opioids in the post-anesthesia care unit (PACU) and showing minute ventilation (MV) below 40% of predicted minute ventilation (MVPRED)- for more than 2 minutes within the 15 minutes following initial opioid administration were defined as experiencing opioid-induced respiratory depression (OIRD). Patients not receiving opioids and showing MV below 40% MVPRED over a period of 10 minutes in the PACU were defined as experiencing post-operative respiratory depression (PORD). OIRD (in opioid patients) showed marginally higher incidence in patients receiving spinal anesthesia. PORD (in nonopioid patients) showed significantly higher incidence in patients receiving spinal anesthesia ($p = 0.008$). (B) A combined analysis looked at incidence of either form of respiratory depression in the PACU across both opioid and nonopioid patients. Patients receiving spinal anesthesia were found to have significantly higher incidence of respiratory depression than patients receiving general anesthesia ($p = 0.004$).

musculoskeletal injuries, have led joint medical providers to consider novel methods for ensuring the safety of combat casualties throughout the continuum of care.[31] This work expands upon previous studies that have shown that respiratory depression, unsafe respiratory patterns, and risk for hypoxemia may be detected early with a noninvasive RVM. Although the RVM has not yet been implemented directly in the military environment, the results from this study population suggest that developing a protocol for generic use of SA may not have the safety advantage anticipated for patients undergoing lower body surgery due to traumatic wounds. The study also strongly suggests a role for the RVM as a means to individualize care regardless of anesthetic technique. The RVM data permits rapid recognition and management of postoperative complications in the contemporary combat casualty environment, improving overall outcomes.

The consensus in recent years is that neuraxial anesthesia is by and large a safer and preferred alternative to GA. There is no context for which this is more accepted than major orthopedic surgery. In particular, major surgeries of the hip and knee have been the focus of a series of large-scale trials and meta-analyses, with the broad conclusion that SA is associated with reduced mortality and reduced complications postoperatively.[12–14] However, recently published practice guidelines by the American Society of Anesthesiologists note that, while safer overall, neuraxial anesthesia may place patients at additional risk for OIRD. Therefore, it is recommended that all patients receiving neuraxial anesthesia should be monitored for "adequacy of ventilation (e.g., RR, depth of respiration [assessed without disturbing a sleeping patient])".[21]

As discussed at length by Gulur et al. the limitations of such expansive research studies are numerous and inevitable.[32] Results tend to be conflicting, with similar large-scale studies reporting no statistical difference in outcomes from general versus neuraxial anesthesia.[32,33] Surgical outcomes are also influenced by a wide variety of confounding factors, which can often go unaccounted for in such work. These

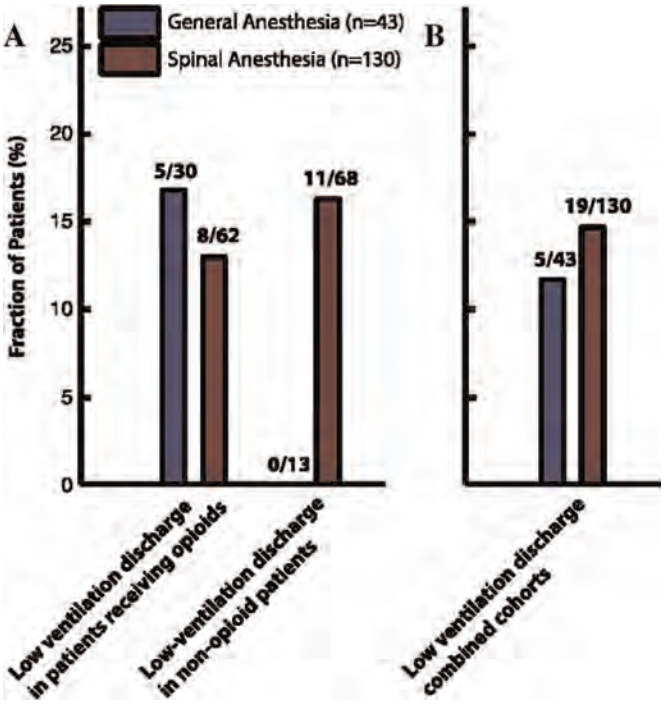

FIGURE 2. Low minute ventilation (LMV) at post-anesthesia care unit (PACU) discharge in patients receiving general anesthesia versus spinal anesthesia. Patients showing MV below 40% MV_{PRED} for 10 minutes during their final 30 minutes in the PACU were defined as exhibiting LMV at discharge. (A) In the cohort receiving postoperative opioids, frequency of LMV discharge was found to be marginally high in general anesthesia (GA) patients than spinal anesthesia (SA) patients, but not statistically different. The opposite was true of the nonopioid cohort. Neither result was statistically significant (Fisher's Exact Test, $p > 0.05$). Zero of 13 GA patients receiving no postoperative opioids exhibited LMV at discharge. (B) A combined analysis of opioid and nonopioid patients showed comparable frequence of LMV discharge between GA and SA cohorts.

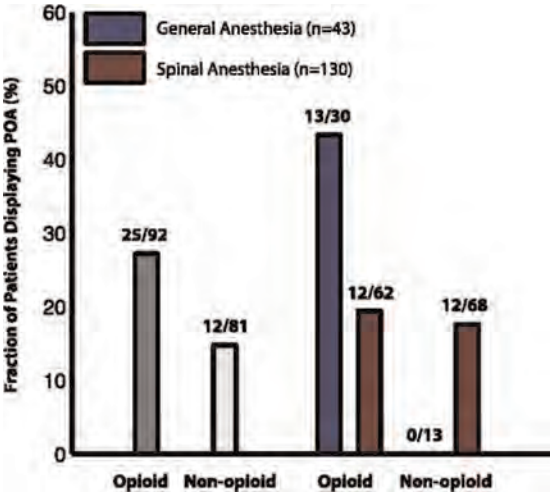

FIGURE 3. Postoperative apnea by anesthesia and opioid use in patients receiving joint replacement surgery: a posthoe analysis. A novel, bio-impedance-based respiratory volume monitor was used to track minute ventilation during and after surgery in patients presenting for total hip or knee arthroplasty. Apneic events were defined as periods of at least 10 seconds with no detected breath. Patients averaging more than five apneic events per hour over the course of their stay in the post-anesthesia care unit (PACU) were defined as demonstrating post-operative apnea (POA). Higher rates of POA were observed in patients receiving PACU opioids than in nonopioid patients ($p = 0.063$). This difference was driven by POA rates in general anesthesia (GA) patients receiving opioids. GA opioid patients showed significantly higher incidence of POA (13/30, 43.3%) than either spinal anesthesia (SA) opioid patients (12/62, 19.4%) ($p = 0.024$) or GA nonopioid patients (0/13, 0%) ($p = 0.004$). Incidence rates were similar among SA opioid and SA nonopioid patients.

may largely explain the observed gaps in mortality and morbidity, which appear to be closing as standards of care continue to improve.[29] Meta-analyses that reach back to cases 10 and 15 years ago to support their conclusions may well be misrepresenting comparative outcomes under current practice. Lastly, it is valuable to recognize that in the context of a specific surgical protocol and individual patient risk factors, 1 anesthetic technique can present clear advantages over the other. To reduce the question of technique to a sweeping, binary conclusion is perhaps to discount the complexity of anesthesia.

Our findings in the present study speak to this point. We sought to evaluate the incidence of respiratory depression in the PACU in relation to primary anesthetic technique, general or neuraxial. To accomplish this, we used novel RVM technology to directly monitor MV in a cohort of patients presenting for total hip and knee arthroplasty procedures. Consistent with general recommendation to patients that neuraxial anesthesia is the safer of the two available techniques, approximately three in four patients preferred SA for their joint replacement procedure after professional consultation.

Our results, however, suggest that with respect to immediate postoperative respiratory compromise, SA may be the higher-risk alternative. Patients receiving opioids in the PACU after SA showed a substantially higher rate of OIRD onset (38.7%) than their GA counterparts (20.0%). Although not quite demonstrating a statistically significant advantage for GA, this result certainly challenges the blanket notion that SA corresponds to reduced complications postoperatively. This higher rate was observed in spite of the SA cohort receiving consistently lower dosages of intraoperative opioids and sedatives than the general cohort, and having a markedly lower mean morphine equivalence for opioids received in the PACU as well (SA: 3.80, GA: 7.67). In other words, GA patients responding to opioid analgesia appear to maintain ventilatory function at least as well, if not better than SA patients, despite receiving substantially higher opioid dosing both during and after surgery.

These OIRD results are mirrored by our examination of PORD incidence in the nonopioid division of the cohort. SA nonopioid patients show a noticeably higher rate of PORD (36.8%) than GA nonopioid patients (15.4%). This finding further implicates SA as a factor in postoperative respiratory compromise.

In light of similar results in the OIRD and PORD analyses, we attempted to increase the statistical power of our analysis by implementing a combined Fisher's Exact Test analyzing incidence of any form of respiratory depression across the combined +opioid/−opioid cohort. As shown in Figure 1B, we found that incidence of respiratory depression was in fact significantly higher in SA patients than in GA patients for the combined cohort (37.7% vs. 18.6%, $p < 0.025$). Keeping in mind that opioid intake was markedly higher in GA patients both intraoperatively and postoperatively, this result is strongly suggestive of an association between SA and an increased risk for early PORD.

Our analysis of respiratory competence at patient discharge from the PACU (Figure 2) was less conclusive, with little difference observed between GA and SA patient ventilation in either opioid-subgroup or combination analysis. Still, among GA patients not receiving opioids, not one patient showed LMV at discharge ($GA^{-opioid}$: 0/11 LMV at discharge, 0%), giving this group a slight advantage over its SA counterpart ($SA^{-opioid}$: 11/67 LMV at discharge, 16.4%). Collectively, our findings suggest that SA provided no advantage to GA with respect to postoperative respiratory compromise in the PACU after major orthopedic surgery. Although surprising, the observation of a higher incidence of respiratory depression among SA patients has potential explanations. Pain is known to act as a physiological antagonist of the respiratory depressant effects of opioid analgesics.[34] It is possible that by reducing pain stimulation relative to GA, patients with SA are more vulnerable to OIRD.

Our results also speak to the dangers of stratifying patient respiratory risk postoperatively according to any generalized set of assumptions. Respiratory compromise is a major concern for PACU staff. Patients may have residual anesthetic, neural muscular blockade, hypercarbia, hypoxemia, airway obstruction, reduced RR, reduced TV, reduced

MV, and varying degrees of sedation. These risks are further compounded by the effects of surgical insult, the use of opioid analgesia, and potential manifestations of latent respiratory risk factors such as undiagnosed obstructive sleep apnea.

In the context of such a complex threat to patient safety, it may be tempting to stratify patient risk for respiratory complications according to anesthesia type, BMI, comorbidities, or any number of other factors, in an attempt to compartmentalize the attention of caregivers. However, as the results of this study show, patterns of respiratory compromise can be unpredictable in the PACU, at times defying traditionally accepted indicators of risk. Even in what are considered to be the safest of patient populations, preventable respiratory complications may arise, leading to increased morbidity, and cost of care. Our findings suggest that there is a need for careful, individual monitoring of ventilation in all postoperative patients, regardless of perceived risk. This is consistent with growing demand for continuous respiratory monitoring in postoperative care over the last 5 years.

Disordered or obstructed breathing, as we have mentioned, is a significant contributor to respiratory risk in the PACU. In the interest of including this phenomenon in the scope of our discussion of respiratory compromise, we were able to conduct a posthoc analysis in which we evaluated the incidence of what we termed POA in patients receiving general and SA. Patients were classified as demonstrating POA if they averaged more than five apneic or hypopneic events per hour over their entire PACU stay. This definition was intentionally blind to cause, as apnea can manifest postoperatively for a variety of reasons, and in the general clinical environment it is difficult if not impossible to identify which is responsible in a given patient.

Here we see that GA patients receiving opioids show a dramatically higher rate of POA than SA patients receiving opioids or GA patients receiving no opioids, whereas POA rates in SA patients are similar regardless of whether opioids were given. This is perhaps suggestive of a synergistic effect between GA and opioid analgesia in eliciting apnea per se. However, the result may also be skewed by the higher opioid dosages among GA patients in this cohort. Further research is required to investigate the potentially interactive effects of anesthesia and opioid analgesia on breathing obstruction. As an aside, it is interesting to note that among GA patients receiving no postoperative opioids, not one patient had an incidence of POA or showed LMV at PACU discharge. The small sample size for such patients (n = 11) limits any conclusion, but this subgroup appears tentatively to be the least prone to respiratory compromise, and further research may be warranted.

This study was limited by an inability to continue monitoring on the hospital floor after discharge from the PACU, which would allow the assessment of respiratory status over a longer period of time than just the first 2 to 5 hours after surgery. Another major limitation of this study was the inability to follow these patients on the floor and determine the impact of a LMV at PACU discharge. In addition, this study was limited to a specific, elective surgical population, and consequently the distributions of age and ethnicity were not completely representative of the general populace.

CONCLUSION

RVM is a novel monitoring modality that was used to identify patients with respiratory depression following elective major lower extremity orthopedic surgery. A surprising finding was a greater association of respiratory depression in patients receiving SA compared to patients who received GA, in the context of recent work where SA was found to be generally associated with reduced complications. While these findings highlight a previously unrecognized potential risk of SA, this study also demonstrates the value of postoperative respiratory volume monitoring. We propose future studies using an RVM to detect and report unsafe respiratory status in combat casualties with major pelvi-perineal and/or lower extremity traumatic injuries.

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