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COMMENTARY

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The problem of postoperative respiratory depression

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Abstract

What is known and Objective: Postsurgical recovery is influenced by multiple pre-, intra- and perioperative pharmacotherapeutic interventions, including the administration of medications that can induce respiratory depression postoperatively. We present a succinct overview of the topic, including the nature and magnitude of the problem, contributing factors, current limited options, and potential novel therapeutic approach.

Comment: Pre-, intra- and perioperative medications are commonly administered for anxiety, anaesthesia, muscle relaxation and pain relief among other reasons. Several of the medications alone or in joint-action can be additive or synergistic producing respiratory depression. Given the large number of surgical procedures that are performed each year, even a small percentage of postoperative respiratory complications translates into a large number of affected patients.

What is new and Conclusion: Due to the large number of surgeries performed each year, and the variety of medications used before, during, and after surgery, the occurrence of postoperative respiratory depression is surprisingly common. It is a significant medical problem and burden on hospital resources. There is a need for new strategies to prevent and treat the acute and collateral problems associated with postoperative respiratory depression.

KEYWORDS
FTR, PACU, PODC, postoperative, respiratory depression, surgical complications

1 | WHAT IS KNOWN AND OBJECTIVE

Except for the downturn due to COVID, the number of surgical procedures continues to increase each year in the United States and internationally.[1] For example, ten years ago, there were 51.4 million inpatient surgical procedures performed in nonfederal hospitals in the United States[1]; last year, there were more than 125 million, with an estimated increase to 144 million by 2023.[2] During the same period, ambulatory centre surgical procedures increased by 300 per cent.[1] Worldwide, the increase was from 234 million to 313 million.[1,3] With such large numbers, even a few per cent of postoperative respiratory complications (PORC) can be a significant number. And because surgery has a profound effect on multiple organ systems, including the respiratory system, even "simple" surgeries can cause substantial respiratory dysfunction.

Generally, PORC are due to either respiratory muscle dysfunction or primary airway disease.[4] Either can occur due to changes in the ventilatory drive. Surgery predisposes to PORC in several ways. Just the act of lying flat reduces functional residual capacity (the volume of air in the lungs at the end of passive expiration) by as much as 1.5 litres.[5] It decreases even further during surgery.[6] In addition, the type of surgery influences the impact on respiratory function. For example, thoracoabdominal surgery can decrease functional residual capacity by 30%, which can take a week or more to return to normal.[6] Likewise, the anaesthetic agent can make a difference. For example, halothane can dramatically diminish responses to hypoxia and hypercapnia.[7]

Oedema occurs in about 2% of postoperative patients; and atelectasis occurs even more frequently.[8] Atelectasis (collapse of part of, or the entire, lung) occurs soon after the start of surgery and can persist into the postoperative period.[5] Mild PORC include sore throat, cough and dyspnoea. Severe complications include a need for prolonged mechanical ventilation, life-threatening hypoxia, sepsis, prolonged postsurgical neuromuscular blockade, pneumonia and cardiorespiratory arrest.[5,9-11]

The most serious PORC are respiratory failure, a patient's inability to respond appropriately "on a moment to moment basis" to hypercapnia or hypoxia.[12] One of the early and more serious markers for persistent respiratory failure is re-intubation.[13] Therefore, risk of re-intubation has become a focus as a quality checkpoint, and risk screens have been developed to assess this potentiality.[13] The Agency for Healthcare Research and Quality, among other organizations, has recommended risk assessment for PORF as well as for failure-to-rescue (FTR; when a progressive deterioration in a patient's condition is not recognized and prevented, and death ensues).[14] PORF has been said to be the fourth most common patient safety event.[15] Pneumonia, failure to wean, and postextubation respiratory failure are second in frequency only to wound infection.[16] Unfortunately, "no single measurement technique can adequately assess the extent of respiratory depression."[12]

In the United States, approximately 2.5 million patients suffer from PORC complications every year.[17] The consequence is greater patient suffering, longer hospital stays, higher costs and even greater mortality.[18-21] It was estimated that in 2013, respiratory depression due to opioids alone resulted in an additional mean length of stay of 5 hospital days and up to $10,000 in additional hospital costs in the United States.[22] Very concerning, there are data to suggest that PORC even extend beyond the postanaesthesia care unit (PACU) – into the postdischarge period.[23] For example, PORC in patients undergoing abdominal surgery are associated with an approximately 10-fold increase in 30-d mortality.[24]

Unfortunately, as mentioned above, PORC are fairly common, especially following surgeries that require hospitalization. The incidence of PORC in general surgery is estimated to be between 0.3 and 17%,[25,26] overall; between 7 and 14% of patients undergoing elective orthopaedic surgery, and about 12% of patients after hysterectomy.[18,27] In a study of liver transplantation patients, postoperative respiratory failure (PORF) occurred in 36.0% of cases.[28] Most (about 88%) postoperative complications occur within 24 hours of surgery, but a significant number are delayed.[29]

2 | COMMENT

2.1 | The PACU

It is inevitable that surgical complications occur in hospitals. However, the quality and timelines of response varies widely.[30] For example, pulse oximetry is used routinely in this setting, but "it is not a substitute for close observation by trained personnel."[31] Investigations show similar results, as observed by the following statement, "these investigations highlight the lack of adequate patient monitoring on surgical wards."[32]

For these reasons, the PACU has become a vital part of almost all hospitals, ambulatory care centres and surgical suites for postoperative care, and provides more intensive care for high-risk surgical patients.[33] These units have greatly improved postsurgical outcomes, but consistency is still an issue. There is significant variation in identification and classification of respiratory complications, partly because anaesthesia practice and patient monitoring are not homogeneous,[26] and partly because the window for classification can differ: from time after admission to the PACU, to days following surgery, to discharge from the PACU. Therefore, the true incidence is difficult to quantify accurately. Due to such a situation, several organizations have proposed continuous monitoring of all postoperative patients. Although this has been shown to improve patient outcomes, other aspects of the process can lead to poor outcomes, for example alarm-fatigue and ICU capacity strain.[34]

2.2 | Failure-to-rescue

FTR as defined above is "hospital deaths after adverse events."[35] Since FTR is usually deemed preventable, this metric has been used as a measure of a hospital's quality of care: "good hospitals" will rescue patients by identifying complications quicker and instituting more timely appropriate aggressive treatment.[36] Some PACUs perform better, when assessed by this metric, than do other PACUs.[37] Since detecting a crisis and instituting preventative measures is clearly the optimal course, defining patients who are at risk is critical.[37] Toward this end, two broad ways of reducing FTR have been highlighted: (1) timely response (the prompt recognition of complications) and (2) appropriate response (the correct management and treatment of the complication).[38] Obviously, PORF is a significant contributor to FTR. Unfortunately, attempts at early recognition of patients who may potentially undergo either respiratory or cardiac arrest have not been fully successful, in spite of the fact that patients will show signs of deterioration even 6 – 8 hours before such events.[39] Obviously, the earlier these patients are identified, the better.[40]

2.3 | Predictable?

Due to the seriousness of the complications and their outcomes, numerous attempts at screening have been developed. Although different in details, they share commonalities. Congestive heart failure, obstructive sleep apnoea, chronic obstructive pulmonary disease, obesity, preoperative anaemia, malnutrition, and an American Society of Anaesthesiology ≥ 3 have all been shown to correlate with PORF.[41] Serum albumin is one of the strongest predictors of PORC, especially if < 35 g/L.[42] There is fair evidence that the patient variables of impaired sensorium, abnormal chest examination findings, alcohol use and weight loss increase the

risk of PORC.[43] Procedure-related risk factors include the surgical site, difficulty/duration of the surgery, anaesthetic technique and emergency vs elective procedure.[43] However, "although valuable, these scoring system do not provide clinicians with a reliable and ongoing method by which to stratify all patients" for development of PORC or PORF.[32] Intermittent assessment of vital signs has been shown to be insufficient. For example, in one study, 38% of the patients experienced hypoxemia despite intermittent vital signs being regularly taken.[44]

Predicting prior to surgery which patient(s) will develop PORC is very challenging.[45] Results from testing oxygen demands at rest and during stress can be significantly different.[5] Preoperative hypoxemia < 90% is associated with increased complications; however, arterial blood gases suggest only part of the clinical scenario. It is critical that "evaluation of the clinical picture" must be thorough.[5] A recent review by Ayad et al. [22] discusses new assessment tools and monitoring devices being developed. These include: integrated monitoring devices (eg pulse oximetry and capnography), integrated delivery plus monitoring devices, acoustic monitors, radar monitors, and bioimpedance and inductance monitors (plethysmography and audiometry).

2.4 | Contributing drugs

Classes of drugs that contribute to PORC include neuromuscular blocking drugs, analgesics and sedatives. They decrease respiratory drive when used alone or in combination (synergistically). Some studies suggest that hypoxia that occurs within 30 minutes of PACU admission might likely be due to neuromuscular blockers, whereas after this time, opioids and sedatives may be the likely cause.[29] It appears that the use of opioids for analgesia and anaesthesia, intra- and postoperatively, will also increase the risks of PORC.[46] Opioids remain "the cornerstone" of analgesia after surgery.[47] However, postoperative opioid-induced respiratory depression is involved in 55% of postoperative deaths and 22% of patients left with severe brain damage.[23] Combinations of an opioid and sedative were responsible for up to 3.8-fold increase in the incidence of cardiorespiratory arrest in hospital patients compared to when these medications were not used.[10] An estimated 97% of PORC cases due to opioids are deemed to be "preventable."[48] Studies in 2015 by a Mayo Clinic team found that 58% of naloxone administrations were delivered within 12 hours of PACU administration and 88% within 24 hours.[49] In spite of multiple attempts to improve pain medicine after surgery, "at least" 80% of patients experience moderate-to-extreme postsurgical pain.[26] This continues to be a significant gap in postoperative care.

Residual paralysis from neuromuscular blocking drugs can delay the return of a patient's spontaneous respiratory function. This problem is widespread, and frequently unrecognized.[50] The estimated range of the presence of residual neuromuscular blockade is from 22 to 34%.[51] In a study conducted in Spain, risk factors for residual paralysis included female gender, longer duration of surgery and use of halogenated anaesthetic.[50] Not using neuromuscular reversal agents is correlated with the risk of residual neuromuscular blockade,[50,52] and the presence of residual neuromuscular blockade increases admissions to the ICU.[53] The reversal of the effect of neuromuscular blocking agents has been "revolutionized" by Sugammadex,[54] which selectively binds to the steroidal nondepolarizing muscle relaxants rocuronium and vecuronium, and reverses their neuromuscular blocking action. Sugammadex is an improvement over the anticholinesterases, because it has a rapid recovery time and can reverse deep neuromuscular block.[55]

2.5 | Good practice

Primary care should be involved in the pre-surgical evaluation and in the treatment of patients scheduled for non-emergent surgeries. The American College of Physicians has developed guidelines for perioperative evaluation and care.[43] A common, and at times overlooked, effort to reduce potential PORC includes smoking cessation. In a Cochrane review, preoperative smoking cessation that began 4 – 8 weeks before surgery had a positive impact on PORC.[56] The American College of Physicians Guidelines suggest the data are "mixed" when it comes to tobacco discontinuation reducing PORC.[43] However, smoking cessation should be a goal of the perioperative evaluation for many obvious reasons. Although published data are mixed, they suggest a modest increase in risk for PORC among current smokers, with the odds ratio for cigarette use being 1.26 (CI, 1.01 to 1.56). It is important to assess a history of current smoking status and support for smoking cessation intervention as early as possible in the preparation for non-emergency surgery. Lung expansion modalities are "better than no prophylaxis at all"; however, the literature does not clarify which modality is best.[43] Optimal blood pressure and diabetic control also help improve postsurgical outcomes and are important goals for the primary-care physician.

In the PACU, close direct monitoring needs to be the rule and not the exception. Since too many alarms can lead to "alarm fatigue," a high ratio of nurses to patients and close personal monitoring are important in reducing PORC, and especially PORF.[34] The ratio of physicians to patients in the ICU has been shown to be a contributor to improved outcomes of patients who experience PORF.[57]

Pain management before, during and after surgery is a critical component, as pain itself causes significant physiological responses that can be detrimental to respiratory function.[58] However, opioids can also increase the risk of postoperative respiratory complications, as mentioned above. Patients' pain needs to be addressed, but so do the risks of complications. The recently approved opioid oliceridine might induce less respiratory depression in the postoperative setting, while providing analgesia.[59] All modalities, including pharmacologic (eg topical and non-opioid analgesics) and non-pharmacologic (eg cryotherapy and a host of others), should all be considered as part of an integrated management plan to alleviate patients' pain and suffering.

2.6 | Respiratory stimulants

Respiratory stimulants have a long history and have been used in the postoperative setting since at least the early 1900s. Doxapram is the one respiratory stimulant that is currently available in the United States. Its mechanism of action is not completely understood but likely includes the inhibition of a subtype of K^+ channels, specifically TWIK-related acid-sensitive K^+ (TASK) channels.[60] Doxapram is currently used to stimulate respiration in patients emerging from anaesthesia and for those with postoperative acute respiratory insufficiency. Clinical scenarios in which doxapram has been used include reducing laryngeal spasm and postoperative shivering, and assisting in blind nasal intubation.[60]

ENA-001 (formerly GAL-021), although currently still in development, has received attention as an "agnostic" respiratory stimulant, because it reverses the effects of a variety of drug classes that induce respiratory depression. It inhibits large-conductance Ca^{2+}/voltage-activated K^+ (BK_{Ca}, Big K) channels.[61] The original research that established ENA-001 as an agnostic respiratory stimulant came from animal studies,[6] where it increased minute ventilation in a dose-related manner, and reversed opioid-, benzodiazepine-, isoflurane- and propofol-induced respiratory depression.[62] It has now been shown to antagonize opioid-induced respiration in healthy human volunteers.[63] A further benefit is that ENA-001 has a rapid onset time/offset which has been said to make "this drug an attractive alternative to naloxone."[64] Currently, however, naloxone still reserves a critically important place and should be administered in opioid-induced respiratory depression. The addition of a respiratory stimulant may have potential benefits in reducing the incidence of PORC and PORF, and thus improve patient outcomes.

2.7 | Conclusion

Residual postoperative respiratory depression induced by peri- and intra-operative medication occurs commonly, decreases outcome and increases healthcare cost. The problem of medication-induced respiratory depression presents a particularly difficult conundrum, because the drugs that cause the problems are medically appropriate and necessary. That is, a certain degree of muscle relaxation is needed to facilitate the surgical procedure, and pain relief is not only humane but favours better recovery and shorter hospital length of stay—so block of pain relief with block of respiratory depression using an opioid receptor antagonist introduces a difficult dilemma. The problem is compounded by the unpredictability of which patient(s) within the incidence statistics will be affected. At present, the only available respiratory stimulant is limited by its adverse effects. A welcome addition to the pharmacologic armamentarium would be a respiratory stimulant "agnostic" to the cause.

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