

Opioids and Respiratory Monitoring Technology

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Overview

Opioids play a central role in postoperative multimodal analgesic therapy but are considered high-alert medications by the Institute for Safe Medication Practices (ISMP) due to the risk of significant patient harm from respiratory depression. This white paper presents an overview of the clinical use of opioids, the associated risks, and a summary of the respiratory monitoring technologies developed to increase patient safety. Finally, the ICU Medical recommendations for respiratory monitoring during opioid therapy are summarized.

Introduction

Respiratory monitoring has been shown to offer valuable insight into a number of medical conditions, and it has been demonstrated that respiratory changes precede significant adverse events such as intensive care unit (ICU) transfers and cardiopulmonary arrest.^{1,2,3,4} Respiratory monitoring is important with the use of opioids because they have characteristic respiratory side effects that can lead to catastrophic morbidity.^{1,5} Evidence of risk includes the analysis of closed anesthesia malpractice claims, which describes how the morbidity associated with opioids may be preventable in 97% of patients with improved monitoring and response^{6,7}. The underlying physiologic drivers of these complications are treatable⁶ and, in the opinion of some, these complications could be described as "never events."⁷

The ISMP lists opioids by oral, intravenous (IV), and transcutaneous routes as high-alert medications due to the risk of patient harm.⁸ Reduction of opioid administration through utilization of alternative analgesic modalities inherently reduces opioid-related complications.

Multimodal analgesia utilizes two or more medications acting through unique central or peripheral pathways to create additive or synergistic pain relief while reducing medication side effects. The use of multimodal analgesia was described as early as 1993 and has grown with the expansion of outpatient medical services, the number of pharmacologic agents and techniques available to clinicians, and the increased recognition of opioid-induced risk. For those hospitalized patients with more severe pain who are not able to tolerate oral opioids, parenteral therapy still may be required.

For patients who require parenteral opioids, two primary opioid administration strategies are utilized: patient-controlled analgesia (PCA) and clinician-initiated dosing. The Guidelines on the Management of Postoperative Pain strongly recommend that when parenteral opioids are required, hospitalized patients should be given PCA for postoperative pain.⁹

Despite a growing understanding of opioid-induced respiratory depression (OIRD) and alternative analgesic options, patients continue to experience significant morbidity and mortality from opioids.¹⁰ OIRD is measured in various ways, including reduced respiratory rate, elevated arterial carbon dioxide levels, decreased oxygen saturation, or the need for an opioid reversal drug.¹¹

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An additional metric of the incidence of respiratory depression is the use of naloxone rescue for respiratory depression, which occurs in approximately 0.3% of postoperative patients.¹⁰

Physiologic drivers of OIRD are multifactorial and include decreased respiratory drive, decreased level of consciousness, and upper airway obstruction.¹² Estimates for the incidence of serious respiratory depression from PCA usage vary from 0.5% by The Joint Commission,¹³ 0.1–1% by the Anesthesia Patient Safety Foundation (APSF),¹⁴ or up to 41% in individual studies.¹¹

Identifying patients at risk for opioid toxicity is complex as patient response to opioids varies widely.^{14,15,16} Specific groups appear to be at higher risk for complication, including those patients with advanced age, central or obstructive sleep apnea, obesity, preexisting respiratory disease, and those on other Central Nervous System (CNS)-acting drugs.^{10,13,14} Despite the known high-risk groups, in one study, medical conditions only predicted 50% of the affected group¹⁰ and APSF expert opinion supports the incidence of a low but unpredictable risk of respiratory depression in young healthy patients.¹⁴ Risk stratification has been demonstrated to be insufficient to eliminate postoperative OIRD.¹⁰ In light of the unpredictability of the risk of patient harm, the APSF and industry experts recommend that all patients receiving parenteral opioids (and neuraxial opioids) have continuous electronic monitoring.^{7,14}

The Joint Commission, the ISMP, and the APSF have issued statements advocating for increased vigilance and improved monitoring strategies for patients on opioids.^{8,10,13,14,17} Monitoring for opioid-induced side effects requires effective clinical strategies. Clinical efforts to reduce opioid complications include patient and clinician education and regular clinical evaluations, including assessments of mental status, sedation level, and respiratory function.^{13,15} While clinician evaluation of patients contributes valuably to patient care, time for in-room examination is limited. As an example, when a patient's vital signs are checked every 4 hours, patients are left unmonitored 96% of the time.¹⁰ The use of sedation scales may make limited clinician time more impactful.

Sedation level may be of particular importance as changes in mental status can be a marker of pending respiratory depression.^{10,18} An example of a screening tool specifically created for opioid-related mental status changes is the Pasero Opioid-Induced Sedation Scale.¹⁹ Other sedation screens widely used in intensive care and adapted for monitoring patients on opioids are the Richmond Agitation Sedation Scale (RASS) and the Ramsey Sedation Scale.¹⁶ Raising additional concerns about the adequacy of clinician evaluation is evidence from closed claims analysis that one quarter of respiratory events occur within 15 minutes of nursing evaluations,⁷ suggesting nursing evaluation may be required every 15 minutes or less for some patients.

To enhance the effectiveness of clinical assessment and account for periods when nurses are out of the room, the APSF, ISMP, and The Joint Commission advocate for the use of continuous electronic monitoring. The APSF states that although no ideal single technology exists, continuous monitoring using available technology likely reduces risk.¹⁴ APSF and industry experts further recommend monitoring of oxygenation with routine pulse oximetry. When patients are receiving supplemental oxygen, the organizations further recommend the use of a ventilation monitor as pulse oximetry may not detect the development of lethal hypercapnia.^{7,17}

From the APSF 2011 statement titled, "No Patient Shall Be Harmed By Opioid-Induced Respiratory Depression":¹⁰

In summary, the consensus of conference attendees was that continual electronic monitoring should be utilized for inpatients receiving postoperative opioids. When supplemental oxygen is not being used, pulse oximetry was thought to be the most reliable and practical monitor currently available. If supplemental oxygen is added, then monitors of ventilation (e.g., capnography) were thought to be necessary to detect hypoventilation ... The issues identified and the actions recommended by this group should mitigate these risks with the goal to eventually eradicate this cause of preventable patient harm.

The remainder of this paper will address respiratory monitoring during opioid administration with a focus on monitors of oxygenation and ventilation.

Monitors of Oxygenation

Monitors of oxygenation detect the amount of oxygen in the blood and include arterial blood gas analysis and pulse oximetry. Due to its invasive nature, the use of blood gas analysis is limited to specific clinical circumstances and will not be included in this discussion.

PULSE OXIMETRY

Pulse oximeters detect the amount of oxygen carried in the blood by assessing the percent of hemoglobin molecules "saturated" or carrying oxygen. These devices are familiar, widely available, and easy to use. Intermittent pulse oximetry is performed on a schedule like other vital signs, limiting measurements to specified time frames that may not capture the development of OIRD. Continuous pulse oximetry involves a patient wearing a device continually, enabling immediate recognition of changes in oxygen saturation. Technologic limitations of pulse oximeters include potential inaccuracy with reduced perfusion at the site of measurement during clinical conditions such as hypotension and hypothermia.¹

In many cases, pulse oximeters are a late indicator of respiratory depression as the adequacy of ventilation and the removal of exhaled carbon dioxide are not measured. Patients may develop significant hypercapnia prior to a change in oxygen saturation, especially when supplemental oxygen is being used.

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Hypercapnia may be lethal through the disruption of blood pH and a reduction of the patient's level of consciousness that creates sedation, additive to the central nervous system effects of opioids.^{10,15} In hypercapnic respiratory failure, changes in oxygen saturation reflect advanced respiratory deterioration when gas exchange is no longer effective and only minutes may remain for effective intervention.

Despite limitations, the APSF recommends routine use of pulse oximetry in patients receiving PCA or neuraxial opioids. Support for the use of pulse oximetry in this setting includes a study by Taenzer, et al. that demonstrated a reduction in rescue events and ICU transfers after the implementation of a continuous patient surveillance system based on pulse oximetry.²⁰ Although imperfect, early identification of desaturation with routine pulse oximetry may enable early intervention and improve outcome.^{7,21}

Monitors of Ventilation

In cases when supplemental oxygen is indicated by patient condition, additional surveillance of respiratory status through ventilation monitoring is recommended.^{10,14,17} Ventilation monitors quantify the adequacy of ongoing respiratory gas exchange by targeting respiratory rate, tidal volume, and exhaled carbon dioxide levels.

While there is agreement on the utilization of pulse oximetry to monitor oxygenation,⁷ less agreement exists in the selection of a ventilation monitoring technology. Options range from well-known techniques, such as capnography and minute ventilation monitoring, to numerous newer systems recently available or under development. Until an optimal technology is determined from clinical trials, clinicians will choose from a range of options, including the technologies described below.^{7,22}

CAPNOGRAPHY

Respiratory depression from opioids may be reflected in variations of respiratory rate and/or CO₂ levels. Capnography measures the carbon dioxide content of exhaled respiratory gas, i.e., end-tidal CO₂ (EtCO₂). The end-tidal CO₂ level is displayed in real time as a waveform. The amplitude of the waveform correlates with arterial CO₂ levels, the waveform frequency corresponds to respiratory rate, and the wave form shape corresponds to various disease states.

Experience with capnography is extensive and utilization of the technology is the standard of care for respiratory monitoring during moderate to deep sedation and general anesthesia in the United States and several other countries.²³ Capnography is applicable for intubated and nonintubated patients. In nonintubated patients who require no or limited oxygen, capnography most commonly utilizes a CO₂ sampling nasal cannula. In patients who require higher levels of supplemental oxygen, an oxygen face mask may be utilized for capnography.

Although the role of capnography in nonprocedural care environments, such as during opioid administration, has not been firmly established, successes have been demonstrated. In studies involving postoperative opioid administration, respiratory depression was detected with capnography prior to changes with pulse oximetry when both monitors were in use.^{11,24} In addition, during postoperative opioid administration, capnography increased the detection of respiratory events and decreased complications.^{11,15,17,24,25,26}

Despite these demonstrated successes, the implementation of capnography for postoperative opioid monitoring faces challenges, including patient compliance, clinician training requirements, expense, patient mobility, dislodged devices, and nuisance alarms.^{17,27} In particular are concerns with patient compliance related to discomfort with nasal cannulas. Currently, despite established market history, published data is not widely available that describes patient comfort and compliance with this monitoring technique. The lack of data has resulted in concern that nasal cannula compliance may affect monitor applicability in this setting.

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MINUTE VENTILATION MONITORING

Minute ventilation monitoring utilizes electrodes placed on the chest wall to calculate tidal volume, respiratory rate, and minute ventilation. It has been observed that patients who develop respiratory depression from opioids and other causes have observable changes in minute ventilation prior to the development of dangerous respiratory depression.⁵ Lynn and Curry describe in "Patterns of unexpected in-hospital deaths: a root cause analysis" that three patterns of respiratory physiology correspond to hospital deaths. One of these patterns—Type II—is the pattern of "CO₂ narcosis" commonly associated with opioids.⁵ This pattern demonstrates a fall in minute ventilation,

followed by an increase of arterial CO₂, which culminates in falling oxygen saturation. The CO₂ narcosis respiratory pattern demonstrates that observing a change in respiratory rate by itself may not be sufficient to demonstrate reduced minute ventilation. Medications, such as benzodiazepines, reduce minute ventilation with unpredictable effects on respiratory rate.⁵ The pathophysiology of CO₂ narcosis indicates that minute ventilation monitoring may be effective to provide early warning of a Type II respiratory pattern.

Minute ventilation monitoring technology has advanced to improve monitoring accuracy.²⁸ Newer respiratory volume monitoring devices have demonstrated quantitative minute ventilation measurements with substantially improved reliability.²⁹ A 2013 study of respiratory volume measurements in hospitalized patients demonstrated that a noninvasive respiratory volume monitor differed from traditional spirometry by an average difference of <10% through a number of breathing patterns.²⁹

The same study demonstrated a significant difference in tidal volume of nonobstructed versus obstructed breathing with obstructed breathing registering tidal volumes in the range of anatomic dead space, which may enable prompt detection of an apneic event.²⁹ Respiratory volume monitoring may be appropriate in a broad range of settings and have application for patients on PCA pumps and postoperative opioids. In the presence of opioid administration, minute ventilation monitoring demonstrated respiratory volume changes that may serve to identify at-risk patients.³⁰

A potential benefit of respiratory volume monitoring is sensor configuration and patient compliance. As the minute ventilation monitors attach to the chest, they may be less susceptible to patient removal—compared to alternatives such as capnography which utilizes airway devices that may be more noticeable and/or irritating to the patient. Data comparing patient compliance of minute ventilation monitoring with alternative monitoring techniques is not currently available.

ACOUSTIC SIGNAL MONITORING

Acoustic monitoring technology uses an adhesive patch placed over the patient's neck to detect gas movement in the trachea during the respiratory cycle. Recent improvements in overcoming noise and motion artifacts have led to products becoming available for use in the United States and Europe. A comparison study of acoustic monitoring and capnography on postoperative patients has shown the acoustic monitor to be an indicator of respiratory rate with reliability similar to capnography.³¹ In a separate study in pediatric patients, acoustic monitoring was associated with respiratory rate monitoring as accurate as capnometry with fewer episodes of the device being dislodged from the patient.²⁷

While a capnograph produces a wave form and associated data, and minute ventilation monitors produce data on minute ventilation, tidal volume, and respiratory rate—the acoustic monitor is limited to respiratory rate. Acoustic monitoring has also been associated with limitations with continuous positive airway pressure (auditory interference) and diaphoretic skin (sensor adhesion problems).³¹

PHOTOPLETHYSMOGRAPHY – PULSE OXIMETRY RESPIRATORY RATE MONITORING

It has been shown that the pulse oximeter waveform (i.e., plethysmogram) contains a number of signals that are modulated by respiration. Algorithmic interpretation of the pulse oximetry wave form enables respiratory rate determination and is now commercially available. In a study of general care floor patients, respiratory rate derived from a pulse oximeter was compared to the respiratory rate from capnography and found to have close agreement.³²

In clinical studies, this technology (piezoelectric monitor) has been shown to accurately trend heart rate and respiratory rate and is associated with a lower number of code blue events and a shorter length of hospital stay.

PIEZOELECTRIC CONTACT-FREE RESPIRATORY RATE MONITORS

A piezoelectric monitor that does not require direct patient contact is available and utilizes a sensor placed under the mattress of a bed or under a seat cushion. The sensor detects the mechanical vibrations of the heart, respiratory system, and musculoskeletal system. Monitoring software analyzes the motion signals and produces heart rate and respiratory rate data.

Potential benefits include high patient compliance and continuous monitoring data when the patient is in the proximity of the sensor in bed or in a chair. In clinical studies,

this technology has been shown to accurately trend heart rate and respiratory rate and is associated with a lower number of code blue events and a shorter length of hospital stay.³³ Further studies are required to understand the impacts of these monitors, including safety implications of unmonitored periods when the patient is not in sensor proximity.

Monitors of Ventilation in Development

REMOTE PHOTOPLETHYSMOGRAPHY – CONTACT-FREE PULSE OXIMETRY RESPIRATORY RATE MONITORING

Traditional pulse oximeters utilize sensors attached to patients' bodies. Remote photoplethysmography utilizes cameras to detect respiratory-induced color variations in patients' skin to determine respiratory rate. This technology appears effective in visible and dark lighting conditions and is designed to detect heart rate and respiratory rate. Initial evaluations have shown monitor effectiveness, although this technology is not yet commercially available.³⁴

DOPPLER RADAR CONTACT-FREE RESPIRATORY RATE MONITORS

Microwave Doppler radar has been evaluated for heart beat and respiratory rate assessment.³⁵ Additional respiratory information these monitors may be capable of capturing are tidal volume and inspiratory expiratory ratios.³⁵ This technology is in early stages of development.

HUMIDIFIED GAS MONITORING

Humidified gas monitoring assesses the humidity of exhaled gas to determine respiratory rate. A comparison of this technology to capnography, manual breath counting, and EKG-derived respiratory rate measurement shows that humidified gas assessment may be an effective respiratory rate monitor.³⁶ This technology is currently under development.

Considerations during Opioid Transitions

ISMP identifies all opioids, by all routes, as high-alert drugs. The risk of OIRD does not cease when patients are no longer receiving PCA or IV opioids. Patients undergo multiple transitions of pain therapy during a hospitalization, including the transition from PCA to oral medications and PCA to oral medication plus clinician-initiated boluses. During these transitions it is possible that the oral medications do not meet opioid requirements, leading to frequent IV boluses for uncontrolled pain, or the oral dose could exceed opioid requirements, leading to opioid toxicity. In either case, patients are at risk of OIRD and vigilant monitoring reduces risk for morbidity. For the pulse oximetry and ventilation monitoring to continue during transition, these devices must be continuously available for the patient. Medical centers take various approaches to respiratory monitoring for patients on opioids.

A subset of facilities adopt strategies to provide monitoring for all patients on opioids, regardless of administration route, due to the risk of OIRD. Other hospitals may target subsets of patients for respiratory monitoring such as those using a PCA. Targeting a limited subset of the population does have inherent risk as those patients most at risk for OIRD are not always predictable.

Furthermore, in the event that a device, such as a capnograph, is integral to a PCA that's discontinued, the patient may lose access to capnography when the risk of OIRD remains. A comprehensive strategy providing monitor availability for all patients on opioids (oral, IV, PCA, neuraxial, transdermal, etc.) may be best equipped to manage OIRD risk during hospitalization, including the transition from IV to oral therapy.

The development of closed loop systems linking opioid PCA delivery and respiratory monitors holds promise, but the prevalence of false alarms and interruptions of therapy with current technology may limit application and effectiveness.

Summary and Future Direction

Whether opioids are administered by oral or parenteral routes, the risk of respiratory depression is present. The selection of an appropriate monitoring strategy will reduce patient risk but is a complex task that requires an understanding of the clinical environment, staff training and education, and the patient population. Fortunately for patients, technologic advances are being combined with education and changes in practice to minimize the risk posed by these important medications.

The development of closed loop systems linking opioid PCA delivery and respiratory monitors holds promise, but the prevalence of false alarms and interruptions of PCA therapy with current technology impact clinician and patient satisfaction and may limit application and effectiveness. Nasal cannula capnography may be poorly tolerated and closed loop pulse oximetry may not be appropriate due to the late indication of OIRD. What is needed is a closed loop system that provides early warning of OIRD with high sensitivity/high specificity and is well tolerated by patients to enable continuous monitoring while a patient is at risk for OIRD. Further study is required to determine which monitor of ventilation best meets the requirements of OIRD monitoring.

There are decisions and trade-offs that exist for the number and types of respiratory monitors made available for use in any facility. In consideration of available technology, healthcare facilities may follow the recommendations of the APSF to utilize pulse oximetry on all patients receiving postoperative parenteral opioids and a continuous ventilation monitor for those patients on supplemental oxygen.

Despite being a late indicator of OIRD, pulse oximetry holds promise in reducing rescue events and ICU transfers²⁰ while being well tolerated by patients. Strengths of pulse oximetry additionally include the prevalence of the monitors in hospitals and clinician familiarity with the technology, which reduce the barriers associated with training and implementation. In the presence of supplemental oxygen, a monitor of ventilation is recommended by the APSF as hypoventilation may lead to lethal hypercapnia in the presence of maintained oxygenation. Although pulse oximetry and ventilation monitors have strengths and weaknesses, implementation of a comprehensive continuous electronic monitoring strategy will likely reduce the probability of patient harm.

Continuous electronic monitoring, while critical, is just part of the equation of managing the risks of opioid administration. Individualized management of PCA therapy remains central to safe care and includes sedation assessments and appropriate dosing, lockout periods, and dose limits. It should also be considered that in individual circumstances, parenteral opioid administration may be best delivered by clinician bolus at the time of a pain and sedation level assessment rather than by PCA.

A comprehensive monitoring strategy during PCA administration is critical, but it is also important to consider respiratory monitoring for patients receiving non-PCA opioids, including during transition from IV to oral medications and in the presence of neuraxial opioids. With an understanding of the unpredictability and potential severity of OIRD, sound clinical practices and a comprehensive electronic monitoring strategy will reduce the number of patients suffering opioid-related morbidity and advance healthcare toward the APSF goal of "No patient shall be harmed by opioid-induced respiratory depression."

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