BJA

British Journal of Anaesthesia, xxx (xxx): xxx (xxxx)

doi: 10.1016/j.bja.2019.05.044
Advance Access Publication Date: xxx
Review Article

REVIEW ARTICLE

Characterisation and monitoring of postoperative respiratory depression: current approaches and future considerations

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Summary

Respiratory depression is common in patients recovering from surgery and anaesthesia. Failure to recognise and lack of timely institution of intervention can lead to catastrophic cardiorespiratory arrest, anoxic brain injury, and mortality. Opioid-induced respiratory depression (OIRD) is a common and often under-diagnosed cause of postoperative respiratory depression. Other causes include residual anaesthesia, residual muscle paralysis, concurrent use of other sedatives, splinting from inadequate pain control, and obstructive sleep apnoea. Currently used methods to identify and monitor respiratory safety events in the post-surgical setting have serious limitations leading to lack of universal adoption. New tools and technologies currently under development are expected to improve the prediction of respiratory depression especially in patients requiring opioids to alleviate acute postoperative pain. In this narrative review, we discuss the various causes of postoperative respiratory depression, and highlight the advances in monitoring and early recognition of patients who develop this condition with an emphasis on OIRD.

Keywords: analgesia; monitoring; opioids; postoperative complications; respiratory depression

Editor's key points

- Use of conventional opioids for the management of acute pain in the postoperative setting is associated with unacceptable adverse events, including opioid-induced respiratory depression.
- Monitoring respiratory safety events is imperative for timely institution of intervention and prevention of catastrophic cardiorespiratory arrest, anoxic brain injury and mortality.
- Currently employed methods used to identify and monitor respiratory safety events have serious limitations that preclude their universal adoption.
- Several new tools and technologies under development may substantially improve risk prediction and monitoring of respiratory complications.
- This narrative review provides an update on opioid pharmacology and physiology along with recent advances in the development of tools that aid in early recognition of patients likely to develop opioid-induced respiratory depression.

Editorial decision: 24 May 2019; **Accepted:** 24 May 2019

Respiratory impairment in the postoperative period is associated with significant morbidity and mortality.[1,2] The risk for respiratory compromise exists well beyond the duration of care in the post-anaesthesia care unit (PACU) extending on to the regular nursing floors where monitoring and early recognition are a challenge. A significant proportion of respiratory events occur in the first 24 h after surgery, and many of these appear to be preventable.[3,4] Amongst the various aetiologies of postoperative respiratory depression, opioid-induced respiratory depression (OIRD) or opioid-induced ventilatory impairment has gained increasing attention as a potentially preventable cause of death and brain damage after surgery.[3] Up to a fifth of all inpatients may experience respiratory impairment secondary to opioids, depending on what monitoring parameter is used to define this condition,[5,6] and intraoperative opioid use has been associated with 30-dy readmission to hospital.[7]

The need for improved pain management after surgery still remains a formidable healthcare challenge with at least 80% of patients experiencing moderate-to-extreme pain after surgery.[8] Whilst parenteral opioids remain the mainstay of therapy for controlling acute moderate-to-severe pain in the postoperative setting,[9–13] their association with postoperative respiratory depression and the antecedent brain damage and death is concerning, particularly in at-risk patient populations.[3,14,15] Moreover, management of opioid-related respiratory events increases resource utilisation and healthcare costs.[16–22] For example, an additional mean length of stay of 5 hospital days and up to $10 000 in hospital costs have been cited in hospitals in the USA as a direct consequence of OIRD events.[23]

The current narrative review aimed to provide an overview of postoperative respiratory depression, with emphasis on OIRD, including a brief description of its reported incidence, at-risk populations, and potential impact on health-economic outcomes. In addition, a summary of measures and methodologies used in clinical studies to characterise and monitor the respiratory safety of opioid analgesics will be presented. Finally, we provide an account of recent advances in monitoring and detecting OIRD in clinical practice and research, including new monitoring technologies in early development. Presentation of this essential information is intended to help improve clinicians' knowledge of OIRD assessment and to develop best practices for optimal monitoring of patients who receive opioids during inpatient hospital stay.

Postoperative respiratory depression

Pulmonary dysfunction after surgery and anaesthesia is common with a reported incidence of 0.3–17% depending upon the metric evaluated.[1,5,24] The heterogeneity in anaesthetic practice and postoperative monitoring strategies used makes it difficult to accurately assess the true incidence of this problem. Postoperative respiratory failure has been rated as the fourth most common patient safety event by the Agency for Healthcare Research and Quality, and is associated with increased mortality and hospital length of stay.[25] Despite the magnitude of this problem and the high likelihood of catastrophic consequences in affected patients, a universal definition is lacking.

Postoperative respiratory impairment occurs as a result of the interplay between modifiable and non-modifiable comorbid conditions, and also surgery- and anaesthesia-related factors. Anaesthetic causes include OIRD, residual effects of anaesthetic agents, residual muscle paralysis, and concomitant use of sedatives and narcotic-based pain medications. Clinically, the immediate postoperative period may be an especially susceptible time for the occurrence of OIRD. This is because most i.v. and inhalational anaesthetics have an additive or synergistic effect with opioids, acting via agonism at the gamma-aminobutyric acid (GABA) receptor.[26–30] To further corroborate the dangers of these interactions, the concurrent use of benzodiazepines with opioids has been associated with a number of opioid-related adverse events (ORAEs) in a large closed claims analysis of events from the general care floor.[3] Surgical risk factors include nature, duration, and type of surgery, whilst patient-related risk factors include sleep-disordered breathing, obesity, diabetes mellitus, male gender, advanced age, increased opioid dose requirement, concomitant use of other sedating medications, co-morbidities (including pulmonary or cardiac disease), opioid use via patient-controlled analgesia (PCA) systems, and smoking.[2,31–33]

Accurate prediction of postoperative respiratory compromise remains an ongoing challenge. Various scoring systems have been devised, which incorporate patient-, surgery-, and anaesthesia-related risk factors to predict respiratory compromise after surgery. The STOP-Bang questionnaire screens for the risk of obstructive sleep apnoea (OSA) in the preoperative period,[34] whilst the Score for the Prediction of Postoperative Respiratory Complications (SPORC) and Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) scores predict the risk of reintubation and postoperative respiratory complications, respectively.[35,36] Whilst these scores have been validated and offer clinicians the option of judicious utilisation of monitoring resources in the postoperative setting, each has its own limitations. For example, the STOP-Bang score is a validated and simple preoperative screening tool for OSA that is associated with oxygen desaturation and hypoventilation. An increasing score (on a scale of 0–8) has been associated with an increasing probability of moderate-to-severe sleep apnoea.[37] However, the score itself has not been shown to be predictive of postoperative hypoxaemia.[38] Whilst OIRD is common, the type of opioids used in post-surgical recovery is not associated with the duration and extent of oxygen desaturation events in these patients.[39] Although best practices for optimal detection of postoperative respiratory depression are still not universally available, experts advocate for the increasing use of capnography (or ventilation monitoring) in addition to pulse oximetry (oxygenation monitoring) at least in those patients receiving opioids. In addition, the judicious use of supplemental oxygen in the postoperative recovery room and general care floor, along with better education of healthcare providers with respect to early recognition of impending respiratory deterioration patterns, is essential.[40] Continuous, portable bedside monitors with an effective central alarm and noise filter will also be essential in decreasing alarm fatigue, whilst maintaining patient safety and vigilant surveillance.[21,41,42]

Respiratory effects of conventional opioids

Opioids generally described under the category of 'conventional opioids' include hydromorphone, morphine, fentanyl, sufentanil, alfentanil, and remifentanil. The primary site of action of the conventional opioids is the μ-opioid receptors, and analgesia is mediated via the G-protein pathway. ORAEs were previously thought to be mediated largely via the β-arrestin pathway; however, recent evidence suggests otherwise. A mouse knock-out model that inhibited the recruitment of β-arrestins showed a diminished development of analgesic

tolerance, but adverse effects were unchanged.[43] G-protein-gated inwardly rectifying potassium (GIRK) channels also contribute to respiratory depression.[44] PZM21, a novel μ-opioid agonist that works via G protein and β-arrestin signalling displays similar respiratory depression characteristics as morphine.[45] Mechanistically, opioids exert depressive effects on respiratory drive,[46] consciousness,[47,48] and supraglottic airway muscle tone,[49–51] which contribute to decreased ventilation and pulmonary gas exchange, and potentially result in hypoxia and hypercapnia.[15] Although the exact pathophysiological mechanisms involved in OIRD are not well understood, opioids appear to depress the ventilatory control system via their effects on μ-opioid receptors located on neurones in brainstem respiratory centres.[52–56] Opioid activation of these receptors and potential consequent respiratory compromise may be temporary in some patients, but, in others, can lead to irregular breathing, apnoea, and even fatal cardiorespiratory collapse.[57]

The most opioid-sensitive aspect of respiration is rhythm generation, and changes in the respiratory pattern are observed at lower opioid doses than change in tidal volume.[58] In this context, this class of opioids inhibits the pre-Bötzinger complex, a small area in the ventrolateral medulla that acts as the rhythm generator during inspiration. Importantly, this area of the medulla works in close association with the retro-trapezoid and parafacial respiratory group that is active during expiration, but insensitive to opioids.[59–62] Opioids tend to cause respiration to slow and become irregular, and the classic picture of opioid overdose is slow and deep breathing.[63,64] Higher opioid doses cause a significant hypoventilatory response characterised by a variability in tidal volumes.[63] One postulated mechanism for this may be decreased tonic inputs from opioid-sensitive chemoreceptors, which are only partly compensated *in vivo* by increases in Pa_{CO_2}, and hence, lead to an overall decrease in minute ventilation.[65] Opioids also tend to shift the CO_2 response curve to the right and cause an almost 50% depression of hypercapnic ventilatory response.[66,67] With a gradual increase in opioid concentrations (as with a constant rate infusion), there is gradual hypercapnia as a result of a progressive increase in opioid receptor occupancy. This contributes to the maintenance of respiration. On the other hand, a fast increase in opioid receptor occupancy resulting from an i.v. bolus would lead to an initial period of apnoea until the Pa_{CO2} rises to its steady-state value and stimulates respiration again.[63] Hence, patients receiving drugs that bind to the μ-receptors more quickly (e.g. alfentanil and remifentanil) should be more closely monitored for immediate respiratory depression post-administration than those receiving drugs with slower receptor binding (e.g. morphine and hydromorphone).[68–70]

Respiratory effects of non-conventional opioids

Non-conventional opioids typically act via mechanisms other than the traditional μ- opioid receptors. Prominent in this class are tramadol and buprenorphine. Tramadol is a weak-to-moderate μ-opioid agonist that acts via the inhibition of uptake of norepinephrine and serotonin in the CNS.[71] Of note, it suppresses the hypercapnic ventilatory response more than the hypoxic ventilatory response.[72] Patients with renal failure may accumulate an active metabolite as a result of altered clearance.[73,74] Buprenorphine is an agonist (high affinity, but low efficacy with slow dissociation kinetics) at the μ-opioid receptor. In addition, it is an agonist for the delta- and opioid-receptor-like-1 receptors. It is also an antagonist at the κ receptor. This unique combination of receptor affinities allows for a ceiling effect on the impairment of the hypercapnic ventilatory response (although not for analgesic effects), ensuring a low likelihood for toxicity even at higher doses,[75,76] although respiratory depression is similar to that of morphine in a recent meta-analysis.[77] Buprenorphine binds tightly to the μ-opioid receptor; therefore, exogenous opioid use confers a minimal reinforcing effect.[78] It also exhibits an extended clinical duration of action and very little potential for physical dependence because of its slow dissociation from the receptor.[79] It can therefore be used to discourage opioid abuse, and its own cessation results in a much milder abstinence syndrome compared with methadone.[80,81] Newer mixed agonists targeting the μ opioid and non-classical nociceptin/orphanin FQ opioid receptors that are in development show analgesic efficacy with reduced respiratory depression and tolerance compared to morphine.[82,84]

Factors influencing prevalence of OIRD

The hallmark of OIRD is a decrease in the effectiveness of ventilatory function after opioid administration. The incidence of OIRD in the postoperative setting is difficult to estimate because of variability in the definitions and assessment methods used. Also, there are differences in the opioids administered, their administration routes and dosages, concomitant medications, and patient-specific factors.[14,15,24,83] An analysis of pooled data from 20 000 patients showed that, for i.m. analgesia, the mean (95% confidence interval [CI]) reported incidence of respiratory depression varied between 0.8 (0.2–2.5) and 37.0 (22.6–45.9)% compared with i.v. PCA, where the mean (95% CI) reported incidence of respiratory depression varied between 1.2 (0.7–1.9) and 11.5 (5.6–22.0)%, and the epidural route, where the mean (95% CI) reported incidence of respiratory depression varied between 1.1 (0.6–1.9) and 15.1 (5.6–34.8)%, using hypoventilation and oxygen desaturation, respectively, as indicators.[24] In the same analysis, the reported incidence of OIRD in patients receiving parenteral opioids via a PCA device after major surgery ranged from 1.2% to 11.5%, depending on the definition and method applied to monitor the event (Table 1).[24] The highest overall estimates of OIRD

Table 1 Reported incidence of OIRD after major surgery in patients receiving parenteral or PCA opioids based on the criteria used to define the event (from Cashman and Dolin[24]). CI, confidence interval; O_2, oxygen; OIRD, opioid-induced respiratory depression; Pa_{CO2}, partial pressure of carbon dioxide in arterial blood; PCA, patient-controlled analgesia.

Definition of OIRD	No. of study groups	No. of patients	Mean incidence of OIRD (%) (95% CI)
Ventilatory frequency below a pre-specified value	35	6922	1.2 (0.7–1.9)
O_2 saturation below a pre-specified value	11	707	11.5 (5.6–22.0)
Pa_{CO2} above a pre-specified value	4	301	1.3 (0.2–7.7)
Naloxone rescue therapy	2	4691	1.9 (1.9–2.0)

incidence were based on oxygen (O_2) desaturation, whereas the lowest were based on ventilatory frequency (VF). Both long- and short-acting opioids administered intravenously may cause the same degree of hypoxaemia. In a sub-analysis of the prospective cohort **V**ascular events **I**n noncardiac **S**urgery pa**t**Ients c**O**hort evaluatio**N** (VISION) study, S_pO_2 values of <95% for ≥20 min h^{-1} were observed in 56% of patients receiving i.v. short-acting opioids (i.e. fentanyl) and 57% of those receiving long-acting opioids (i.e. morphine or hydromorphone) via PCA systems after noncardiac surgery, with similar results seen at S_pO_2 thresholds of <90% and <85% (Fig. 1).[39]

The risk of postoperative respiratory compromise with opioid medication is greatest in the immediate recovery period,[85] but persists after patients leave the operating room, PACU, and ICU. Outcomes of OIRD occurring with subsequent additional opioid treatment in patients on the wards or whilst in transit to or after returning home are potentially catastrophic. Based on an analysis of closed malpractice claims associated with OIRD, this ORAE can lead to catastrophic outcomes, with as many as three quarters of the OIRD-related malpractice cases linked to severe brain damage or death.[3] The hazards associated with this occurrence are a major factor leading to restricted opioid dosing and inadequate analgesia.[65]

Certain patient types are at greater risk for OIRD after surgery, including patients diagnosed with OSA and those who are morbidly obese with a high risk of OSA, who snore, or who smoke.[17,22,33,86–91] Old age has also been shown to convey greater risk of OIRD,[17,85,92–94] as have pre-existing pulmonary/cardiac disease/dysfunction, major organ failure, and concurrent administration of other sedating drugs.[3,17,22,91] Patients with OSA may present challenges with perioperative opioid-based management because of concerns of severe ventilatory compromise. OSA is characterised by intermittent hypoxia, including nocturnal hypoxaemia and sleep fragmentation. Patients on chronic opioid therapy and especially those that have co-existing OSA typically present with nocturnal hypoxaemia.[95] Components of OSA, such as sleep fragmentation and intermittent hypoxia, may modify pain behaviour and also increase sensitivity to opioid analgesia.[96] At the same time, opioids can exacerbate sleep-disordered breathing after operation and may worsen hypoxaemia. Considering all these factors, patients with OSA may be predisposed to a higher risk of OIRD, and hence, requiring use of non-opioid analgesics as a part of multimodal analgesia to reduce opioid dosing along with intense and prolonged respiratory monitoring. In a 2012 Sentinel Event Alert dedicated to the safe use of opioids amongst hospital inpatients, The Joint Commission encouraged organisations to educate the staff about the need to screen patients for these OIRD risk factors to help avoid its occurrence.[91]

The development of cardiopulmonary/respiratory arrest and potential administration of naloxone rescue therapy in patients with OIRD substantially increase resource utilisation, including length of hospital stay and healthcare costs.[97–100] Findings from the Premier Perspective database indicated that hospital stays were approximately 8 days longer and hospital costs $28 000 higher for opioid-treated patients who experienced cardiopulmonary/respiratory arrest or required respiratory resuscitation *vs* those who did not.[97] Malpractice claims against healthcare providers filed for cases of OIRD also may pose a substantial economic burden.[3]

Challenges in assessing the respiratory safety of opioid analgesics

One of the main obstacles slowing progress in OIRD management and investigation is the absence of standard definitions and lack of consistent assessment methods for OIRD in clinical practice and research.[14,24,101–103] Numerous different

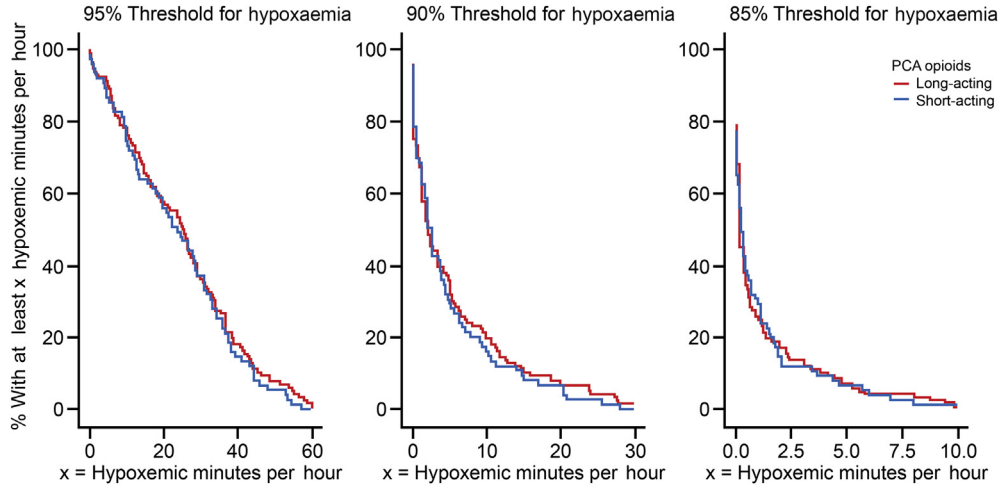

Fig 1. Raw S_pO_2 data showing the incidence (percentage) of patients with an average number of minutes per hour of hypoxaemia more than a set threshold during continuous oxygenation monitoring.[39] Three thresholds for hypoxaemia were considered as 95%, 90%, and 85% of S_pO_2. The red line represents patients receiving long-acting PCA opioids, and the blue line represents patients receiving short-acting PCA opioids. The y-axis is the percentage of patients with at least 'x' minutes of hypoxaemia per hour, and the x-axis is the number 'x' of hypoxaemic minutes per hour. There was no significant difference in the amount of hypoxaemia in patients receiving long- or short-acting opioids via a patient-controlled analgesia system.

parameters have been used to detect and define OIRD, alone and in combination, including respiratory rate, O_2 saturation, partial pressure of carbon dioxide (CO_2) in the arterial blood, exhaled end-tidal CO_2 ($ETCO_2$), and HR below and above variable thresholds.[6,42,89,104] This makes the accurate identification of patients with OIRD challenging. According to practice guidelines from the ASA, clinical signs of OIRD are respiratory rate <10 bpm, arterial O_2 saturation <90%, or arterial CO_2 tension >6.66 kPa.[105] However, other manifestations of OIRD are also frequently considered, such as sedation and somnolence, which often precede decreased ventilatory function and qualitative signs of respiratory distress (e.g. apnoea, snoring, or cyanosis), which may require intervention via jaw lift or positive airway ventilation.[3,105]

A uniform methodology applicable across future clinical trials of opioid analgesics to assess respiratory safety is lacking. Flaws in existing methodology in previous clinical trials to assess respiratory events have curtailed broader acceptance/adoption of specific techniques. For example, certain methodologies may be unreliable because of frequent false positives and false negatives.[21,103,106–111] Because OIRD is a multifactorial event, the definition of OIRD based on a single criterion may not be adequate or reliable.[103] Single-measure readings, such as O_2 saturation, can be confounded by patient factors (e.g. comorbid conditions) and by administration of supplemental O_2.[103,112–115] In addition, O_2 saturation measurements can stay in the 90–100% range even in patients with advanced hypercarbia, particularly with O_2 supplementation, and can decline rapidly in near respiratory arrest.[103,112,115] Evidence from CO_2 studies of opioid analgesics suggests that CO_2 response curves are also poor measures of OIRD.[116]

Although multiple parameters are frequently combined to assess sedation and respiratory status in patients treated with opioid analgesics (e.g. respiratory rate, O_2 saturation, and $ETCO_2$), a standardised assessment approach integrating these parameters has generally not been accepted or validated.[17,103] Significant opioid overdose necessitating naloxone reversal is uncommon in highly controlled clinical trial settings.[24] Surrogate markers of milder hypoxaemia would be valuable, but may be prohibitively expensive to incorporate into the protocols of large controlled treatment studies. The reversal of OIRD by naloxone is also problematic because it frequently leads to a decrease or loss of analgesia, and may cause serious cardiovascular complications.[117–120] Finally, the timing, pattern of onset, and duration of OIRD events are also important for the assessment of OIRD, but are often poorly documented or not reported, because continuous monitoring in the clinical setting is not established as a standard practice.[5,101,121] Thus, an unmet need remains for a comprehensive, clinically meaningful, and reliable approach to evaluating the respiratory safety of postoperative opioid therapy in the clinical trial setting.

Current methods for OIRD assessment

Improvements in monitoring are needed to reduce the serious risk to patient safety posed by OIRD, but the best way to evaluate opioid-related ventilatory dysfunction in clinical practice or trials has yet to be identified. A review of the characteristics of commonly used methods, such as monitoring respiratory rate, tidal volume, O_2 saturation, and $ETCO_2$, underscores the strengths and weaknesses of each individual method, and suggests that a comprehensive, multimodal monitoring approach may be warranted (Table 2).[19] In the USA, the continuous use of some or all of these monitoring modalities is certainly not the current standard of care on the general care floor. However, data do suggest a trend to improved outcomes with continuous rather than spot-check-based monitoring.[122]

Ventilatory assessments

Monitoring vital signs of ventilatory function is a valuable and widely implemented approach for the detection of OIRD. A reduction in respiratory rate frequently precedes changes in other respiratory parameters in patients who develop OIRD, thus serving as an expedient indicator of this adverse event. Respiratory rates lower than a predetermined value (e.g. <8 or <10 bpm) are common criteria for OIRD in clinical studies of the respiratory effects of postoperative pain therapy.[24] The standard technique for monitoring respiratory rate is intermittent visual assessment of patient breathing and use of transthoracic impedance pneumography. Thoracic impedance between two EKG electrodes is measured, and the changes in impedance as a result of thoracic movement produce a waveform on the monitor screen. The monitor then counts the waveform cycles to calculate the respiratory

Table 2 Strengths and weaknesses of OIRD monitoring methods commonly used in the postoperative period (adapted from Weinger and Lee[19]). Sensitivity: positive in the presence of OIRD (i.e. low false-negative rate); specificity: negative in the absence of OIRD (i.e. low false-positive rate); reliability: accuracy/availability (i.e. likelihood of an accurate and available reading at the time of OIRD); response time: average time from OIRD onset to abnormal reading. *When $ETCO_2$ is high, this method is highly specific for OIRD; when $ETCO_2$ is low (e.g. because of unknown dead space), this method is limited to measuring ventilatory frequency. †Respiratory rate alone may not be an adequate measure of OIRD in some patients. $ETCO_2$, end-tidal carbon dioxide; O_2, oxygen; OIRD, opioid-induced respiratory depression; Pa_{CO2}, partial pressure of carbon dioxide in arterial blood; S_pO_2, peripheral O_2 saturation.

Monitoring method	Sensitivity	Specificity	Reliability	Response time
$ETCO_2$ (intubated)	High	High	High	Fast
S_pO_2 (no supplemental O_2)	High	Moderate to high	High	Fast
$ETCO_2$ (unintubated)	High	Moderate to high*	Moderate	Fast
Pa_{CO2}	High	High	High	Slow
S_pO_2 (with supplemental O_2)	Moderate	Moderate	High	Slow
Clinical assessment (skilled clinician)	Moderate	Moderate to high	Moderate	Slow
Respiratory rate (newer technology)	Moderate	Moderate†	Moderate	Medium
Tidal volume (unintubated)	Moderate	Moderate	Low	Medium
Clinical assessment (less skilled clinician)	Low to moderate	Low to moderate	Low to moderate	Slow

rate.[123] Impedance pneumography has limitations when used alone.[124] Any patient motion, including cardiogenic artefacts and signal degradation with change in position, can cause a change in the impedance signal, thus providing a false-positive result. Although impedance pneumography effectively monitors respiratory effort, it does not measure the actual respiratory airflow. For example, a blockage of the airway may severely restrict the amount of air entering the lungs (obstructive apnoea), but because the chest wall continues to move (as the patient attempts to breathe), impedance pneumography will register respiratory movement. Automated respiratory rate monitoring modalities using pulse oximetry are currently in development and may provide accurate assessment of respiratory effort.[125]

Ventilatory assessment has the advantage of allowing for clinical judgement and expertise; conversely, its benefits may be limited by inadequate observer skill, proficiency, and knowledge.[106] Even when conducted by trained healthcare professionals, manual assessment of respiratory rate may be inaccurate and unreliable in hospitalised patients.[126,127] Its dependability may be particularly questionable in certain patient subgroups, such as patients with OSA, in whom airway obstruction is not typically associated with decreased respiratory rates and chest movement may be observed without effective ventilation because of airway obstruction.[106]

Differences in the practices and training of clinical staff within each participating clinical site may result in substantial variability in respiratory rate estimation, when reported in clinical trials.[14] The reliability of ventilatory assessment may also be hampered by inconsistencies in the frequency of monitoring. Furthermore, clinical studies of opioid analgesics for acute postoperative pain lack a standardised consensus on the frequency of respiratory rate monitoring (e.g. at least every hour or every 2–6 h), leading to a significant variability in measurements.[128] This variability reflects divergent protocol specifications for monitoring respiratory status amongst clinical studies and discrepancies in the monitoring recommendations of professional organisations, including the ASA and Centers for Medicare & Medicaid Services.[105,129]

O_2 saturation measured by pulse oximetry

The development of postoperative OIRD is also often assessed by measuring via pulse oximetry, a noninvasive, safe, inexpensive electronic device that can be used either continuously or during spot checks. Whilst an acceptable normal range for patients without pulmonary pathology is from 95% to 99%,[130] the threshold for low O_2 saturation that defines respiratory depression in clinical studies of postoperative pain varies (e.g. 90%, 85%, and 80%).[24]

Hypoxaemia in the postoperative period is common, persistent, potentially severe, and highly unpredictable.[5,39] In a prospective cohort study of the frequency, duration, and severity of post-surgical oxygen desaturation in noncardiac surgery patients, 37% of patients had at least one hypoxaemic episode, defined by S_pO_2 of <90%, which persisted for ≥1 h, and 11% had such an episode persisting for ≥6 h (Fig. 2).[5] Severely hypoxaemic episodes (S_pO_2 <80%) lasting for ≥30 min were reported in 3% of patients. This analysis was based on continuous and blinded oxygen saturation monitoring after noncardiac surgery. It therefore highlighted the amount of hypoxaemia that was going unnoticed in these patients. Importantly, there was no assessment of relationships with clinical outcomes.

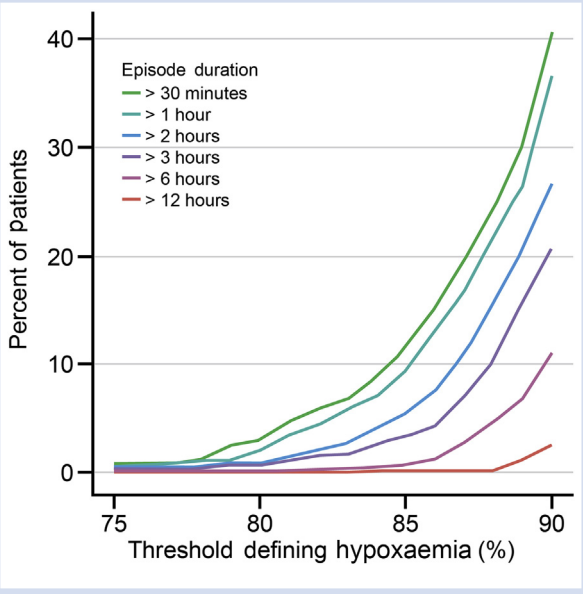

Fig 2. Smoothed S_pO_2 data from continuous monitoring of postoperative patients showing the incidence of at least one single hypoxaemic episode of varying minimal duration (under 90%, 85%, 80%, and 75%) under progressive S_pO_2 thresholds characterising hypoxaemia.[5] The x-axis is the varying thresholds of hypoxaemia, the y-axis is the percent of patients under a given threshold, and the different colours indicate the duration of time spent under a given threshold of hypoxaemia.

However, unseen hypoxaemia remains a serious safety issue. In its latest statement on OIRD, the Anesthesia Patient Safety Foundation (APSF) called for the use of continuous electronic monitoring with pulse oximetry, preferably using paging systems and centralised alarms, in all patients prescribed opioids who were not receiving supplemental O_2 in the postoperative period.[106] In a recent systematic review and meta-analysis of studies comprising surgical patients administered opioids after operation, the odds of detecting desaturation were significantly higher in the group monitored by continuous pulse oximetry than in the group monitored by intermittent nurse spot checks.[122]

Because pulse oximetry does not measure ventilation and hypoxaemia is a late sign of hypoventilation, especially in an O_2-enriched environment, the ability of oximetry to detect OIRD before it becomes clinically important is limited,[17,103] and its use may thus delay optimised care.[131] Moreover, pulse oximetry may indicate high O_2 saturation regardless of the presence of OIRD and significant hypercapnia in patients receiving supplemental O_2.[112,113,132,133] Finally, the waveform provided on the oximeter is considered unreliable, and the device is prone to frequent false alarms caused by such factors as low perfusion states, pigmented skin, light interference, and patient movement, leading healthcare professionals to ignore the alarms by silencing them or turning them off.[134,135]

CO_2 measured by capnography

Capnography is noninvasive, continuous, and electronic, providing an immediate assessment of the patient's condition.[136] Routine electronic monitoring with capnography is

supported by the APSF in all opioid-treated patients who are receiving supplemental O_2 after operation.[106] This technique is a near-surrogate measure of ventilation and perfusion,[17] and is more sensitive than oximetry because it measures ventilation rather than oxygenation, serving as an early indicator of OIRD.[17,136–139] In a study of postoperative patients, Hutchison and Rodriguez[137] reported that respiratory depression was detected at a significantly higher rate with capnography than with pulse oximetry. In another study, capnography was shown to detect compromised respiratory status earlier than both oxygen desaturation and diminished chest excursion.[138] In addition, capnography has been shown to identify OIRD earlier than oxygen desaturation in patients receiving supplemental oxygen.[140]

Perhaps the biggest shortcoming of capnography is that it is difficult to correlate $ETCO_2$ to arterial CO_2 (Pa_{CO2}). There is always a gradient between the two values and one, which may vary substantially depending on patient pathophysiology. The accuracy of $ETCO_2$ measurement is only correlated with alveolar $ETCO_2$ when patients take a full vital capacity breath, an unusual occurrence in the postoperative setting.[104] Another limitation of capnography is that its sensitivity may lead to high false-positive rates of alarms.[104] Imperfect positioning of the nasal cannula, patients' unique nasal anatomy, nasal obstruction or mouth breathing, and O_2 administered by mask may distort capnography findings. In addition, evidence is lacking that conclusively shows capnography directly improves patient outcomes.[17]

Sedation assessment

Excessive sedation has long been incorporated in clinical studies as an endpoint of imminent respiratory depression.[141] Depression of consciousness, or sedation, is one of the essential depressant effects of opioids on the CNS, reducing ventilation and pulmonary gas exchange.[15] The sedative effects of opioids may become apparent earlier than their respiratory effects, particularly when these analgesics are administered with other CNS depressants, and may therefore serve as an early warning sign of potential OIRD.[15,142–145] Sedation that results in unconsciousness is estimated to occur in patients with arterial CO_2 concentrations of 6.39–19.73 kPa.[146] Opioid-related sedative effects increase patients' risk of aspirating and losing the ability to clear airway obstruction.[15]

Simple sedation scoring systems, which are inexpensive and generally easy to use, can help monitor patients for increasing sedation after surgery.[17,143,147–149] Although dozens of valid sedation scales are available, those commonly implemented in clinical studies of opioids include the Moline–Roberts Pharmacologic Sedation Scale (MRPSS),[142] the Pasero Opioid-Induced Sedation Scale (POSS),[150] the Ramsay Sedation Scale (RSS),[151] the Richmond Agitation–Sedation Scale (RASS),[148] and the Riker Sedation–Agitation Scale (SAS).[152] The MRPSS and POSS rank levels of sedation on a continuum from alert to unresponsive, and provide guidance on appropriate pain management for each level. The RSS, RASS, and SAS are conventional sedation scoring tools developed to evaluate goal-directed sedation during surgery and in critical care patients, not specifically in the pain management setting.

The use of objective methods, such as the EEG, might be useful in detecting opioid-mediated sedation before the development of OIRD. Opioids produce a dose-related decrease in the frequency and amplitude of the EEG. Low-dose opioids show a loss of beta waves (high frequency; >14 Hz) and a slowing of alpha waves (7.5–13 Hz), moderate doses lead to diffuse theta waves (3.5–7.5 Hz), and some delta waves and at high doses there is presence of delta waves (high amplitude, slow waves 0–4 Hz).[153] Recent work by Montandon and colleagues[154] in paediatric patients has shown a correlation between morphine-induced reduction in respiratory rate and changes in EEG activity, and further studies are needed for wider adoption of this monitoring modality in the postoperative setting.

Despite the benefits of these tools, monitoring sedation is associated with several problems. To date, no single definition of sedation has been established, nor has a single sedation scoring system been universally accepted. Measurement of opioid-induced sedation can be challenging because it involves accessing arousal (i.e. response to stimuli) and concentration (i.e. ability to remain alert), and is influenced by many factors, including patient characteristics, the opioid administered, and treatment response.[48] In addition, similar to other potential measures of OIRD, sedation monitoring modalities have limited specificity and sensitivity.

Opioid reversal with naloxone

The competitive μ-opioid receptor antagonist, naloxone, may be required in the postoperative period to reverse the adverse effects of opioid intoxication, including OIRD.[33,155] Rescue therapy with naloxone effectively reverses opioid-induced ventilatory and CNS depression, improves patients' respiratory efforts in cases of excessive opioid dosing, and is generally indicative of a serious opioid-related respiratory event.[155,156] Naloxone utilisation often includes its use during rapid response team calls for clinical respiratory depression, and includes situations where a clear history of opioid intake may not exist. In actuality, significant opioid overdose necessitating naloxone reversal is rare in highly controlled clinical trial settings.[24,104] Naloxone has a clinical onset of action within 2 min of i.v. administration. However, an inadequate response or re-narcotisation after the administration of a single dose (0.4 mg i.v.) of naloxone may occur within 30–45 min after administration. This is because naloxone, being highly lipid soluble, has both a rapid uptake and a rapid elimination across the blood–brain barrier.[157,158] A naloxone infusion may best prevent the recurrence of OIRD.[159]

Reversal of OIRD using novel therapies

Drugs that act through non-opioid receptor systems may be of great benefit in the postoperative setting, as they may restore breathing and may also prevent OIRD without affecting analgesia. Three drug classes (potassium channel blockers, ampakines, and 5-hydroxytryptamine [serotonin, 5HT] receptor agonists) have shown promising results. The oldest and best-known K^+-channel blocker that stimulates breathing is doxapram; however, its use is associated with significant side-effects,[160] and there are concerns that it might mitigate the analgesic effects of opioids whilst at the same time reducing OIRD.[161] GAL-021, a novel developed K^+-channel blocker, is a respiratory stimulant acting predominantly at the carotid bodies and has the potential to reverse OIRD without affecting anti-nociception.[160] Animal studies show that ampakines increase respiratory rate by their action at amino-3-hydroxy-5-methyl-D-aspartate receptors in the

Table 3 Advantages and disadvantages of new OIRD monitoring technology that may be used in the postoperative period (adapted from Gupta and Edwards[128]). EtCO2, end-tidal carbon dioxide; MV, minute ventilation; RR repiratory rate; S_pO_2, oxygen saturation; TV, tidal volume.

Monitor	Parameters	Advantages	Disadvantages
Integrated Pulmonary Index	S_pO_2, $EtCO_2$, RR, and HR	Easy clinical interpretation Integrates HR with primary respiratory parameters into a single-digit numerical output	Not validated across all patient populations, including those inpatients on opioids
Integrated delivery and monitoring devices	S_pO_2, $EtCO_2$, and RR	Monitor tied to drug delivery Use of algorithms Interrupt drug delivery before notifying clinicians	Expensive Not widely available Both CO_2 sampling line and oximeter required
Acoustic monitor	RR	Better tolerated (e.g. children) Detects and VF Detects apnoea	Prone to motion and noise artefacts High false positives Alarm fatigue
Radar monitor	RR	No patient contact Better tolerated (e.g. children) Detects and VF Detects apnoea	Prone to motion artefacts High false positives Alarm fatigue
Bioimpedance	RR, TV, and MV	Sensitivity to ventilation Detects apnoea Detects ventilation before S_pO_2	Expensive Cumbersome to wear Prone to motion artefacts High false positives Alarm fatigue False negatives with obstructive apnoea
Inductance plethysmography and audiometry	RR, S_pO_2, and airway patency	Sensitivity to ventilation Detects apnoea Detects obstructive apnoea Detects ventilation before S_pO_2 Detects isolated S_pO_2	Expensive Cumbersome to wear Prone to motion artefacts High false positives Alarm fatigue

pre-Bötzinger complex,[162] an important area that is involved in respiratory rhythm generation.[162] Similarly, animal studies have shown that serotonin agonists increase respiratory drive via actions at 5HT1A, 5HT7, and 5HT4a receptors, but data in humans are lacking.[163] Subanaesthetic doses of esketamine can also counter OIRD.[164]

New tools and technologies for predicting risk and monitoring respiratory safety

Broader adoption of continuous electronic cardiorespiratory monitoring promises to improve early detection of respiratory compromise and reduce the incidence of OIRD and its complications, but questions remain about which parameters and patients to include when implementing this approach. In the recently completed PRediction of Opioid-induced Respiratory Depression In Patients Monitored by capnoGraphY (PRODIGY) trial, researchers evaluated the occurrence of OIRD detected by continuous multi-parameter monitoring (i.e. HR, respiratory rate, $ETCO_2$, and S_pO_2 via capnography and pulse oximetry) in patients on the hospital ward who received parenteral opioids for post-surgical or non-surgical pain, with the primary goal of deriving a risk prediction score.[42] The validated risk prediction tool that is in development based on the PRODIGY trial findings is expected to allow clinicians to ensure a safer recovery for patients after surgical and medical procedures by enabling a more accurate prediction of who is at risk of opioid-related respiratory events and earlier response to deteriorating respiratory function.

Given the limitations of existing assessment approaches, it is not surprising that many new assessment tools/monitoring systems are in development, including new monitors with smarter alert systems.[128] For example, 'smart' algorithms are currently under investigation that combine multiple individual parameters to create a single alarm threshold.[165] In the future, introduction of new systems that will analyse changing patterns amongst several combined vital signs is expected. These systems may allow for earlier alerts of impending respiratory depression, earlier intervention, and reduced morbidity. The Integrated Pulmonary Index (IPI) algorithm is one such fuzzy logic inference mathematical model combining S_pO_2, respiratory rate, PR, and $PetCO_2$ into a single value between 1 and 10 (higher numerical values indicating worsening status) that summarises the adequacy of ventilation and oxygenation. The validity of the index was tested on 523 patients, and correlated well with expert interpretation of the continuous respiratory data ($R=0.83$; $P<<<0.001$), with an agreement of −0.5 (1.4). Highest levels of sensitivity and specificity were seen based on IPI thresholds 3–6.[166]

Integrated monitoring of respiratory status (e.g. pulse oximetry and capnography), medication-delivery systems, and i.v. PCA devices permit the concurrent assessment of, and intervention for, emerging signs of respiratory depression.[128] A monitor using smart algorithms is able to identify early signs of respiratory depression, discontinue further opioid administration, and alert the medical staff. Whilst respiratory rate can currently be measured with capnography via a sampling line, other methods have also been evaluated, one of which is acoustic monitoring. The latter method is an attractive option because it does not require direct patient contact and has shown good reliability when used in extubated patients in PACU.[167,168] However, frequent errors and false alarms have slowed the development of acoustic monitoring and ventilation-monitoring radar

systems. Bioimpedance technology is being developed to estimate respiratory rate, ventilation, end-tidal volume, and apnoea via surface electrodes on the patient that capture changes in electrical conductance in the chest.[128] Using this technology, respiratory-volume monitors can detect imminent respiratory depression earlier than capnography alone. Table 3 details these and another newer technology that has potential clinical applications in the monitoring of OIRD in the postoperative period.

Conclusions

Postoperative pain remains inadequately controlled in a substantial proportion of patients, and can pose a heavy clinical, quality-of-life, and cost burden. Conventional opioids are the foundation of acute pain management in the peri-/postoperative setting, but opioid doses required to achieve maximum analgesia may result in unacceptable adverse events, including OIRD, particularly in at-risk patients.

The methodologies currently implemented to characterise and monitor respiratory safety events in patients receiving conventional opioids in clinical practice and trials, such as single-measure readings of respiratory function and opioid-reversal therapy, are not without potentially serious limitations. Several new tools and technologies are on the horizon that may substantially improve risk prediction and monitoring of respiratory complications in patients who require opioids to alleviate acute postoperative pain. However, more comprehensive and reliable approaches remain urgently needed to allow standardisation of respiratory safety assessment and comparison of respiratory safety amongst different therapeutics tested within the same trial and amongst different trials.

Authors' contributions

All authors made substantial contribution to the conception and design of this narrative review, acquisition of data, analysis and interpretation of data, and drafting the article or revising it critically for important intellectual content; provided final approval of the version to be published; and were in agreement to be accountable for all aspects of the work, thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

The authors thank Frances Chung of the University of Toronto for her initial guidance in the review's content, and Kunal Karamchandani, Penn State Health Milton S. Hershey Medical Center (Hershey, PA, USA) for his assistance in writing the manuscript. Editorial support for the first draft, figures, and styling for initial submission was provided by Kevin Wang of Xelay Acumen (San Mateo, CA, USA) and Donna McGuire of Engage Scientific Solutions (Philadelphia, PA, USA), and was funded by Trevena, Inc. (Chesterbrook, PA, USA).

Declaration of interest

SA is a consultant for Trevena, Inc. AKK is a consultant for Medtronic. SUI was an employee of Trevena, Inc. at the time of manuscript development. NS is an employee of Lotus Clinical Research, LLC, contracted by Trevena, Inc., to conduct Phases II and III studies of oliceridine.

Funding

Trevena Inc. (Chesterbrook, PA, USA).

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Handling editor: J.G. Hardman