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Postoperative Opioid-Induced Respiratory Depression: Who Are at the Greatest Risk?

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Abstract— **Opioid-induced respiratory depression (OIRD) is a life-threatening complication in postoperative patients receiving opioids for pain management. Identifying patients at higher risk for OIRD is crucial to preventing adverse events associated with opioids. This narrative review aims to evaluate the risk factors associated with postoperative OIRD. The review synthesizes evidence from 22 studies, involving over 1.8 million postoperative patients, to understand the complexities of OIRD. It highlights significant variability in the incidence of OIRD, ranging from 0.1% to 46%. This variation is attributed to differences in monitoring techniques, definitions of respiratory depression, methods of opioid administration, and patient-specific factors. Certain characteristics, comorbidities, and surgical and anesthetic factors are associated with a higher incidence of OIRD. Key intrinsic patient factors influencing OIRD include age, sex, BMI, opioid naïveté, and comorbidities such as obstructive sleep apnea, pulmonary, and cardiac diseases**

Keywords— **opioids; analgesia; risk factor; postoperative complications; respiratory depression**

I. Introduction

Opioid analgesics are routinely used to relieve pain in hospitalized patients. There has been a significant transition in the perioperative use of analgesic medications over the past two decades. The concept of pain as the fifth vital signs and regulatory emphasis on adequate postoperative pain management led to a dramatic rise in the administration of opioids for surgical procedures [1]. However, these medicines are associated with major adverse effects, including unexpected sedation progression, respiratory depression, and hypoxic and anoxic brain injury with subsequent death [2]. Patients with opioid-induced respiratory depression (OIRD) may experience longer hospital stays (by 55%), higher healthcare expenses (by 47%), an increased risk of 30-day readmissions (by 36%), and a 3.4-times higher risk of inpatient mortality [3].

The incidence of opioid-induced respiratory depression varied from 0.1 to 37% in the studies included in the review, [4-6] depending on the monitoring equipment used to identify respiratory depression (RD) and definitions of respiratory depression, as well as different administrations of opioids, routes of administration, opioid dosage, concurrent medication, and patient-specific characteristics [4-6]. The lowest estimates were recorded when the criteria for respiratory depression was naloxone delivery, and higher estimates were based on respiratory rate, hypercarbia, and oxygen desaturation [7, 8].

Opioids exert depressive effects on respiratory drive, level of consciousness, and airway muscle tone, leading to decreased ventilation and pulmonary gas exchange. This may further be characterized by increased arterial carbon dioxide concentration (hypercapnia), reduced tidal and minute volume (MV), as well as hypoxia. These characteristics can lead to irregular breathing, apnea, and even fatal respiratory arrest [9-12]. An improved comprehension of factors that increase susceptibility to OIRD might pave the way for more effective preventive measures. The main aim of this review was to assess existing studies to discover potential links between characteristics of patients and procedures, and the occurrence of OIRD in postoperative period. Understanding these risk factors will assist clinicians in implementing suitable precautionary measures, strategizing risk reduction, adjusting opioid dosage, and applying advanced monitoring for patients at greater risk.

II. Methods

This narrative review was conducted to locate, evaluate, and synthesize relevant studies. We included evidence that reports both OIRD events and risk factors that predict or are associated with the occurrence of OIRD. The

MEDLINE bibliographic database was searched to identify relevant literature. The search strategy included Medical Subject Headings (MeSH) terms and keywords. The main search concepts consisted of "Opioids, postoperative period, respiratory depression, and risk". These broad concepts were searched, and results were combined using the appropriate Boolean operators (AND, OR). The retrieval was restricted to the human population with English-language material published between January 1, 2003, and November 15, 2023.

This review included adult hospitalized patients (≥18 years), who were administered opioids during their postoperative period and had OIRD events. We included experimental and quasi-experimental study designs, including randomized controlled trials (RCTs), non-RCTs, before and after studies, and interrupted time-series studies. In addition, observational studies, including prospective and retrospective cohort studies, case-control studies, and cross-sectional analytical studies, are considered for inclusion. High-level evidence from systematic reviews was also eligible. Duplicate publications, conference abstracts, and editorials were excluded. Multiple publications of the same trial (companion reports) were excluded unless they contain additional outcome data of interest and meet the selection criteria outlined above. Studies that do not meet the selection criteria (e.g., do not mention the risk factors of OIRD), take place outside the hospital, or are not published in English were excluded.

The titles and abstracts of all citations retrieved from the literature search were assessed. Then full-text articles of the remaining studies were evaluated based on the selection criteria. To ensure rigor during the screening phase, titles and abstracts were screened, followed by the full text, using COVIDENCE software. Data extraction followed an iterative process, as the charting table is updated if additional unforeseen data are found. The charting table included descriptive data such as the first author, year of publication, study design, aim, study population, setting, sample size, number of patients with OIRD, location (post anesthesia care unit/ general ward) and time of OIRD (first 24 hours or after), type of surgery and anesthesia, medical comorbidities, outcomes reported, and risk factors for OIRD. Synthesis involved grouping evidence from similar reported risk factor or OIRD incidence.

III. Results

The initial Medline database search yielded a total of 372 articles. Additionally, 54 more articles were found through manual screening. Overall, 74 publications were selected after the title and abstract evaluation. A total of 52 articles were excluded after full-text reading, leaving 22 studies eligible in the review. The PRISMA flowchart was used to depict the study selection process (figure 1). Our analysis encompassed a diverse range of surgical procedures and patient demographics, drawing from a total of **1,831,994 surgical patients** across 22 studies.

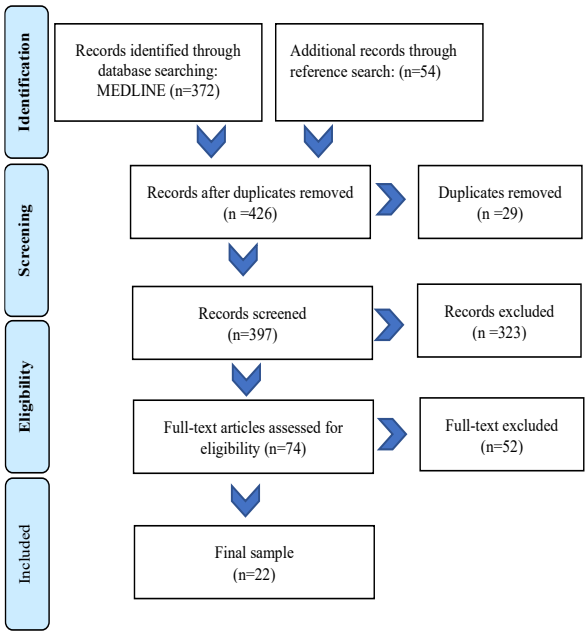

Fig. 1 PRISMA Flow Diagram

The incidence of OIRD varied significantly across studies, ranging from 0.1% to 46 %. This variation can be attributed to differences in monitoring techniques, definitions of respiratory depression, methods of opioid administration, and patient-specific factors. Notably, the use of advanced monitoring methods like continuous pulse oximetry and capnography revealed higher incidences of OIRD than traditional approaches.

A. Intrinsic patient factors

Several studies reported that older patients exhibited a significantly higher risk of OIRD [7, 8, 13-20], where with those aged over 80 years having 8.7 times the risk compared to younger age groups [19]. However, a retrospective cohort reported that advanced age might decrease (OR: 0.971; 95% CI: 0.968 to 0.973) the incidence of OIRD [21]. In several studies, a higher proportion of women were reported to have experienced OIRD [19, 21]. However, in a few studies male has been reported as a risk factor for OIRD [7, 20]. Higher BMI also reported as a risk

factor for RD events in postoperative period [14, 16, 20, 22]. Laporta at el. 2021 reported patients with lower body weight are at the higher risk of OIRD [15]. Current smoking status also introduced as significant risk factors for OIRD events (OR 1.91, 95% CI 1.12–3.42; p=0.023) [14]. Interestingly, opioid naivety was introduced as an important risk factor for OIRD [7]. However, Roy et al., 2022 reported that history of drug abuse might increase the OIRD incidence [21]. Patients with OIRD events had 3.4 times higher risk of inpatient mortality compared to those with no opioid related adverse drug events [23].

B. Surgical/anesthetic factors

Key risk factors for OIRD included presence of comorbidities such as obstructive sleep apnea (OSA) [7, 16, 19, 24-26], pulmonary disease (such as COPD) [8, 17, 19, 26], cardiac disease (CHF, CAD, cardiac dysrhythmia) [7, 8, 19, 24], diabetes mellitus [19, 24, 26], hypertension [19, 24], neurologic disease [19], renal disease [8, 19]. Furthermore, patients with opioid dependence, those receiving patient-controlled analgesia [19], and those receiving opioids on a scheduled rather than as-needed basis [21], and those with different routes of opioid administration [19], especially when combined with sedatives [19, 27] , showed a higher risk. Surgeries with general anesthesia, long acting sedatives and preoperative gabapentin can cause higher RD events [28]. Massive surgeries (digestive, musculoskeletal) were also associated with higher incidence of OIRD [21, 22]. There is a correlation with surgery time and OIRD incidence [22].

IV. Discussion:

While individual symptoms indicative of respiratory depression can be readily detected with modern technologies, the challenge in actual determination and classification of respiratory depression arises from the variability in reporting criteria and the intricate combination of symptoms a patient might experience. Although patients are monitored heavily after medical operations, OIRD remains elusive in many studies. This review reveals that the wide variability observed in the reported incidence of OIRD, ranging from 0.1% to 46%, indicates that there are multifactorial aspects contributing to OIRD. A possible contribution towards this variability in occurrence of OIRD is differences in monitoring techniques, leading to conflicting intrinsic patient risk factors (sex, age, comorbidities), as well as surgical/anesthetic risk factors being reported in these studies. Notably, the use of advanced monitoring methods [7], and classification techniques did uncover higher incidences of OIRD than more traditional approaches such as naloxone administration alone. Therefore, a more robust and standardized method of determining and classifying OIRD is needed moving forward to uncover the true occurrence of respiratory depression in postoperative patients.

Patients with pre-existing cardiac, pulmonary conditions or known OSA exhibited a heightened risk of experiencing postoperative OIRD [7, 8, 16, 17, 19, 24-26]. While chronic underlying illnesses are linked to an elevated incidence of postoperative issues, the exact pathways for these connections remain undefined. Such conditions might indicate a general decline in health and a reduced cardiorespiratory capacity, leading to compromised tolerance for postoperative opioid painkillers. Using patient-controlled analgesia (PCA) for pain relief might result in the administration of increased total opioid dosages, thereby heightening the likelihood of OIRD [19, 21, 29]. Additionally, this review highlighted patients were concurrently administered sedatives and opioids are more likely to have an episode of OIRD. The use of gabapentin preoperatively in individuals undergoing laparoscopic surgeries was linked to a heightened incidence of postoperative OIRD [19, 25, 27] . A closed claims analysis revealed that in 34% of the cases of postoperative OIRD, there was coadministration of sedatives and opioids [20].

The Anesthesia Patient Safety Foundation (APSF), The Joint Commission, and American Society for Pain Management Nursing (ASPMN) strongly recommended assessing the opioid-induced respiratory depression risk in all hospitalized patients who receive different types of opioids for postoperative pain management. By identifying individuals at high risk for opioid-induced respiratory depression, improving the education of healthcare professionals, and improving the assessment and monitoring of patients receiving opioids for pain management, patient harm associated with opioid-induced respiratory depression can be prevented [30-32].

V. Conclusion

In conclusion, the review emphasizes the complexity of OIRD in postoperative settings, influenced by factors like patient demographics, comorbidities, and surgical/anesthetic variables, highlighting the need for strategies to identify high-risk patients receiving opioid analgesia.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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