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Review

Use of Fentanyl in Pediatric Patients and Its Association with Postoperative Respiratory Events

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Abstract

Fentanyl is widely employed in pediatric anesthesia due to its rapid onset, potent analgesic properties, and favorable hemodynamic profile. Its use spans a range of procedures, from minor day-case surgeries to complex operations requiring deep sedation and prolonged analgesia. However, the pharmacologic advantages of fentanyl must be carefully weighed against its potential to induce postoperative respiratory events, particularly in young and vulnerable patients. Immature respiratory control mechanisms, reduced metabolic clearance, and altered protein binding in neonates and infants increase sensitivity to fentanyl's respiratory depressant effects. Variability in pharmacokinetics, driven by age, genetic polymorphisms, and comorbidities, further complicates standardized dosing. Postoperative respiratory events such as apnea, hypoventilation, airway obstruction, and oxygen desaturation are disproportionately common in pediatric patients administered fentanyl, especially those with conditions like obstructive sleep apnea, obesity, or neurological impairment. These events often occur during the immediate postoperative phase but may also present later during ward recovery, underscoring the importance of continued surveillance beyond the post-anesthesia care unit. Risk mitigation involves strategic dosing, use of non-opioid adjuncts, and regional anesthesia to reduce fentanyl exposure. Continuous monitoring through pulse oximetry and capnography enables earlier detection of respiratory compromise, improving clinical response times. Institutional protocols emphasizing individualized care, standardized monitoring, and multidisciplinary communication enhance safety in opioid-based pediatric pain management.

Keywords: *fentanyl, pediatric anesthesia, respiratory depression, postoperative monitoring, opioid safety*

Introduction

Fentanyl, a synthetic opioid approximately 50 to 100 times more potent than morphine, is widely used for perioperative analgesia due to its rapid onset, short duration of action, and high lipid solubility. In pediatric anesthesia, fentanyl has become a mainstay agent for both intraoperative and postoperative pain control, particularly because of its predictable pharmacokinetics and ease of titration. However, its use in children is complicated by unique developmental pharmacological factors and an elevated sensitivity to respiratory depressant effects, which poses significant clinical concerns, especially in the postoperative period (1).

Postoperative respiratory events (PREs) are among the most serious complications in pediatric patients receiving opioid analgesia. These events include apnea, hypoventilation, hypoxia, and airway obstruction, often requiring interventions ranging from oxygen supplementation to reintubation. The immaturity of respiratory control mechanisms in infants and younger children, compounded by pre-existing conditions such as obstructive sleep apnea, neuromuscular disorders, or obesity, increases the likelihood of adverse respiratory events following opioid administration. Furthermore, opioids like fentanyl exert a dose-dependent suppression of the brainstem respiratory centers, and even small miscalculations in dosage can lead to significant respiratory compromise (2).

The risk is exacerbated in the immediate postoperative phase when children are transitioning from the monitored environment of the operating room to less intensively observed settings such as the post-anesthesia care unit (PACU) or general wards. During this transition, residual sedation, analgesic needs, and individual pharmacogenomic variability in opioid metabolism can create a critical window in which respiratory events are most likely to occur. Several studies have demonstrated that fentanyl, due to its high potency and potential for accumulation with repeated dosing or continuous infusion, carries a higher risk of delayed respiratory depression compared to shorter-acting agents like remifentanil (3).

Despite these risks, fentanyl remains indispensable in pediatric anesthesia due to its effectiveness in blunting hemodynamic responses to surgical stimulation and reducing the requirement for inhalational anesthetics. Balancing effective analgesia with patient safety is therefore a critical concern. Clinicians must carefully assess patient-specific risk factors such as age, weight, comorbidities, and surgical context when selecting fentanyl dosing regimens. Moreover, the application of multimodal analgesia strategies—combining opioids with non-opioid agents such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), and regional techniques—has emerged as a valuable approach to minimizing opioid consumption and reducing the incidence of PREs (4). As the demand for pediatric surgical procedures increases and enhanced recovery protocols are more widely implemented, understanding the pharmacodynamics of fentanyl and its association with respiratory outcomes is essential. Ongoing efforts in monitoring technologies, risk stratification models, and individualized pharmacologic strategies are vital to ensuring safer use of fentanyl in children undergoing surgery.

Review

The use of fentanyl in pediatric patients, while highly effective for pain management, necessitates vigilant consideration of associated respiratory risks. Children, especially infants and toddlers, exhibit heightened sensitivity to opioids due to immature respiratory centers and variable metabolic clearance. This vulnerability significantly increases the risk of postoperative respiratory events, which can lead to hypoxia, prolonged PACU stays, and even reintubation if not promptly managed. A study by Sadhasivam et al. demonstrated that genetic polymorphisms influencing opioid metabolism can further alter fentanyl pharmacokinetics, making some children more susceptible to respiratory depression despite standard dosing protocols (5). Additionally, the route and method of administration play a critical role in determining safety; continuous infusions, though useful for steady analgesia, may lead to drug accumulation,

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particularly in patients with impaired hepatic or renal function.

In recent years, the trend has shifted towards incorporating multimodal analgesia strategies to reduce the opioid burden. Regional anesthesia and non-opioid adjuvants such as dexmedetomidine have shown promise in minimizing the need for high-dose fentanyl without compromising analgesia (6). Ultimately, individualized approaches that consider patient-specific risk factors and incorporate non-opioid techniques are essential for balancing effective pain control with the mitigation of respiratory complications in pediatric surgical populations.

Pharmacological Properties of Fentanyl and Pediatric Considerations

Fentanyl, a potent synthetic μ-opioid receptor agonist, exhibits unique pharmacological characteristics that distinguish it from other opioids used in pediatric anesthesia. Its high lipid solubility enables rapid penetration across the blood-brain barrier, resulting in a swift onset of analgesic and sedative effects. In children, the onset can be even faster due to a relatively higher cerebral blood flow in infancy and early childhood, which enhances central nervous system exposure. This rapid effect profile is advantageous for managing acute procedural pain but presents a narrower therapeutic window, particularly in vulnerable pediatric populations (5, 7).

Volume of distribution (Vd) for fentanyl in neonates and infants is notably larger compared to adults due to a higher proportion of total body water and reduced fat content. This increased Vd contributes to a prolonged elimination half-life in neonates, even though the drug itself has a short context-sensitive half-time under normal conditions. Hepatic metabolism, primarily via CYP3A4-mediated N-dealkylation, converts fentanyl to norfentanyl, an inactive metabolite. However, hepatic enzyme activity in neonates and infants is immature, reducing clearance and enhancing systemic exposure. This immaturity leads to dose accumulation when administered repeatedly or by infusion, elevating the potential for delayed respiratory depression (8).

Respiratory sensitivity in the pediatric population is heightened by fentanyl's central action on the medullary respiratory centers. Infants, in particular, exhibit an irregular breathing pattern and underdeveloped response to hypercapnia and hypoxia. When exposed to fentanyl, these vulnerabilities can manifest as prolonged apneas, oxygen desaturation, or hypoventilation, especially in the postoperative setting. The drug's impact on respiratory drive is dose-dependent, yet in neonates, even lower doses may produce exaggerated effects. This is further complicated by interindividual variability, which is more pronounced in children due to differences in genetic polymorphisms affecting drug metabolism and receptor sensitivity (9).

Distribution and metabolism are only part of the picture. Protein binding also plays a critical role in fentanyl's pharmacologic behavior. Fentanyl binds primarily to α1-acid glycoprotein, a plasma protein with lower concentrations in neonates than in older children and adults. The reduced protein availability results in a larger free (active) drug fraction in circulation, enhancing both therapeutic and adverse effects. During stress, surgery, or illness, α1-acid glycoprotein levels may fluctuate, altering drug dynamics in unpredictable ways. This requires constant reassessment of dosing strategies, particularly in infants under six months of age.

Age-specific dosing regimens are necessary not only because of these pharmacokinetic differences but also due to variability in receptor expression and sensitivity. The density of μ-opioid receptors in the central nervous system increases postnatally, with a corresponding shift in analgesic responsiveness. Studies in animal models suggest that early-life exposure to opioids like fentanyl may induce long-term changes in receptor expression, potentially altering pain thresholds and opioid requirements later in life. Though clinical data in humans remains limited, these findings prompt caution in both dosing and repeated exposure (10).

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The formulation and route of administration influence fentanyl's pharmacokinetics in pediatric patients. Intravenous bolus dosing produces rapid peak concentrations, which may cause abrupt respiratory suppression. In contrast, continuous infusions offer steadier plasma levels but carry a risk of accumulation, especially in low-weight infants with immature clearance mechanisms. Transmucosal and transdermal routes are seldom used in acute pediatric care but remain options in select chronic settings. The intranasal route, gaining traction for procedural sedation in older children, offers rapid absorption and non-invasive delivery, yet demands precise dosing to avoid overdose or inadequate analgesia.

Beyond the clinical application, pharmacodynamics in pediatrics must be contextualized within the child's developmental physiology. Neonates and infants have a higher cardiac output relative to body weight, altered organ perfusion, and immature blood-brain barrier integrity. These elements combine to produce divergent fentanyl effects when compared to adults. Sedation, bradycardia, and muscle rigidity are more commonly observed in the youngest patients, requiring readiness to intervene with airway support or opioid antagonists such as naloxone (11, 12). Pediatric anesthesiologists, therefore, must navigate a pharmacological landscape shaped by age-dependent physiology, variable metabolism, and sensitivity to opioid effects. Fentanyl's clinical utility hinges on a comprehensive understanding of these principles, tailored dosing, and vigilant perioperative monitoring to ensure both efficacy and safety across all pediatric age groups.

Incidence and Risk Factors of Postoperative Respiratory Events

PREs remain a prominent source of morbidity in pediatric patients receiving opioids, particularly fentanyl. These events, ranging from mild oxygen desaturation to life-threatening apnea or airway obstruction, tend to cluster in the early recovery period. Data from multicenter analyses show that opioid-related respiratory depression accounts for a disproportionate number of adverse events in pediatric anesthesia, especially within the first 30 to 60 minutes post-extubation (13). The incidence varies with age, type of surgery, pre-existing comorbidities, and the intensity of monitoring, with reported rates as high as 20% in high-risk populations. Notably, these complications are often underreported in routine clinical settings due to inconsistent documentation and variable definitions across institutions.

The youngest children, particularly those under six months of age, show the highest vulnerability. Immature respiratory control mechanisms, including a blunted response to hypercapnia and increased susceptibility to central apnea, interact unfavorably with fentanyl's potent depressant effects. Premature infants, even when corrected for gestational age, carry residual risk due to altered neurochemical control of ventilation. Studies have documented prolonged apnea episodes in this group following standard opioid dosing, especially when no formal apnea monitoring is applied in the recovery setting (14). Furthermore, children with craniofacial anomalies, neuromuscular disorders, or a history of central hypoventilation are more likely to experience severe forms of PREs.

The presence of obstructive sleep apnea (OSA) significantly amplifies the risk profile. Even in cases where OSA has not been formally diagnosed, features such as habitual snoring, observed apneas during sleep, or daytime somnolence should alert clinicians to a higher baseline risk. OSA alters pharyngeal muscle tone and increases the likelihood of upper airway collapse under sedation. Fentanyl's suppression of arousal mechanisms further exacerbates this tendency. A large retrospective cohort study found that children with suspected or confirmed OSA had more than triple the odds of requiring unplanned respiratory interventions in the PACU following opioid administration, with fentanyl being the most frequently implicated drug (15).

Obesity also contributes to a higher incidence of respiratory complications. Altered lung mechanics, including decreased functional residual capacity and increased airway resistance, reduce the margin for ventilatory stability under sedation. These changes

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are magnified when supine positioning and residual anesthetic effects are present. Dosing errors due to weight misclassification—using total body weight instead of lean body weight—further complicate opioid titration in obese children. Respiratory compromise may not manifest immediately but can evolve insidiously in the hours following fentanyl administration, particularly with repeated boluses or background infusions. Surveillance beyond the PACU period is often warranted in these patients, yet standard protocols may not address this extended vulnerability (16).

Procedural context matters. Airway surgeries, such as tonsillectomy or adenoidectomy, carry intrinsic risks for airway obstruction postoperatively. When combined with intraoperative opioid use, especially fentanyl, the incidence of PREs increases significantly. This has led to modified analgesic strategies in these settings, often minimizing or eliminating intraoperative fentanyl in favor of non-opioid alternatives or regional anesthesia. Likewise, surgeries requiring neck flexion or positioning that compromises airway patency tend to be associated with a higher rate of desaturation episodes during emergence and in the PACU. Muscle rigidity induced by high or rapid fentanyl bolus dosing—particularly chest wall rigidity—can mimic upper airway obstruction and further complicate recovery (17).

Environmental and systemic factors also influence the occurrence of PREs. Inadequate monitoring in the early postoperative period remains a recurring theme in adverse event analysis. Many institutions rely on intermittent vital sign checks rather than continuous monitoring of oxygen saturation or capnography, especially once the patient leaves the PACU. Pediatric patients who appear stable initially may still be at risk, especially if their sedation depth and ventilatory function are not consistently reassessed. Staff-to-patient ratios, recovery room layout, and the training level of personnel tasked with monitoring can directly affect early recognition and intervention. Delayed responses to desaturation or apnea events often result from this systemic gap in surveillance (18).

Strategies for Risk Mitigation and Clinical Monitoring Protocols

Minimizing the occurrence of postoperative respiratory events in pediatric patients exposed to fentanyl requires a blend of tailored pharmacologic choices and vigilant, context-aware monitoring. There is no single intervention that eliminates risk, but several strategies—both preventive and responsive—have been shown to reduce adverse respiratory outcomes when integrated into perioperative care plans. Individualized risk assessment remains the starting point. Age, comorbidities such as sleep-disordered breathing or neuromuscular disease, obesity, and the nature of the surgical procedure must all be factored into preoperative planning. These risk profiles help determine whether fentanyl is appropriate and what dosing thresholds should be observed (19).

Dosing adjustments are particularly necessary for infants and children with impaired metabolism or increased drug sensitivity. Employing lean body mass rather than total weight when calculating opioid dosages prevents inadvertent overdose in obese children. Similarly, reducing the rate of intravenous bolus administration lowers the likelihood of chest wall rigidity and abrupt respiratory compromise. Some centers opt for low-dose fentanyl in combination with non-opioid adjuncts—acetaminophen, NSAIDs, or dexmedetomidine—to achieve sufficient analgesia while minimizing opioid exposure. This multimodal model, when appropriately applied, supports both analgesic effectiveness and improved safety outcomes in the postoperative phase (20).

Regional anesthesia offers additional benefit, not only by limiting the need for systemic opioids but also by promoting earlier extubation and less postoperative sedation. Caudal epidurals, peripheral nerve blocks, and local infiltration techniques are effective in a wide range of pediatric surgeries, and their use has expanded in part due to mounting concern over opioid-related adverse events. In procedures where regional techniques are not feasible, intraoperative strategies such as remifentanil infusions with early conversion to non-opioid analgesics in the recovery room have been

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employed with some success. These regimens preserve intraoperative hemodynamic control while reducing postoperative fentanyl burden.

Monitoring protocols plays a decisive role in detecting early signs of respiratory compromise. Standard pulse oximetry is widely used but has limitations, especially in patients receiving supplemental oxygen, where desaturation may be masked until ventilation is severely impaired. Capnography provides a more immediate reflection of respiratory status, capturing changes in carbon dioxide exhalation that often precede oxygen desaturation. Continuous capnography, when paired with oxygen saturation monitoring, delivers a clearer picture of ventilatory adequacy and sedation depth, and has been associated with faster intervention when respiratory events occur. Despite this, routine capnography is underused outside the operating room and intensive care settings, largely due to logistical and cost barriers (21).

Institutional protocols have a measurable impact on outcomes. Hospitals with formalized postoperative opioid monitoring policies tend to report fewer unanticipated respiratory events. These policies include standardized sedation scores, routine nurse education on opioid effects, early warning systems for deteriorating patients, and criteria for when anesthesiology or pain services should be consulted. Implementation of these systems often coincides with improved response times to hypoventilation or apnea episodes. In some cases, clinical decision support tools embedded within electronic medical records have been used to prompt dosage checks, risk stratification, or alerts for cumulative opioid exposure in real-time (22).

Careful planning must also extend beyond the PACU. Many adverse events occur after discharge from intensive monitoring environments, especially in patients transferred to general wards. High-risk individuals may benefit from prolonged surveillance, including overnight oximetry or step-down unit admission. Where feasible, advanced monitoring systems with integrated alarm thresholds and remote notification systems improve situational awareness for bedside staff. Engagement of parents or guardians in recognizing early signs of respiratory distress adds another layer of vigilance, especially when discharge is planned on the same day. The continuity of care from OR to PACU to ward becomes the critical scaffold on which patient safety is built (23). Prevention of fentanyl-related respiratory events is less a matter of avoiding the drug entirely than of building an anticipatory system of care around its use. That system relies not only on pharmacology and technology but also on institutional culture, clinician training, and consistent implementation of risk-sensitive workflows.

Conclusion

Fentanyl remains a valuable analgesic in pediatric perioperative care but demands cautious, individualized use. Understanding age-specific pharmacology and patient risk factors is central to minimizing respiratory complications. Comprehensive monitoring and multimodal analgesic strategies enhance safety without compromising efficacy. An integrated, anticipatory approach across surgical settings ensures optimal outcomes for children.

Disclosures

Author contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Ethics statement

Non-applicable.

Consent for publications

Not applicable.

Data availability

All data is provided within the manuscript.

Conflict of interest

The authors declare no competing interest.

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