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- Received Date: 01 July 2026
- Accepted Date: 07 July 2026
- Publication Date: 13 July 2026

Keywords

Epidural morphine; Neuraxial opioids; Respiratory depression; Postoperative analgesia; Opioid toxicity; Naloxone reversal; Delayed adverse event

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Delayed Neuraxial Morphine-Induced Respiratory Depression; a Rare but Possible Adverse Event

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Abstract

Introduction: Effective postoperative pain management is essential for enhanced recovery and shorter hospital stays. Epidural morphine remains a widely used neuraxial analgesic due to its prolonged duration of action; however, it carries a rare but significant risk of delayed respiratory depression. This adverse event is often underrecognized, particularly when epidural rather than intravenous opioids are administered.

Case Report: We report the case of a 70-year-old woman who underwent sigmoidectomy for recurrent diverticulitis. General anesthesia was achieved with fentanyl, midazolam, propofol, and rocuronium, followed by 4 mg epidural morphine at the end of the procedure. The surgery and immediate recovery were uneventful. Approximately 11 hours later, the patient developed sudden unresponsiveness, pinpoint pupils, and a respiratory rate of 8–10 breaths per minute, although oxygen saturation remained above 95%. No additional opioids were administered postoperatively. Supportive measures were initiated, and intravenous naloxone produced immediate improvement in mental status and respiratory effort. The epidural catheter was removed, and the patient was transitioned to non-opioid analgesics. Her subsequent hospital course was uneventful, and she was discharged home on postoperative day four.

Discussion: Delayed respiratory depression following neuraxial morphine is a known but uncommon complication, often occurring up to 24 hours after administration. Risk factors include advanced age, renal impairment, sleep apnea, and co-administration of sedatives. This case underscores the importance of vigilant monitoring—particularly respiratory rate, oxygenation, and consciousness—beyond the immediate postoperative period. Current guidelines recommend structured monitoring intervals, yet real-world adherence varies, leaving patients vulnerable to delayed toxicity.

Conclusion: Our case reinforces that epidural morphine, though effective for pain control, carries the potential for severe delayed respiratory depression. Clinicians must maintain a high index of suspicion for opioid toxicity even in the absence of intravenous dosing. Early recognition and prompt administration of naloxone can be lifesaving, and structured multidisciplinary communication is vital to ensuring patient safety in the postoperative setting.

Introduction

Effective postoperative pain management relies on a multimodal approach that incorporates different classes of analgesics, administered via intravenous, subcutaneous, regional anesthesia techniques, or patient-controlled methods. Properly managed postoperative pain has been associated with shorter hospital stays, lower healthcare costs, and improved recovery times. While opioids remain a cornerstone of postoperative pain control in some institutions, other modalities, such as epidural anesthesia, are also utilized based on varying protocols. Epidural analgesia may serve as the primary anesthetic method or be combined with other techniques [1]. In certain surgical procedures—including abdominal, thoracic, vascular, gynecologic, and lower extremity orthopedic surgeries—intrathecal opioid administration can be used alongside

general anesthesia [2].

Morphine was the first opioid approved by the U.S. Food and Drug Administration (FDA) for regional anesthesia. Epidural administration of morphine sulfate at a dose of 5 mg is an effective method for postoperative pain relief, offering analgesia that can last up to 24 hours. The overall risk of respiratory depression from neuraxial opioids is estimated to be less than 1%, a rate comparable to that of parenteral opioid administration. However, morphine use—regardless of the route of administration—can be associated with side effects such as constipation, nausea, vomiting, sedation, dizziness, bradycardia, hypotension, urinary retention, and pruritus [3].

This report presents a case of epidural morphine overdose in an elderly patient who exhibited significant opioid-related toxicity but demonstrated a remarkable response to naloxone treatment.

Citation: Hassanesfahani M, Bucci L, Alla M, Louis MA. Delayed Neuraxial Morphine-Induced Respiratory Depression; a Rare but Possible Adverse Event. Surg Res J. 2026;6(1):1-3.

Case Report

A 70-year-old woman underwent a sigmoidectomy for recurrent diverticulitis under general anesthesia, which included 100 mcg fentanyl, 2 mg midazolam, 100 mL propofol, and a total of 70 mg rocuronium, administered at 8:00 AM. She weighed 65 kg, with a baseline glomerular filtration rate of 75 mL/min and normal renal function parameters. The procedure began at the same time, and at 10:30 AM, she received 4 mg of morphine via an epidural catheter. Surgery concluded at 11:00 AM, with the patient tolerating the procedure well and experiencing no intraoperative complications. Her intraoperative urine output was 280 mL, and postoperatively, she maintained a urine output exceeding 0.6 - 0.7 mL/kg/h.

Initially, she remained hemodynamically stable in the recovery room. However, approximately 11 hours after epidural morphine administration, she became unresponsive, with pinpoint pupils and a respiratory rate of 8–10 breaths per minute, though her oxygen saturation remained above 95%. Supportive care was initiated, and she promptly responded to naloxone administration (dosage to be specified), with an immediate improvement in respiratory rate and pupillary size. Notably, she had not received any additional opioids or pain medications postoperatively, as she never reported pain.

The epidural catheter was removed without complications, and she was transitioned to oral non-opioid analgesics for pain management. Her subsequent hospital course was uneventful, and she was discharged on postoperative day 4. She has since completed adjuvant chemotherapy as an outpatient and is currently doing well.

Discussion

Opioids are widely regarded as one of the most effective options for managing postoperative pain. Morphine, being hydrophilic, has a slower onset of action but provides prolonged analgesia compared to more lipophilic opioids like fentanyl and sufentanil. When administered epidurally, a lower dose of morphine is required than when given intravenously, primarily due to its enhanced selectivity for the spinal cord. However, its use should be approached with caution, as it carries the risk of rare but potentially serious adverse effects [4].

Morphine toxicity is most commonly associated with accidental overdose. Dahl et al. documented a case in which 400 mg of morphine was mistakenly administered epidurally instead of intravenously [5]. Another report described a 31-year-old woman at 39 weeks of gestation who received 25 mg of intrathecal morphine instead of bupivacaine [6]. Both patients developed respiratory depression and required naloxone infusion for reversal. Ritter et al. identified a strong correlation between opioid overdose and cardiac arrest, consistent with findings from other hospital-based studies. These observations align with the established pathophysiology of opioid toxicity, emphasizing the potential risks of respiratory failure and cardiac complications [7].

Opioid-induced respiratory depression is estimated to affect approximately 0.5% of patients receiving opioids for acute postoperative pain, though the risk exists for all individuals undergoing opioid therapy [8]. Notably, epidural administration of morphine carries the potential for delayed respiratory depression, which may manifest up to 24 hours following a single dose. The absence of standardized diagnostic criteria in the literature makes it challenging to determine the exact incidence of this rare complication [9].

Opioid-induced respiratory depression can be effectively reversed with opioid antagonists like naloxone, which has been a key treatment for over 50 years and plays a vital role in addressing the opioid crisis. As a competitive μ -opioid receptor antagonist, naloxone is commonly utilized by emergency responders and law enforcement personnel [10]. However, its use in opioid reversal can trigger adverse effects, including pain, psychological distress, sympathomimetic reactions, and, in severe cases, pulmonary edema, due to the sudden release of catecholamines through central mechanisms [9,11].

Current guidelines on preventing respiratory depression from neuraxial opioids remain limited and emphasize careful risk stratification and monitoring. Patients with underlying respiratory conditions—such as COPD, acute asthma, obstructive sleep apnea, obesity, or renal impairment—are at higher risk, and thorough pre-administration assessment is essential. This includes reviewing medical history, baseline vital signs, concurrent medications, and prior adverse reactions to opioids. Monitoring protocols recommend close observation of ventilation, oxygenation, and consciousness, particularly within the first 24 hours, as delayed respiratory depression has been reported even after single-dose neuraxial administration [9,12,13].

Elderly patients present an additional challenge due to reduced hepatic and renal clearance, which increases susceptibility to drug accumulation and delayed toxicity. Lower initial dosing and intensified monitoring are advised for this population. Our case reinforces that respiratory depression and toxicity are not limited to intravenous administration; similar vigilance is warranted following epidural morphine to ensure early recognition and prompt management of this potentially life-threatening complication [14].

Conclusion

Opioids play a crucial role in managing postoperative pain and facilitating recovery; however, they are not without risks. In our case, morphine overdose occurred 11 hours postoperatively, underscoring the need for vigilance in monitoring patients for delayed adverse effects. Clinicians should consider opioid toxicity in the differential diagnosis of perioperative changes in consciousness and vital signs. Effective communication among anesthesiologists, surgeons, and recovery teams is essential to ensuring awareness of administered medications and their potential side effects. Prompt administration of naloxone is critical for opioid reversal, as delays can have life-threatening consequences. This article highlights the importance of maintaining a high index of suspicion for opioid-related complications and reinforces the need for seamless interdisciplinary communication during patient handoff and postoperative care.

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