



EDITORIAL:

Reconsidering Opioid-Sparing Anesthesia— The Case for Individualized Multimodal Analgesia Care

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INTRODUCTION

Efforts to reduce perioperative opioid exposure have accelerated over the past decade in response to the opioid epidemic, enhanced recovery pathways, and growing awareness of opioid-related adverse events. Opioid-sparing anesthesia has emerged as one strategy to address these concerns, emphasizing multimodal analgesia including regional anesthesia, nonopioid systemic analgesics, and adjunctive modalities to eliminate intraoperative and postoperative opioid use. While the goals of minimizing opioids are well intentioned, elimination of opioids without individualized consideration of patient physiology, surgical pain mechanisms, and postoperative care capacity may introduce unintended patient safety risks. Patient safety is best supported by thoughtful, individualized clinical decision-making rather than rigid adherence to protocolized targets.¹ In this context, the choice of analgesic strategies warrants careful examination. Opioid elimination may shift analgesic risk toward other modalities such as exclusive nonopioid medications and regional anesthesia techniques, each of which carries risks potentially resulting in inadequate analgesia, increased physiological stress, renal injury, bleeding, or unsupervised opioid escalation after discharge.²

THE RISK OF INADEQUATE PAIN MANAGEMENT

One of the major concerns when employing new pain management techniques is inadequately treated pain, which can increase the risk of postoperative delirium, delayed recovery, and chronic pain development.³ A blind spot exists in research of nonopioid analgesia techniques that focus on the reduction of opioid milligrams without regard to analgesic efficacy.⁴ The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group reviewed 73 randomized controlled trials of opioid-sparing analgesic approaches and reported only 18% included pain as a primary outcome.⁴ While reductions in opioid use are desired, few would advocate reducing opioids without adequate pain relief. Demonstrating that nonopioid methods can effectively manage pain while simultaneously reducing



opioids should be the focus of clinical, safety-driven research. Researchers are encouraged to incorporate pain measures either through using multiple primary endpoints (i.e., opioid use and pain), incorporating a single composite endpoint that includes opioid use and pain, or including a noninferiority study design for the pain outcome.⁴

INCREASED RISK OF DRUG-DRUG INTERACTIONS

A hallmark of multimodal analgesia is the inclusion of drugs targeting different receptors and pathways involved in pain processing; however, as the number of drugs increase, so does the risk for drug-to-drug interactions. Taking 5 or more medications leads to an 80% risk of potential cytochrome P450-mediated interactions, and multimodal pain management protocols often include 3 or more medications.^{2,5} The CYP2D6 enzyme is particularly concerning as it metabolizes most oral opioids (oxycodone, hydrocodone, tramadol).⁶ The concurrent consumption of another medication metabolized by CYP2D6 can result in competitive inhibition by stronger-affinity CYP2D6 substrates and to non-competitive inhibition interactions by CYP2D6 inhibitors. Strong CYP2D6 inhibitors include commonly prescribed antidepressant medications (e.g., fluoxetine, bupropion, paroxetine), and the moderate CYP2D6 inhibitors duloxetine

and celecoxib are often included in multimodal analgesic protocols. In an orthopedic trauma study, individuals taking a CYP2D6 inhibitor exhibited significantly longer duration of postoperative opioid use than those not taking a CYP2D6 inhibitor (median 33 days vs. 4 days, $p < .001$).⁷ Similar findings were reported after total joint replacement surgery.⁸ A recent examination of geriatric patients receiving polypharmacy reported that, after controlling for age, co-morbidities, and kidney function, each additional CYP2D6 inhibitor drug taken decreased the CYP2D6 enzyme activity by half.⁹ The inclusion of multiple medications increases the risk of drug-to-drug interactions leading to increased adverse effects and may even increase the risk of prolonged opioid use if CYP2D6 inhibitors are co-administered.

NONOPIOID ANALGESIC RISKS

Beyond increasing the risk of drug interactions, common nonopioid drugs included in multimodal analgesia protocols present additional adverse effects. Gabapentin is associated with reports of respiratory and central nervous system depression and cognitive dysfunction, particularly when combined with rescue opioids.^{10,11} Concerns for gabapentinoid misuse are also increasing as this drug class replaces opioid analgesics.¹²

Nonsteroidal anti-inflammatory drugs (NSAIDs) and cyclooxygenase-2 (COX-2) selective inhibitors are frequently substituted for opioids in opioid-sparing protocols, and concerns about kidney injury with the use of these medications combined with fluid-minimization has been a controversial topic in early recovery after surgery (ERAS) conversations.¹³ While recent large meta-analyses report that overall these medications are safe, certain populations such as older patients, as well as those undergoing cardiac, urological, or robotic procedures, are at increased risk of acute renal injury.¹³⁻¹⁵ Bleeding risk is another concern. Although COX-2 inhibitors reduce platelet inhibition compared with nonselective NSAIDs, they do not eliminate bleeding risk, especially in procedures with high bleeding potential or in patients receiving antiplatelet therapy.¹⁶ Substituting opioids with NSAIDs may therefore shift rather than eliminate perioperative risk, underscoring the importance of individualized analgesic selection.

Tramadol is often included in multimodal protocols as a rescue opioid with the belief that, as a weaker mu-agonist, it confers fewer risks. However, tramadol use has been associated with an increased risk of dementia and an increased risk of prolonged postoperative opioid use compared to other opioids.^{17,18}

PERIPHERAL NERVE BLOCK SELECTION AND ANALGESIC ADEQUACY

Peripheral nerve blocks are central to many opioid-sparing strategies; however, inappropriate block selection may result in incomplete analgesia. Somatic nerve blocks may not adequately address visceral pain components associated with abdominal, pelvic, or thoracic

procedures where thoracic or lumbar epidural could have been a better choice. Inadequately treated visceral pain is associated with sympathetic activation, increased myocardial oxygen demand, impaired respiratory mechanics, and delayed recovery.¹⁹

A related concern is the potential for a false sense of analgesic adequacy following technically successful regional anesthesia. Peripheral nerve blocks may provide incomplete or time-limited analgesia, and inadequate pain control may not become apparent until block resolution. This may delay recognition of insufficient analgesia and postpone timely administration of rescue pain medications.^{20,21} Poorly controlled postoperative pain is not solely a comfort issue; it has been associated with increased postoperative complications, prolonged hospitalization, and decreased patient satisfaction.^{22,23}

SINGLE-INJECTION BLOCKS AND THE TIMING MISMATCH PROBLEM

Single-injection peripheral nerve blocks are commonly used in opioid sparing protocols due to ease of placement and limited resource requirements. However, the 12-24 hour duration of single-injection blocks often does not align with the trajectory of postoperative pain, which frequently peaks after block resolution.^{21,22} This timing mismatch may result in abrupt rebound pain following discharge, often occurring in unmonitored home settings.

Rebound pain has been associated with increased opioid consumption, unplanned healthcare utilization, and patient distress.²⁰ In opioid naïve patients, sudden severe pain may prompt unsupervised opioid escalation at home, increasing the risk of adverse events. Continuous peripheral nerve blocks, when feasible, may better align analgesic duration with

the perioperative stress response and inflammatory cascade, potentially reducing reliance on unsupervised rescue opioids.²¹

VARIABILITY IN EXECUTION OF ADVANCED ANALGESIC STRATEGIES

Availability of advanced analgesic modalities varies across institutions and care settings. Techniques such as continuous peripheral nerve blocks, advanced regional anesthesia approaches, and adjunctive technologies require specialized expertise, equipment, and postoperative follow-up. Variability in access may influence how opioid-free strategies are implemented in practice.

When continuous regional techniques or structured follow-up are less feasible, clinicians may rely more heavily on single-injection nerve blocks or systemic nonopioid medications. While these approaches can be effective, they may not provide the same duration or consistency of analgesia for all patients. Aligning perioperative analgesic strategies with available monitoring and follow-up resources may help reduce unintended analgesic gaps after discharge and support patient safety.²⁴

ADJUNCT TECHNOLOGIES: PROMISE AND PRACTICAL LIMITATIONS

Adjunctive modalities such as hot and cold compression devices and perioperative cryoneurolysis have demonstrated potential to reduce postoperative pain and opioid consumption as well.^{25,26} However, access to these technologies may be limited by cost, insurance coverage, and institutional resources. In addition, long-term safety data and standardized implementation guidelines continue to evolve. Consideration of these practical limitations is important when incorporating adjunctive therapies into perioperative analgesic planning.

REFRAMING THE GOAL: OPIOID-SPARING, PATIENT-CENTERED ANALGESIA

The goal of perioperative analgesia should not be absolute opioid elimination but rather safe, effective, and individualized pain control. Opioid-sparing multimodal strategies allow judicious opioid use when appropriate while balancing analgesic efficacy with patient safety. Multimodal analgesia that integrates regional techniques, nonopioid medications, and low dose opioids when indicated has been shown to improve pain control and functional recovery while minimizing opioid-related adverse events.²

In clinical practice, optimizing patient safety requires careful preoperative assessment and individualized planning. Evaluation of coexisting diseases, baseline renal function, hydration status, and potential drug-drug interactions



can help guide analgesic selection and reduce the risk of complications such as acute kidney injury and bleeding, particularly when nonopioid agents such as NSAIDs or COX-2 inhibitors are used. Incorporating these assessments into perioperative workflows allows clinicians to tailor analgesic strategies to patient-specific risk profiles.

Frequent reassessment is central to individualized care. Pain scores alone are insufficient; clinicians should also evaluate sedation, respiratory status, ability to ambulate, participation in pulmonary hygiene or therapy, adverse drug effects, and overall functional recovery. This allows the analgesic plan to be adjusted dynamically as the patient's condition evolves. In some cases, escalating opioid-sparing measures may reduce the need for opioids; in others, cautious opioid administration may be the safest way to avoid uncontrolled pain and its downstream consequences.

Rigid adherence to “zero-opioid” targets may inadvertently compromise patient safety by prioritizing metric achievement over individualized care. A safer and more practical approach is to embed individualized decision-making into perioperative workflows through preoperative risk stratification, procedure-specific planning, functional goal setting, flexible multimodal pathways, and ongoing postoperative reassessment. Aligning analgesic plans with patient physiology, surgical factors, and postoperative care capacity is more consistent with the broader mission of perioperative safety than enforcing uniform opioid-avoidance targets.

CONCLUSION

As the pendulum swings toward reduced opioid use, caution is advised to avoid the unintended consequences of ignoring risks associated with alternate opioid-sparing analgesic techniques. Opioid-sparing anesthesia offers potential benefits for selected patients; however, rigid, or nonindividualized application may introduce unintended patient safety risks related to inadequate analgesia, timing mismatches, renal and bleeding complications, and postoperative monitoring challenges. A flexible, patient-centered, opioid-sparing multimodal approach rather than absolute opioid elimination may better support perioperative safety and recovery while addressing the complexities of surgical pain management.

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