Opioid free anesthesia: feasible?

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Purpose of review
The present review aims to address the feasibility of opioid free anesthesia (OFA). The use of opioids to provide adequate perioperative pain management has been a central practice of anesthesia, and only recently has been challenged. Understanding the goals and challenges of OFA is essential as the approach to intraoperative analgesia and postsurgical management of pain has shifted in response to the opioid epidemic in the United States.

Recent findings
OFA is an opioid sparing technique, which focuses on multimodal or balanced analgesia, relying on nonopioid adjuncts and regional anesthesia. Enhanced recovery after surgery protocols, often under the auspices of a perioperative pain service, can help guide and promote opioid reduced and OFA, without negatively impacting perioperative pain management or recovery.

Summary
The feasibility of OFA is evident. However, there are limitations of this approach that warrant discussion including the potential for adverse drug interactions with multimodal analgesics, the need for providers trained in regional anesthesia, and the management of pain expectations. Additionally, minimizing opioid use perioperatively also requires a change in current prescribing practices. Monitors that can reliably quantify nociception would be helpful in the titration of these analgesics and enable anesthesiologists to achieve the goal in providing personalized perioperative medicine.

Keywords
enhanced recovery after surgery protocol, multimodal anesthesia, nociception monitoring, opioid epidemic, opioid free anesthesia

INTRODUCTION

Opioids are often prescribed in the perioperative period for intraoperative analgesia and postsurgical pain management. Intraoperatively, intravenous opioids have been used to maintain anesthesia and blunt the sympathetic response, which is often used as a surrogate for pain, during surgery [1▪]. Similarly, in the postoperative period, intravenous and oral opioids are used to help manage moderate to severe pain. Opioids, both exogenous and endogenous in response to noxious stimuli, modulate signal transduction and gene expression in the peripheral and central nervous system [2]. The binding of opioid agonists to opioid receptors activate G proteins and modulate calcium and potassium ion channels, causing hyperpolarization of cells and reduction of neuronal excitability [3]. However, in an effort to provide adequate perioperative pain management, the overuse and over prescription of opioids have contributed to the opioid crisis in the United States. Reports indicate the number of overdose deaths from prescription and illicit opioids have quadrupled since 2000 from opioid diversion, misuse, and addiction [4]. Studies have shown that new persistent opioid reliance after surgery is prevalent after both minor and major surgeries, which has led to significant morbidity and mortality [5,6]. The cellular and molecular changes that occur at opioid receptors are also likely responsible for the tolerance, dependence, and sensitization to opioids [2,3]. Although we all know the potential benefits of opioids, we often forget their side effects, and the intraoperative use of opioids has been such a central part of the anesthesia practice that it has only been challenged recently. In a nutshell, if pain is a subjective experience with some physiological consequences

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KEY POINTS

- The opioid epidemic has led to significant morbidity and mortality in the United States, prompting a paradigm shift towards an OFA approach in the management of intraoperative analgesia and postoperative pain.
- OFA, a 'radical' form of an opioid sparing technique, has been made possible by MMA, which emphasizes neuraxial anesthesia, peripheral nerve blocks, and nonopioid adjuncts.
- ERAS protocols, often under the auspices of a perioperative pain service, have helped guide and promote opioid reduced and OFA, without negatively impacting perioperative pain management or recovery.
- Some of the limitations of OFA include managing patient expectations, the potential for adverse drug effects and drug interactions with nonopioid medications, inadequate treatment of cancer pain, and the need for anesthesia providers skilled in regional anesthesia.
- The development of novel monitors that can accurately quantify intraoperative and postoperative nociception would be an vital tool to improve the titration of analgesics, as the few current monitors available have limitations and are only surrogate measures of nociception.

(activation of the sympathetic system), why do we use analgesics such as opioids in unconscious patients? Why do not we avoid the use of opioids in unconscious patients and approach the physiological consequences of nociception with drugs specifically targeted at blunting the sympathetic system? This provocative approach is the basis of opioid free anesthesia (OFA). In this review we will discuss the side effects of opioid use and especially some of the most recent findings about their potential long term effects, the concept of OFA and how it is defined, novel perioperative care processes such as enhanced recovery after surgery (ERAS) under which opioid sparing techniques and OFA approaches have flourished, the limits of OFA approaches and their potential risks, and finally new ways of monitoring nociception so that titration of opioids can be more informed and patient-centered.

SIDE EFFECTS OF OPIOIDS

The potential side effects of opioids can be described as a three-fold negative impact from the immediate adverse reaction in the patient to the long-term sequela of chronic effects, eventually resulting in systemic healthcare system burdens. First, opioids have a multitude of acute side effects including nausea, pruritis, respiratory depression, and constipation [1▪]. These adverse effects can lead not only to prolonged hospital admissions, but to unplanned hospital admission, dependence, addiction, hyperalgesia, and development of chronic pain as well [7]. Patients with opioid-related adverse events can have nearly twice the treatment costs, double the length of stay, and significantly higher readmissions to the hospital compared to patients who did not have an opioid related adverse event [8]. One study in 2013 reported 12% of surgeries had some kind of opioid related adverse event [9]. On a larger scale, the opioid epidemic has become a major public health issue when inadequately treated acute pain transitions into chronic pain, driving up healthcare costs and reducing patient satisfaction [10].

Another side effect of opioids that has more recently been gaining evidence in literature, is the role of opioids in cancer recurrence. One study by Gupta *et al.* [11] found that morphine has been associated with stimulation of microvascular endothelial cell proliferation and angiogenesis leading to tumor progression. Similarly, another investigation found that higher mu opioid receptor expression and greater opioid requirements have been correlated to shorter progression-free survival in patients with metastatic prostate cancer [12]. Other studies found a possible direct effect of mu opioid receptor on growth factor signaling leading to proliferation and lung cancer progression [13,14]. However, the opinion on opioid use for cancer pain is mixed. Other studies suggest poorly controlled pain and stress can also contribute to cancer progression [15,16].

WHAT IS OPIOID FREE ANESTHESIA?

OFA is essentially the practice of intraoperative anesthesia without the use of intraoperative opioids. It can be considered a 'radical' form of an opioid sparing technique. As more light has been shed on the adverse effects of opioids, there has been a shift in the prescribing practices of opioids. Physicians and medical providers have placed more emphasis on minimizing or eliminating opioid consumption in the perioperative period. Strategies to increase nonopioid adjuncts, regional techniques, and neuraxial anesthesia have become more popular and the goal of providing OFA has been made possible by multimodal analgesia (MMA), or balanced analgesia with an opioid sparing approach [17]. MMA is based on the synergistic use of drugs with different modes of action, leading to additive pain management that works at different nociceptors along the pain pathway [18].

Nonopioid medications that are currently available include acetaminophen, nonsteroidal anti-inflammatory drugs (ketorolac, ibuprofen, celecoxib),

alpha-2 agonists (dexmedetomidine, clonidine, tizanidine), N-methyl-d-aspartate (NMDA) receptor antagonists (ketamine, amantadine, dextromethorphan), gabapentioids (gabapentin and pregabalin), antidepressants (amitriptyline, desipramine, duloxetine), esmolol, lidocaine, caffeine, glucocorticoids (dexamethasone), muscle relaxants (methocarbamol, cyclobenzaprine), and magnesium [17,19]. Multimodal approach includes a combination of these adjuncts, and so it is important to be cognizant of potential drug–drug interactions and safety profiles of these medications [20].

Regional anesthesia including upper extremity, lower extremity, and truncal blocks have minimized opioid use in the perioperative period and increased patient satisfaction [21]. Brachial plexus blocks are used for shoulder, arm, and hand surgeries and have decreased opioid consumption and pain scores [17]. Interscalene, supraclavicular, infraclavicular, axillary, and suprascapular blocks have all been well documented in the literature [17,22–24]. Lower extremity blocks have also become routine for knee, hip, and foot surgeries and have not only improved pain scores and minimize opioid use, but they have also helped patients decrease the length of their hospital stay and improve the time to physical therapy [25]. Femoral, sciatic, popliteal, adductor, fascia iliaca, and interspace between the popliteal artery and posterior capsule of the knee (iPACK) blocks are often offered to patients to help with pain control during and after surgery [26,27]. Truncal blocks such as transversus abdominis plane and quadratus lumborum are beneficial for abdominal and gynecological surgeries, and pectoral and serratus anterior nerve blocks have been studied for mastectomies and rib fractures [28]. Erector spinae blocks have been performed for rib fractures and thoracotomies [29]. Single injection and continuous catheters are both available techniques for nerve blocks, depending on the institution, availability of regional anesthesiologist, cost, and cooperation of the patient. The effectiveness of dexamethasone, dexmedetomidine, and clonidine in prolonging the duration of peripheral nerve blocks has also been studied with mixed results [30–32].

Neuraxial techniques have also minimized perioperative opioid use in thoracic, urology, orthopedic, obstetric, and general surgeries [17]. Following open abdominal and thoracic surgeries, epidurals are often used for analgesia in the peri-operative period [33]. Paravertebral blocks are another alternative for thoracotomies but it is important to follow the regional guidelines for the use of antithrombotic or thrombolytic therapy with neuraxial blocks according to the American Society of Regional Anesthesia [34]. As orthopedic procedures are moving towards outpatient procedures, intrathecal and combined spinal–epidural techniques are often performed to decrease hospital length of stay and pain while improving patient satisfaction [26,35].

ENHANCED RECOVERY AFTER SURGERY PROTOCOLS

Neuraxial anesthesia, peripheral nerve blocks, and nonopioid adjuncts are the foundation of a multimodal approach to analgesia. ERAS protocols have promoted these opioid alternatives to provide opioid reduced anesthesia (ORA) and OFA to patients [18]. OFA not only minimizes the adverse effects of opioids outlined above, but enables earlier ambulation and return of bowel function [36]. One of the key elements of the implementation of ERAS protocols is to help patients minimize opioid use, without negatively impacting perioperative pain management or recovery [37]. This approach prevents the sequela of adverse drug reactions associated with use of larger doses of one agent, specifically opioids [38]. However, it is important to note that the ERAS pathway also promotes minimally invasive surgical approaches, discontinuation of nasogastric tubes, and early ambulation, which likely have the strongest impact on recovery after surgery [39,40▪▪]. The use of these strategies has been shown to decrease the length of stay in recovery rooms and reduce the burden in healthcare resources, while improving patient quality of life and satisfaction [41].

In large hospital centers, a perioperative pain service is often available to help supervise and conduct these pathways to ensure surgical patients are appropriately managed. It has also been suggested that such a service should be multidisciplinary, involving the expertise of pain medicine physicians, hospitalists, addiction medicine, psychologists, and possibly social workers. The goal of such a group should be to assess individual patients' needs while providing a comprehensive plan to optimize pain management and assessment during preoperative, intraoperative, and postoperative phases and discharge. The measurable long-term goal of this transitional pain team would be prescription use after discharge to assess the incidence of inadequately treated perioperative pain [42].

WHAT ARE THE LIMITATIONS OF OPIOID FREE ANESTHESIA?

OFA is not without challenges. Some of those include resources to provide patients with multimodal alternatives to opioids, dealing with patient

expectations regarding pain control, the potential for adverse drug effects and drug interactions with nonopioid medications, and inadequate treatment of cancer pain [43]. There needs to be a collaboration between surgeons, anesthesiologists, patients, and their caregivers, requiring more planning and personalization. Neuraxial anesthesia and peripheral nerve blocks require a certain skill set, and patients that receive neuraxial anesthesia need to be monitored closely postoperatively.

Managing pain expectations can also be difficult for both opioid naïve and opioid tolerant patients. However, studies have shown that patient education and strict opioid restricting protocols can help. A study by Mark *et al.* [44] successfully decreased the amount of opioids prescribed to patients who underwent gynecological and abdominal surgeries without significant difference in pain scores or medication refill requests. A review by Rucinski and Cook [45] investigated and suggested a multimodal approach of using at least two forms of patient education to enforce opioid education in the perioperative period can be effective in reducing opioid prescription, requests and filling. In 2016, a recent publication of perspectives of patients discharged from an emergency room revealed that one in four patients were unaware that opioids could be addictive [46]. These efforts to guide patient care and pain management ideally would require a dedicated transitional pain management team to help educate and implement these opioid minimizing and sparing guidelines. The resources to establish this integrated transitional pain team may not necessarily be available at every healthcare institution.

Drug–drug interactions for opioids and nonadjuncts have been well studied [17,18,20]. The challenge lies in the unanticipated adverse effects that may arise from the use of multimodal analgesics [47]. Individual analgesics have unique mechanisms of action, potency, side effect profiles, and adverse drug–drug interactions [48]. Nonsteroidal anti-inflammatory drugs (NSAIDs) can be harmful to the gastrointestinal system and can cause serious kidney damage and lead to bleeding when used in conjunction with glucocorticoids [49]. Acetaminophen can be hepatotoxic and has been associated with agranulocytosis, and local anesthetics at high doses can result in neurological and cardiac complications. Dexmedetomidine should be given over at least given over 10 min to avoid hypertensive episodes, bradycardia, and even asystole [50,51]. Clonidine in low dose has an increased risk of clinically relevant hypotension [52]. As MMA approaches have more widespread implementation, individual monitoring and titration needs to be followed to minimize the discovery of more unanticipated adverse reactions. Additionally, few studies have looked at whether the side effects of nonopioid analgesics have an impact on hospital length of stay and should be a consideration for investigation in the future.

Cancer pain management is also an area that requires more studies. Opioids are thought to promote tumor progression; however, stress and pain are also associated with cancer progression [15,43]. There are conflicting studies on whether opioids are beneficial or harmful to cancer patients, but this is likely because of the multitude of different signaling pathways, inflammatory mediators, and environmental factors involved in oncogenesis [15,53]. Overall, minimizing opioids is beneficial to all patients; however, not all patients with cancer are candidates for neuraxial anesthesia and certain nonopioid medications may be contraindicated. Thus, it is important to find a balance with ORA and OFA in providing adequate analgesia [43].

Another challenge in reaching the long-term goals of OFA includes addressing the current state of prescription practices. A recent retrospective study looking at prescribing practices at a single center found that 70% of ERAS patients who demonstrated minimal pain in the immediate hospitalization were discharged with an opioid prescription [36]. This highlights that prescription practices adds a layer of vulnerability in eliminating opioid reliance and prescription diversion. Not surprisingly, there is an association that patients leaving the hospital with opioid prescriptions appear to be at a higher risk of long term opioid dependence, fueling the epidemic [54]. If physician behavior towards discharge prescription practices remain the same, in hospital efforts to provide ORA and OFA to minimize widespread opioid misuse use will continue to be counterproductive.

Finally, it is important to address that studies have not shown that the use of intraoperative opioids has led to significant negative long-term effects [40▪▪]. In the United States, postoperative pain is still poorly controlled, and longer acting opioids such as methadone may have a role in managing postoperative pain in both ambulatory and major inpatient surgeries [55]. Methadone, which is an NMDA receptor antagonist, has a half-life of 24 to 36 h depending on the dose [56]. Although studies have shown that patients who were administered methadone required significantly less postoperative opioids and had lower pain scores without significant respiratory depression, clinical trials have been limited by small sample sizes [57▪]. Methadone can be an effective drug, but more studies are needed to investigate its potential role as part of a MMA pathway.

CAN WE MONITOR NOCICEPTION AND TITRATE PAIN MEDICATION?

As we head towards minimizing opioid use, the monitoring of nociception during titration of perioperative pain medication will be an important tool to minimize long-term adverse effects of opioids. There are currently a few commercially available monitors that measure sympathetic tone, pupillary response, and nociceptive flexion reflex as a proxy for nociception [58▪]. However, these devices all have limitations to them and have not consistently been shown to be a reliable surrogate for nociception. Additionally, medications, fluid status, age, emotions, and neuromuscular blockade can confound the accuracy of these monitors. The analgesia nociception index uses heart rate variability as an objective measure of pain by the numeric rating scale or the visual analog scale, and although it is theoretically sound, recent publications providing preliminary evidence did not find a strong correlation between these parameters and different states of acute postoperative pain [59]. More studies are needed to evaluate the effectiveness of current monitors, and investigate new technology to measure pain objectively. The development of novel monitors that can accurately quantify intraoperative and postoperative nociception would be a vital tool to improve the titration of analgesics.

CONCLUSION

If the question is: 'Is Opioid Anesthesia Feasible?' the answer is clearly yes. However, whether OFA is beneficial and can improve short-term and long-term patient outcomes remains unknown. It is clear today that many drugs and approaches can help reduce the use of opioids during surgery. We are moving from a practice where years ago anesthesiologists would be using massive doses of opioids during anesthesia to an era when anesthesiologists are able to titrate each of the drugs in their arsenal based on patients' characteristics, achieving the goal of personalized perioperative medicine.

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Conflicts of interest

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- ▪ of special interest
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