Managing Perioperative Pain

A clinical review and perspective on pharmacologic options for managing pain prior to, during, and following medical procedures.

By Dmitry M. Arbuck, MD [1]

The mounting scrutiny over opioid prescribing in the United States has led to increased attention on alternate pain treatments not just in primary and specialty care, but also as part of the perioperative pain control cycle. Preoperative patients currently taking opioids or presenting with a history of opioid addiction, and those living with chronic pain, in particular, may require a unique approach, for which agreed-upon standards are lacking in such cases. While the pain management community seeks solutions to and guidance on the evolving situation, this paper offers a clinical perspective and review of full and partial mu opioid agonists, as well as alternative pharmacologic treatments, for perioperative pain control.

[2]

Preoperative History & Planning

Appropriate use of steroids, antibiotics, and presurgical patient education are well-established methods

for decreasing pain and minimizing opioid consumption leading up to and following a major medical procedure. More intricate pharmacologic approaches are often necessary in complex cases where the surgical patient presents with chronic pain and/or pain-related comorbidities. The following section provides a range of available options as presented in the literature and currently used in clinical practice.

Pharmacologic Presurgical Pain Control

It has been extensively reported that preventive preoperative use of gabapentin may result in decreased doses of required opioids and the likelihood of central sensitization post-surgery.[1] A 900 mg to 1200 mg single dose has been deemed effective for these purposes.[2] Not all studies support this notion, however, potentially due to their focus on the gabapentin's effect on anxiety versus pain, or due to too low doses of the medication.[3,4]

A high initial dose of gabapentin may be poorly tolerated by many patients, so it is reasonable to start with lower doses in the two to three days before surgery (if the patient is not already on this medication) and increasing the doses as tolerated, ending with a maximal dose in the immediate preoperative period. The author recommends continuing gabapentin for 7 to 14 days after surgery.

Reported post-surgical regimens and doses vary greatly, with doses as low as 400 mg/day, deemed effective.[5] The use of alternative, long-acting formulations of gabapentin and gabapentin enacarbil may be considered as well.

Pregabalin, expectedly, provides a similar effect on pain control and a decrease in opioid reliance.[6] Unfortunately, optimistic results have not been universal: a Cochrane meta-analysis suggested a modest but statistically significant reduction in the incidence of chronic pain after surgery following treatment with ketamine but not with gabapentin or pregabalin[7] (see also, sidebar–"Overprescribing Concerns").

Preoperative use of celecoxib has also received much attention. This medication showed a modest decrease in pain and post-surgical opioid consumption.[8,9] Cox-2 receptors are not present on platelets, so celecoxib should not influence bleeding time, but surgeons universally tend to avoid even a remote chance of coagulation problems.

Successful preoperative use of muscle relaxants and acetaminophen also have been reported.[10] Of note, many muscle relaxants may be sedating and add to the risk of gait instability and confusion, as well as swallowing and respiratory problems.

The use of N-methyl D-aspartate (NMDA) receptor antagonists, including amantadine, in theory, may help to prevent pain chronification and opioid dependence.[11] Ketamine may offer promising relief as well, but due to potential mental effects and potentially addictive nature, ketamine should be used with caution.[12,13]

For the Opioid-Managed Patient

There is no current consensus in the pain management community on how to effectively handle patients who are in need of surgery and already taking prescription opioids for related or unrelated condition(s), or who are undergoing opioid addiction treatment with, for example, methadone. Patients with a history of ongoing opioid use or addiction, mental health conditions (especially borderline personality disorder, anxiety, depression, and somatization), and/or a history of childhood or ongoing abuse should be considered at high risk of developing chronic post-surgical opioid abuse. Research by Sun et al,[14] found that male gender, age older than 50 years, and a preoperative history of benzodiazepine or antidepressant use were also associated with chronic opioid use even among opioid-naive surgical patients.

Some physicians may instruct such patients to cease their opioid treatment for one, two, or even four weeks prior to a scheduled surgery. Motivated patients are likely to comply, particularly when the physician makes clear why preoperative dosage cessation may be beneficial long-term. To avoid potentially unnecessary suffering and contention, however, physicians may instead propose that patients decrease their full mu agonists' dosages rather than go off opioids completely. A 50% reduction in a maintenance opioid dose for a brief period before surgery may be more practical and attainable, for instance. A rapid preoperative opioid detoxification has also been suggested,[15] but has been associated with possible complications of its own.

When serious warning signs are exhibited, such as complete refusal of a patient to decrease high opioid dosages, active use of illicit substances, or ongoing psychiatric crisis, the situation may warrant delaying a scheduled surgery until reasonable stability is achieved. Consultation and clearance by an addiction or mental health specialist may be sought as a precondition to surgery.

In the case of an emergency surgery, a patient's history and any prior opioid use or abuse needs to be identified and addressed in the immediate post-surgical period by the surgeon in consultation with appropriate social and psychiatric services.

For the Patient on Buprenorphine

A patient taking prescribed maintenance buprenorphine for pain or opioid dependence presents a unique challenge. This partial mu agonist exhibits potency of about 30 times that of morphine, thereby controlling pain reliably and decisively. At the same time, buprenorphine produces much-diminished euphoria and, as such, is often less preferred by patients with addiction challenges.

Patients who are established on such treatment may be prescribed an additional opioid to manage surgical and post-surgical pain if needed. Note that this method does not work the other way around; a patient taking a prescribed opioid who is then given buprenorphine may have the original opioid displaced and experience withdrawal symptoms.[16] Experimental animal studies support the preoperative use of buprenorphine.[17] In comparison with morphine and fentanyl, only buprenorphine is reported to prevent the neuroendocrine and immune system post-surgical alterations.[18]

There is no existing uniform strategy to manage a presurgical patient on an established buprenorphine maintenance plan. Various recommendations call for discontinuing buprenorphine 24, 48, or 72 hours prior to surgery, while others call for discontinuation 5, 7, 14 or more days before the surgery.

The author recommends that patients on buprenorphine continue their buprenorphine dosage before surgery and maintain it in the post-surgical period. Clinically, this approach has worked well and demonstrated that the theoretical constructs of buprenorphine interference with the efficacy of "add-on" full mu agonists are far from universal. This method was echoed by a new Stanford University Medical Center policy released in 2017,[19] based on findings that patients who had discontinued buprenorphine before surgery "consumed significantly greater amounts of opioid in the immediate post-operative period, yet the pain scores for the two groups were not at all that different."

The author has seen an endless number of previously stable patients in crisis and uncontrolled post-surgical pain after surgeons have discontinued their buprenorphine. It is prudent, therefore, that practitioners consider outcomes beyond the immediate post-surgical period in a chronic pain patient. The process of switching a patient back from full mu agonists to buprenorphine may be difficult and cause unnecessary suffering.[20]

For the Anxious Patient

Many patients may present with anxiety leading up to surgery. The use of preoperative benzodiazepines, however, should be avoided whenever possible as they may complicate anesthesia recovery, potentiate sedating agents, and increase likelihood of respiratory depression. With

appropriate patient education and preoperative care in non-ambulatory surgery, alprazolam, for example, is no more effective than a placebo.[21] The use of a hypnotic sleeping pill may be sufficient to control presurgical anxiety.[21] In addition, there are reports of natural aids such as melatonin, essential oil lavandin, and citrus aurantium blossom[22-24] proving successful in pre- and post-operative anxiety control.

Intraoperative Pain Control

Following surgery, approximately 10% of patients develop chronic post-surgical pain.[25] Proper intraoperative pain control may improve their outcome. Based on the multimodal analgesia principle, the use of local anesthetic, regional anesthesia, and opioids are at the forefront of current intraoperative pain control. Medications such as ketamine, dexamethasone, and ketorolac also may be used on a case-by-case basis.[26,27] Interest in ketamine use has heightened recently,[28] but not all practitioners agree with its use in the perioperative environment.[29]

In pediatric surgical patients [3], opioids remain the standard of pain care. A systematic review conducted by Zhu, Benzon, and Anderson[30] concluded that not enough data exist from which to draw conclusions on the intraoperative use of gabapentin, magnesium, dextromethorphan, lidocaine, amantadine, pregabalin, esmolol, or caffeine. Further research is needed to justify these and other pharmacologic modalities in the pediatric population. It is worth noting that the FDA has issued broad warnings against the use of codeine and tramadol in children.[31]

Epidurals, Dexmedetomidine, Naloxone, & Vitamin C

Epidural analgesia is widely used for pain control during a variety of surgeries, but not all patients may be suited to, or benefit from, this method as regards post-operative recovery. Lidocaine has been investigated in several studies for its multimodal use to reduce post-operative pain and enhance surgical outcome. A Cochrane review revealed only low to moderate evidence of benefit from this intervention.[32]

Another Cochrane review showed that dexmedetomidine, when administered intraoperatively for acute pain after abdominal surgery in adults, had an opioid-sparing effect.[33] Use of this medication in wider surgical scenarios has been published as well.[34]

A recent study of intraoperative naloxone showed a reduction in post-operative hyperalgesia when combined with a high dose of remifentanil for elective thyroid surgery.[35] Also, it was reported that 50 mg/kg vitamin C by intravenous (IV) infusion immediately following induction of anesthesia decreased post-operative pain during the first 24 hours and reduced morphine consumption in the early post-operative period.[36] Similarly, according to a study by Ayatollahi et al,[37] administration of 3 g vitamin C IV intraoperatively reduced post-operative pain without increased side effects in patients undergoing uvulopalatopharyngoplasty with tonsillectomy.

Nerve-Based Surgeries

Animal studies of post-traumatic nerve injury pain demonstrate that there is a critical timeframe before and immediately after nerve injury in which specific interventions may reduce the incidence and intensity of chronic neuropathic pain behaviors, or so-called “preventative analgesia.” In these cases, perineural local anesthetic, systemic intravenous local anesthetic, perineural clonidine, systemic gabapentin, systemic tricyclic antidepressants, and minocycline have each been shown to reduce pain behaviors (and, therefore, opioid demand) days to weeks after treatment.[25]

Ambulatory Surgeries

Esmolol is often utilized in patients undergoing ambulatory surgery and in those expected to have mild

post-operative pain. The beta-1 receptor antagonist may reduce post-operative pain and opioid consumption, according to research by Gelineau and colleagues.[38] Possible mechanisms responsible for this clinical outcome include voltage-gated calcium channels and NMDA regulation.[39]

Post-Operative Pain Management

Despite pre- and intraoperative pain management strategies, combined with improved analgesics and sophisticated drug delivery systems, surveys indicate that more than 80% of patients report moderate to severe pain post-operatively.[40] Inadequate post-operative [4] pain [4] relief may prolong recovery and hospital stay, increase healthcare costs, and reduce patient satisfaction.

A multimodal approach in the post-surgical period is therefore crucial to the overall success of long-term pain control. Both pharmacologic and nonpharmacologic aspects of pain care should be considered, including: a patient's mental status, education, and management of expectations; and alternative treatments, such as electrical stimulation, acupuncture, herbs, supplements, hypnosis, and music therapy.

Opioids and Common Alternatives

Opioids remain the standard of care for post-operative analgesia and appropriate prescribing—typically 5 to 10 days post-surgery, or longer depending on the severity of the trauma.[41,42] Opioid use, as known, may however be associated with adverse effects, including ileus, which can prolong the patient's hospital stay, or it may lead to addictive behavior when inappropriately used or overprescribed.

Lidocaine: In a study by McCarthy et al,[43] post-operative opioid consumption was reduced by up to 85% in intravenous lidocaine-treated abdominal surgery patients when compared with controls, demonstrating lidocaine's potential benefit beyond intraoperative use.

Pumps: Continuous wound infusion pumps may have great potential in an ambulatory setting, while the incorporation of non-opioids, local anesthetics, and regional techniques may enhance current post-operative analgesic regimens.[40]

Antagonists: The use of small doses of opioid antagonists post-operatively has been utilized over many years.[44] As reported by Movafegh and Shoeibi,[45] an ultra-low dose of naloxone infusion proved to reduce morphine need as well as the incidence and severity of opioid-induced nausea and vomiting following hysterectomy. Maxwell and Kaufmann concluded that in children and adolescents, a small-dose naloxone infusion may significantly reduce the incidence and severity of opioid-induced side effects without affecting opioid-induced analgesia.

The researchers recommended that, when initiating morphine IV patient-controlled analgesia for the treatment of moderate to severe pain, clinicians strongly consider starting a concomitant small-dose naloxone infusion.[46] Concomitant use of morphine and naloxone in patient-controlled analgesia did not show a decrease in the post-operative opioid requirement in an earlier study.[47]

Acetaminophen, Gabapentin, and Celecoxib: The use of acetaminophen post-surgery should not be underestimated,[48] especially in combination with nonsteroidal anti-inflammatory drugs (NSAIDs). Intravenous acetaminophen [49] or the intravenous formulation of meloxicam may provide post-surgical pain relief.[50] In meta-analysis performed by Han,[51] a significant decrease in opioid consumption in the post-surgical period was connected to gabapentin administration. The use of celecoxib, however, was not necessarily effective in the post-surgical period, at least after tonsillectomy.[52]

The Genetic Link

Attention to CYP-450 enzymes may enable a surgical team to avoid expected drug interactions and to

match opioids or other medications to the patient's profile.[53] Genetic testing, which is becoming more common, may reveal that a patient may have ORM1 mutation consistent with decrease in opioid efficacy. This information may explain why some patients respond to all opioids poorly. Problems with CYP-450 2D6, 3A4, and other mutations also may explain why a patient may respond better to one opioid over another.

While such genetic testing may impact all aspects of the perioperative pain management strategy, it remains largely overlooked in common practice. As part of routine outpatient care, it may be prudent, however, to determine whether a patient has ORM1 result consistent with a predictable decrease in opioid efficacy. In such patients, higher doses and longer uses of opioids may be replaced with other means of pain control.

Post-Operative Options with Growing Potential

As is common in complex scenarios such as the post-surgical situation, the quality of evidence, sample size, and heterogeneity of trial designs are pertinent to the designation of optimal and patient-specific analgesic regimens.[54] Many reports are anecdotal in nature and driven by investigator preference. However, the search for pain relief before, during, and after surgery is intense, and will undoubtedly bring new discoveries and practical applications.

Stem cell technology, for example, is quickly moving to the forefront of pain management, including for post-operative pain control. Recent studies suggest that bone marrow stem cells or bone marrow stromal cells may produce powerful analgesic effects in animal models of inflammatory pain, neuropathic pain, and cancer pain.[55] Mesenchymal cells of either autologous or allogenic origin, when involved in connective tissue regeneration, have been shown to aid in both wound healing and pain control.[56]

In Conclusion

As always, the primary goal of any medical practice is safety. This brief review of primarily pharmacologic options available today aims to provide physicians working in the perioperative environment with systematic approaches for successful long-term patient outcomes.

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Sidebar: Overprescribing Concerns in a Surgical Setting

-Reported by Jodi Godfey, MS, RD, and Angie Drakulich

Nearly 3 million individuals who underwent a surgical procedure in 2016 were deemed persistent opioid

users, providing a strong indication that post-surgical patients presented a high-risk group for opioid overuse or misuse.[1] Prompted by the growing opioid crisis, IQVIA Institute for Human Data Science (a merger of Quintiles and IMS Institute) was commissioned to conduct an independent analysis of opioid use following surgery. Released in September 2017, this comprehensive analysis offers the most current data on national trends regarding opioid prescribing for post-surgical pain.

According to the report, opioid prescriptions were written for 9 out of 10 patients to manage post-surgical pain, with many of them taking opioids for three to six months after their procedure. In addition, patients left 3.3 billion pills unused, leaving them available for potential diversion or abuse.[1]

Women's Higher Risk

The IQVIA analysis further uncovered evidence that opioids may pose a higher risk for women following surgery.[1] In fact, 40% more women than men became dependent on opioids following a surgery. Middle-age women (40-59 years old) appeared particularly vulnerable, receiving twice as many prescriptions as similarly aged men after surgery. Most troubling, 13% of middle-aged women were found to be reliant on opioids long after their procedure date.

Although the overall risks are greatest for this population, researchers found that when looking at specific surgeries, Generation X women (ages 35-44), who had undergone total knee replacement also showed a post-surgical persistence in opioid use, with 23% continuing to use opioids three to six months after their surgery.[1]

Gabapentinoid Data

In a separate but related study, the use of gabapentinoids was reported to be on the rise, despite lack of long-term safety data. Prescriptions for this class of opioid alternatives, including pregabalin and gabapentin, have risen significantly since 2002, according to an early 2018 paper by Johansen.[2]

Both pregabalin and gabapentin are FDA indicated for partial seizers and postherpetic neuralgia, among other conditions, but have been used off-label in pain management, including in perioperative settings, for many years. Johansen reviewed the CDC's Medical Expenditure Panel Surveys from 2002 to 2015. The reports document more than 346,000 patient-reported medical conditions and their identified prescriptions for gabapentinoid, benzodiazepine, opioids, and more.

During the time period analyzed, gabapentin and/or pregabalin use increased from 1.2% to 3.9% between 2002 and 2015, with the most significant increases of gabapentin taking place after 2008 and pregabalin plateauing after that time. Increases were further concentrated among those patients who were older, had diabetes or other chronic diseases, or who were already taking prescribed opioids or benzodiazepines.

The rise is in prescriptions for these medications is not surprising given the country's focus toward opioid alternatives but, cautioned Johansen in assessment, these opioid-sparing options do not have long-term safety data yet and may also lead to addictive behavior.

The IVQIA study was funded by Pacira Pharmacueticals, a specialty pharmaceutical company focused on developing acute care products for post-surgical analgesia.

Sidebar Sources

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