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REVIEW ARTICLE

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Perioperative multimodal analgesia: a review of efficacy and safety of the treatment options

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Abstract

Pain in the postoperative period is a common patient experience that can subsequently lead to other postoperative complications if not managed appropriately. While opioids are a common pharmacologic tool for managing pain, there are risks associated with liberal opioid use. Multimodal analgesic strategies, however, can adequately manage postoperative pain and minimize the risks associated with opioids. In this review, common pharmacological treatments for multimodal analgesia will be reviewed for efficacy, risks, and benefits, including gabapentinoids, opioids, alpha-2 agonists, ketamine, Non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids. While this may not be a comprehensive list of medication options, it represents some of the most commonly used pharmacologic techniques for managing pain in the perioperative period. In addition, newer regional anesthetic techniques will be discussed to review their efficacy, risks, and benefits as well. The goal of this review is to summarize the various options for a multimodal analgesic protocol that we encourage providers to utilize when managing postoperative pain to facilitate conservative opioid usage and improve patient outcomes overall.

Keywords Postoperative pain, Multimodal analgesia, Postoperative complications

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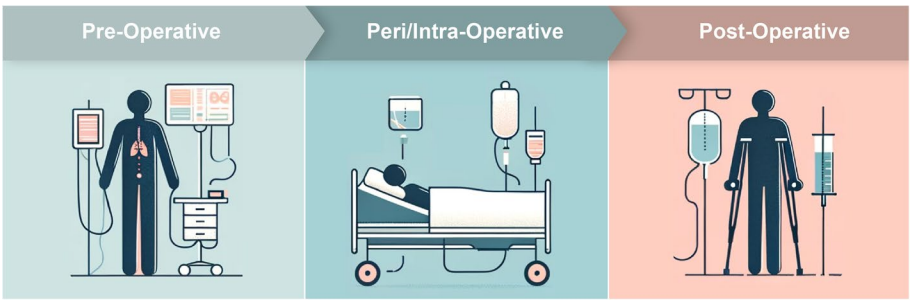
Graphical Abstract



1 Introduction

In the postoperative period, one of the more often reported complaints by patients is pain [1]. Not only is the pain itself difficult for patients, but poorly controlled pain can also lead to increased risks of other complications which can result in further healthcare utilization and possibly even revision surgeries. After an initial surge in opioid usage during its introduction into medical practice as a wonder-drug for pain management, it was eventually understood that too liberal of opioid usage can be more detrimental to overall outcomes, not to mention the risks of dependence and over usage. Therefore, modern anesthesia practice has shifted to more of an opioid-sparing mindset with a multimodal approach to targeting pain. These approaches include not only additional pharmacologic sources for pain control, but regional anesthetic procedures as well. Throughout this review, we will expand on prior reviews that have discussed multimodal analgesia through exploration of various pharmacologic, as well as regional anesthesia options, and review the risks and benefits associated with each approach [2]. Multimodal analgesia is defined here as the use of more than one pharmacologic class of medications, often targeting different receptors in the pain pathway, for the management of pain [3].

According to prior reports from the U.S. Institute of medicine, it is estimated that at least 80% of patients report some form of postoperative pain and acute postoperative pain is experienced among patients undergoing both soft and hard tissue operations [4]. Poorly controlled pain in the postoperative period has been linked to various additional adverse outcomes such as delirium, delayed recovery, increased morbidity, and the development of chronic pain syndromes [4, 5]. Therefore, poorly controlled postoperative pain remains a significant clinical concern for health-related quality of life and postoperative outcomes [6].

In particular, older patients or those with existing cognitive impairment experiencing poorly controlled postoperative pain have increased risk of developing delirium, or an acute state of mental confusion, which can lead to increased morbidity and hospital utilization, higher likelihood of discharge to a long-term care facility, and increased mortality [7, 8]. Prior studies have supported this link between postoperative pain and delirium by showing an association between higher pain levels and the development of delirium, thereby indicating that improved postoperative pain control could reduce the rates of delirium in higher risk populations [9].

Furthermore, the development of chronic pain in patients with poorly managed postoperative pain, also known as persistent postsurgical pain, is a significant area of concern given the long-term implications for patients [6]. In prior studies assessing thoracotomy patients, it has been shown that the patients who developed chronic pain conditions had experienced more severe pain in the immediate postoperative period, thus suggesting that earlier intervention and management of pain after surgery could play a role in minimizing the burden of chronic pain conditions [10].

Finally, poorly managed pain can have a great impact on patient quality of life and functional status, thereby impacting a patient's health in other ways over time. Prior studies have shown that poorly controlled pain after surgery correlated with the patients' decreased abilities to recover, perform activities of daily living, and with worsening quality of life overall [11–13]. Thus, the management of pain in the perioperative period is imperative in reducing overall complications and ensuring patients can recover functionally with minimal impacts to overall quality of life.

1.1 Opioids

1.1.1 Medication overview

Opioid medications are one of the most often used treatments for postoperative pain as a central and peripheral nociception modulator. These drugs can be given

in many ways including oral, intramuscular, and intravenous, allowing it to be easily utilized in a variety of patients with pain. Some of the opioids often utilized include morphine, hydromorphone, oxycodone, fentanyl, or its derivatives. The opioids that act as agonists at the μ receptor can promote hyperpolarization at both the central and peripheral nervous system thereby inhibiting pain signal transmission [14].

One of the more common methods for administering opioids, particularly if intravenous delivery is desired in the postoperative period, is through the patient-controlled analgesia (PCA) pump. Prior reviews have assessed the efficacy of PCA delivery of opioids for pain management and had found only moderate evidence that the PCA has improved analgesic coverage compared to non-patient-controlled regimens, even when slightly higher opioid consumption was found in the PCA group. Interestingly, there were no observed increases in opioid-related adverse effects in the PCA group, despite the slightly higher opioid usage [15].

1.1.2 Medication efficacy

While there has been a large political and social narrative surrounding the dangers of opioid prescription and usage related to the opioid epidemic in the United States, opioids gained significant favor after their introduction into clinical practice owing in large part to their significant improvements in the management of chronic pain [16]. However, there has been many efforts to limit postoperative opioid consumption to decrease the risks of long-term opioid use and dependence [17]. Various studies have shown the efficacy of opioids in the perioperative setting to assess their utility in managing acute postoperative pain as well. Given many opioids have quick times to onset, they can be desirable in the acute setting when pain control is important for ultimate recover and return to baseline for rehabilitation needs postoperatively. Some studies have shown specific qualities of different opioids for improvement in neuropathic pain (buprenorphine and tramadol) [18–20], acute pain requiring rapid cessation (fentanyl) [21], and others for relieving more visceral experiences of pain (oxycodone) [22].

Furthermore, systematic reviews have also compared the efficacy of opioids in bolus versus PCA pump dosing. Some of these studies reported similar opioid consumption, opioid-related adverse effects, and overall pain relief between the two administration methods, with improved patient satisfaction and analgesic effect with the PCA administration in the postoperative setting [23]. Other studies, however, demonstrated that PCA administration is superior for analgesia [24]. Regardless of the means of administration for opioids in the perioperative setting, the data from these systematic reviews demonstrates how opioids do improve postoperative pain control to the minimal-moderate ranges based on the visual analog scale scoring.

1.1.3 Medication side effects

However, even though opioids have shown good analgesic coverage in the postoperative period, there are important limitations to be wary of when administering these medications, particularly if it is the only modality being utilized for pain management. Some side effects include constipation, respiratory depression, nausea, vomiting, pruritus, and altered mental status or delirium [25]. While the pharmacologic mechanism explaining these side effects is not fully understood, it has been proposed that there are many opioid receptors in central, peripheral, and enteric nervous system neurons that can be the target of opioid agonism, in addition to potential downstream effects in other non-opioid receptors and signaling cascades [26]. More concerning and severe adverse effects such as cardiac or respiratory arrest and death have also been seen in patients on opioid therapy for pain management. In fact, Izrailtyan et al. retrospectively analyzed factors that may increase the risk of in-hospital cardiopulmonary and respiratory arrest for patients on opioid and sedative therapies and concluded that the former and latter therapies are independent but additive predictors for cardiac or respiratory arrest. This was found to be particularly concerning for patients with chronic obstructive pulmonary disease, liver disease, and elevated body mass index [27, 28]. Additionally, other studies have shown that opioid naïve patients given opioids postoperatively for pain are at higher risk for chronic opioid use, especially if they were men, over the age of 50, and using other medications such as antidepressants or benzodiazepines [29].

While opioids have demonstrated clinically significant coverage for managing pain, especially in postoperative patients, there are serious and important adverse effects to be mindful of as listed above. Further, the opioid epidemic adds another layer of caution that providers should be wary of when prescribing opioids, particularly if used as the only analgesic on board for postoperative management. Given these factors, it is important to utilize the analgesic tools afforded by opioids in a multimodal strategy to adequately manage pain and reduce the risk of the many adverse effects associated with opioid usage [30]. The more recent development of enhanced recovery after surgery pathways for a few key patient populations have helped with standardization of the postoperative pain management protocol and it has been shown in prior studies that multimodal approaches with minimal opioid use leads to better recovery in these patient groups [31, 32].

1.2 Non-steroidal anti-inflammatory drugs

1.2.1 Medication overview

Non-steroidal anti-inflammatory drugs (NSAIDs) are a type of commonly used medication that can act not only as an analgesic but as an antipyretic and anti-inflammatory agent for a variety of uses. Many are even available over the counter, such as salicylates (aspirin) and ibuprofen. NSAIDs are available in the two classes of selective cyclooxygenase (COX) 2 inhibitors and non-selective COX inhibitors (COX1 and 2). Examples of selective inhibitors include celecoxib which can be found in the United States, as well as parecoxib and etoricoxib. These selective COX2 inhibitors are ideal for patients who have prior history of, or risk for, gastrointestinal bleeding as the specificity to COX2 acts more towards inflammation and analgesia, without widespread platelet aggregation inhibition [33–35]. A recent systematic review and meta-analysis demonstrated that celecoxib, parecoxib, and etoricoxib are linked to a decreased risk of intraoperative and postoperative bleeding, and that perioperative, single-dose, or short courses of these COX-2 inhibitors may be used safely in patients undergoing surgery or at risk for bleeding [36]. Some non-selective NSAIDs include aspirin, ibuprofen, diclofenac, naproxen, and indomethacin. These medications are more readily available without a prescription, however their mechanism of action and nonselective nature renders these medications riskier for patients with preexisting cardiac disease, stroke, or cerebrovascular disease [37].

1.2.2 Medication efficacy

For their role in analgesia, many researchers have analyzed the effects of both types of NSAIDs for use in a multimodal treatment approach. Namely, prior systematic reviews have described how the use of nonselective NSAIDs in the postoperative period can have significant effects in pain reduction, ultimately resulting in minimal opioid use. However, selective NSAIDs did not show significant reduction in the opioid related adverse effects such as nausea, vomiting, and sedation, compared to the nonselective NSAIDs [38]. While this result suggests a potentially better role for nonselective NSAIDs due to their reduction in opioid consumption and adverse effects, other studies demonstrated that selective COX2 inhibitors alone, in fact, provided sufficient analgesia when compared to placebo, thus making them promising therapeutics to be used for a multimodal strategy [39]. Hong et al. also showed in a systematic review and meta-analysis of eleven included randomized controlled trials (RCTs), that the selective COX2 inhibitor, parecoxib, can reduce postoperative nausea and vomiting after total knee and hip surgeries. The 24-h postoperative analgesia was better than the placebo in these studies, but there was no difference to placebo found at 48 h postoperatively [40]. Finally, Zhang et al. showed in their multicenter RCT that in patients getting hip arthroscopy surgery, starting NSAIDs preoperatively had better short-term analgesia and patient satisfaction compared to only using it postoperatively, with no differences in adverse events [41].

1.2.3 Medication side effects

NSAIDs are not without their own adverse effects, however, even if available in some formulations as an over-the-counter medication. Some side effects include gastrointestinal upset and peptic ulcer disease, while more serious effects can include significant gastrointestinal bleeding, acute kidney injury, and possible cardiovascular or cerebrovascular events in patients with elevated risk [42, 43]. Furthermore, since nonselective NSAIDs are known to inhibit prostaglandin synthesis which can lead to decreased platelet aggregation, not only is gastrointestinal bleeding a risk but overall bleeding risks are elevated. While this is a known mechanism of action for these medications, prior studies have demonstrated variable results when it comes to the actual risk of postoperative bleeding when NSAIDs are utilized in an analgesic regimen [36, 44]. Additionally, highly selective COX2 inhibitors such as celecoxib, parecoxib, or etoricoxib have little to no effect on platelet activity and have been demonstrated to be safe in the perioperative setting [45]. When NSAIDs are utilized for postoperative pain management, it is therefore important for the risks and benefits of these potential adverse effects to be weighed alongside the potentially significant analgesic effects NSAIDs are known to have [46–48].

1.3 Acetaminophen

1.3.1 Medication overview

Acetaminophen, also named paracetamol, is another medication that many are likely familiar with given its widespread use as an antipyretic for over-the-counter needs. However, in addition to its antipyretic properties, acetaminophen can also provide pain relief by mechanisms which are thought to be related to the cannabinoid receptor pathway in the medulla [49]. As such, it can be a very useful adjunct in a multimodal perioperative strategy for analgesia. Now that it has been approved for intravenous administration, under the name OFIRMEV (acetaminophen) by the Food and Drug Administration (FDA), it has become increasingly attractive for its use intraoperatively to provide initial analgesic effect as a patient may be waking up from surgery. While its use should be limited in patients with acute liver failure or cirrhosis, or those with allergic or hypersensitivity reactions to acetaminophen products, it is one of many useful analgesic adjuncts in the perioperative setting [50].

1.3.2 Medication efficacy

The use of acetaminophen postoperatively for analgesia has been studied in a wide variety of settings. When looking broadly at the use of acetaminophen versus placebo alone for postoperative analgesia, a large Cochrane review showed that even a single dose can provide analgesia for about half of the patients studied [51]. To further assess the role of acetaminophen for providing analgesia postoperatively, other studies looked at the use of acetaminophen in combination with opioids as a multimodal strategy, and it was found that the use of acetaminophen reduced the morphine requirements for patients in the immediate postoperative period when compared to placebo. Of note, these studies also demonstrated no reduction in opioid related adverse events when opioids were combined with acetaminophen [52, 53]. Furthermore, the use of acetaminophen has been studied for a large variety of surgeries including orthopedic, gynecologic, and more. In the orthopedic surgical population, large retrospective analyses of data have shown that the use of intravenous acetaminophen with concurrent opioids reduced overall hospital length of stay and costs but lacked subgroup analyses stratifying by orthopedic procedure [54]. In smaller studies focused on specific orthopedic procedures, such as those receiving total knee arthroplasty, there was no difference in overall length of hospital stay when the combination of acetaminophen with opioid analgesia was administered [55]. Furthermore, when looking specifically at shoulder surgeries, the use of acetaminophen in a multimodal strategy, particularly in the intravenous form, has shown promise in overall reduction of pain and hospital length of stay [56].

While these studies looked particularly at intravenous acetaminophen, there are cost and economic implications that may limit the utility of just intravenous administration. As such, oral and rectal administration must also be assessed for efficacy and utility in postoperative analgesia [57]. In looking at the comparison of oral acetaminophen to intravenous, in many different surgical settings, some studies point to favorable analgesic outcomes with oral administration, while others still show less conclusive data on any differences in pain reduction regardless of the route of administration [58]. Finally, in specifically assessing the role of oral versus intravenous acetaminophen in reduction of opioid consumption postoperatively for gynecologic surgeries, retrospective analysis showed no difference in opioid consumption between oral or intravenous routes [59]. Thus, if economic efficiency is of particular concern, the use of oral or even rectal administration of acetaminophen can still be considered for an effective multimodal analgesic strategy in potentially a large variety of post-surgical patients.

1.3.3 Medication side effects

Given acetaminophen is available to be purchased over the counter in some formulations, one may assume it has limited side effects. Compared to other analgesic modalities discussed in this review, that may be the case. However, it is not without some important contraindications and side effects that must be considered before incorporating into a multimodal strategy. For one, if a patient has any underlying hepatic impairment including cirrhosis or liver failure, acetaminophen must be used with great caution as it is primarily metabolized by the liver. It may be considered as a complete contraindication in patients with severe hepatic impairment or severe active hepatic diseases. Since acetaminophen is metabolized by the liver, it can cause additional or new hepatotoxicity which may be dose related. Thus, to limit any new liver damage in an otherwise healthy patient, it is best not to exceed administration greater than 4 g per day. For a patient with underlying liver dysfunction, this dosage is lwered to a level closer to 2 g per day [60, 61] Furthermore, if a patient has any underlying hypersensitivity reaction to acetaminophen products, it should not be administered.

Other more common side effects that patients may experience include dyspepsia, possible hypotension with intravenous administration and possibly the development of asthma if used during pregnancy or early childhood [62].

1.4 Gabapentinoids

1.4.1 Medication overview

Another class of medications that has become a newer addition to multimodal analgesic strategies are the gabapentinoid medications. Gabapentinoids, as the name implies, are structurally similar to gamma-aminobutyric acid (GABA), a potent inhibitory neurotransmitter that acts on the aptly named GABA receptors. However, gabapentinoids do not bind the GABA receptors to exert their effects. The overall mechanism of action for analgesia is not well understood for these medications. It is postulated that they may bind to presynaptic voltage-gated calcium channels to downregulate excitatory neurotransmitter release, thereby producing a similar effect as endogenous GABA [63, 64]. These medications have been used very frequently in the treatment of neuropathic pain in particular but have not been as thoroughly studied for their utility and efficacy in general postoperative pain management. Data thus far has suggested most of the efficacy for gabapentin use in the reduction of postoperative pain and opioid consumption, however, this effect is most often observed with multiple doses rather than a single dose of gabapentin [65].

1.4.2 Medication efficacy

When assessing the efficacy of gabapentin for postoperative pain management, prior systematic reviews have detailed how preoperative administration was shown to decrease pain scores and overall opioid consumption in the 24-h postoperative period, among 8 RCTs analyzed [66]. Furthermore, Ladich et al. demonstrated that three of four RCT's in their systematic review showed statistically and clinically significant reductions in postoperative pain using gabapentin, and all four RCT's had reduced opioid consumption and improved patient satisfaction scores in the immediate postoperative periods [67]. There may even be important roles for gabapentin in reducing other opioid-related complications, such as reduction of nausea and vomiting after surgery. Analyses such as these have been carried out in various clinical settings as well, including in video-assisted thoracoscopic surgery and bariatric surgery patients, demonstrating similar results [68–70]. However, even with these promising results, the efficacy of gabapentin in management of postoperative pain is unclear, as other studies have shown no clinical significance when gabapentin was utilized for postoperative analgesia [71]. Moreover, the consensus on optimal dosage for analgesic effect has not been widely agreed upon through existing research studies, so further work is needed to determine if the dosages required to achieve clinical benefit in a multimodal strategy is feasible for practice [72–74].

1.4.3 Medication side effects

Finally, it is important to also consider potential side effects associated with gabapentinoid usage. Overall, these medications have relatively favorable side effect profiles, but there have been serious reports of concerns for respiratory depression and even CNS depression. As a result of some of these findings, researchers developed risk scoring tools to stratify patients who may be at higher risk for developing these side effects [75–78]. Given these findings, the FDA has recommended caution while using gabapentinoids, particularly in conjunction with other central nervous system (CNS) depressants like opioids. As such, these medications may be most useful in multimodal strategies in which no opioids are utilized at all, and with caution to higher risk groups such as the elderly, those with obstructive sleep apnea, or kidney injury [79].

1.5 Ketamine

1.5.1 Medication overview

Another medication used throughout the anesthesiologist's practice, often for induction or sedation, is ketamine. Ketamine is a phencyclidine analogue with N-Methyl-D-aspartic (NMDA) receptor antagonism as its primary role, but has additional interactions with the μ opioid, GABA, and muscarinic acetylcholine receptors. These various interactions help to give it sedative, analgesic, and sometimes also dissociative effects [80]. Specifically, the NMDA receptor interactions of ketamine have been found to produce the anti-hyperalgesic effects when used alongside opioids, while subanesthetic doses can potentiate opioid analgesia in a productive manner for multimodal pain regimens. Furthermore, the sympathomimetic effects allow for ketamine to be used easily in rapid sequence induction for patients who are not hemodynamically stable [81–83].

1.5.2 Medication efficacy

Ketamine has been widely studied for its various effects as mentioned above. Multiple prior systematic reviews and meta-analyses have demonstrated ketamine playing a role in reducing postoperative opioid consumption, overall pain scores, and nausea and vomiting for a variety of surgical conditions [84–86]. Furthermore, for its role in potentiating analgesia when used alongside opioids, it has also been demonstrated that its efficacy for analgesia may persist even in patients with opioid dependence, and reduce the hyperalgesia that may be experienced from prolonged opioid use [87–89]. To manage postoperative pain with ketamine, it is possible to utilize it as a single agent or in a multimodal strategy. Prior studies have looked at various dosage strategies for single intravenous bolus doses as well as with continuous infusions to determine optimal strategies when utilized [90]. Some have also looked at the use of ketamine in a PCA in conjunction with morphine and have shown a reduction in overall morphine requirements. This may be increasingly beneficial in patients who are at risk of respiratory depression as well, as the lower morphine requirement may decrease the risk of opioid-related respiratory depression [91, 92].

1.5.3 Medication side effects

Ketamine is not without its own side effects that must be considered. As mentioned, ketamine has sympathomimetic properties as well as known dissociative effects. The delirium emergence reaction, often accompanied by vivid dreams and hallucinations, has been linked to dosages of more than 1 mg per kilogram, and can occur in anywhere from 10–20% of patients. These reactions can, of course, result in various interactions between patients and hospital staff, but there are many cases where patients may become uncontrolled or violent and require additional sedation through benzodiazepine administration until the reaction subsides [93]. Furthermore, while the risks of CNS side effects may be present, the perioperative administration of ketamine has been shown

to significantly reduce overall opioid requirements and postoperative nausea and vomiting, which may outweigh the risks of emergence delirium in certain cases [94]. Finally, as ketamine may act as a sympathomimetic agent, it may be undesirable for usage in patients who already have elevated blood pressures, arrhythmias, or myocardial infarction [95].

1.6 Alpha-2 agonists: clonidine and dexmedetomidine

1.6.1 Medication overview

Another medication class that may have a potential role in managing postoperative pain are alpha-2 agonists such as tizanidine, clonidine, or dexmedetomidine. Stimulate of the alpha-2A and 2C sybtype receptors may lead to sedation and analgesia at both supraspinal and spinal sites. This occurs via a cascade of receptor-mediated and biochemical suppression of neural firing via the locus coeruleus, which in turn inhibits norepinephrine release and reduces activity of ascending noradrenergic pathways, resulting in sedation and hypnosis. Alpha-2 receptor stimulation, specifically in the dorsal horn of the spinal column inhibits nociceptive neurons and decreases substance P release, which produces most of the analgesic reaction [96]. A study by Buerkle and Yaksh demonstrated that spinal analgesic effects of the alpha-2 agonist effects are mediated by two sites, while there is a common supraspinal site that mediates sedation [97]. Some additional effects that each medication may mediate include the following: clonidine as an anxiolytic, tizanidine with reduced muscle spasticity, and dexmedetomidine for minimal cardiovascular and respiratory effects.

1.6.2 Medication efficacy

Each of these medications has demonstrated analgesic properties when used singularly. The real value in using these medications lies in their role in potentiating a much more significant analgesic effect when combined with other common agents such as opioids. Prior clinical trials have shown that systemic administration of alpha-2 agonists in the perioperative period resulted in significantly lower postoperative opioid requirements [98–101]. Tian et al. demonstrated that, for bariatric surgery patients, dexmedetomidine usage resulted in significantly lower postoperative opioid requirements at 24 h, and reduced pain scores in the post-anesthesia care unit compared to control groups. This shows how alpha-2 agonists are a potentially useful tool not only in a multimodal strategy, but also as standalone agents if appropriate clinical conditions are met [100]. Another important effect that has been reported is a potential decrease in postoperative delirium when dexmedetomidine is utilized, possibly due to the decrease in neuroinflammation and improved sleep [102–105].

1.6.3 Medication side effects

While clonidine and dexmedetomidine are frequently used medications for analgesia and sedation in the anesthesiologists practice currently, they are also not without important side effects that must be carefully monitored. First, given their mechanism of action, hypotension is a concern, especially in patients with already low blood pressure or existing cardiovascular disease in which hypotension cannot be tolerated. There can also be profound bradycardia with their use, and thus must be carefully considered for patients with conditions such as heart block. These side effects have been demonstrated in a few studies with variable reports. These studies acknowledge the ability of medications such as clonidine or dexmedetomidine in reducing overall pain postoperatively but note these significant clinical side effects that must be carefully considered before administration in either a single or multimodal analgesic protocol [106–109].

1.7 Corticosteroids

1.7.1 Medication overview

Systemic corticosteroids are another pharmacologic option that can be utilized in the perioperative treatment and management of pain, as well as to manage postoperative nausea and vomiting. Corticosteroids have various actions in reducing inflammation, the immune response overall, and cell proliferation as a result of their ability to bind to and modify the nuclear transcription of target genes. Endogenous glucocorticoids often have tissue specific gene interactions which determine their overall effect in homeostatic function. When corticosteroids are administered systemically, however, they act to downregulate the immune and inflammatory responses often seen in autoimmune, general inflammatory, or even hematologic-oncologic conditions [110].

1.7.2 Medication efficacy

Dexamethasone has been relatively well studied for its utility in managing postoperative pain, nausea, and vomiting to name a few. Prior systematic reviews have shown significantly lower postoperative pain scores at various dosages and clinical conditions studied [111]. Furthermore, as described in more detail in the regional anesthesia section, dexamethasone is also often added as an adjunct for regional anesthetic procedures in order to prolong the efficacy of medication. It has been shown that this multimodal strategy can ultimately lead to significantly reduced pain scores and opioid requirements postoperatively [112].

1.7.3 Medication side effects

As with many medications, corticosteroids are also not without side effects that are important to consider.

Systemic steroids are associated with hyperglycemia in some reported studies [113], but other studies reported that perioperative dexamethasone did not increase blood glucose levels postoperatively in patients with pre-existing diabetes mellitus [114]. Another important side effect of systemic steroids to be considered includes risk of infection and delayed wound healing, which may be particularly important to consider in a postoperative setting. However, in prior systematic reviews looking specifically at corticosteroid use in the perioperative setting, there was no significant increase in infection or delayed wound healing in various clinical studies [115]. These side effects may be more concerning if prolonged corticosteroid use is being considered.

1.8 Lidocaine

1.8.1 Medication overview

Finally, intravenous lidocaine has emerged as an attractive perioperative pain intervention and is convinently inexpensive and can be administered with ease. It is used largely in the postoperative setting to accelerate recovery via its analgesic, anti-hyperalgesic, and anti-inflammatory properties [116–119]. Lidocaine acts via inhibition of sodium channels, G protein-coupled receptors, and N-methyl D-aspartate receptors [117]. Perioperative lidocaine infusion is an effective alternative analgesic in patients that may have relative contraindications to neuraxial anesthesia [120].

1.8.2 Medication efficacy

Intravenous lidocaine use in open laparoscopic abdominal surgeries has been well studied and has demonstrated a variety of effects, such as decreased postoperative pain, improvements in postoperative fatigue and bowel function, and decreases in hospital stays soon after abdominal surgery [117, 121, 122]. Benefits have also been found in patients undergoing major spinal surgeries [123]. Adequate plasma lidocaine concentrations may reduce the amount of volatile anesthetics necessary in patients [117, 124], as well as decreased in postoperative opioid use [120]. With regards to cardiac and hip surgery, studies have not demonstrated significant differences in postoperative pain or opioid use in patients who received lidocaine infusions versus placebo [125, 126].

1.8.3 Medication side effects

Examples of side effects from perioperative intravenous lidocaine infusion include symptoms such as drowsiness and blunted response to tracheal extubation, as well as symptoms commonly associated with local anesthetic systemic toxicity such as tinnitus, perioral numbness, lightheadedness, dizziness, visual changes, and more seriously arrhythmias and seizures [121, 127–129].

2 Regional anesthesia

Regional anesthesia techniques have enhanced perioperative pain control and decreased opioid use related to numerous surgical procedures. While regional anesthesia techniques are associated with risk of complications, the risk is generally small. Innovation involving ultrasound guidance, enhanced needle tracking, and nerve stimulators have reduced risks of intravascular and intraneural injection. There still exist block specific complications, typically related to structures nearby which can be injured during the block procedure, as well as risks involving potential local anesthetic toxicity. In most major surgeries, the benefits rendered by perioperative multimodal anesthesia, particularly regional anesthesia blocks, outweigh safety concerns.

2.1 Standard and novel blocks

2.1.1 Epidural anesthesia

Epidural anesthesia is one of the oldest and widely applied forms of intraoperative and postoperative regional anesthesia in which local anesthetics are delivered to the epidural space to target nerve roots as they exit the spinal dura sheath. It is often used in thoracic surgery, orthopedic surgery, and obstetrical procedures. When used with local anesthetics, it creates both sensory and motor blockade while affecting the autonomic nervous system [130]. Ropivacaine has demonstrated a great degree of motor and sensory separation, with higher selectivity for pain-transmitting fibers over large, myelinated motor fibers. Bupivacaine is a more lipophilic anesthetic agent that demonstrates increased penetration of large, myelinated motor fibers, resulting in increased motor blockade compared to ropivacaine [131]. A benefit of epidural anesthesia is the attenuated cardiovascular response and stress response from surgery, when used in combination with general anesthesia [130, 132]. Risks of epidural anesthesia include unintentional dural puncture and possible post-dural puncture headache, epidural hematoma, and epidural abscess. The risk of post-dural puncture headache risk with labor epidural was 0.9% as observed in a ten-year cross-sectional study [133]. A study analyzed 35,628 epidural anesthesia procedures in patients undergoing obstetrical and gynecological procedures and reported a 0.1% incidence of overt cerebral spinal fluid leak along with a 0.01% risk of seizure and neurogenic bladder [134].

2.1.2 Paravertebral block

The paravertebral block involves the delivery of local anesthetics to the paravertebral space near the spinal nerves emerging from the intervertebral foramen [135]. While it was initially a landmark based procedure, ultrasound guided technique has now also been described [136]. The paravertebral block is considered

an established and reliable technique for reducing pain in the immediate postoperative period after breast surgery [137–139], however there is insufficient evidence to prove any long-term benefits of the paravertebral block in preventing long-term pain after surgery [139, 140]. There are variable risks involving potential pneumothorax, which was reported at 0.7% with use of the landmark technique [141]. Another study reported 2,163 cases of paravertebral injection under ultrasound guidance and determined a 0.1% risk of pleural puncture [142]; while yet another study with 1,427 patients reported no such incidence of pleural puncture [143].

2.1.3 Upper limb nerve blocks

Upper limb nerve blocks are employed due to the high incidence of postoperative pain in upper limb surgeries. The interscalene block has typically been a widely used approach for shoulder surgery, however there are many reports of potentially severe complications, including phrenic nerve damage, Horner syndrome, and dyspnea [144]. Several improved approaches for the shoulder and upper limb have been described to avoid such complications, namely the suprascapular and axillary, and are considered to be rapidly evolving novel block modalities [145]. The suprascapular block and axillary block have been reported to be a safe and alternative form of analgesia, with equivalent pain relief to the interscalene block, but without the potentially severe complications related to weakness as described above [146–148]. Postoperative pain has been well documented with upper limb surgery. In a study of 336 axillary nerve block cases, 4% of cases reported neurological symptoms that persisted between 3 weeks and 36 months [149]. Another study reported the risk of nerve injury to be between 0.4–4% [150]. In an analysis of 2,953 infraclavicular block cases, there were no nerve injuries reported [151].

2.1.4 Transverse Abdominis Plane Block

The transverse abdominis plane (TAP) block involves the delivery of local anesthetics to the fascial plane between the internal oblique and transverse abdominus muscles [152]. It has been used extensively for colorectal surgeries and obstetrical procedures, with excellent analgesic efficacy and decreased use of postoperative opioids [153, 154]. TAP has also proven to have a lower risk of adverse events, is less invasive, and has comparable postoperative pain control outcomes when compared to thoracic epidural anesthesia for colorectal surgeries [155]. A potential risk of the TAP block is accidental intraperitoneal needle placement, which can be as high as 18% if ultrasound guidance is not used [156]. However, ultrasound guidance reduces this risk to less than 0.05% [157, 158]. The TAP block is easier to perform than the quadratus lumborum block as well and requires less expertise [159]. Risks do exist however; a retrospective analysis of 2,382 patients that had QL block demonstrated lower limb weakness in 15% of the patients, with the risk higher in anterior quadratus lumborum (QL) block due to its effect on the spinal nerves [160].

2.1.5 Quadratus lumborum block

Quadratus lumborum block is an umbrella term for several block techniques, which deposits local anesthesia around the quadratus lumborum muscle and covers T6-L1. It was developed to cover a larger sensory block and to potentially provide both visceral and somatic pain control, in comparison to TAP blocks, all while using a similar anesthetic dose [145, 159]. The techniques are effective for abdominal, obstetric, pelvic, and renal surgeries [161]. Studies show that the quadratus lumborum block offers benefits with respect to both postoperative analgesia and limiting opioid consumption in patients that do not receive long-acting intrathecal or epidural morphine [159, 162], and may enhance functional recovery in patients when added to general anesthesia [163]. The great proximity of the quadratus lumborum muscle to the lower pole of the kidney, as well as nearby lumbar arteries originating from the aorta must be avoided during the procedure to avoid any complications [145].

2.1.6 Erector spinae block

The ultrasound-guided erector spinae block is a fascial plane technique used to treat both acute and chronic pain, with many applications ranging from head and neck, thoracic, abdominal, and lower extremity procedures [86, 164], and is considered to be a rapidly evolving novel block [145]. Several investigations have concluded that the erector spinae block is effective at reducing intraoperative [165] and postoperative [166, 167] opioid consumption in patients [168]. Additionally, it provides superior perioperative analgesia, with reduced pain scores postoperatively compared to controls [166, 167]. It has been regarded as a safe technique, but more studies need to be completed in order to further understand the efficacy and potential complications of this block.

2.2 Mechanisms to improve block efficacy

2.2.1 High echogenicity needles

The advent of ultrasound guided regional anesthesia has ushered in the development of high echogenicity needles. Increased echogenicity (and therefore visibility) of an ultrasound needle under ultrasound guidance has been accomplished by incorporating ultrasound reflectors in the needle surfaces [169], allowing for better needle tip tracking during the procedure, and subsequently improved safety. Enhanced needles may also reduce the

technical difficulty, needle redirection, and time taken to complete the procedure but have been found to have no significant difference with regards to procedure complication rates [170–172].

2.2.2 Local anesthetic adjuncts

A limitation of peripheral nerve blockade via regional anesthesia techniques is the rather limited time of effect that the anesthetic may have. Most notably, the use of local anesthetic adjuncts has been explored and found to enhance the efficacy and characteristics of peripheral nerve blocks. Typically, adjuncts are composed of one or more pharmacological agents that are administered around a peripheral nerve, fascial plane, or plexus [173]. Novel anesthetic adjuncts include dexmedetomidine and dexamethasone, which both increase the duration of the block when combined with long acting local anesthetics [173] and have shown to result in significantly less postoperative opioid use in colorectal surgery [174] and in epidural anesthesia [175].

2.2.3 Single shot versus continuous local anesthetic infusion

Continuous catheter anesthetic infusion via delivery of potent analgesia postoperatively may enhance the efficacy of regional anesthesia after surgery. Typically, this incorporates a basal local anesthetic loading infusion, followed by subsequent patient-controlled boluses, and has been determined to be highly effective after both minor and major shoulder surgeries [176, 177]. Opioid use and postoperative pain levels are demonstrated to be decreased with use of continuous catheter anesthetic infusion in shoulder surgery [178]. However, there has been limited benefit of using continuous infusion in patients undergoing knee surgery [179]. Depending on the anatomical site of surgery, among other pre- and postoperative considerations, the anesthesiologist may consider using continuous anesthetic infusion postoperatively for enhanced pain management in patients.

2.2.4 Long-acting local anesthetics

Local anesthetic pain control postoperatively remains a highly attractive option for significant pain control within 48–72 h after surgery, especially considering alternatives such as opiates, non-steroidal anti-inflammatory drugs, acetaminophen, and steroids. However, limited duration of action, or lack of readiness for discharge from continuous infusion systems (while effective for delivery analgesia) [177], has further demonstrated the necessity of an extra-long-acting local anesthetic that will reduce postoperative pain for longer periods than current nonopioid methods offer. Recent advancements and efforts to increase the length of analgesia in pre-existing local anesthetics has yielded the development of EXPAREL liposomal bupivacaine and SABER bupivacaine, with other medications currently awaiting FDA approval for use in the clinical setting. These medications have significantly reduced postoperative pain levels up tp 72 h, diminishes use of rescue opioids overall, increased length of time to first rescue opioid medication use, and reduced hospital stay [180]. More advancements in such long-acting local anesthetics will likely enhance the landscape for regional anesthesia and acute pain care moving forward.

2.2.5 Local anesthetic volume considerations

With increasing use of ultrasound-guided regional anesthesia may come a reduced volume of required local anesthetic to maintain a successful peripheral nerve block, due to heightened precision with medication delivery. However, a recent study demonstrated that block duration is affected by local anesthetic volume and concentration, which is important to consider while there is a general trend towards using smaller anesthetic volumes [181]. Another study demonstrated that craniocaudal block spread, particularly for the serratus anterior block, was enhanced when a higher volume of ropivacaine was used in breast surgery patients. However, in this case, the time until the need for first postoperative analgesic rescue was equivalent between the standard dose and a higher dose [182]. Further investigation is warranted to assess the effects of anesthetic volume and block efficacy, especially across different types of blocks.

2.3 Toxicity and injury

2.3.1 Local anesthetic toxicity

Local anesthetic drugs act by blocking the action potential through targeted nerves, via blockade of sodium channels [183]. This mechanism has effects on potassium and calcium levels, and as a result, high plasma concentration of local anesthetic can result in life-threatening arrhythmias and convulsions, termed as local anesthetic systemic toxicity (LAST) [184]. Local anesthetic drugs can enter systemic circulation via reabsorption from the interstitium into the bloodstream, or from accidental intravascular injection [184–187]. The extent of reabsorption and systemic toxicity from local anesthetic is dependent on location as well as patient factors such as age and comorbidities [183, 188].

Among a cohort of 12,668 patients evaluated across an eight-year period, the risk of unintended vascular puncture during a regional anesthesia procedure was less than 0.2% and risk of seizure was less than 0.1% [189]. Ultrasound guided regional anesthesia procedures demonstrated no cases of local anesthetic toxicity in a cohort of 7,092 procedures, when compared to a cohort study of 9,062 patients undergoing regional anesthesia procedures without ultrasound guidance the risk of LAST was

0.1% in this group [190]. A recent larger cross-sectional study of 710,327 patients reported that overall incidence of LAST was 0.1% [191].

2.3.2 Nerve injury

Neurological deficit after administration of regional anesthesia may occur due to needle-induced mechanical trauma or from intraneural injection of local anesthetic and subsequent postprocedural hematoma formation [192, 193]. The regional anatomy may render only a small margin of error between what would be accurate perineural delivery of local anesthetic versus unintentional intraneural injection. Ultrasound guidance and nerve stimulator monitoring may reduce the risk of intraneural injection.

In a study evaluating 12,668 patients, the risk of neurological symptoms lasting beyond five days was 0.18%, while the risk of symptoms lasting more than 6 months was 0.9% [189]. A subsequent study that investigated over 26,251 cases reported that transient symptoms (time period less than ten days) were reported in up to 14% of patients, while prolonged symptoms (greater than six months) were identified in 0.02% to 0.1% of patients [194]. The risk of prolonged neurological symptoms were 0.18% and 0.01% for landmark and ultrasound guided techniques respectively, indicating that ultrasound guidance significantly reduces the risk of nerve injury, and represents a promising mechanism with which to further enhance patient outcomes in the realm of perioperative multimodal analgesia [190].

3 Conclusions

Overall, many advancements have been made in the study of various medications that can be utilized for postoperative analgesia. As we learn more about the efficacy and side effect profiles of each of these pharmacologic options, a push towards multimodal strategies has become prominent in not only targeting pain from a variety of receptors and signaling pathways, but also to limit the overall opioid consumption and occurrence of adverse effects. Since postoperative pain is one of the most common complaints by patients after surgery, and if left untreated can cause significant complications or development of chronic pain syndromes, it is imperative we work to establish new protocols for multimodal analgesia strategies to manage pain effectively and promptly in the perioperative setting. Not only have there been new advancements in our study and understanding of the mechanism of action of various medications, but new regional anesthetic techniques have also been developed and can be employed in a multimodal approach. A limitation of this review, however, is that this was not a systematic review of all the literature on multimodal analgesic strategies. Thus, there are other possible indications for the pharmacologic agents discussed, as well as multiple potential dosing strategies and methods based on the use case that must bec considered, In the future, it will be critical for researchers and clinicians to study various multimodal protocols in large-scale randomized controlled trials, and in various patient populations, in order for the field of anesthesiology to accumulate enough high-powered evidence to formulate standards of care in the future.

Abbreviations

COX	Cyclooxygenase
ERAS	Enhanced recovery after surgery
FDA	The Food and Drug Administration
GABA	Gamma-aminobutyric acid
LAST	Local anesthetic systemic toxicity
NMDA	N-Methyl-D-aspartic
NSAIDs	Non-steroidal anti-inflammatory drugs
PCA	Patient-controlled analgesia
QL	Quadratus lumborum
RCTs	Randomized controlled trials
TAP	Transverse abdominis plane

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