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Authors

Gabriel, Rodney A

Swisher, Matthew W

Sztain, Jacklynn F

et al.

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REVIEW

State of the art opioid-sparing strategies for post-operative pain in adult surgical patients

Rodney A. Gabriel[a,b,c], Matthew W. Swisher[a,c], Jacklynn F. Sztain[a], Timothy J. Furnish[a], Brian M. Ilfeld[a,c] and Engy T. Said[a]

[a]Department of Anesthesiology, Division of Regional Anesthesia and Acute Pain, University of California, San Diego, La Jolla, CA, USA; [b]Division of Biomedical Informatics, University of California, San Diego, La Jolla, CA, USA; [c]Outcomes Research Consortium, Cleveland, OH, USA

ABSTRACT

Introduction: There are various important implications associated with poorly controlled postoperative pain in the adult surgical patient – this includes cardiopulmonary complications, opioid-related side effects, unplanned hospital admissions, prolonged hospital stay, and the subsequent development of chronic pain or opioid addiction. With the ongoing national opioid crisis, it is imperative that perioperative providers implement pathways for surgical patients that reduce opioid requirements and pain-related complications.

Areas covered: In this review, the authors discuss the components of a multimodal opioid-sparing analgesia pathway as it pertains to the perioperative environment. Medications reviewed include gabapentinoids, acetaminophen, non-steroidal anti-inflammatory drugs, ketamine, intravenous lidocaine, dexmedetomidine, and glucocorticoids. The use of peripheral nerve blocks and neuraxial analgesia are also discussed.

Expert opinion: In appropriate cases, regional anesthetic interventions are extremely useful for postoperative analgesia, including peripheral nerve blocks and neuraxial analgesia and while newer postoperative analgesics have been postulated, the literature on such is presently controversial. Coordinated approaches to pain management are recommended to reduce the need for opioids and to improve patient satisfaction post-surgery.

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Multimodal analgesia; acute pain service; opioid; perioperative

1. Introduction

Pain is one of the most common and significant postoperative events experienced by many surgical patients. The implications of poorly controlled postoperative pain are substantial, including cardiopulmonary complications, opioid-related side effects, unplanned hospital admissions, prolonged hospital stay, and the subsequent development of chronic pain or opioid addiction [1]. With the ongoing national opioid crisis [2], it is in both the patients' and public's interest for perioperative providers to implement pathways for surgical patients that reduce opioid requirements and pain-related complications. In this review, we discuss the components of multimodal opioid-sparing analgesia pathways as it pertains to the perioperative environment in the adult patient (Figure 1). We focus on evidence-based medicine and discuss process changes that may aid in the implementation of such clinical pathways and promising novel therapies.

2. Non-opioid medication for perioperative analgesia

Multimodal analgesia should begin in the preoperative period, extend into intraoperative management, and finally during the acute postoperative period. Preemptive analgesia is defined as a preoperative antinociceptive treatment that prevents the establishment of central sensitization caused by incisional and inflammatory injuries [3], and is achieved by administering analgesics prior to the surgical insult. Intravenous or oral analgesic medications most commonly studied in the context of opioid-sparing preemptive analgesia include gabapentinoids, non-steroidal anti-inflammatory medications (NSAIDs), acetaminophen, ketamine, dexamethasone, magnesium, and dextromethorphan. Many of the agents commonly used in both pre-emptive analgesia and intraoperative management may be continued during the postoperative period. Here, we summarize some of those agents and discuss the evidence behind their utilization.

2.1. Gabapentinoids

Gabapentinoids, such as gabapentin and pregabalin, have been studied as part of a multimodal analgesic regimen to provide analgesia in the perioperative period. Their mechanism of action involves the presynaptic voltage-gated calcium channel receptor in both the central and peripheral nervous systems [4]. A number of meta-analyses have been performed to investigate the effect of preoperative administration of gabapentinoids on postoperative analgesia.

CONTACT Rodney A. Gabriel ragabriel@ucsd.edu Department of Anesthesiology, University of California, 200 W Arbor Dr, MC 8770, San Diego, CA 92103, USA

Article highlights

- Multimodal opioid-sparing analgesia is an effective approach to postsurgical care
- Pharmacological non-opioid agents for pain control include the gabapentinoids, non-steroid anti-inflammatory drugs, magnesium, lidocaine, NMDA-antagonists, glucocorticoids, and alpha2-agonists.
- When appropriate, regional anesthesia interventions are extremely useful for postoperative analgesia, including peripheral nerve blocks and neuraxial analgesia
- Newer agents for postoperative analgesia include HTX-011, SABER-bupivacaine, and liposomal bupivacaine, although the literature is still controversial
- A coordinated approach to pain management, including an Acute Pain Service or Enhanced Recovery After Surgery pathway, may aid in reducing opioid requirements and improving patient satisfaction in the surgical population.

This box summarizes key points contained in the article.

2.1.1. Gabapentin

Two meta-analyses found significantly lower pain scores and/or opioid consumption for 24 h with preoperative gabapentin [5,6]. An additional systematic review and meta-regression analysis of 133 placebo-controlled RCTs revealed improved postoperative nausea and vomiting, pruritis, preoperative anxiety, and patient satisfaction [7].

Possible side effects with gabapentinoids include sedation and respiratory depression: one retrospective review found a 50% increased risk of respiratory depression [8]. Relatedly, this class of analgesics has also been associated with an increased risk of naloxone administration and delayed recovery room discharge [9,10]. Although distinct from preoperative gabapentinoid administration, recent data demonstrate an association between outpatient opioid-related deaths and concomitant treatment with opioids and gabapentin [11]. Thus, caution must be exercised, especially with the continuation of gabapentinoids past the perioperative period.

2.1.2. Pregabalin

There is no consensus regarding the optimal type (e.g. gabapentin versus pregabalin) or dose for gabapentinoids. In a meta-analysis investigating 11 RCTs, they reported that perioperative pregabalin was not associated with postoperative pain intensity; however, it reduced 24-h opioid consumption and some opioid-related adverse events [12]. In a more recent meta-analysis that included 43 studies, they also reported reduction in analgesic usage associated with perioperative pregabalin usage [13]. One placebo-controlled RCT demonstrated no analgesic superiority between gabapentin (600 mg) and pregabalin (150 mg) during the first 48 postoperative hours following laparoscopic cholecystectomy in terms of postoperative shoulder pain, although it failed to evaluate opioid consumption [14]. In contrast, another RCT involving lumbar spine surgery showed improved postoperative opioid consumption for preoperative pregabalin in comparison to gabapentin [15]. This study used a higher dose of pregabalin (300 mg) in comparison. Similarly, a comparative randomized trial did find decreased opioid consumption and pain scores with pregabalin (150 mg) compared to gabapentin (900 mg) [16]. Comparative results for other surgical populations have also shown conflicting results. Given the lack of consensus and limited data, further prospective controlled trials are required.

2.2. Non-steroidal anti-inflammatory drugs

Both nonselective non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors improve postoperative analgesia in a myriad of surgical populations. A recent meta-analysis of 20 randomized controlled trials (RCT) documented a decrease in 24-h opioid consumption, pain scores, and postoperative nausea and vomiting with preoperative celecoxib administration for non-cardiac surgery [17]. Similarly, a systematic review of 22 placebo-controlled RCTs involving preoperative COX-2 inhibitors also found

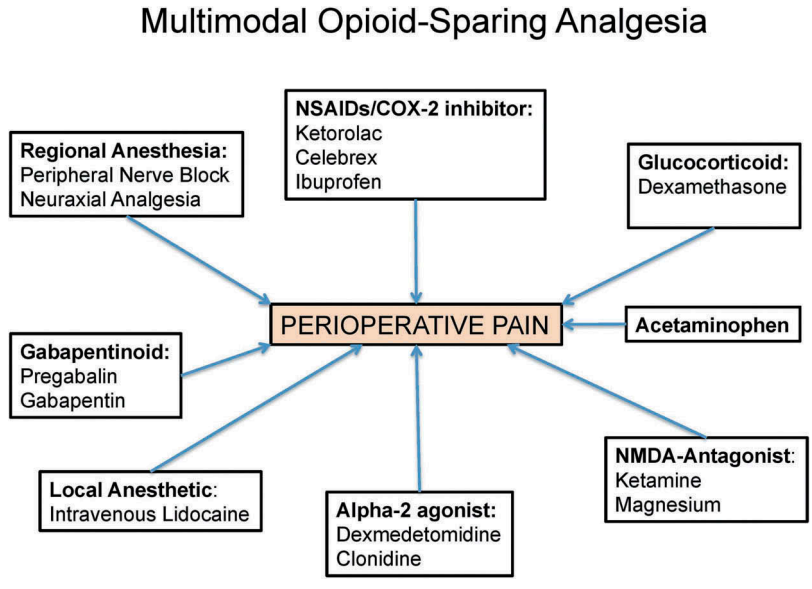

Figure 1. Diagram illustrating components of a multimodal opioid-sparing regimen.

improved postoperative pain scores, analgesic consumption, and patient satisfaction [18]. Another meta-analysis of eight RCTs involving specifically lumbar spine surgery similarly reported improved pain scores in patients receiving NSAIDs, especially with selective COX-2 inhibitors [19]. Another meta-analysis by Oliviera et al. involving 13 RCTs evaluated perioperative ketorolac [20], finding an improvement in early pain scores but only a decrease in opioid consumption with the higher ketorolac dose of 60 mg. Overall, there is a significant heterogeneity with the available studies investigating NSAIDs for preemptive analgesia with respect to specific NSAID administered, dosage, and schedule of administration (preoperative, intraoperatively, and postoperatively). Further randomized controlled trials are needed to better delineate the potential risks and benefits of this class of medication.

While a plethora of data demonstrate that perioperative administration of NSAIDs improves postoperative analgesia, the optimal timing of administration initiation remains unknown (e.g. preoperative versus postoperative). An RCT by Sun et al. demonstrated that celecoxib administration after major plastic surgery procedures had no benefit of when administered preoperatively [21]. In contrast, an RCT by Zhou et al. reported a benefit to preoperative compared with postoperative celecoxib administration for arthroscopic knee surgery [22]. Similar RCTs for parecoxib have also shown conflicting results for hip arthroplasties and colorectal surgery [23–25]. Interestingly, a recent RCT studying celecoxib in geriatric patients undergoing total knee arthroplasty showed a decreased incidence of early postoperative cognitive dysfunction, thus highlighting some of the potential non-analgesic benefits to anti-inflammatory therapy perioperatively [26].

Nonselective NSAIDs have been associated with adverse perioperative side effects due to prostaglandin synthesis inhibition, most noticeably to the gastrointestinal, renal, cardiovascular, and hematologic systems. Selective COX-2 inhibitors minimize some of these side effects by their relative sparing of COX-1 activity. The absence of COX-2 receptors on platelets and subsequent prospective studies have led to the consensus that selective COX-2 inhibitors have no effect on platelet function and perioperative bleeding [27].

2.3. Acetaminophen

Acetaminophen has been demonstrated to provide preemptive analgesia. The analgesic mechanism of action remains incompletely understood, but may be due to indirect central COX inhibition or modulation of the endogenous cannabinoid system [28]. Given its advantage of having intravenous, oral, and rectal formulations with a minimal side effect profile, acetaminophen has been extensively used as a perioperative analgesic adjunct. The main safety concern with acetaminophen is its dose-dependent hepatotoxicity. Thus, when administered perioperatively, care must be exercised to not exceed the recommended maximum daily dose (4 g in adults).

The preoperative administration of acetaminophen has been recently studied. One RCT by Moon et al. demonstrated decreased opioid consumption and opioid-related side effects in patients receiving preoperative intravenous acetaminophen for abdominal hysterectomies [29]. Another RCT compared preoperative oral acetaminophen to postoperative rectal acetaminophen for pediatric tonsillectomies and reported decreased pain scores and need for rescue opioids postoperatively in the oral acetaminophen cohort [30]. Similarly, an RCT by Arci et al. compared preoperative and pre-skin closure acetaminophen to placebo following abdominal hysterectomy and reported superiority for preoperative administration over pre-skin closure and placebo in terms of postoperative opioid consumption [31]. In contrast, an RCT by Unal et al. evaluated open nephrectomy patients and reported decreased opioid consumption in patients receiving preoperative or postoperative acetaminophen compared to placebo but did not find a difference between the two [32]. Similarly, an RCT by Khalil et al. for lower extremity surgery done under spinal anesthesia showed superiority of preoperative and postoperative acetaminophen compared to placebo but no difference between preoperative and postoperative administration [33]. Based on the available data, perioperative acetaminophen provides postoperative analgesic and opioid-sparing benefits; however, it remains unclear if there is an optimal timing for administration relative to surgery.

The optimal dosage and route of administration of acetaminophen for preemptive analgesia have not been established. Due to the high bioavailability of oral acetaminophen, the use of the intravenous formulation is typically reserved for patients who cannot tolerate the oral formulation. There is limited data comparing oral to intravenous acetaminophen for preemptive analgesia. One such RCT by Politi et al. discovered no difference between these two formulations as part of a multimodal analgesic regimen continued for 24 h after total joint arthroplasty [34]. While not specifically examining preoperative oral versus intravenous acetaminophen, another RCT by Hickman et al. also found no difference between preoperative oral acetaminophen versus intraoperative intravenous acetaminophen for patients having total joint arthroplasty [35]. Based on the available evidence, the optimal dosage and route of administration of acetaminophen for preemptive analgesia remain undetermined.

2.4. Ketamine

Ketamine is a phencyclidine derivative, which was developed in the 1960s as a general anesthetic [36]. At subanesthetic doses, ketamine exhibits analgesic and anti-hyperalgesic properties [37] primarily *via* N-methyl-D-aspartate (NMDA) receptor antagonism [38,39]. Its non-competitive antagonism of NMDA receptors prevents central sensitization, therefore attenuating opioid-induced hyperalgesia, and decreasing opioid tolerance [40]. Initially, the use of ketamine was limited due to its adverse effects such as delirium and nausea, but low dose infusion has more-recently gained favor as part of a multimodal opioid-sparing analgesia regimen for the treatment of acute pain. It has been included at some institutions as standard care for the management of postoperative pain in opioid-tolerant patients [41]. Similarly, ketamine is now incorporated into many orthopedic multimodal analgesic pathways and shown to reduce opioid requirements and/or pain scores for opioid-tolerant patients undergoing spine [42,43] and joint replacement surgeries [44,45].

Three studies [46–48] found an average 42% reduction in morphine consumption at 24 h postoperatively after a single intraoperative 0.15 mg/kg bolus of ketamine, although another [49] found no such difference after the same dose. Four studies [43,50–52] investigated dosing with an intraoperative bolus followed by a low-dose infusion (0.15 mg/kg + 0.12 mg/kg/h to 0.5 mg/kg + 0.6 mg/kg/h) and found an average 39% reduction in opioid consumption at 24 h postoperatively [41]. In contrast, two studies [53,54] using doses within the same range found no reduction in 24-h opioid consumption.

The limited data involving a ketamine infusion alone without an initial bolus is limited but suggests that the opioid-sparing effect is surgical site dependent. Patients undergoing surgery with anticipated severe postoperative pain such as lower abdominal, intra-abdominal, and orthopedic (limb and spine) procedures have shown the greatest benefit in opioid reduction with ketamine [41,55]. Opioid tolerant or opioid-dependent patients also experience significant benefits [55].

The reported dose of ketamine is variable, ranges from single dose boluses (up to 1 mg/kg) to continuous IV infusions (up to 0.18 mg/kg/h for 48 postoperative hours) [56,57]. Based on a 2015 review, IV ketamine has a definite effect on reducing opioid consumption, although a clear dose-response could not be determined [41]. However, when given as an intraoperative infusion with or without an accompanying 24-h infusion, it has been associated with less long-term effect of residual pain in comparison to single dose bolus [41].

Side effects to ketamine include neuropsychiatric effects, psychomimetic effects such as hallucinations, vivid dreams, diplopia, blurred vision, nystagmus, or dysphoria. Nausea and/or vomiting, as well as sedation, are also noteworthy [58]. Schwenk et al. concluded that during low-dose infusions, adverse drug effects were minimal and nearly 95% resolved immediately after discontinuation of infusion [59].

2.5. Intravenous lidocaine

Another older medication that has found a resurgence in popularity is intravenous lidocaine, an amide local anesthetic and Class 1b antiarrhythmic first described as an analgesic in 1951 [60]. Lidocaine interacts with several receptors, including NMDA, however, the exact mechanism of action of systemic lidocaine in prevention of acute pain remains elusive [61,62]. Van der Wal et al. in 2016 concluded that its analgesic and anti-hyperalgesic effect is obtained through inhibition of the voltage-gated sodium channels, voltage-gated calcium channels, various potassium channels, NMDA receptors, glycine system, and G protein pathways [61]. Lidocaine has been associated with reduced opioid consumption, earlier return of bowel function, faster rehabilitation, and shorter hospital stays [63–65]. There is evidence that intravenous lidocaine prevents hypersensitization and hyperalgesia [66]. The anti-inflammatory properties of lidocaine protect cells from inflammation by blocking the priming neutrophils and inhibiting the release of superoxide anions and interleukin-1B [67]. Several clinical studies suggest that perioperative administration of systemic lidocaine is associated with attenuation of surgical-induced release of pro-inflammatory cytokines [68–70]. Cahana et al. used PET scans to demonstrate lidocaine may have a specific site of action in the thalamic region of the brain, suggesting a mechanism of action for chronic neuropathic pain [71].

The most recent Cochrane review of perioperative lidocaine included 68 trials with varying IV lidocaine doses (1–5 mg/kg/h) and infusion termination (the end of surgery to several days later) determined it was uncertain whether perioperative lidocaine has any impact on early (0–4 h) postoperative analgesia, gastrointestinal recovery, postoperative nausea, or opioid consumption [72]. The quality of evidence for the benefit of IV lidocaine was very low due to inconsistency, imprecision and study quality [60,72]. However, like ketamine, IV lidocaine may show surgery-specific perioperative benefit. Several studies demonstrate that patients undergoing open or laparoscopic abdominal surgery with lidocaine infusions of at least 2 mg/kg/h intraoperatively – and continuing for up to 8 h after surgery – reduced opioid consumption and postoperative pain and improved return of bowel function [73–75]. There is also some evidence that systemic lidocaine decreases postoperative pain and opioid consumption in open prostatectomy, thoracic and major spine procedures [75]. Fortunately, toxicity from perioperative lidocaine is exceedingly rare.

Perioperative use of IV lidocaine can have a beneficial effect as a prophylactic measure to prevent the development of chronic pain. For breast cancer patients, perioperative IV lidocaine was effective in reducing the severity of persistent post-surgical pain at 3 months [76,77] and mastectomy patients had 20 times less the relative risk of the occurrence of post-surgical chronic pain when compared with placebo [78]. Similarly, patients undergoing complex spine surgery had overall lower opioid consumption and improved quality of life with administration of perioperative IV lidocaine [79].

Reported perioperative lidocaine infusion dosing varies from 1 to 5 mg/kg/h (after a bolus of 0–1.5 mg/kg) in patients undergoing open or laparoscopic abdominal surgery [80,81]. Koppert et al. found that a dose of 1.5 mg/kg/h of lidocaine started preoperatively and continued until 1 h following surgery provided analgesic benefits for up to 72 h following surgery [64]. Optimal dose, initiation timing, and administration duration remain undetermined.

There have been no reports of increased risk of life-threatening events such as cardiac arrhythmias, although clinical studies have not always addressed adverse events [80]. In a retrospective case series analysis of 122 lidocaine infusions, the most common side effects were drowsiness (31%), perioral numbness (13%), nausea (6%), and minor fluctuations of blood pressure (4%) [82]. Lidocaine infusion is contraindicated for patients with anaphylaxis to lidocaine, and electrocardiogram monitoring is recommended especially in the setting of known cardiac arrhythmias.

2.6. Alpha-2 agonists

2.6.1. Dexmedetomidine

In 1999, dexmedetomidine – a2-adrenoceptor agonist – was approved for use in clinical practice as a short-term sedative (<24 h). Agonism of this alpha receptor induces multiple downstream effects including a decrease in sympathetic

tone, attenuation of the neuroendocrine and hemodynamic response to surgery, reductions in anesthetic and opioid requirements, and induction of sedation and analgesia. There have been several studies assessing its benefit for postoperative analgesia when used during the perioperative period with mixed results [83–96]. However, many studies have demonstrated reduce postoperative opioid use when the drug is administered intraoperatively, specifically following laryngectomy[83], abdominal surgeries [84,95], bariatric surgery [91,96], cesarean section[86], off-pump coronary artery bypass surgery [87], knee surgery [88,94], tonsillectomy [90], and total abdominal hysterectomy [93]. A few studies have found a lack of benefit involving other types of procedures, including major spine [89] and some abdominal surgeries [85]. The dosing of dexmedetomidine for these studies differed significantly and ranged from a single pre-incision bolus to a continuous intraoperative infusion. Given that several studies have demonstrated benefit, its use seems appropriate in a multimodal opioid-sparing analgesic pathway for specific types of surgery, although more data is required before definitive recommendations may be provided. Side effects of dexmedetomidine include cardiovascular depression, but it has the benefit of minimal respiratory depression compared to other analgesics such as opioids.

2.6.2. Clonidine

Clonidine is another alpha-2 agonist that has antinociceptive properties and have been used in the perioperative setting for analgesia. In a clinical trial investigating patients undergoing spinal fusion, subjects were randomized to receive a clonidine infusion versus placebo [97]. The results demonstrated that clonidine decreased pain scores and time to first request of opioid injection. In a prospective study, the efficacy of perioperative clonidine was studied in patients undergoing major abdominal surgery [98]. Here they showed that intraoperative clonidine reduced opioid consumption while not exacerbating sedation or side effects. Another clinical trial investigated the optimal intravenous dose of perioperative clonidine (defined as the dose providing minimal analgesic request, minimal sedation, and stable hemodynamics) after lumbar hemilaminectomy for herniated disk repair [99]. Among the four cohorts studied, the trial reported that 3 mcg/kg bolus dose followed by a continuous infusion of 0.3 mcg/kg/hour was considered the optimal intravenous dose. Based on these studies, perioperative clonidine appears to be an effective agent included in a multimodal analgesia plan if hemodynamics allow.

2.7. Glucocorticoids

Dexamethasone is a glucocorticoid steroid commonly used perioperatively for the prevention of postoperative nausea/vomiting; however, it contains analgesic properties as well. Glucocorticoids reduce prostaglandin synthesis by inhibiting phospholipase enzyme and cyclooxygenase type II. In addition, they modulate the inflammatory system *via* mechanisms that involve tumor necrosis factor-alpha, interleukin 1B, and c-reactive protein [100]. The optimum dosing for dexamethasone remains undetermined and may differ depending on the patient population, route of administration, and surgical procedure. Jokela et al. studied the effective analgesic dose of dexamethasone after laparoscopic hysterectomy and reported that intravenous dexamethasone (15 mg) just prior to induction of anesthesia decreases postoperative oxycodone consumption, whereas doses as low as 5 mg has negligible effects on analgesia [101]. Of note, anti-emetic doses (4 mg) did not improve analgesia in a previous study [102]. In a randomized controlled trial, an 8 mg dose did not help reduce analgesia requirements following cesarean sections [103]. Its use when provided as an adjuvant for peripheral nerve blocks have demonstrated benefits in many studies [104], although the optimal route of introduction – intravenous or perineurally – remains controversial.

2.8. Magnesium sulfate

Several studies have investigated the use of perioperative intravenous magnesium sulfate for postoperative pain with mixed conclusions. In a meta-analysis, 20 RCTs with 1,257 subjects were analyzed and demonstrated that magnesium improved pain at rest and at movement and reduced postoperative opioid consumption, while no studies reported clinical toxicity related to magnesium [105]. Another meta-analysis investigated 22 trials, which also demonstrated decreased pain scores and opioid use with magnesium use [106]. Perioperative magnesium appears to be a safe addition to a multimodal opioid-sparing approach to postoperative analgesia.

3. Regional anesthesia for acute pain management

3.1. Peripheral nerve blocks

The analgesic and opioid-sparing effects of peripheral nerve blocks have long been studied for upper extremity, lower extremity, and truncal surgeries. The degree of analgesic benefit is dependent on the specific surgery and type of nerve block performed. One of the most widely studied surgical procedures for postoperative analgesia includes total knee arthroplasties. A recent Cochrane review showed that femoral nerve blocks provided more effective analgesia than opioid alone with less nausea/vomiting [107]. More recently, adductor canal blocks have been used for total knee arthroplasty given their association with improved short-term functional recovery secondary to decreased quadriceps weakness and similar analgesia compared to femoral nerve blocks [108]. Adductor canal blocks as part of a multimodal analgesic pathway for knee arthroplasty patients have been shown to be associated with reduced hospital length of stay and decreased opioid consumption [109].

Although less widely studied, brachial plexus blocks have been associated with improved pain scores, decreased opioid consumption, and even decreased length of stay after such procedures as shoulder arthroplasty and rotator cuff repair [110,111]. For oncologic and reconstructive breast surgery, paravertebral nerve blocks have also been shown to improve postoperative analgesia, decrease opioid consumption, and decrease opioid-related side effects [112,113].

With respect to long-term outcomes, recent studies have evaluated the effect of peripheral nerve blocks on persistent postsurgical pain with varying results. There is limited data suggesting that peripheral nerve blocks for breast, foot, knee, and hip surgery is associated with a decreased incidence of persistent postsurgical pain [114,115]. Given the recent emphasis on the opioid epidemic and postoperative opioid prescribing practices, recent retrospective reviews showed no association between peripheral nerve blocks and persistent opioid use after surgery; however, prospective studies are lacking [116,117].

Peripheral nerve blocks include single-injection and continuous techniques. While many adjuvants have been studied to prolong the analgesia of single-injection techniques beyond the first postoperative day, the placement of a catheter with multi-day infusion of local anesthetic allows for an extended duration of postoperative analgesia that can be utilized for both in- or outpatient surgery. Compared to opioid analgesia alone, continuous peripheral nerve blocks (CPNB) have been shown to be associated with superior analgesia, decreased opioid consumption, and decreased opioid-related side effects [118]. When comparing single-injection peripheral nerve blocks to CPNBs, continuous techniques tend to be associated with improved postoperative analgesia, improved patient satisfaction, and decreased total opioid consumption for certain surgeries; however, randomized controlled trials directly comparing the two techniques are rather limited [119–121]. The main limitations of CPNBs in comparison to single-injection techniques include block performance time, cost, logistical maintenance of patients with continuous infusions, infection, and catheter dislodgement.

The most commonly cited risks associated with peripheral nerve blocks include nerve injury, bleeding, infection, intravascular injection, systemic local anesthetic toxicity, and injury to surrounding anatomic structures. The incidence of nerve injury associated with peripheral nerve blocks has been difficult to accurately determine given the multifactorial nature of perioperative peripheral nerve injuries. More commonly, early transient postoperative neurologic symptoms are quite common but rarely result in long-term neurologic sequelae [122]. Infectious risks of single-injection techniques remain very low; however, cPNBs have been shown to be associated with a 0–1% risk of infection depending on the duration of catheter use and site [123,124]. More common site-specific risks include quadriceps weakness and falling for femoral nerve blocks, pneumothorax for brachial plexus and thoracic truncal blocks, and phrenic nerve blockade for some brachial plexus blocks. For thoracic truncal blocks, more superficial interfascial plane blocks such as pectoral plane blocks and erector spinae plane blocks have been newly developed and require prospective investigation to document and quantify analgesic potency.

3.2. Neuraxial analgesia

Thoracic epidural analgesia (TEA) plays an important role for patients undergoing open abdominal or thoracic procedures. It is well recognized as a superior analgesic choice to intravenous opioids in patients undergoing major open abdominal surgery [125], and considered the gold standard for postoperative pain following thoracic surgery [126]. Benefits of TEA include reduced postoperative ileus duration after major abdominal surgery by an average of 36 h [127,128]. The mechanism by which TEA may shorten the duration of ileus may include a decrease in sympathetic tone, stress response, and inflammatory processes. Most recent meta-analysis demonstrates that an epidural infusion provides superior postoperative analgesia, decreased perioperative pulmonary-cardiac morbidity, and earlier return of gastrointestinal tract function in comparison to systemic analgesia [129]. Despite these benefits, TEA has not been shown to decrease hospital length of stay [127]. Over time, TEA has become an integral part of anesthesia-based Acute Pain Services (APS) and Enhanced Recovery After Surgery (ERAS) especially abdominal surgery [129–131]. Opioid sparing adequate analgesia is a cornerstone to APS/ERAS, and TEA serves as an adjunct in fast-track recovery, as it minimizes opioid-related sedation, and allows for more effective mobilization [132].

Analgesic agents for TEA infusions include local anesthetics alone, opioids alone or a combination of both. The use of local anesthetic alone provides analgesia without opioid-related side effects but is often limited by vasodilation-induced hypotension and/or decreased sensation and weakness of the lower extremity (for catheters inserted closer to the lumbar plexus). Since opioids do not induce a sympathectomy or motor/sensory block, they may be added to improve analgesia without the risk of these complications. However, epidurally administered opioids can exhibit side effects similar to systemic opioids such as prolonged postoperative ileus, nausea and vomiting, respiratory depression, and mental status changes. There is no clear evidence for the superiority of thoracic epidurals when the infusion consists of only opioids versus parenteral opioids [133], though it can be considered in the short term in patients with marginal hemodynamics [134]. Several studies and reviews conclude that local anesthetic-based TEA with or without opioids following abdominal surgery accelerates the return of gastrointestinal transit and decreases pain [135–137]. However, there was no difference in the incidence of vomiting or anastomotic leakage [135].

Despite TEA's numerous benefits, its use is sometimes limited by catheter insertion difficulties. The optimal insertion site targets the level of the midpoint of the surgical incision. However, this can become challenging for upper abdominal surgery requiring a catheter above T11 due to the extreme caudad angulation of the mid-thoracic spinous processes: a conventional midline approach to the epidural space can be difficult and a paramedian approach is often necessary [134]. This technique is thought to be more hazardous due to perceived increased risk of injury to the spinal cord [Manion21606825]. In patients undergoing abdominal or abdominal–thoracic surgery, the predicted maximum risk for permanent neurologic complication is 0.07% [138].

Additional complications include epidural hematoma or abscess. The incidence of hematoma is 1 in 150,000 and usually in the setting of impaired anticoagulation [139]. The American Society of Regional Anesthesia and Pain Medicine recently released updated guidelines for the management of patients in

the setting of anticoagulation [140]. Epidural abscess remains rare and is influenced by factors such as TEA catheter duration and perioperative use of antibiotics [141]. Other undesirable but less serious risks include catheter migration (intrathecal or intravascular), back pain, and post-dural puncture headache [142].

3.3. Surgical wound infiltration

Surgical wound and intra-articular injection with local anesthesia has also been demonstrated in some studies to be effective for postoperative analgesia. This was demonstrated in patients undergoing cesarean section [143], knee replacement surgery [144], and laparoscopic cholecystectomy [145]. However, there are reported negative studies in patients undergoing hip arthroscopy [146] and knee replacement surgery [147].

4. Newer therapies

4.1. HTX-011

HTX-011 (Heron Therapeutics, San Diego, CA, USA) is an extended-release, fixed-ratio product that contains bupivacaine and low-dose meloxicam incorporated in a bioerodible polymer. The purpose of meloxicam is to enhance the effect of bupivacaine. Once HTX-011 is administered directly into the surgical wound, the polymer undergoes a steady hydrolysis that releases bupivacaine and meloxicam slowly over 3 days. Recently, Heron Therapeutics announced the results of two Phase 3 clinical trials (EPOCH1 [NCT number: NCT03295721] and EPOCH2 [NCT number: NCT03237481]), in which HTX-011 was compared to standard bupivacaine and placebo in randomized controlled trials for patients undergoing bunionectomy and hernia repair, respectively. For both trials, all primary and secondary endpoints were achieved, in which there was a statistically significant reduction in both pain scores and opioid consumption through 72 h. Further research will be required in other surgical procedures and with use in peripheral nerve blocks if and when HTX-011 is approved by the United States Food and Drug Administration and becomes commercially available.

4.2. SABER-bupivacaine

Sucrose acetate isobutyrate extended-release bupivacaine (SABER-Bupivacaine) (DURECT Corporation, Cupertino, California, USA) is another depot formulation that provides continuous release of bupivacaine following surgical infiltration. The sucrose acetate isobutyrate is a biodegradable compound that stores bupivacaine. In one double-blinded, randomized controlled trial, 124 subjects undergoing open inguinal hernia repair received either SABER-bupivacaine or SABER-placebo administered to the surgical wound. The results demonstrated improvement in both pain scores and opioid use while there were no differences in adverse events [148]. To date, there have been no other published randomized controlled trials evaluating its efficacy.

4.3. Liposomal bupivacaine

Exparel (Pacira Pharmaceuticals, Parsippany, New Jersey, USA) is the only currently available liposomal formulation of local anesthetic. This form of bupivacaine is slowly released continuously over approximately 72 h as the bupivacaine-containing liposomes gradually break down. It was initially approved by the US Food and Drug Administration in 2011 for surgical infiltration specifically for postoperative analgesia. More recently, it received approval for use in transversus abdominus plane and interscalene brachial plexus blocks. The preponderance of evidence from the 13 randomized, controlled trials published at the time of this writing suggests that there are few, if any, benefits in switching from intraoperative infiltration with unencapsulated bupivacaine to liposomal bupivacaine [149]. In contrast, early evidence from the use of liposome bupivacaine within peripheral nerve blocks appears promising, although far more research is required to document and quantify any analgesia-related benefits [150].

4.4. G-protein pathway modulating opioids

There is a class of medications – μ-G-protein pathway selective (μ-GPS) modulators – currently in development that may prove to be a significant advance over existing mu opioid receptor agonists. The first agent in this class now going through phase 3 clinical trials is Oliceridine. Our prototypical opioid, morphine, along with most of the other clinically used opioids, mediate their primary analgesic effects via the μ-opioid receptor. The adverse effects of these agents are also mediated at the same receptor. The μ-opioid receptor, along with the other opioid receptors (δ-opioid, κ-opioid, and NOP receptors) is a G-protein coupled receptor. An opioid ligand binds the opioid receptors and activates antinociception as well as opioid-related adverse effects (ORAEs) [151]. Of note, the FDA recently communicated its decision to not approve this drug.

5. Conclusion

A multimodal opioid-sparing analgesia technique is ideal for surgical patients. This approach includes a variety of drugs from different families, each with its unique mechanism of action and side effect profile. In addition, multimodal analgesia should include regional anesthesia techniques, including neuraxial and peripheral nerve block approaches. With the ongoing opioid crisis and rising costs of opioid-related morbidity and mortality, it is important that for any multimodal analgesia pathway, the concept of opioid-sparing is prioritized.

6. Expert opinion

State-of-the-art drug therapy for postoperative pain management should include a multimodal opioid-sparing strategy. Implementation of a postoperative analgesic strategy is optimized with inter-departmental collaboration (e.g. anesthesiologists, additional pain specialists, surgeons, palliative care providers, pharmacists, etc.) through either consult services such as an APS [152], protocolized formal pathways such as

ERAS [153] or Perioperative Surgical Home [154], or simple pathways led by surgical services. Many of the medications and regional anesthesia techniques discussed in this review should play an integral part of these pathways but is dependent on a myriad of factors, such as the surgery procedure, patient comorbidities (e.g. opioid dependency), and hospital resources. In the following section, we provide an example pain pathway for patients undergoing open abdominal surgery. This protocol may be adapted, as needed, for other surgical procedures and will vary based on regional anesthetic approach (if appropriate), tolerance to oral diet, and discharge milestones.

Postoperative management challenges following open abdominal surgeries include ileus, pain, physical therapy, and dehydration, among others. Adequate pain management while concurrently minimizing opioid consumption can decrease the time to reach important milestones [152]. We propose the following components for perioperative pain management in this adult patient population (Figure 2). Immediately prior to surgery, providers should consider administering oral gabapentinoid if no contraindications exist (i.e. gabapentin 300 mg or 600 mg), oral acetaminophen (650–1000 mg), and an oral NSAID (i.e. celebrex 200 mg). If a patient is on any home dose of opioids, this should be administered prior to surgery. TEA is highly recommended in this patient population and, ideally, can be inserted in the preoperative holding area to provide a less-pressured catheter insertion and minimize operating room inefficiency. The use of a relatively high-concentration intermediate-acting local anesthetic via the epidural catheter will provide a potent regional anesthetic without the requirement of opioids. Alternative regional anesthetic techniques to TEA include bilateral paravertebral nerve blocks (with optional continuous infusions), intrathecal opioids, or transversus abdominus plane block (although the efficacy of this block for midline open abdominal procedures is minimal relative to the other regional anesthesia techniques).

Intraoperatively, opioid administration should be limited to reduce opioid-induced hyperalgesia and side effects. Pre-incision ketamine, dexamethasone, and dexmedetomidine boluses should be considered. Continuous ketamine (0.1–0.6 mg/kg/h) and dexmedetomidine infusions should be part of the anesthetic plan if appropriate, especially in patients with pre-existing chronic pain. If a TEA is present and no concerns for hemodynamic instability, this should be started intraoperatively to reduce the total required anesthetic for surgery and initiate postoperative analgesia. When no local anesthetic infusion through an epidural/perineural catheter is available, providers should consider administering an intravenous lidocaine infusion (1–3 mg/kg/h) intraoperatively.

Postoperatively, patients should have the following analgesics available: TEA with bupivacaine infusion (typical concentration at our institution ranges from 0.0625% to 0.15% at 8–10 mL/h with a 5 mL patient-provided bolus available every 20 min), lidocaine transdermal patches applied near the surgical incision, standing acetaminophen orders (oral when patient tolerating diet), standing gabapentinoids (when patient tolerating oral diet and no contraindications), standing NSAID (if no surgical concerns), and low-dose opioids either *via* nursing provided intravenous bolus or patient-controlled analgesia apparatus. Medications may be titrated up and down, as needed, with the goal of minimizing opioid use. For patients with pre-existing chronic pain or those with high postoperative opioid requirements, a postoperative ketamine infusion is also recommended and can range from 0.1 to 0.6 mg/kg/h, although higher doses may be used. In the event that no regional anesthetic is available, the combined use of continuous ketamine and lidocaine infusions should be considered. Transition to oral medications is encouraged as rapidly as possible depending on patient tolerance. The duration of epidural use will depend on postoperative recovery.

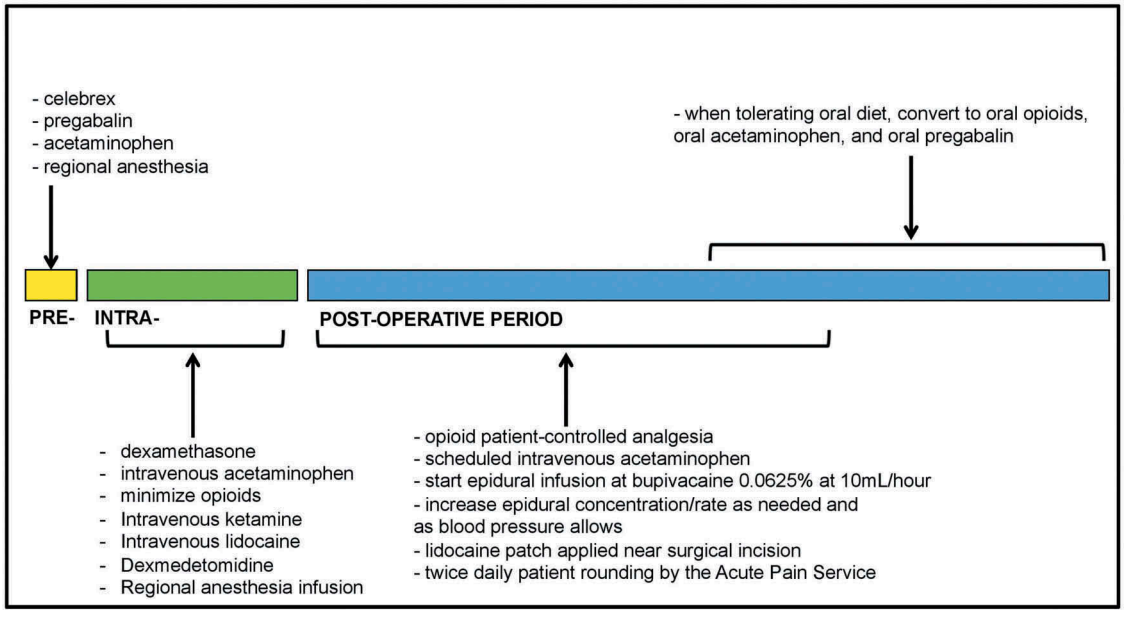

Figure 2. Example protocol for perioperative pain management for major abdominal surgery.

For abdominal surgeries, it is recommended to maintain TEA until patient tolerates oral pain medications unless there is concern for catheter infection (whichever comes first).

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