Opioid-Sparing Perioperative Analgesia Within Enhanced Recovery Programs

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KEYWORDS

• Opioid • Nonopioid • Opioid-sparing • Multimodal • Analgesia • Recovery • Side effects • Intravenous

KEY POINTS

- Opioid-based analgesia can provide excellent pain control but exposes the patient to avoidable side effects and complications.
- Optimal analgesia is an approach that targets the fastest functional recovery with adequate pain control while minimizing side effects.
- Opioid-sparing analgesia appears to be of benefit in the perioperative period.
- Many different options for nonopioid multimodal analgesia exist and have been shown to be efficacious, with certain modalities being more beneficial for specific surgeries.

INTRODUCTION

Perioperative pain management plays a central role in functional recovery after surgery and can be related to overall patient satisfaction with the surgical and anesthesia experience.[1,2] Although opioids are extremely effective to treat pain, they do so at the expense of adverse side effects that can interfere with functional recovery.[3] In addition, acute exposure to opioids in the perioperative period can also lead to the long-term risk of developing persistent postoperative opioid use (PPOU).[1,4] Recognition of these drawbacks has prompted providers to shift away from opioid-only based regimens and has encouraged the exploration of alternative analgesic strategies.

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Abbreviations	
ERP	Enhanced Recovery Program
NOMA	non-opioid multimodal analgesia
PPOU	persistent postoperative opioid use
CWIC	continuous wound infiltration catheters
TEA	thoracic epidural analgesia
RCT	randomized controlled trial

The concept of an Enhanced Recovery Program (ERP) is a multicomponent approach aimed at reducing the stress of surgery experienced by the patient and improving the metabolic response, thereby speeding the return of functional recovery.[5] One of the central principles of ERP is the application of nonopioid multimodal analgesic (NOMA) interventions to reduce the reliance on opioid-based medications.[5] ERPs provide a framework to decrease the amount of perioperative opioids used while still targeting excellent pain control. Compared with traditional care, ERPs have been shown to successfully reduce perioperative opioid use and complications while still providing adequate analgesia.[6] This is particularly important in the opioid epidemic era, as clinicians are looking for guidance on the management of acute postoperative pain and the appropriate use of opioids.

Recent consensus statements have discussed potential strategies to address acute postoperative pain management with focus on preventing PPOU, and the feasibility and relative merits, if any, of opioid-free anesthesia and analgesia for ERPs.[4,6–8] Specifically, the reports noted that opioid-free, or at least opioid-minimizing, ERP care pathways are feasible and able to be used in routine practice. Opioid reduction has been associated with reduced postoperative ileus and length of stay.[9,10] In light of recent, conflicting reports of the effect of some multimodal agents, such as gabapentinoids, on postoperative complications,[11,12] and the recent report that opioid-free analgesia may be associated with harm,[13] it is important to consider the evidence behind a practical approach to appropriate opioid minimization in the perioperative period.

Within any ERP, the goal should be to deliver “optimal” or “effective” analgesia, which has been defined as a “technique that optimizes patient comfort and facilitates functional recovery with the fewest medication side effects,” regardless of the particular analgesics used (**Fig. 1**).[7] It has been noted that this may not correspond with the lowest pain score possible, which is important to discuss with patients during the preoperative education phase. As such, a practical goal is that the pain is “tolerable,” which is best defined as not keeping the patient from sleeping, not waking the patient from sleep, and not inhibiting them from participating in their recovery (eg, drinking, eating, ambulating). In short, the goal is to reduce pain interference in the recovery process while also preventing side effects from the analgesics used. Thus, the approach to treating pain should be multifaceted, including a combination of techniques such as neural blockade, intravenous (IV), and oral multimodal analgesia. The overall combination of analgesic components is not as important as targeting the goal of optimal/effective analgesia.

However, opioids have been the backbone for treating perioperative pain and are still used extensively, if not exclusively, in most surgical specialties. In light of the fact that opioids are excellent analgesics, many perioperative physicians may ask why there is such a focus on opioid minimization or elimination from perioperative care. In short, *minimizing opioid analgesia for patients reduces the adverse effects of opioid use.* The short-term side effects of opioids, including nausea, vomiting, ileus,

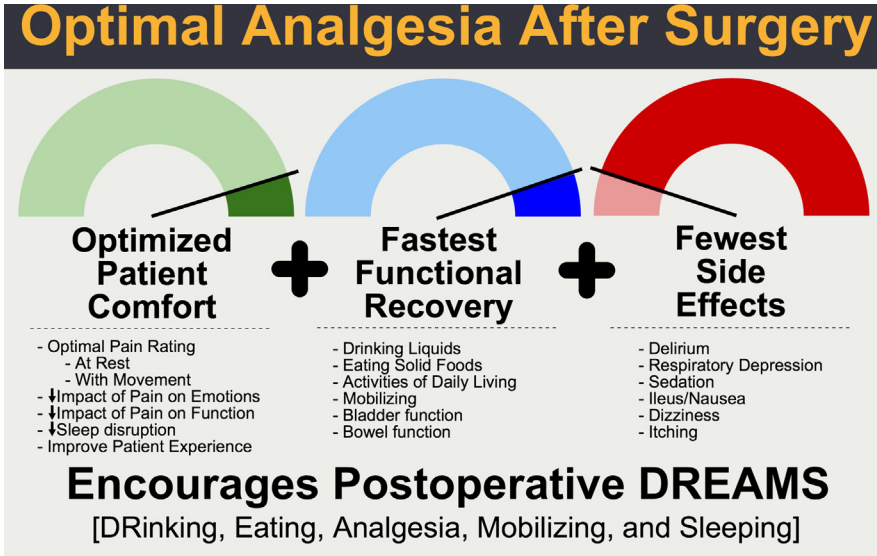

Fig. 1. Optimal analgesia. This figure illustrates the core components of providing optimal analgesia. Pain after surgery can have profound effects on patient recovery. However, the complete elimination of pain may also have untoward effects, as listed in the figure. Optimal analgesia after surgery is an approach to pain control that facilitates a positive patient experience through optimized patient comfort that facilitates functional recovery while minimizing adverse drug events. (Reproduced with permission from POQI, www.thepoqi.org.)

urinary retention, and somnolence can cause patient distress and delay enteral intake, mobilization, and hospital discharge in the surgical patient.[14] In addition, postoperative delirium (itself a risk factor for the development of dementia and longer-term cognitive dysfunction) in the elderly patient is a frequent complication that delays discharge and can be caused both by uncontrolled pain and its treatment with opioids.[15–17] Finally, traditional use of an opioid-based pain management regimen is likely to be associated with developing tolerance and hyperalgesia.[14] In contrast, non–opioid-based approaches may reduce the incidence of developing chronic postsurgical pain, and could potentially decrease the recurrence of and increase survival for certain cancers based on tumor biology, although there is conflicting data concerning the latter.[18,19] These advantages have led to the adoption of a multifaceted approach using various analgesic components to greatly reduce the need to give any opioids during the perioperative period. For all the reasons detailed earlier, opioid-sparing pathways should be considered a best practice.[20]

PERSISTENT POSTOPERATIVE OPIOID USE

Epidemiology

In light of the opioid epidemic in the United States and many other countries, anesthesiologists and surgeons are uniquely positioned to play a significant role in reducing opioid use for surgical patients, for whom opioids continue to be first-line analgesic agents while nonopioid medications are inconsistently prescribed.[1,2] Crucially, several studies suggest that surgery is associated with an increased risk of long-term opioid use, a phenomenon known as PPOU.[3,4] As such, efforts to reduce the risk of PPOU can have a direct effect on opioid use at the population level. In addition, decreasing

the risk of PPOU could also have indirect benefits on population-level opioid use by reducing the incidence of diversion and overdose, particularly in the light of studies suggesting a substantial amount of opioid overprescription and large amounts of unused pills among surgical patients.[5,6,7]

Incidence

A wide range of PPOU rates have been reported—approximately 1% to 20% for opioid-naïve patients and 35% to 77% for patients with previous opioid exposure—depending on the definition used. Kent and colleagues recently proposed definitions of what would constitute PPOU to reduce this incidence reporting variability. For opioid-naïve patients, PPOU is defined as having filled at least a 60-day supply of opioid in the period from 3 to 12 months after surgery, which allows for normal postoperative weaning from opioids. For patients who used opioids before surgery, PPOU was defined as an increase above baseline during this same period. Regardless, PPOU is a significant population health problem. Major risk factors for PPOU are listed in **Box 1**.

DEFINING ERP STRATEGIES

A key component of developing an analgesic strategy for an ERP is to be clear on the goal and the overall approach. As such, definitions for terms such as opioid-based, opioid-sparing, and opioid-free analgesia are important when applied operationally to patient care. Traditional perioperative pain management was *opioid-based*, meaning that the primary medications used for analgesia were opioids, and nonopioid therapies were seldomly used in a scheduled or structured fashion. In contrast, the current trend in perioperative care includes a massive reduction in the use of opioid-based patient-controlled analgesia (PCA) regimens.[21] *Opioid-free* analgesia is an approach to pain management that strictly avoids the use of opioids, which is sometimes confused as a goal rather than a strategy. There have been reported successes with this approach, and early evidence suggested that not only can this strategy be used in routine practice, but pain scores and patient satisfaction may be better.[6] Nonetheless, total abstinence from opioid use does not ensure an uncomplicated postoperative course, as nonopioid analgesics can also be associated with side effects that inhibit surgical recovery. Finally, *opioid-sparing* strategies promote structured and

Box 1
Risk factors for persistent postoperative opioid use

- Preoperative opioid use
- History of psychiatric disorder
- History of substance use disorder
- Presence of preoperative pain conditions
- History of smoking
- Type of surgery
  - Total knee arthroplasty
  - Thoracotomy—open or video-assisted
  - Breast surgery
  - Spine surgery
  - Craniotomy

scheduled use of NOMAs, including regional and neuraxial analgesia, to achieve the goal of optimal analgesia. However, the judicious use of opioids is not viewed as a failure, and if opioids are required, there are clear guidelines for doing so.[20,22]

APPROACH TO AN OPIOID-SPARING ERP

A practical approach to implementing an opioid-sparing strategy is to adhere to the principle that nonopioid agents are used first, used in a scheduled manner, and discontinued last (**Fig. 2**). Conversely, opioids are used last, used only as needed, and discontinued first. To deliver optimal analgesia using such a strategy, a well-structured and planned multimodal approach should be constructed that covers the entire perioperative care arc, from the preoperative period into the postdischarge recovery phase (**Fig. 3**).[7,8] It should be noted that the literature is replete with a wide variety of successful opioid-sparing analgesic combinations across many types of surgery.[21,23–25] From the published literature to date, it would appear that reducing opioid use is beneficial in the perioperative period, and high compliance with opioid-sparing ERP care pathways is strongly associated with an overall reduction in opioid consumption and improved patient outcomes. In the following discussion, we present an overview of the most recent data on a wide variety of nonopioid analgesic options, including information about the benefits of use and areas of controversy. In the accompanying tables, we will present a summary of which components have been associated with opioid reduction for specific types of surgery.

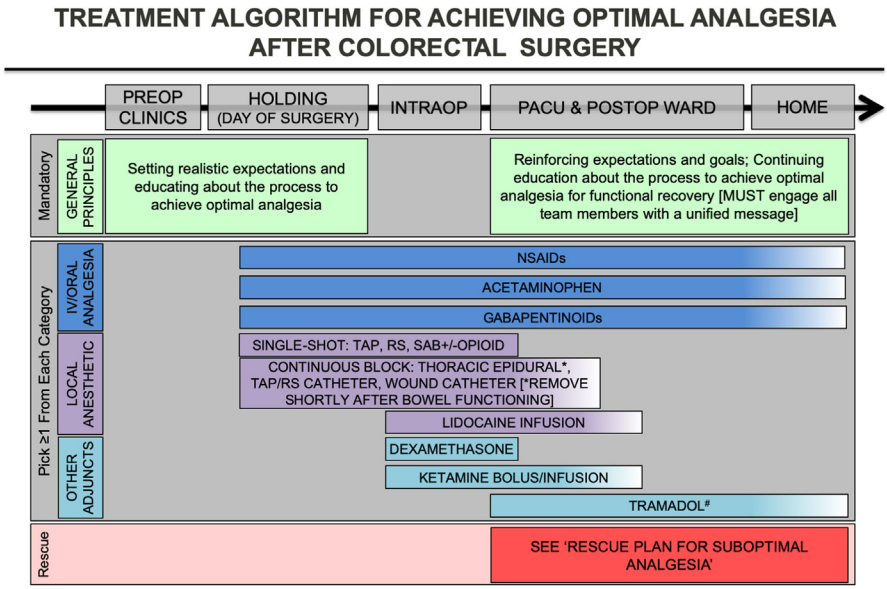

Fig. 2. Multimodal plan within ERAS. This figure illustrates suggested components of a multimodal approach to pain management in an ERP for colorectal surgery. Of note, the plan should be comprehensive, encompassing all phases of perioperative care from preoperative to postdischarge. However, current evidence is insufficient to determine how many components should be selected to maximize pain control, reduce opioid burden, and avoid the side effects of all analgesics used. See **Table 1** for specific dosing recommendations for different analgesic components. ERP, Enhanced Recovery Pathway. (Reproduced with permission from POQI, www.thepoqi.org.)

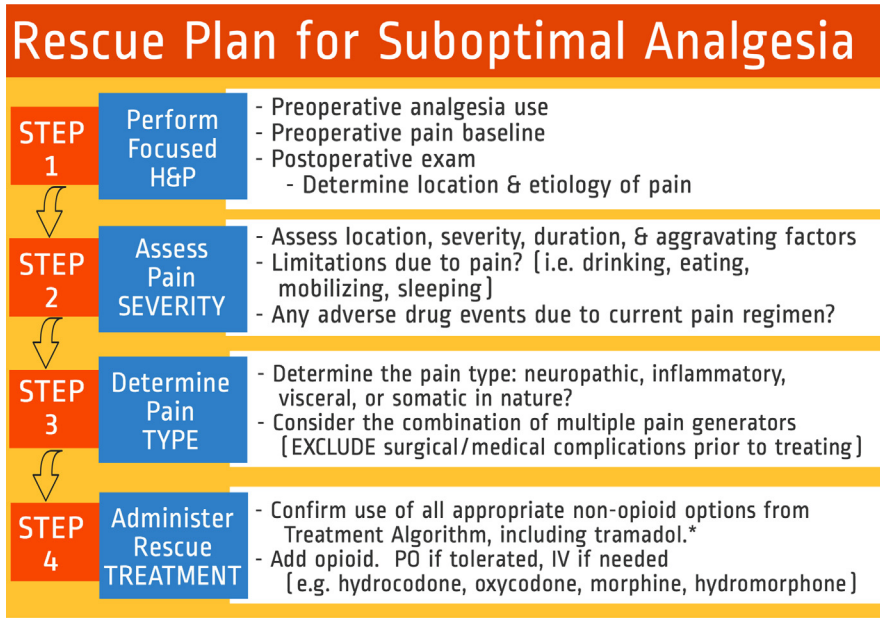

Fig. 3. Structured rescue plan. This figure illustrates a structured approach as a rescue plan for a patient experiencing suboptimal pain control. Except in extreme cases, this step-by-step process should lead to appropriate management that continues the principles being used with the goal of delivering optimal analgesia. See **Table 1** for specific dosing recommendations for different analgesic components.

MULTIMODAL ANALGESIA

Primary Options—Regional Anesthesia/Analgesia

Neuraxial analgesia

Thoracic epidural analgesia. Compared with parenteral opioid-based analgesia, thoracic epidural analgesia (TEA) has been shown to be associated with superior postoperative pain control,[26,27] reduced pulmonary morbidity,[28] and earlier return of bowel function for open abdominal surgery.[29,30] However, in the era of minimally invasive surgery, the overall benefit of TEA for patients undergoing laparoscopic colorectal procedures is uncertain.[31,32] From a practical perspective, using TEA as a routine care component of ERPs for open abdominal surgery is of benefit.[33] In addition, TEA may be particularly beneficial for specific populations, such as those with significant pulmonary disease or a history of chronic pain.[34] To ensure that TEA does not prolong the length of stay, it is prudent to have a plan to wean the infusion and remove the catheter within 2 to 4 days after surgery, depending on the typical recovery timeline (eg, colorectal surgery [CRS] vs Whipple) while supplementing with oral, nonopioid multimodal agents as soon as possible in the postoperative period. Whether TEA can be supplanted by other regional techniques, such as rectus sheath catheters (RSCs), is being investigated.[35] This is important to note as recent meta-analyses have reported TEA failure rates as high as 30% in some centers and that ~20% of patients experience postoperative hypotension, a complication increasingly known to be associated with acute kidney and myocardial injury.[36–39]

Intrathecal opioids. Two meta-analyses of randomized controlled trials (RCTs) have reported that the use of a single-shot of intrathecal hydrophilic opioid (eg, morphine,

hydromorphone, and diamorphine) is associated with significantly lower pain scores and reduced opioid requirements.[40,41] These benefits are likely more pronounced in patients undergoing abdominal surgery as opposed to other types of surgery. Interestingly, these meta-analyses included studies covering large dose ranges (100–4000 μg). Current research and practice trends suggest that lower doses are more commonly used (eg, <300 μg) because of dose-dependent side effects and respiratory depression.[42] Of note, this finding was replicated in the most recent meta-analysis on intrathecal opioids, but only with intrathecal morphine doses of greater than 500 μg[41] From a practical perspective, some centers use a spinal dose of bupivacaine as a carrier for the opioid and to cover the stimulation and pain from the incision in the immediate perioperative period; there is often a resulting sympathetic block that can require management of hypotension intraoperatively; however, this is typically not severe. There is a practical benefit of hybrid techniques where intrathecal opiates are used to provide visceral analgesia and then truncal blocks without or with continuous infusion catheters are used for somatic pain. This is becoming a more common approach in the United Kingdom for nonseptic emergency laparotomy or rescue of laparoscopic colorectal cases converted to open and is gaining traction in North America as well.

Truncal and chest wall plane blocks

Advances in ultrasound technology have led to an exponential rise in the incorporation of truncal and chest wall blocks for routine analgesia of abdominal and thoracic surgery (**Table 1**).[43] Meta-analyses indicate that truncal blocks for abdominal surgical procedures are associated with superior analgesia and decreased postoperative opioid consumption compared with opioid analgesia alone.[44–48] Some of these blocks are technically simple to perform and have minimal side effects and complications (eg, rectus sheath and erector spinae), while some are quite challenging (eg, quadratus lumborum). Some studies have boasted equivocal analgesic efficacy compared with neuraxial analgesia, although data are mixed.[49–51] Although wound infiltration offers similar short-term analgesia, these plane blocks provide superior long-term analgesia in the setting of a multimodal analgesic regimen.[52,53] The placement of these blocks preoperatively, rather than postoperatively, may offer some benefit in terms of early analgesia and opioid consumption.[54] However, the full impact of preoperative versus postoperative placement on longer-term outcomes remains unknown.

Concerning the choice of local anesthetic, ropivacaine, bupivacaine, and liposomal bupivacaine have all been used in ERPs with good results, although liposomal formulations have recently been challenged.[55–58] In short, the latest evidence would suggest

Table 1
Examples of chest wall and truncal blocks

Chest Wall	Paravertebral
	PECs (PECtoralis and serratus plane blocks)
	Erector spinae plane (ESP)
	Transversus thoracis plane
Truncal/ Abdominal Wall	Paravertebral
	Q Quadratus lumborum blocks (QL)
	Transversus abdominus plane (TAP) blocks/catheter
	Rectus sheath block/catheters (RSC)
	Wound infiltration and continuous wound infusion catheters (CWIC)

that there is no difference when using any of these local anesthetic formulations. However, it should be noted that additives, such as dexamethasone, epinephrine, and opioids, are effective at prolonging the duration of regional blocks.[59]

Continuous wound infiltration catheters

Continuous wound infiltration catheters (CWICs) offer sustained postoperative analgesia through wound infiltration analgesia using specially designed wound soaker catheters.[60] RSCs seem to be superior to them for midline in at least 1 RCT but they have the advantage of simplicity for 2 reasons. First, the surgeon can place them into the length of the wound in the preperitoneal space before closing. Second, CWICs can be used in any wound orientation, unlike RSC, which are for midline incisions only. A practical example of this is used as a rescue technique in laparoscopic hepatobiliary surgery that gets converted to an open approach. At the start of the case, one might use intrathecal opiate and IV lidocaine as primary analgesia; then, once converted to open the surgeon could place CWIC in the incisions that are often subcostal or in a "hockey stick" shape and the lidocaine infusion could be discontinued.

Tables 2 and **3** delineate details for how these regional anesthesia techniques can be applied for various operations.

Nonopioid Adjuvants

Lidocaine

IV lidocaine infusions are effective to reduce systemic inflammation and are indicated as part of a multimodal analgesic approach for visceral surgery when other local anesthetic approaches such as regional analgesia are not possible. In open and laparoscopic abdominal surgery, IV lidocaine infusions have been shown to result in a significant reduction in postoperative pain intensity at rest, with cough, and movement, as well as opioid consumption for up to 48 hours postoperatively.[61–64] From a functional recovery perspective, IV lidocaine infusions are associated with earlier return of bowel function and shorter length of stay.[61–64] Lidocaine infusions should be used with caution in patients with any cardiovascular instability and concomitant use of alpha agonists or certain beta-blockers (eg, sotalol), and in patients with allergies to other amide local anesthetics. Side effects are more pronounced in patients with liver dysfunction, pulmonary diseases when the predominant problem is carbon dioxide retention, and congestive heart failure. Lidocaine is typically administered as a bolus (100–150 mg or 1.5–2.0 mg/kg) followed by an infusion of 1 to 2 mg/kg/h through the end of surgery. The most recent meta-analyses suggest that continued perioperative administration of IV lidocaine is associated with a decrease in postoperative pain and opioid consumption and possibly faster return of bowel function and decreased length of hospital stay.[65–67] Of note, the ALLEGRO study, which is nearing the end of recruitment in the United Kingdom, is a large multicenter NIHR funded study of lidocaine versus placebo in CRS with primary end-point reduction in ileus/speed return of bowel function. The results of the trial have the potential to standardize the use of lidocaine as prophylaxis for ileus in CRS, which remains the greatest factor in the prolonged length of stay (https://srmrc.nihr.ac.uk/trials/allegro-2/).

N-methyl-D-aspartate antagonists

Ketamine. Perioperative inhibition of N-methyl-D-aspartate (NMDA) receptors with clinically available NMDA antagonists such as ketamine may be associated with improved perioperative pain and decreased opioid use.[68–71] Ketamine has also been shown to be of particular benefit in patients on chronic opioids, but this has not been specifically tested in chronic pain patients undergoing CRS.[72] Perioperative

Table 2
Suggested use of local anesthetics in blocks and intravenous by type of elective surgery

	IT LA ± opioid ± LA in joint	TEA	RSC	CWIC (catheter infusion in surgical donor site)	IV Lidocaine gtt	Hybrid – Intrathecal opiate + RSC	Hybrid – Intrathecal opiate + CWIC
Oesophagectomy		X					
Major colorectal—laparo/open transverse	X				X		
Major colorectal—open midline		X	X			X	X
Major liver resection—laparoscopic	X				X		
Major liver resection—open		X					X
Whipple (pancreatectomy)—laparo	X				X		
Whipple (pancreatectomy)—open		X					X
Radical cystectomy—laparo with Pfannestiel	X				X		
Radical cystectomy—open midline		X				X	X
Major open vascular		X					
Major gynae—laparo/open transverse	X				X		
Major gynae—open midline		X				X	X
Hip/Knee replacement	X						
Radical neck dissection with free flap				X			
Radical neck dissection w/o free flap					X		

Abbreviations: FI, fascia iliaca; gtt, infusion; IT, intrathecal; LA, local anesthetic; SIFI, suprainguinal fascia iliaca.

Table 3
Suggested use of local anesthetics in blocks and intravenous by type of emergency surgery

	Spinal (LA + Opioid)	TEA	RSC	CWIC	IV Lidocaine gtt	Hybrid– Intrathecal Opiate + RSC	Hybrid – Intrathecal Opiate + CWIC	Peripheral Nerve Block Infusion – Surgically Placed	Facscia Iliaca Block (FI or SIFI)
Emergency midline laparotomy	X	X	X	X	X	X			
Neck of femur	X								X
Vascular surgery amputations	X	X						X	

ketamine, including boluses as well as intraoperative and postoperative low-dose infusions for up to 48 hours, has been shown to result in significant reductions in pain, opioid consumption, and postoperative nausea and vomiting (PONV) with no significant side effect profile.[73–75] The intraoperative boluses ranged from 0.15 to 1 mg/kg and perioperative infusions ranged from 1 to 5 μg/kg/min, with a postoperative infusion rate of 2.5 mcg/kg/min.

Magnesium. Systemic infusions of perioperative magnesium may reduce postoperative pain and opioid consumption.[76–78] The optimal dosing is uncertain, as some studies include both a bolus followed by an infusion, whereas others only use an infusion without a loading bolus. Typical boluses are 30 to 50 mg/kg and the infusion rates range from 4 to 15 mg/kg/h. None of the studies in a systematic review reported clinical toxicity related to toxic serum levels of magnesium.[76]

Memantine. Although traditionally used in the treatment of Alzheimer dementia, memantine has recently emerged as a nonopioid analgesic alternative.[79] It is a long-acting NMDA antagonist with a half-life between 60 and 80 hours.[80] It also has a lower side effect profile and is generally better tolerated than ketamine.[81] Memantine preferentially binds to pathologically active channels, suggesting promise in areas of opioid-induced hyperalgesia and central sensitization.[82,83] Although most data support its use for chronic neuropathic pain[84–86] and fibromyalgia,[87,88] it is gaining popularity in the perioperative setting. The limited evidence available is promising, showing reductions in pain intensity and analgesic consumption.[89,90] It can also be used as an oral agent to help transition patients from ketamine infusions.[82]

Steroids

Glucocorticoid steroids may have analgesic benefits possibly related to anti-inflammatory properties and should be considered as part of a multimodal perioperative pain regimen. Several meta-analyses examined perioperative dexamethasone and indicated that patients who received dexamethasone (4–10 mg or >0.1 mg/kg) had lower pain scores, used less opioids, and required less rescue analgesia.[91–93] Glucocorticoids are also powerful antiemetics, thus providing an additional value to ERPs.[94] The concern for significant hyperglycemia (>180 mg/dL) has not been confirmed, even in bariatric patients receiving these doses of dexamethasone.[95] Meta-analysis review revealed glucocorticoid administration only slightly increases average peak glucose concentrations by 20 mg/dL, which is unlikely to have a significant clinical impact.[96] In addition, this same analysis addressed the theoretic concerns of immunosuppression and determined the concerns for wound infection were unfounded.

Acetaminophen (paracetamol)

Acetaminophen (paracetamol), when administered as part of a multimodal regimen, is associated with a significant reduction in pain and opioid usage, which may result in a decrease in some opioid-related side effects.[97–103] One meta-analysis concerning studies using a single dose of IV acetaminophen (paracetamol, typically 1g) given before surgery was associated with significantly lower early pain at rest and movement, postoperative opioid consumption, and PONV versus placebo.[98] A separate meta-analysis concerning studies using 1g or 15 mg/kg of IV acetaminophen (paracetamol) given 10 to 30 minutes before induction/incision (vs the same dose given 10–30 min before the end of surgery/before skin closure) was associated with a reduction in 24-h opioid consumption and a lower incidence of postoperative vomiting in the preventive acetaminophen (paracetamol) group.[97] Some studies including

pharmacokinetic outcomes reported higher postoperative plasma concentrations and larger proportions of patients achieving target plasma concentrations after IV dosing compared with oral dosing.[104] However, for patients who can take oral medications preoperatively, there does not appear to be evidence of a clear benefit of the IV formulation if the oral dose is given 30 to 60 minutes to surgery.[104] As such, decision-making should take into account both convenience and cost.[104]

Nonsteroidal anti-inflammatory drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs), whether nonselective or selective cyclooxygenase-2 inhibitors (COX-2), when administered as part of a multimodal regimen, are associated with a reduction in pain and opioid usage, which may result in a decrease in some opioid-related side effects.[105–110] A systematic review noted that preoperative COX-2 inhibitors significantly reduced postoperative pain, analgesic consumption, antiemetic use, and improved patient satisfaction compared with preoperative placebo.[107] In the studies examining celecoxib, the doses used were 200 or 400 mg PO, and for parecoxib, they were 40 mg PO.[111]

The use of COX-2 inhibitors has minimal effect on coagulation, even at supratherapeutic doses.[112] However, it is uncertain whether the perioperative use of NSAIDs carries additional risk of harm. Although it is unlikely that NSAIDs increase the risk of renal injury in euvolemic patients who do not have contraindications to receiving these medications,[113] caution should be undertaken in patients who are hypotensive or thought to be hypovolemic. In addition, there is a concern for the potential for an association with increased anastomotic leak, but the literature surrounding this question is inconclusive and some studies show no risk of harm specifically in an ERP for CRS.[114,115] As such, insufficient evidence is available to recommend against routine use of NSAIDs, especially COX-2 inhibitors, as these medications are effective in treating pain and reducing opioid use in the perioperative period.[116,117]

Gabapentinoids

Several meta-analyses including studies concerning intra-abdominal surgery suggest that gabapentinoids (gabapentin and pregabalin) when given as a single dose preoperatively are associated with a decrease in postoperative pain and opioid consumption at 24 hours.[118–124] For gabapentin, a preoperative dose of 300 to 1200 mg is associated with lower pain scores (both at rest and with movement) and reduced opioid consumption.[120,122,123] It should be noted that one small RCT found that a single preoperative dose of gabapentin 600 mg PO did not significantly reduce opioid consumption or pain scores on postoperative day 1 or 2 for patients presenting for colectomy.[125] However, opioid consumption and pain scores were lower at all time points in the gabapentin group compared with placebo, but there were only 36 patients per group and it was underpowered to detect any difference. As noted by the authors, continuing doses in the postoperative period may confer added benefit given the pharmacokinetics of gabapentin. This corresponds with the dosing regimens reported in successful ERPs for CRS where gabapentin is used as one component to reduce opioid consumption in the perioperative period.[21,25] However, the exact contribution of gabapentin to these positive outcomes is unknown. For pregabalin, a recent meta-analysis indicated that pain scores at rest were reduced with all doses of pregabalin (mostly 75–300 mg) but pain scores with movement were only reduced with the 300 mg dose. There were no significant differences in side effects between the 3 dose levels of pregabalin. The opioid-sparing effect of pregabalin appeared to be limited to doses 100 mg to 300 mg but not $\leq$75 mg at 2h after surgery.[121] Although most of the studies in the meta-analysis involve abdominal hysterectomy and cholecystectomy, none were in

CRS patients. A more recent meta-analysis found no difference between gabapentinoids and placebo in terms of pain scores.[126] However, the authors did note approximately a 30% reduction in opioid consumption with the use of gabapentinoids, as well as a significant reduction in PONV, while also noting an increase in postoperative dizziness. Overall, the evidence would suggest that gabapentinoids may be of benefit for reducing opioid consumption in the perioperative period, but use can come with an increase in some side effects, which is likely most pronounced in the elderly. From a practical perspective, the institutions at which the authors work use a structured plan for gabapentinoid use and assessment of side effects. These plans recommend standard dosing for adult patients that can be reduced based on renal function and age or possibly increased if the patient takes a larger dose at home on a regular basis.

Alpha-2 adrenergic agonists

A Cochrane review of dexmedetomidine infusions for pain found reduced opioid consumption, but no significant difference in pain scores compared with placebo, and there was more hypotension in the dexmedetomidine group.[127] Dexmedetomidine has been added both perineurally to nerve blocks and intravenously to prolong nerve block.[128,129] However, the extended duration provided by the IV administration of dexmedetomidine is shorter than that provided by perineural administration. A recent extensive review of perioperative alpha agonists comparing dexmedetomidine and clonidine found similar reductions in opioid consumption and weak antiemetic effects, but as expected, both drugs had adverse effects on hemodynamics.[130] In summary, perioperative administration of dexmedetomidine or clonidine can reduce morphine consumption up to 24h and to a similar extent as acetaminophen (paracetamol), but not as much as other NSAIDs. These alpha agonists have other side effects such as sedation and hypotension that have to be considered.[131] Typical dose ranges are 1 to 5 mcg/kg orally, IV or perineurally for clonidine and 0.5 mcg/kg IV bolus followed by an infusion of 0.2 to 0.7 mcg/kg/h or 0.5mcg/kg perineurally for dexmedetomidine.

Special Opioids

Tramadol

Overall, there is limited evidence for the use of tramadol in CRS. However, one study compared postoperative pain control with an opioid IV-PCA to IV tramadol and found that the patients in the non-PCA (tramadol) group needed less rescue analgesia, and none required escalation of analgesic therapy to IV-PCA.[132] In addition, another study included scheduled tramadol as part of an ERP.[133] Although this was only one component of the ERP, overall pain scores and other outcomes were improved. If tramadol is to be used, one study would suggest caution with its use in patients undergoing major abdominal surgery who are more than 75 years, American Society of Anesthesiologists (ASA) 3 or 4, or have impaired mobility or frailty, as use in this setting was associated with delirium.[134] Based on the evidence that exists in CRS, we recommend considering tramadol as an analgesic adjunct.

Methadone

Methadone has a complex pharmacologic profile. It exerts agonist activity at the μ, kappa, and delta-opioid receptors, and functions as an antagonist at NMDA receptors. It has a rapid onset with variable metabolism.[135] The prolonged duration of action of methadone has been used to significantly reduce postoperative opioid consumption.[136–139] A meta-analysis of 10 RCTs demonstrated that methadone results in better patient satisfaction, lower pain scores, and reduced opioid consumption compared with alternative opioid regimens.[140,141] In addition, 2 recent RCTs demonstrated

significant reductions in postoperative opioid use and pain in the first few days after surgery and out to 1 year.[141] In short, methadone may be the opioid that helps greatly limit the use of other opioids. The exact role and possible benefit of methadone within ERPs remain to be elucidated.[142]

Practical Implementation

At this point, it is important to consider the practical application of the preceding data for someone implementing an ERP. At a high level, **Fig. 2** illustrates a summary view of perioperative planning and the components to be considered. **Tables 2 and 3** detail how these components can be best used according to the type of surgery and whether it is elective or emergent. **Table 4** displays the recommended dose ranges

Table 4
Recommended dosing strategies by phase of care for nonopioid multimodal analgesics

	Phase of Care		
Analgesic Component	**Preoperative**	**Intraoperative**	**Postoperative**
Oral Medications			
Celecoxib	200-400 mg	n/a	200-400mg q12
Clonidine	0.1-0.3 mg	n/a	0.1-0.3 mg q12h
Gabapentin	300-1200 mg	n/a	300-1200 mg q8h
Ketorolac	20 mg	n/a	10 mg q4-6h
Memantine	5-10 mg	n/a	5-10 mg q12
Paracetamol/ Acetaminophe n	1000 mg	n/a	1000 mg q8
Pregabalin	75-300 mg	n/a	75-300 mg q12
Tramadol	50-100 mg	n/a	50-100 mg q4-6h
Intravenous Medications			
Clonidine	n/a	1-5 mcg/kg	n/a
Dexamethasone	n/a	4-10 mg or >0.1mg/kg	n/a
Dexmedetomidine	n/a	0.5 mcg/kg bolus followed by an infusion of 0.2-0.7 mcg/kg/h	0.2-0.7 mcg/kg/h infusion
Ketamine	n/a	0.15-1 mg/kg bolus followed by infusion 1-5 micrograms/kg/min	2-2.5 mcg/kg/min infusion
Ketorolac	15-30 mg		15-30 mg q6h
Lidocaine	n/a	1.5–2.0 mg/kg bolus followed by infusion 2 mg/kg/h	1-2 mg/min infusion
Magnesium	n/a	30-50 mg/kg bolus followed by infusion 4-15 mg/kg/h	4-15 mg/kg/h infusion
Methadone[a]	5-20 mg		n/a
Paracetamol/ Acetaminophen	1000 mg		1000 mg q8h
Parecoxib	40 mg		20-40 mg q12h
Tramadol	50-100 mg		50-100 mg q4-6h

for each analgesic component and any specific contraindications (relative or absolute) that have been reported in routine practice. Finally, any ERP should have a structured plan for rescue analgesia when the typical pathway is not sufficient to meet the needs of the patient.[8] **Fig. 3** provides an example of what a rescue plan should entail, although individual implementations of this may vary by program.

FUTURE DIRECTIONS

Much of the push toward opioid minimization has come through enhanced recovery after surgery (ERAS). However, as some have pointed out, even though many publications and guidelines note that opioid minimization is associated with improved outcomes, many ERAS protocols contain unproven elements in regards to analgesia.[33] As such, future research should include a more thorough investigation of the current components used to reduce opioids and opioid-related adverse events in the perioperative period. Major ongoing RCTs include trials investigating the efficacy of lidocaine and ketamine.[a] As there is debate in the literature as to the benefit (or lack thereof), additional research should also include prospective trials concerning gabapentinoids, NSAIDs, muscle relaxants, and other commonly used nonopioid analgesic components. Finally, as opioid-free anesthesia and analgesia may work for some patients, research on the role of methadone as an opioid-sparing opioid within ERPs is warranted.[142]

SUMMARY

Traditional opioid-based analgesia in the perioperative period can provide excellent pain control, but this approach exposes the patient to avoidable side effects and possible harm. Optimal analgesia within an ERP, an approach that targets the fastest functional recovery with adequate pain control while minimizing side effects, can be achieved with opioid minimization. Many different options for nonopioid multimodal analgesia exist and have been shown to be efficacious, with certain modalities being more beneficial for specific surgeries. However, much research remains to be done to better define the optimal approach for opioid minimization to maximize patient outcomes.

CLINICS CARE POINTS

- Opioid-based analgesia can provide excellent pain control, yet exposes the patient to avoidable side effects and complications
- Optimal analgesia is an approach that targets the fastest functional recovery with adequate pain control while minimizing side effects
- Opioid-sparing analgesia appears to be of benefit in the perioperative period
- Many different options for nonopioid multimodal analgesia exist and have been shown to be efficacious, with certain modalities being more beneficial for specific surgeries

[a] IMPAKT (https://clinicaltrials.gov/ct2/show/NCT04625283?term=raymond+and+ketamine&draw=2&rank=1); ROCKET (https://medicine.unimelb.edu.au/research-groups/critical-care-research/critcare/about-us/the-rocket-study); and Lidocaine (https://clinicaltrials.gov/ct2/show/NCT04176419?term=lidocaine+AND+intraoperative&recrs=a&cntry=US&draw=2&rank=6).

DISCLOSURE

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Neuraxial and Regional Blocks	Intrathecal	Epidural	Perineural
Clonidine	15-75 mcg	1-2 mcg/kg	150-300 mcg
Dexmedetomidine	5 mcg	1 mcg/kg	50–60 mcg
Dexamethasone	4-8 mg	4-10 mg	4 mg
Epinephrine	100-200 mcg	1-5 mcg/mL	100-300 mcg

[a] Studies performed with methadone versus other opioids have typically used doses of 10-20 mg IV, but some have gone as high as (0.3mg/kg); use of lower doses of opioids may be needed if other adjuncts are used but lower doses of methadone are also noted to have pharmacokinetics/dynamics similar to hydromorphone rather than what is achieved with higher doses of methadone and longer half-lives.

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