Opioid Management in the Setting of Enhanced Recovery After Surgery (ERAS) Protocols

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Abstract: Enhanced Recovery After Surgery (ERAS) protocols have been implemented across multiple surgical specialties, including OB/GYN, to improve patients' perioperative experiences. ERAS protocols typically include multimodal pain regimens; opioids are frequently utilized. In the perioperative setting, nonopioid analgesics, including acetaminophen, NSAIDs, dexamethasone, gabapentinoids, ketamine, antidepressants, and local anesthesia may be used, which impacts perioperative opioid utilization. In some patients, opioid-sparing analgesia may be possible. Postdischarge, patients should utilize a multimodal pain regimen similar to that of their inpatient stay, with limited opioid quantities prescribed. Postoperative prescribing should balance optimal pain control while considering the risks and side effects of opioid analgesics.

Key Words: enhanced recovery after surgery (ERAS), opioid, opioid-sparing, multimodal pain regimen

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Enhanced Recovery After Surgery (ERAS) protocols are a complex perioperative bundle of orders, procedures, and medications to improve patients' postoperative recovery. One important aspect of ERAS protocols is the inclusion of multimodal therapies for postoperative pain management. Historically, opioid medications have been the cornerstone of treatment of postoperative pain. However, liberal opioid use has been curbed over the past decade due to several factors.

Most importantly, surgeons have become increasingly aware of their role in the opioid epidemic. This epidemic was declared by the Department of Health and Human Services after opioid overdoses increased by nearly a third from 2016 to 2017 in 45 states.[1] While much of the focus to curb the epidemic was changing opioid management for chronic pain, surgeons also played a role in the contribution of opioids available to be misused. Studies have shown that in the recent past, patients were prescribed 3 to 4 times more opioids than consumed following gynecologic procedures.[2–5] In addition, acute opioid prescription after any type of surgery can lead to persistent opioid use or opioid use disorder in up to 7% of patients, although this is likely closer to 0.5% in the gynecology population.[6] Research suggests that over 39,000 women undergoing hysterectomy in the United States

annually will be prescribed opioids long term; of those women, roughly 3600 will develop an opioid use disorder.[7]

Beyond opioid stewardship, clinicians have become more cognizant that despite their effective analgesic properties, opioids' multiple side effects impair postoperative recovery. These side effects may include nausea and vomiting, pruritus, respiratory depression, delirium, hyperalgesia, and delayed return to normal bowel function, including constipation and ileus. All of these side effects can counteract the expedited recovery ERAS protocols are designed to achieve.[8]

While many ERAS protocols attempt to minimize opioid use, their use in perioperative care will be necessary for the foreseeable future. The focus of this review is to present the existing evidence related to opioids within an ERAS protocol. Mirroring ERAS protocols' timed interventions, this review will organize the evidence behind opioid management at each step in a patient's perioperative journey: preoperative (before the day of surgery), perioperative (immediately before the operating room, intraoperative, and inpatient recovery if applicable), and postdischarge. Table 1 summarizes the recommendations that are reviewed in depth within the manuscript. In addition, the authors have included a final section of considerations for special populations of patients, including those with opioid use disorder or chronic opioid use. Outside of the scope of this review is the use of regional or neuraxial anesthesia.

PREOPERATIVE

Preoperative Education/Counseling

There is some evidence that preoperative education may have some benefits for postoperative pain outcomes. Specifically, the ERAS society recommends preoperative counseling, including setting expectations for postoperative pain levels, as this may have a benefit on patient-reported satisfaction.[9] Preemptive psychoeducation in this preoperative period may be helpful to reduce opioid prescription. This can include setting expectations for anticipated pain, determining strategies to reduce pain and anxiety, an informed consent on the risks of perioperative opioid use, and shared decision-making regarding minimization or avoidance of opioids postoperatively.[9,10] Educational interventions, including handouts or formal slide presentations, have been associated with reduced postoperative opioid prescriptions after some gynecologic procedures.[11] These preoperative discussions are associated with lower levels of patient anxiety, decreased postoperative pain, and improved functional scores[10] as well as overall optimization of postoperative recovery and length of stay.[12]

Identifying at Risk Patients

Patients with pre-existing chronic pain are a group of patients that require specific attention preoperatively.

TABLE 1. Summary of Evidenced Based Analgesics in Enhanced Recovery After Surgery (ERAS) Protocols

	Preoperative	Perioperative	Postoperative	Discharge
Opioids			Oxycodone IR 5 mg Q 4 hrs PRN*; Tramadol 100 mg Q 6-8 PO PRN; Fentanyl 50mcg IV Q 30 min PRN for uncontrolled pain; PCA as last resort	Oxycodone IR 5 mg Q 4 hrs PRN (max 3-5 d)*
Acetaminophen	1000 mg PO 1-2 hrs preoperatively*		Scheduled 1000 mg Q 6 hrs IV/PO*	750-1000 Q 6 hrs PRN*
NSAIDs	Celecoxib 200-400 mg PO 1-2 hrs preoperatively*	Ketorolac IV 15 mg*	Ibuprofen 600 mg Q 6 hrs*	Ibuprofen 600 mg Q 6 hrs*
Dexamethasone		Intraoperative 15 mg IV		
Gabapentin	Gabapentin 600 mg**		300 mg 1-3x per day PRN	
Ketamine		Intraoperative dose at subanesthetic level		
Duloxetine	Duloxetine 600 mg		Duloxetine 600 mg on postoperative day #1	
Local Anesthetics		Injection of port sites before/after closure*; Consider paracervical block before hysterectomy. Consider continuous infusion in laparotomy for malignancy	TAP block for open procedures	

*Strong evidence supporting use.
hrs indicates hours; IR, immediate release; IV, intravenous; min, minutes; NSAIDs, nonsteroidal anti-inflammatory drugs; PCA, patient-controlled analgesia; PO, by mouth; PRN, as needed; TAP, transverse abdominus plane.

Preoperative neuropathic pain is important, as this is a significant risk factor for higher postoperative pain scores and opioid consumption.[1]

One important screening tool used for patients with chronic pain and patients with mood disorders is the pain catastrophizing scale.[13] While this tool has been used in studies on opioid prescribing, patients with higher catastrophizing scores were only prone to higher postoperative pain scores but not postoperative opioid use.[1,10] However, a review looking at postoperative opioid consumption and prescription in gynecology notes that persistent opioid use in patients who recently underwent hysterectomy was linked to higher Fibromyalgia Survey Scores preoperatively.[14]

Patients with nicotine dependence have also been found to require more opioids within 72 hours after surgery compared with nonsmokers. Because nicotine has analgesic properties, withdrawal at and around the time of surgery can lower patient's pain tolerance and increase postoperative opioid requirements.[15]

Perioperative

After implementation of an ERAS protocol, one commonly studied outcome is perioperative opioid use, which ideally is as low as possible while still achieving adequate pain management. Depending on the patient and procedure, a goal of opioid-free anesthesia may be possible. Decreased perioperative opioid use after ERAS implementation can be significant, as much as 64%, with parallel improvement in postoperative pain scores.[16] Many ERAS protocols recommend an option such as the following: acetaminophen 1000 mg orally every 6 hours, ibuprofen 600 mg orally every 6 hours, and an opioid of choice with an intravenous (IV) breakthrough option.

The perioperative period, for this review, will include immediately before the operating room as well as throughout recovery and postoperative admission, if applicable. This is intentional, as multiple studies of ERAS protocols report medications used in both settings. While the focus of this review is on opioids in ERAS protocols, each medication or class often used in combination with or in lieu of opioids will be reviewed pertaining to its impact on opioid utilization.

Acetaminophen

Acetaminophen is a common component in ERAS protocols. Preoperative and scheduled postoperative use are associated with decreased pain and decreased opioid use perioperatively, both in the hospital and as an outpatient.[1,17–19] Given the medication's effectiveness and relative safety, acetaminophen is a cornerstone of multiple society-supported ERAS guidelines.[8,20–24] There are numerous studies in ERAS protocols demonstrating the effectiveness of acetaminophen on reducing opioid use and even hospital costs compared with opioid alone.[25] This is especially important in obstetrics, as multiple other medications used in ERAS protocols are not to be used in pregnancy.

Typical doses for acetaminophen range from 750 to 1000 mg. Notably, as comparisons of enteral and parenteral acetaminophen demonstrate no difference between routes of delivery, this significantly less expensive option should be recommended routinely.[26–28] This has been specifically studied after laparoscopic hysterectomy, and the oral formulation was found to be noninferior.[29]

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are the second cornerstone of multimodal therapy in ERAS protocols; use of these medications is another outcome often studied after ERAS implementation. Like acetaminophen, NSAIDs are universally included in multiple society-endorsed ERAS protocols.[8,20–24] They may be even more important than acetaminophen; one study comparing acetaminophen and ketorolac found that patients using ketorolac used fewer opioids.[30]

Celecoxib, a COX-2 inhibitor, if given before surgery is associated with less perioperative opioid use.[17] The American College of Obstetrics and Gynecology (ACOG) recommends a combination of celecoxib 400 mg, gabapentin, and acetaminophen as part of their preoperative multimodal medication regimen.[31] Typically, preoperative celecoxib is given followed by postoperative ibuprofen, which leads to decreased intraoperative and postoperative opioid use as well as decreased opioid prescriptions at discharge.[18] AAGL's White paper on ERAS protocols recommends the use of intravenous ketorolac 15 mg at the time of the surgical case.[24]

NSAIDs should be scheduled postoperatively as well. A retrospective analysis looking at ERAS implementation involving a multimodal analgesic protocol including naproxen orally or ketorolac IV found that post-ERAS, patients required lower rates of rescue opioids postoperatively.[32] Importantly, increasing the dose of ketorolac to 30 mg compared with 15 mg did not decrease opioid use or pain scores.[33]

One important consideration for these medications is their ceiling effect. Increases beyond this limit, 400 mg for ibuprofen, will not positively impact the drug's anti-inflammatory effects.[34] A potential concern of inclusion of NSAIDs in ERAS protocols is their effect on GI bleeding, although this risk can be reduced with celecoxib.[35] In addition, there are risks with prolonged use, including renal toxicity, cardiovascular toxicity (especially in patients with coronary artery disease), anastomotic leak following bowel surgery, and postoperative bleeding.[36]

Dexamethasone

Like NSAIDs and acetaminophen, another component of many published ERAS protocols is the use of intraoperative dexamethasone.[10,21] This steroid has a dose-dependent relationship with reducing postoperative opioid consumption as well as other benefits, including less sore throat, muscle pain, confusion, insomnia, and nausea.[37]

Gabapentin

For gabapentin and related medications, multiple studies have shown that use of these medications in ERAS protocols' multimodal pain management can minimize opioid use, both in the recovery room and during admission.[17] Various doses have been reported. ACOG recommends consideration of preoperative gabapentin 600 mg.[23] Other studies report lower doses, including 300 mg preoperative repeated 12 hours later or 150 mg the night before, 30 minutes before surgery, and 6 hours postoperative.[38] Due to only have a modest effect on postoperative pain and opioid requirements, gabapentin was recommended, although not strongly in urogynecology procedures.[22] However, a recent meta-analysis looking at preemptive gabapentin and its effects on postoperative pain revealed no clinically significant effects on postoperative acute, subacute, or chronic pain. In addition, adverse effects like sedation, gait imbalance, and visual disturbances were noted by some patients.[39] Importantly, when combined with opioids, these medications have been shown to compound the risk of postoperative respiratory depression requiring noninvasive ventilation. As a result, anesthesia associations have recommended against the routine use of gabapentinoids in ERAS protocols.[40]

Ketamine

Perioperative administration of ketamine has been shown to have an opioid-sparing effect with a decrease in pain scores and opioid consumption in the immediate postoperative period.[15] Importantly, this should be given at subanesthetic doses, as this will preferentially affect analgesia and not cause hallucinations and other dissociative side effects.[36] However, the level of support for widespread protocolized use of ketamine in gynecologic ERAS protocols is not wide enough for inclusion in multiple society guidelines.[41]

Duloxetine

Duloxetine is a serotonergic and noradrenergic reuptake inhibitor that ultimately blocks nociceptive input via descending inhibitory pain tracts. A recent trial in patients undergoing abdominal hysterectomy showed that duloxetine 60 mg administered preoperatively and one day later resulted in lower pain scores and opioid requirements and improved quality of recovery.[42] An additional meta-analysis revealed that duloxetine was associated with a significant reduction in postoperative pain and opioid use, although there was no difference at 2 weeks postoperatively.[36]

Local Anesthesia

Infiltration of surgical wounds in the operative room is common practice. Review of the evidence suggests local anesthetics should be injected at the conclusion of the surgery during incision closure.[38] Multiple society guidelines include recommendations to use local anesthetics at the incision site for vulvar/vaginal surgery as well as consideration of paracervical and vaginal cuff blocks.[22,43] There is conflicting evidence on the role of paracervical block before hysterectomy to improve postoperative pain scores.

Use of local anesthetics via posterior or subcostal transversus abdominus plane (TAP) blocks after laparotomy for gynecologic oncology surgery has been shown to reduce postoperative pain scores as well as opioid consumption at 24 hours postoperative.[44] ACOG's ERAS guideline states to consider traditional local wound infiltration or TAP block depending on incision site.[23]

Extended-release liposomal bupivacaine has been studied in various gynecologic surgeries. There is evidence that it reduces opioid use in patients following staging laparotomy or complex cytoreductive surgery in gynecologic oncology.[45] However, liposomal bupivacaine did not reduce postoperative opioid use in vaginal surgery.[46]

Continuous intraoperative and postoperative lidocaine infusions in patients undergoing laparotomy for gynecologic malignancy have been shown to reduce total opioid use and length of stay.[47]

Opioid-Sparing Anesthesia

Multiple studies have investigated using completely opioid-free analgesia (OFA) in the operating room. A randomized trial of OFA in patients undergoing laparoscopic gynecologic surgery found that patients with opioid-

free analgesia (preoperative acetaminophen and gabapentin, intraoperative flurbiprofen and ropivacaine, and postoperative acetaminophen and celecoxib) required less opioid postoperatively and had fewer rescue analgesics in the recovery room. In addition, pain scores were lower postoperatively.[48] A study looking at opioid-free anesthesia and analgesia in patients undergoing gynecologic oncology surgery found that when corrected for preoperative pain perception, there was no difference in postoperative analgesia in patients who received OFA versus those who received opioids.[49] Other studies have supported OFA reducing opioid requirements[50] and not affecting readmission rates.[51] Another study on OFA in a limited resource setting used magnesium sulfate, lidocaine, clonidine, ketamine, and dexamethasone in combination with paralytics and inhaled anesthetics. This analgesic regimen was associated with a significant reduction in pain and higher patient satisfaction scores up to 24 hours postoperative as well as no morphine use.[52]

Perioperative Opioid Management

When immediate postoperative opioids are ordered for patients, these should be short-acting only, ordered as needed instead of scheduled, and the lowest effective dose. Surgical teams should be aware that some factors may be associated with increased opioid needs, including younger age, obesity, preoperative pain, greater operative blood loss, and longer operating time.[5,53,54] In addition, patients who cannot use NSAIDs may use more opioids.[55] Even in an oncologic population, IV opioids, including patient-controlled anesthesia (PCA) should only be used as last resort in patients after they have failed multimodal nonopioid analgesia with NSAIDs, oral acetaminophen, and repeated intravenous opioid rescue attempts.[51] Notably, ACOG recommends considering scheduled tramadol if a patient cannot take NSAIDs,[23] which has been studied in some ERAS protocols.[56] It is important to note that this medication is still an opioid, with all the known risks, but additionally the side effect profile of a serotonin-norepinephrine reuptake inhibitor.

Nonpharmacologic Interventions

Studies have shown some benefit in nonpharmaceutical interventions postoperatively to minimize opioid use. One frequently utilized intervention is the use of ice packs. A randomized trial of an opioid-sparing pain regimen found that a combination of ice packs, acetaminophen, and ketorolac was more effective in treating postoperative pain up to 96 hours when compared with standard protocol, including opioids, acetaminophen, and NSAIDs.[38] This did not affect patient satisfaction scores or scores on quality of recovery questionnaires.[57] Another study found that ice packs and acetaminophen/NSAIDs were noninferior to a standard opioid regimen.[58] Ice packs, in addition to guided imagery (musical/visual) have been shown to reduce pain and opioid requirements in urogynecology patients.[22]

In addition, a review looking at strategies for reducing opioid consumption noted reducing dietary restrictions, encouraging ambulation in the early postoperative period, urinary catheter removal, encouraging oral fluid intake and supplementing with fluids when necessary, and implementing a bowel regimen as additional tactics for improving postoperative pain and reducing opioid requirements.[10] These strategies should not be forgotten as key items in an ERAS protocol. Another important perioperative factor

that has been shown reduce opioid use is maintaining an insufflation pressure that is as low as possible.[59]

Postdischarge Management

After discharge, it is imperative that patients continue to utilize multimodal pain relief given the previously listed evidence for these synergistic medications. Use of acetaminophen and NSAIDs is associated with decreased pain scores as well as readmission.[36] Expert consensus is for patients to use NSAIDs in alternation with acetaminophen with opioids prescribed for as needed use only.[24]

Postdischarge Opioid Quantities

ERAS protocols have been associated with decreased postoperative opioid prescribing,[60–64] which remains true even years after implementation of the protocols[65] and may have an even greater effect on women older than 75 years.[66] There have been multiple publications on recommended postdischarge quantities for a typical patient based on type of procedure and anticipated postoperative pain. While other specific opioids may be prescribed, the most commonly used is oxycodone 5 mg tablets.[60] Regardless of the specific drug, it should be immediate release (not long-acting) with daily doses of no greater than 30 morphine milli-equivalents (MME) and no more than 3 days (maximum of 5 days if pain is expected for a longer duration).[67] In addition, patients should receive the same opioid dose at discharge as they received inpatient to optimize pain control and patient safety.[15] A suggested table of prescribing quantities is provided in Table 2.

For minor gynecologic procedures, 0 to 8 tablets may be appropriate with consideration of only up to 15 tablets after minimally invasive surgery, including hysterectomy.[24,38,68] Specifically in the urogynecology literature, studies have supported prescribing no more than 5 to 11 tablets of opioid at discharge.[69–71]

Beyond minimizing opioid quantities, patients may also be safely discharged with no opioid prescription. One study found that over 80% of patients after minimally invasive hysterectomy and 50% of patient after laparotomy were discharged without opioids with no difference in requested refills or postoperative pain.[72] Even in a gynecologic oncology population, 15% of patients used no opioids following discharge and all patients were satisfied with pain control.[73]

While surgeons may be concerned about limiting patients' opioid prescriptions, studies demonstrate no impact on patient satisfaction or pain control.[69,70,74,75] In addition, requests for postoperative opioid refills are low despite smaller quantities provided, typically between 7% and 15%.[69,70,75,76]

Individualized Prescription Planning

There is growing evidence for using tailored opioid strategies for individual patients, based on patient factors or created calculators. One gynecology oncology group reduced opioid over-prescribing to only 25% with median number of prescribed opioids of 3 to 6 tablets based on invasiveness of surgery.[77] Another study used discharge timing, route of surgery, and whether opioids were used inpatient to determine postoperative quantities prescribed. No differences were noted in refills or patient pain scores and total opioids prescribed were reduced.[78] Multiple studies on tailored opioid prescription after cesarean section have been shown to reduce quantities of opioids

TABLE 2. Postoperative Opioid Prescribing by Procedure

Procedure	Oxycodone IR 5 mg	Considerations
Hysterectomy	0-15 tablets	20%-24% of patients will require 0 tablets after MIH
Minor GYN procedure	0-8 tablets	Average requirement: 1.5-8 tablets
Major GYN procedure	5-20 tablets	Average requirement: 5-11 tablets
URPS procedure	0-11 tablets	Consider 0 if no inpatient use

GYN indicates gynecologic; IR, immediate release; MIH, minimally invasive hysterectomy; URPS, urogynecology and reconstructive pelvic surgery.

prescribed.[79,80] Some studies have used inpatient opioid use as a tool to plan opioid prescribing with some improvement, although this is of limited utility with the increase of same-day discharge.[81]

Predictors of Opioid Use

Invasiveness and type of surgery are 2 components commonly used to decide on postoperative quantities of opioids needed.[82,83] However, specific surgery type is another way. Patients undergoing prolapse or incontinence procedures use no more than 3 to 4 tablets of oxycodone 5 mg,[5] and 25% of patients use no opioids following vulvar cancer surgery.[55] For urogynecology, hysterectomy with prolapse repair compared with uterine-sparing surgery and use of mesh are also associated with increased opioid prescribing.[82] Notably, studies do not show a difference in postoperative opioids needed between conventional and robotic-assisted laparoscopic surgeries.[84,85]

Patient-specific factors may also predict increased postoperative opioid requirements. This includes younger age (especially < 65 years of age),[82,83,86] a history of recent opioid prescription or substance use disorder,[3,87] and neighborhood details, including urban status and highest income quintile. Postoperative diagnoses are associated with increased opioid use, including infertility, adnexal mass, and endometriosis.[86] Models have been created to predict postoperative opioid requirements based on patient age, educational attainment, smoking history, anticipated pain medication use, anxiety about the procedure, operative time, and preoperative pregabalin administration.[88] Refills are more likely to be needed in patients with chronic pain, higher BMI, history of substance abuse, or presence of preoperative opioid use, and those with higher immediate postoperative use.[87]

Disposal of Medications

Even though ERAS protocols have decreased opioid prescribing, patients often have excess tablets postoperatively. The US Food and Drug Administration has published guidelines on opioid disposal, prioritizing take-back programs, combining tablets with coffee grounds or other food waste and dispose of them in the trash, or flushing if no other safe option.[89] However, only 17% of OB/GYNs counsel patients on opioid disposal with only 20% of patients reporting a disposal plan. Importantly, patients who received education about disposal were more likely to abide by the protocol.[10] An in-person discussion of opioid disposal in addition to EMR reminders is effective in increasing opioid disposal rates from 30% to 83%.[90]

Special Populations

Patients With Chronic Opioid Use

For patients with preoperative opioid use, the inclusion of pain specialists in the preoperative arena should be used to help monitor and treat pain. This may involve the use of controlled substance agreements, as they have been shown to reduce outpatient utilization of opioids.[91] On the day of surgery, patients should take their morning maintenance medications, including opioid or gabapentin and related medications. In addition, a pain medicine specialist may be warranted to determine discharge quantities and doses.[24]

Patients With Opioid Use Disorder

It is important to counsel patients before surgery that they are at high risk for relapse during this period of opioid exposure and likely pain. Even in patients who are in remission without medication, surgeons should consider a substance use disorder consultation. As inpatients, non-opioid medications and ERAS multimodal therapies should be considered. Postoperatively, consideration should be taken for naloxone prescription and direct counseling about overdose prevention.[92]

For patients on methadone, the prescribing clinic should be contacted. Patients should continue methadone during their inpatient stay and avoid partial-acting opioid agonists. At discharge, patients should be given short-acting opioids only with a clear plan for tapering. In addition, they will need a letter to confirm their last inpatient methadone dose.[92]

Patients using buprenorphine preoperatively should attempt cessation before invasive procedures, although this must occur 3 to 7 days preoperatively. Continuation may lead to worsened postoperative pain control and require higher-than-expected doses of opioids. As such, discontinuation is the best option in this patient population.[91]

CONCLUSIONS

ERAS protocols have multiple components and goals. After implementation, they can be incredibly successful at minimizing opioid use postoperatively while simultaneously improving postoperative pain management.[61,93–99] Importantly, this reduced opioid use is still associated with good patient satisfaction and decreased length of stay.[100] In an era of opioid stewardship and desire for improving outcomes, surgeons should be aware of the evidence for opioids' ongoing use in surgical care.

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