Chapter 12
Use of Opioid Analgesics in Postsurgical and Trauma Patients

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Introduction

One of the primary objectives for patients admitted to the intensive care unit (ICU) following surgery or traumatic injury is optimal pain control. Not only is adequate analgesia a component of compassionate care, it is essential for maintaining satisfactory hemodynamics and respiratory function. It is also necessary for effective physical therapy and rehabilitation following injury and/or operative intervention. Opioids have long been the mainstay of analgesia in postsurgical and trauma patients, and appropriate selection of opioid analgesics is one of the pillars of effective analgesia. However, equally important is to establish reasonable expectations for pain control, understand the key transition points for shifting from parenteral to enteral analgesics, and recognize the risk for dependence and addiction to these medications following a patient's discharge from the ICU and subsequently the hospital. Additionally, multiple studies have shown that opioid analgesic prescribing practices in the postoperative setting vary widely and lack standardization thus placing patients and providers at risk for over and under prescribing narcotics.

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Pain Assessment

Pain is frequently undertreated in the ICU which can result in serious physiologic and psychologic sequelae for patients [1, 2]. Uncontrolled postoperative pain or following a traumatic injury has been associated with increased sympathetic activity and physiologic stress [1, 2]. It has also been shown to cause long-term psychological effects such as post-traumatic stress disorder and post-intensive care syndrome [2]. The primary method of assessment of pain in postsurgical and trauma patients is by using a patient's own self-report of pain intensity. However, frequently patients in the ICU are unable to communicate that they have untreated pain. In these settings it is useful to utilize validated pain assessment scores. The critical care pain observation tool (CPOT) is a frequently used pain scale in the ICU. This tool has four fields that include: facial expressions, body movements, muscle tension, and ventilator compliance (or voice use in non-intubated patients). Each domain has a score range of 0–2 with a possible score variation of 0–8, with a score of 2 indicating a patient has uncontrolled pain and may benefit from analgesic administration. The Behavioral Pain Scale (BPS) is an additional validated pain assessment tool in the ICU. This scale has three domains which include: facial expression, upper limb movements, and compliance with mechanical ventilation. Both of these scores have been validated as reliable assessments of pain in patients who are unable to verbalize or communicate pain severity [2].

Expectation Management

There is evidence that opioid use following surgical procedures is reduced if reasonable expectations for postoperative pain management have been established preoperatively [3, 4]. Many patients present to the ICU following elective and semi-urgent procedures that would have benefited from pre-procedural counseling about realistic pain management goals following surgery. This is not necessarily the role of the intensive care provider, though this is an excellent opportunity to influence the patient experience by collaborating with surgical colleagues. Often this is a component of the pre-procedural or pre-anesthetic evaluation.

It is important for providers to recognize that many patients' expectations are that they will suffer no pain at all. Patient and provider definitions of controlled pain frequently differ. Analgesic administration has in large part been driven by the assessment of pain based on patient subjective report. The inclusion of pain as the "fifth vital sign" was associated with patients requesting, and receiving, increased amount of opioid analgesics [5]. This approach became increasingly utilized in response to an *Institute of Medicine* report that analgesia in cancer patients was routinely not adequate [5]. This method of monitoring and treating pain has often been associated with unrealistic patient expectations of pain control. It is also widely regarded as a significant factor contributing to the opioid

epidemic [5]. Assessing pain strictly from a subjective patient report and through observation of vital signs can lead to significant overdosing of opioid pain medications. Unfortunately, certain routinely used hospital quality indicators still favor liberal administration of analgesics in response to a pain score, even though this may not be in the patient's best interest [5].

Many patients will present to the ICU emergently, some with neurological impairment, others, having already sustained traumatic injury or undergone an emergent surgical procedure. In such patients, establishing analgesic expectations may be difficult. A consistent approach by the entire care team is needed to set and maintain appropriate expectations as well as develop and modify analgesic plans. Providing the expectation that pain will be controlled to the best extent possible which will allow patients to participate in their care and therapy is reasonable and should be addressed early on with patients and their families following surgery or traumatic injury.

Dependence and Addiction

This topic is discussed in depth in other parts of this book. However, appropriate prescription and administration of opioids to ICU patients warrants a discussion of the screening techniques and a consideration of the risk of addiction. The National Institute on Drug Abuse, as well as many state medical boards, provides screening tools to assess risk for future opioid dependence and potential for addiction. One such tool, provided by the National Institute on Drug Abuse, has five domains that include: a family history of substance abuse (including alcohol and prescription medications), personal history of substance abuse, a history of sexual abuse, age, and psychological disease [6]. A patient who scores 3 or less on this assessment is considered low risk for developing opioid dependence issues. A patient who scores greater than 8 is considered high risk for developing dependence issues [6]. Critically-ill, postoperative, and trauma patients will all have a need for opioids for adequate analgesia. However, careful consideration of the type of opioid prescribed, the duration of therapy, and supplementing analgesia with non-opioid adjuncts is highly recommended as part of an effort to reduce opioid abuse and tolerance.

Protocols and Variability in Practice

Initiating opioid therapy in a patient who has undergone surgery or suffered a traumatic injury requires consideration of the type of surgery or extent of injury, a patient's prior use of opioids, and a clear assessment of anticipated course of recovery. A large multicenter review of postoperative opioid prescribing practices reported that there is significant variation in amounts of oral morphine equivalents

prescribed postoperatively for identical procedures [7]. Similar findings have been shown in multiple studies [8, 9], highlighting the poor standardization in the prescription of opioid analgesics and in the management of postoperative pain.

Given the identification of this wide variation in prescribing practice, and the significant morbidity and mortality associated with inappropriate opioid administration, many advocate for definitive standardization of opioid prescriptions in the postoperative setting. One strategy has been to limit the opioids prescribed, forcing the patient to be re-assessed when seeking ongoing prescriptions.

Effects of Opioid Use Prior to Surgery or Traumatic Injury

Patients can present to surgical or trauma ICUs with a history of long-term opioid use. Providers must be vigilant and elicit any history of long-term opioid use as there are important potential adverse physiologic and psychologic effects that may ultimately result. Patients may have tolerance to opioid analgesics which may necessitate increased doses, in turn subsequently placing these patients at increased risk for respiratory depression and delirium [10, 11]. Use of a multimodal analgesic regimen is paramount in these settings to reduce the need for opioid escalation. Additionally, long-term effects of opioids can be associated with hyperalgesia in postoperative patients or following injury [10, 11]. Gastrointestinal effects, including constipation and nausea, may also result from long-term opioid use and can exacerbate postoperative or post-traumatic ileus [10, 11]. Respiratory system effects include central and obstructive sleep apnea and CO_2 retention. Chronic opioid use can also cause suppression of the hypothalamic-pituitary-adrenal axis. Opiates have been shown to affect the release of all hormones including adrenocorticotropic hormone, which can cause a relative adrenal insufficiency, in turn influencing the normal host immune response of critically ill patients [10, 11].

Physiologic Effects of Uncontrolled Pain

Severe pain can cause significant physiologic derangements and can induce psychological distress and impairment. Uncontrolled pain can induce sympathetic activity that can result in tachycardia, hypertension, and increased myocardial oxygen demand, potentially inducing myocardial ischemia [1, 12]. Pain from surgical incisions in the thorax and abdomen can impair diaphragm function resulting in altered pulmonary mechanics, tachypnea, atelectasis, and impaired gas exchange [1, 12]. Impaired sleep, delirium, and agitation can result from uncontrolled pain and may be associated with long-term sequalae [1, 12]. Finally, pain has also been shown to cause immunosuppression, increased protein catabolism, and impair wound healing [1, 10–12].

Premedication and Opioid-Sparing Analgesics (Table 12.1)

The use of non-opioid analgesics preoperatively such as acetaminophen, gabapentin, and nonsteroidal anti-inflammatory drugs (NSAIDs) has also been shown to improve postoperative pain control and reduce the use of opioid analgesics after surgery.

Mild to moderate pain in the ICU can be effectively treated with acetaminophen. When used in conjunction with opioids, acetaminophen has been shown to reduce the need for opioids in the postoperative setting [12–14]. Some studies have also shown a reduction in ICU length-of-stay, and delirium incidence and duration with the use of scheduled acetaminophen administration [13, 14]. Intravenous (IV) and oral formulations are available. Intravenous acetaminophen has not been shown to be superior to enteral formulations given its high availability via enteral absorption [15]. If a patient is able to absorb enteral medications, the enteral route of administration is preferred given the significantly lower cost per dose. Acetaminophen has a maximum dose of 4 g in a 24-hour period to prevent risk of liver injury. Special considerations to maximum daily dose are needed when administering this drug to patients with impaired liver function or a history of alcohol ingestion.

NSAIDs produce analgesia via inhibition of cyclooxygenase [1, 12]. This can provide significant analgesia and antipyretic effects. As a class these drugs have been shown to significantly reduce the amount of opioids administered in the postoperative setting; however, they can have significant side effects and should be cautiously used in critically ill patients [1]. NSAID side effects include risk for gastrointestinal bleeding and nephrotoxicity, morbidities common in the critically ill [1, 12, 16]. There has also been controversy regarding NSAID use in patients suffering traumatic fractures as these agents have been associated with impaired bone healing and remodeling [17]. The evidence for this is not robust and has been called into question recently. Ketorolac is an IV NSAID that can be used postoperatively and is metabolized in the liver and excreted in the kidney so the dose may need to be adjusted or held in patients with hepatic and renal impairment [1]. Prolonged use of ketorolac for greater than five days is not recommended as this increases the risk of gastrointestinal bleeding significantly as well as at operative sites [1, 12].

Gabapentin, pregabalin, and carbamazepine are effective medications for the treatment of neuropathic pain [1, 12]. Use of these medications in the ICU has been shown to reduce the total opioid dose administered after surgery. Unfortunately, these drugs must be administered enterally. Also, these drugs have several drawbacks including sedation and impaired cognition, and their use should be with caution in patients at risk for postoperative cognitive dysfunction and delirium [1, 12]. Clinicians should be aware that abrupt discontinuation of these medications may be associated with withdrawal symptoms.

Ketamine is an n-methyl-d-aspartate (NMDA) receptor antagonist. There is also evidence that ketamine acts at mu, kappa, and delta opioid receptors [12, 18]. Ketamine has several properties that make it a good adjunct to opioids in

Table 12.1 Opioid adjuncts commonly used in the ICU

	Intermittent dosing	Infusion dose	Mechanism of action	Metabolism	Critical illness considerations
Acetaminophen [62]	650 mg–1000 mg q6h	N/A	Cyclooxygenase inhibitor, no anti-inflammatory action	Hepatic glucuronidation/CYP oxidation	Do not exceed 4 g/day. May need reduced dosing in patients with hepatic dysfunction
Ketorolac [63]	30 mg q6h(IV)	N/A	Cyclooxygenase inhibitor	Hepatic glucuronidation	Avoid in GI bleeding and patients with AKI/ESRD
Gabapentin [64]	Start 100–300 mg TID may uptitrate	N/A	Unclear, high affinity binding to calcium channels in CNS inhibiting excitatory neurotransmission	Renal clearance, unmetabolized	Reduced dose in kidney dysfunction, potential for sedation
Ketamine [65]	0.1–0.5 mg/kg q6h	0.1–0.5 mg/kg/min	NMDA receptor antagonism	Hepatic N-dealkylation	Direct myocardial depression. Caution in patients with heart failure
Dexmedetomidine [66]	N/A	0.2–2 mcg/kg/hr	Alpha receptor agonism; 1600:1 alpha2:alpha1	Hepatic glucuronidation/CYP oxidation	Caution in patients with bradycardia/ myocardial dysfunction

postoperative and trauma ICU patients. It has sympathomimetic properties that give it a favorable hemodynamic profile and has been shown to augment cardiac output in healthy patients [1, 12]. The effects of ketamine on respiratory function are advantageous for patients in the ICU as it acts as a bronchodilator, and there is minimal respiratory depression associated with analgesic doses of ketamine [1, 12]. Ketamine has been used for many years in burn patients. It has been shown to reduce hyperalgesia and allodynia associated with thermal injuries [19]. For many years, the military has used ketamine as part of a multimodal analgesic regimen for wounded or injured soldiers [20]. Its perioperative use in cardiac surgery patients has further demonstrated a reduction in opioid use and potentially a reduction in the rate of chronic post-sternotomy pain [17]. In patients who have undergone major abdominal surgery, ketamine has also been shown to reduce postoperative opioid requirements and it is thought that this effect may also promote the earlier return of bowel function [21, 22]. There is also strong evidence for the opioid-sparing property of ketamine in patients who have a history of chronic pain with significant opioid use prior to surgery [23].

Although ketamine has shown significant promise and there are many advantages to its use, there are also certain drawbacks to its administration in critically ill patients. Despite the favorable hemodynamic profile there is controversy over ketamine's direct effects on the myocardium. Some investigators have suggested it depresses myocardial function in patients with longstanding congestive heart failure [24]. Furthermore, ketamine increases pulmonary vascular resistance and may be problematic in patients with concomitant pulmonary arterial hypertension [25]. Additionally, ketamine-related tachycardia can be detrimental to patients with severe valvular stenosis or coronary artery disease as it will increase myocardial oxygen demand [1, 12, 24]. It is unclear if these effects are significant at analgesic doses. Ketamine is also a potent sialogogue and secretion burden can become significant following its administration [19]. Ketamine has also been shown to be associated with unpleasant psychoactive effects including hallucinations and emergence delirium [1, 12]. Lastly ketamine has long been associated with increased intracranial pressure, though the clinical significance of this has been called into question in recent years [26].

Dexmedetomidine is an alpha-2 receptor agonist that has sedating and analgesic properties with a favorable hemodynamic profile, though minimal respiratory depression but with some risk of bradycardia [12, 27]. Dexmedetomidine causes analgesia at multiple sites of action, including in the locus ceruleus and inhibition of pain signals through the dorsal horn of the spinal cord. Dexmedetomidine also inhibits the release of norepinephrine from presynaptic terminals and prevents the transmission of pain signals across synapses. Due to these analgesic properties, dexmedetomidine has been studied in multiple surgical populations and shown to reduce opioid consumption as well as pain intensity in patients postoperatively [27].

Regional Anesthesia

There are many regional anesthetic techniques that can provide effective pain control for a patient undergoing a surgical procedure or who has suffered traumatic injury. The use of epidural anesthesia can reduce the use of opioids in postsurgical patients including cardiac, thoracic, intra-abdominal, and orthopedic surgeries [27–30]. Patients who sustain traumatic injuries to the chest and/or abdomen can also see a reduction in opioid consumption when epidural analgesia is used [31]. The benefits of this type of analgesia must be weighed against the risks of the frequent need and use of anticoagulants for venous thrombosis prophylaxis. Careful timing of initiation and discontinuation of neuraxial anesthesia must consider anticoagulation dosing and administration. Additionally, the use of neuraxial regional techniques may cause hypotension as they can block sympathetic nervous system output in the spine with resulting splanchnic vasodilation.

Methadone

Methadone is a unique opioid. For much of its existence it has found its primary use as a treatment for heroin addiction [32]. However, the opioid epidemic has generated new interest in its use in the perioperative setting. Methadone is available in enteral and parenteral formulations. Of the opioids used in clinical practice, it has the longest half-life with enteral formulations estimated to last between 15 to 55 hours while IV methadone between 8 and 59 hours [32, 33]. When administered at doses of 20–30 mg, the effective duration of analgesia can be from 24 to 36 hours [33]. The principal mechanism of action is similar to other opioids, acting on central and peripheral mu_1 receptors. However, further investigation has shown that it also antagonizes the NMDA receptor [32, 33]. Additionally, methadone has been shown to decrease reuptake of serotonin and norepinephrine [32, 33], see Chaps. 3 and 4.

Opioids with shorter half-lives have the problem of wide variability in plasma concentrations. Even with the use of patient controlled analgesia (PCA) pumps, patients in the ICU and other postoperative settings can range between inadequate analgesia and significant overdosage side effects of opioids such as respiratory depression.

Given the unique properties of methadone and the persistent reporting of inadequate analgesia in the postoperative period, methadone is of great interest in treating acute pain. Studies in patients undergoing complex spine surgery have shown that methadone administration at induction of anesthesia is effective in reducing postoperative opioid use [34]. Investigation into the role of methadone in cardiac surgery patients has shown similar results [35]. In these patients, methadone has been shown to significantly reduce overall use of opioids postoperatively and improve pain scores as compared to patients who instead received fentanyl as the sole analgesic during surgery. Investigations have demonstrated

that methadone can be effective in preventing the development of hyperalgesia and allodynia [36]. Additionally, methadone has been shown to decrease opioid tolerance and has been effective in the treatment of neuropathic pain which may develop in the postoperative period [32]. These benefits are thought to be mediated via the antagonism of the NMDA receptor [32, 33].

Despite potential benefits of methadone in the perioperative setting, it nonetheless also has a side effect profile similar to other opioids including respiratory depression, delayed gastric emptying, urinary retention, pruritus, and urticaria [32]. Like other narcotics such as fentanyl, methadone is also associated with development of serotonin syndrome, perhaps related to serotonin reuptake and metabolism [32, 33]. Additionally, methadone can prolong the QT interval placing patients at risk for ventricular arrhythmias, particularly when used in combination with other drugs that prolong the QT interval such as certain antiemetics and antidepressants [32, 33]. An electrocardiogram should be obtained on all patients prior to initiation of methadone therapy.

Opioids Conventionally Used in the Acute Post-Traumatic and Postoperative Period (Table 12.2)

Pain following surgery or traumatic injury follows a different course than some other types of pain (chronic pain, fibromyalgia). The peak pain intensity is on postoperative day 0 and 1. It is expected that as time progresses from the initial insult, the severity of pain and analgesic requirements will decrease. Currently, the mainstay of analgesia in the postoperative and traumatic injury setting is the use of opioid analgesics as part of a multimodal pain regimen. As a class, narcotics reliably provide effective analgesia and have a favorable hemodynamic profile. In the immediate post-injury or postoperative setting IV opioids with rapid onset are preferred, given the acuity and severity of pain these patients will be experiencing as well as concerns regarding drug absorption barring enteral or transcutaneous routes of administration.

Fentanyl is a synthetic opioid with a rapid onset of action making it favorable following surgery or traumatic injury [1, 11]. Fentanyl has an approximately 50-fold greater potency as compared to morphine [1]. When given as a single bolus dose, the duration of action of fentanyl is relatively short, only lasting 25–30 minutes [1, 11]. However, continuous fentanyl infusions can be used when a patient will need continuous sedation and is likely to require analgesia, such as in postoperative and trauma patients who will remain intubated for a prolonged period. The concept of context sensitive half-life is important in this setting. Due to the high lipid solubility of fentanyl, it will accumulate in tissues throughout the body. As a result, increased duration of infusions will result in increased duration of effects, including sedation and respiratory depression even persisting after the infusion is discontinued. Fentanyl can be used as an analgesic in patients who are hemodynamically unstable

Table 12.2 Dosing and considerations of IV opioids commonly used in the ICU [1, 33, 57, 58, 59, 60, 61]

	Morphine	Hydromorphone	Fentanyl	Methadone	Remifentanil
IV bolus dose	2–4 mg	0.5–2 mg	25–100 mcg	5–20 mg	N/A
Infusion dose	1–10 mg/hr	0.5–5 mg/hr	50–20 mcg/hr	N/A	0.5–5 mcg/kg/hr
Hemodynamic effects	May cause hypotension	Negligible, may cause hypotension	Negligible	QTc prolongation, potentially arrhythmogenic	Bradycardia
Use in renal failure	Do not use	Dosing adjustments required	Safe to use	Safe to use	Safe to use
Use in Hepatic Failure	Dosing adjustment required	Dosing adjustments required (50% dose)	Dosing adjustment required, may cause encephalopathy	Increased half-life	No dosing adjustment, may cause encephalopathy
Time to Onset	<10 min	<10 min	<1 min	20–30 min	<5 min
Duration of Action(Bolus)	2–3 hours	2–3 hours	30 min	10–36 hours	N/A

as it has little effect on circulation. Fentanyl is safe for use in patients with end-stage renal disease or acute kidney failure as it is cleared through hepatic metabolism [1, 11]. However, dosing adjustments will be required in patients with impaired liver function.

Remifentanil is another synthetic opioid that is described as being ultra-fast acting. It has a half-life of 5–10 minutes and is metabolized by plasma esterases with no active metabolites [1, 11]. It is typically used as an infusion and can be infused for extended durations with little increase in duration of action. Remifentanil has the potential drawback of producing hyperalgesia if it is suddenly discontinued without initiation of other analgesic therapy [1, 11]. It can also cause significant bradycardia and, therefore, should be used with caution in patients at risk for heart block or who are on concurrent beta blockade.

Morphine has many qualities that make it less desirable for use in the ICU. Morphine has an active metabolite, morphine-6-glucuronide, that can accumulate in patients with renal impairment and cause central nervous system and respiratory depression [1, 11]. Additionally, morphine may cause histamine release which is not ideal in hemodynamically unstable patients [1, 11].

Hydromorphone is a semisynthetic opioid that is slightly more potent than morphine and has a similar time to onset. The duration of action is 2–3 hours for a single bolus dose [1, 11]. There is little histamine release associated with hydromorphone administration with less effects on hemodynamics as seen with morphine. Hydromorphone has had a history of dosing errors owing to its increased potency over morphine. Also, there is the potential for accumulation of its active metabolite (hydromorphone-3-glucuronide) in kidney failure which can be neurotoxic, though this is significantly less of a concern than with morphine administration [1, 11].

Oxycodone is an enteral opioid that binds mu and kappa receptors [37]. Both immediate and extended release formulations are available. Immediate release is most appropriate in postsurgical or trauma patients given its quick onset of action within 10–15 minutes [37]. A single dose can be effective for 3–6 hours [37]. Oxycodone has similar side effects to other opioids including respiratory depression and constipation. However, similar to hydromorphone, there is little histamine release with oxycodone administration [37].

Meperidine is a synthetic opioid derivative and has little modern use in postoperative or traumatic injury analgesia [1, 38]. Meperidine is metabolized to an active metabolite, normeperidine, that can accumulate and induce seizures in experimental models [38]. The primary use for meperidine is in the control of shivering thought to be mediated via its effects on the kappa opioid receptor and alteration of the thermoregulatory set point [38].

Tramadol is an analgesic that has a mixed mechanism of action. It is a moderate mu opioid receptor agonist that also acts centrally to block the reuptake and enhance the effects of serotonin [39, 40]. This combined mechanism of action results in less respiratory depression than pure mu agonist analgesics [39]. Additionally, serotonin antagonist antiemetics have been reported to reduce the efficacy of tramadol in the postoperative period [41].

Fentanyl, morphine, remifentanil, and hydromorphone can be delivered by PCA which can be implemented when a patient regains the ability to guide their own analgesic therapy. PCA offers several benefits in the acute postoperative or traumatic injury setting. There is a more reliable plasma level of analgesic due to more regular administration, as well as ease of nursing workload and increased patient satisfaction [42].

As patients regain ability to tolerate enteral administration of medications they should also have less associated traumatic injury or surgical pain. There will be an increased distinction between pain at rest and pain with activity such as coughing and pulmonary hygiene as well as with therapy and rehabilitation. In this subacute phase of pain, enteral analgesics are a reasonable transition from basal IV narcotic infusions and PCA. Timing of administration of medication in this phase of care is important given the delayed analgesic effect associated with enteral administration. This delay should be anticipated by bedside providers and appropriate timing of analgesic administration with physical therapy and rehabilitation services will increase patient satisfaction and their ability to participate in these important activities. Various narcotics are available in transdermal and intranasal routes of administration. The pharmacokinetics of these routes of administration are less favorable for critically ill patients. Hydromorphone and morphine are available in enteral formulations. Multiple dosages and formulations of these drugs are available that include immediate and extended release. They are available as tablets, liquids, and suppositories. The side effect profile remains similar to the IV forms.

Drug Metabolism of Opioids: Consideration of Specific Populations

Opioids are metabolized in the liver and excreted via the kidneys. Each can differ in the way in which they undergo metabolism. Studies of population pharmacokinetics have found differences in opioid metabolism when stratified by age, sex, and ethnicity [40]. CYP-mediated oxidation accounts for metabolism of most opioids. Variation in CYP enzyme function derived from differences in age, sex, and genetic variation, as well as concomitant drug administration has the potential to result in significant drug-drug interaction [40], see Chap. 4. In addition to individual differences in drug metabolism activity, hepatic and renal function are frequently impaired in the critically ill. It is exceedingly difficult to predict the extent to which patients in the ICU will metabolize opioids [40]. Given that many patients in the ICU can have an extensive medication administration regimen, careful titration of any opioid to safe clinical effect is paramount.

Some opioids used in the ICU can have clinically active metabolites. Morphine and hydromorphone are frequently used to treat postoperative and post-trauma pain; both have active metabolites. Morphine is converted to morphine-6-glucuronide as well as morphine-3-glucuronide [40]. These active metabolites can accumulate in patients with end-stage renal disease and cause respiratory depression, gastrointestinal side effects, and increased sedation. Tramadol must be metabolized to its active metabolite to have

full clinical effect. Tramadol and its active metabolite both have μ receptor activity; however, the Tramadol parent compound also affects serotonin and norepinephrine uptake [40]. Fentanyl and methadone are both metabolized by the CYP enzyme system. While this places them at high risk for causing drug interactions with medications metabolized via these pathways, they do not produce clinically active metabolites [40].

In the future, as understanding of the genetic variation in drug metabolism is improved and the impact of environmental factors and critical illness is clarified, personalized drug regimens could be implemented to provide maximal therapeutic benefit with minimal side effects [43]. However, this is in the distant future, and currently critically ill patients require careful and active bedside titration and understanding that these variations exist and one opioid may not be as effective as another for a given patient and a given pain profile.

Specific Cases and Considerations

Sternotomy is the most common wound following cardiac surgery and poorly controlled sternotomy pain can contribute to poor pulmonary function and nonadherence to rehabilitation therapy in the postoperative setting [44]. Sternotomy pain has multiple aspects that make it a particularly painful incision and predispose to chronic pain. First, the sternum is often re-approximated using sternal wires; however, in the early postoperative period, there can still be significant sheer of the sternum when a patient breaths deeply or coughs [45]. Additionally, sternal wires have been implicated in developing significant amounts of pain following cardiac surgery in the acute and chronic phases. Both the sheer effects and the role of sternal wires' impact on sternotomy pain have been attenuated by the introduction of rigid fixation devices [45]. The pharmacologic management of sternotomy pain has shifted to a multimodal model of pain control. Administration of long-acting methadone preoperatively, combined with immediate release oxycodone or hydromorphone postoperatively, in addition to acetaminophen, lidocaine patches and GABA analogues are commonly employed perioperatively for the management of sternotomy pain [35, 46]. NSAIDs should be used with caution in this patient population who are at increased risk for acute kidney injury. Regional analgesia techniques, specifically epidural analgesia, are controversial in cardiac surgery [46]. The medically induced coagulopathy from heparin administration during cardiopulmonary bypass and frequent need for continued anticoagulation postoperatively make timing of placement and removal of epidural catheters difficult. Additionally, thoracic epidural analgesia has not been convincingly shown to be superior to multimodal pharmacologic management of pain following cardiac surgery [2, 47].

Thoracotomy, like sternotomy, can have significant impact on patient respiratory and physical function following surgery. Trauma to the intercostal muscles and nerves during surgery can cause significant pain in both acute and chronic phases of recovery [48]. Some studies have found that up to 50% of patients will develop chronic pain following a thoracotomy [48]. Analgesia for thoracotomy is similar to that for

sternotomy, utilizing a multimodal regimen outlined above. However, regional analgesia can play a much larger role in thoracotomy pain management with options that include epidural analgesia, intercostal, and paravertebral nerve blocks [49].

Laparotomy for intra-abdominal surgery can also be associated with poor pulmonary hygiene and nonadherence to rehabilitation following abdominal surgery [50]. However, it is also associated with an increased incidence of postoperative ileus. Incidence of ileus following abdominal surgery can be up to 40%, and perioperative opioid use can contribute to the development of paralytic ileus [51]. Thus, the management of postoperative laparotomy pain must balance pain control with the risk for ileus. Reducing opioid administration through the use of non-opioid adjuncts including regional analgesia, acetaminophen, GABA analogs, and ketamine can effectively control pain and reduce the risk of ileus following surgery [51].

Challenges of COVID-19

The COVID-19 pandemic has posed a variety of challenges in caring for critically ill patients. The disease remains poorly understood, and as a result, optimal sedation and analgesia is yet to be defined. Many reports, mainly describing clinical experience, seem to indicate that patients with COVID-19 ARDS have significantly increased sedation and analgesic requirements [52, 53]. One retrospective review of COVID-19 patients has shown analgesia requirements to be up to threefold higher when patients require mechanical ventilation than previously studied ARDS populations [53]. At the time this review was written, there were no data on changes in analgesic requirements attributable to COVID-19 in postsurgical and trauma patients. Perhaps insight will be gained utilizing data from research consortiums that have developed during the pandemic to better understand COVID-19.

ICU Discharge

Many patients will likely need to continue opioid analgesia therapy through the duration of their ICU stay following surgery or a traumatic injury. As patients progress through their recovery, their opioid therapy should progress with them and the assessment of a patient's analgesic regimen should be part of the decision to downgrade them from the ICU. Providers should have a standard protocol ensuring patients are discontinued from high-potency, rapid-onset opioids prior to leaving the ICU. Studies have shown that many medications including antipsychotics and stress ulcer prophylaxis medications prescribed while the patient was critically ill are unknowingly continued throughout hospitalization and upon discharge [51, 54, 55]. Recent data have shown similar trends with opioids [56]. Assessment of patient analgesic needs as the critical illness and immediate insult resolves should result in a discontinuation of analgesics when no longer necessary.

Summary

Patients presenting to a postsurgical or trauma ICU have a myriad of concerns in managing their analgesia and careful consideration of an appropriate opioid regimen is essential to effectively managing their critical illness. Uncontrolled pain can result in increased physiologic derangement as well as predispose patients to long-term physical and psychological disturbances. Appropriately assessing patient pain, through validated assessment tools and the ability to participate in rehabilitation are more appropriate than solely relying on subjective patient reports of pain. There is significant variation in the prescribing practices for opioids following surgery which can result in inadequate or excessive opioid administration. Appropriate assessment, in concert with protocols for managing acute pain, may help to reduce prescribing variation. Additionally, it is advisable that appropriate patients initiated on opioid therapy undergo screening for risk of dependence and addiction. Patients may present to the ICU with longstanding opioid use prior to surgery or traumatic injury. Chronic opioid use prior to presentation may impact baseline physiology and may increase requirements for opioids in the acute setting. Many patients will present to surgical ICUs following interventions that will require effective analgesia for appropriate respiratory function as well as participation in rehabilitation therapies. There are many adjuncts that can be employed in the perioperative setting that can be used to reduce opioid consumption and their associated side effects. Use of less conventional, long-acting opioids in the perioperative setting can help to decrease the use of high-potency, rapid-onset opioids. Regional and non-opioid analgesics have also been shown to reduce opioid requirements. As a patient recovers from their insult and prepares to transition out of the ICU, it is important that a careful review of prescribed medications including opioids is performed. Patients should not continue the most potent opioids as they progress to the next level of care and prepare for discharge. Non-opioid adjuncts may be sufficient for controlling pain in these settings and should be favored.

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