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Optimizing Pain Control and Minimizing Opioid Use in Trauma Patients

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ABSTRACT

Adverse effects of opioids and the ongoing crisis of opioid abuse have prompted providers to reduce prescribing opioids and increase use of multiple nonpharmacologic therapies, nonopioid analgesics, and co-analgesics for pain management in trauma patients. Nonopioid agents, including acetaminophen, nonsteroidal anti-inflammatory drugs, gabapentinoids, ketamine, central α_2 agonists, and lidocaine, can be used as adjuncts or alternatives to opioids in the trauma population. Complementary therapies such as acupuncture, virtual reality, and mirror therapy are modalities that also may be helpful in reducing pain. Performing pain assessments is fundamental to identify pain and evaluate treatment effectiveness in the critically ill trauma patient. The efficacy, safety, and availability of opioid-sparing therapies and multimodal pain regimens are reviewed.
Key words: complementary therapy, multimodal pain management, opioid sparing, trauma

Trauma patients in intensive care units (ICUs) and intermediate care units (IMCUs) experience moderate to severe pain from their injuries and from interventions performed (eg, operative interventions, catheter insertions, mobilization) that can be categorized as background pain and intermittent pain.[1] Acute pain in the critically ill trauma patient can be challenging to manage, particularly when the patient has a history of preinjury opioid use. Rates of preinjury opioid use in patients admitted to a level I trauma center vary between 16% and 20% in the literature.[2,3] Severe pain has deleterious effects, and optimizing pain control is important to mitigate psychological, anatomical, and physiological changes (eg, respiratory compromise, immunosuppression, cardiac instability).[4-6] One potential long-term outcome of inadequate treatment of acute pain is the progression to chronic pain.

Traditionally, opioids have been the preferred treatment for acute pain in most ICU settings.[6] Although opioids are considered an important part of acute pain management in high-acuity settings, attention to their effect on pain as well as their potential adverse

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consequences is required. Adverse effects of opioids include nausea, vomiting, constipation, ileus, sedation, and opioid-induced respiratory depression. Another potential long-term adverse outcome can be the development of chronic opioid use.[7,8] Half of patients with chronic opioid use initially received opioids in the acute care setting for pain after surgery to treat an acute injury.[9]

At the same time that we are questioning the chronic use of opioids, the United States is facing a national emergency: the opioid crisis. The risk of opioid misuse and abuse remains a concern when prescribing opioids, especially for traumatically injured patients with preexisting history of substance use disorder. Health care providers and organizations can look to alternatives, such as the use of multimodal analgesia, to help decrease acute to chronic pain while re-evaluating the effectiveness of long-term opioids.

Multimodal analgesia is the simultaneous use of different classes of analgesic medications to minimize adverse effects and maximize synergistic analgesic properties. Multimodal analgesia can consist of the combined use of a nonopioid pharmacologic intervention, with or without opioids, as well as nonpharmacologic complementary therapies.[10] Use of a multimodal analgesia strategy may improve pain control and reduce opioid consumption, as well as improve short- and long-term patient-centered outcomes.[6] A multimodal pain management approach may ameliorate the acute adverse effects of opioids and help mitigate misuse of opioids. Although opioids and nonopioid agents should be considered for trauma patients experiencing moderate to severe acute pain in ICUs and IMCUs, integrating complementary therapies may also be beneficial in treating pain, although more research is needed to validate effectiveness of these interventions in high-acuity settings.

Complementary medicine is defined by the National Institutes of Health's National Center for Complementary and Integrative Health as the incorporation of complementary approaches into mainstream health care.[11] Complementary medicine is the use of nonmainstream therapies in conjunction with conventional medical care.[12] The Joint Commission for Accreditation of Healthcare Organizations' standards for pain management state, "While evidence for some nonpharmacologic modalities is mixed and/or limited, they may serve as a complementary approach for pain management and potentially reduce the need for opioid medications in some circumstances."[13(p2)] Federal agencies such as the Department of Defense, Veterans Health Administration, National Institutes of Health, Food and Drug Administration, and Centers for Disease Control and Prevention are promoting a comprehensive patient-centered and health-focused approach to pain management.[14]

Nonopioid Analgesics and Co-Analgesics for Pain Management

Acetaminophen

Mechanism of Action. Acetaminophen (APAP) has been used as an analgesic and antipyretic since the 1950s. Its mechanism of analgesia has not been fully elucidated but is thought to be due to reduction of prostaglandin synthesis in the brain by inhibition of cyclooxygenase (COX) enzymes.[15] Other contributory mechanisms may include central stimulation of descending serotoninergic pathways, activity of metabolites on the endocannabinoid system, and inhibition of nitrogen oxide formation, and substance P–induced hyperalgesia.[16] Acetaminophen does not have known anti-inflammatory properties.

Medication Use and Characteristics. Acetaminophen has an established use in the setting of mild to moderate noninflammatory pain. It is recommended as a component of a multimodal regimen to decrease pain intensity and spare opioid use in postoperative and ICU settings for patients without contraindications.[17,18] Patients with isolated limb trauma experienced similar analgesia after 1000 mg of intravenously administered APAP or 10 mg of intravenously administered morphine.[19] Patients with acute postoperative pain who received intravenously administered APAP required 26% less opioid over 4 hours and 16% less over 6 hours.[20] Among ICU patients, those who received 24 hours of APAP had reduced behavioral pain scores, opioid consumption, postoperative nausea and vomiting, and sedation as well as decreased time to extubation after major surgery.[21] Acetaminophen has an analgesic ceiling of 1000 mg/dose.[22] More patients achieved 50% pain relief with 1000 mg of APAP than with doses of 500 mg or 650 mg.[23,24] Suggested dosing regimens are listed in Table 1. Efficacy in treating acute pain may be optimized if doses are scheduled

Table 1: Acetaminophen Dosing for Adults[a]

Population	Dosing Schedule	Maximum Single Dose	Maximum Daily Dose
Adult, weight ≥ 50 kg	1000 mg IV or orally every 6-8 h	1000 mg IV or orally	4000 mg IV or orally
	650 mg IV or orally every 4-6 h		
	650 mg rectally every 4-6 h	650 mg rectally	Six suppositories (3900 mg)
Adult, weight < 50 kg	15 mg/kg IV or orally every 6 h 12.5 mg/kg IV or orally every 4 h	15 mg/kg up to 750 mg	75 mg/kg/day, up to 3750 mg

Abbreviation: IV, intravenous.

[a]Data were derived from DRUGDEX System Micromedex 2.0.[25]

versus given as needed. Acetaminophen is available in a variety of oral, intravenous, and rectal dosage forms. When administered orally, APAP is rapidly and almost completely absorbed from the gastrointestinal tract, achieving peak levels at 1 hour.[25] Analgesia onset is faster after an intravenously administered dose, occurring at 5 minutes after completion of a 15-minute infusion, but analgesia with APAP has a shorter duration of 2.9 hours versus 4.6 hours after oral administration.[26] Intravenous administration of APAP achieves higher concentrations in the cerebrospinal fluid, although this does not appear to confer a clinically significant difference in efficacy.[27] Rectal administration results in lower overall concentration and longer time to peak concentration at 2.5 hours than either oral or intravenous administration; it also has the longest duration of action.[28] Because of the higher cost of intravenously administered APAP, oral or rectal dosing formulations may be preferred whenever feasible and clinically appropriate. Acetaminophen is hepatically metabolized by glucuronidation or sulfation to nontoxic metabolites or via cytochrome P450 2E1 to the highly toxic metabolite, *N*-acetyl-*p*-benzoquinone imine (NAPQI). When sufficient glutathione is available, NAPQI is rapidly conjugated to nontoxic metabolites.[29]

Adverse Effects. Acetaminophen is generally well tolerated with minimal side effects when used at recommended doses. The risk of toxicity increases when usual metabolic pathways are overwhelmed or shifted to increase the production of NAPQI or glutathione stores are insufficient to complete rapid detoxification.[30-33]

Acute or chronic use of doses above the recommended 4-g daily maximum is a longstanding and widely recognized factor that increases the risk of APAP-induced liver injury. Acetaminophen-induced hepatotoxicity is the leading cause of acute liver failure.[30] In a review of more than 30 000 patients included in prospective studies use therapeutic APAP dosing, serious liver injury was not observed; only 0.4% of patients experienced elevated aminotransferase levels.[31] In patients with higher aminotransferase levels, the average daily APAP dose was significantly higher at 3.7 g versus 2.7 g in those without increased aminotransferase levels. A separate analysis of more than 9000 patients included in retrospective reviews found elevated aminotransferase levels were reported in 96 patients (1%) and acute liver failure in 32 (0.03%).[31] The reported mean (SD) daily APAP dose in patients with any type of hepatic adverse effect was 2.4 (1.2) g.

Reports of hepatotoxicity at therapeutic APAP doses have prompted investigation into patient-specific factors that may increase risk. Several have been identified, including regular heavy alcohol consumption; malnutrition; fasting; acute illness; advanced or decompensated cirrhosis; and concurrent administration of medications that increase production of NAPQI, such as isoniazid, phenytoin, valproic acid, carbamazepine, simvastatin, rifampicin, zidovudine, and trimethoprim-sulfamethoxazole.[32,33] When APAP use is needed in these patient populations, or in patients with severe traumatic liver injury when concern exists for reduced hepatic metabolic capabilities, daily maximum doses or monitoring for toxicity should be considered.

Considerations for Use in Select Populations. For patients with chronic liver disease, APAP is an important nonopioid analgesic because of concerns regarding safety and side effects of other analgesics in this population. Because the liver is the site of both APAP metabolism and drug-induced injury, there is concern that

these patients may be at risk for toxicity when using APAP within the therapeutic dose range. In a small study of patients with stable chronic liver disease, APAP 4 g/d for 13 days did not produce adverse effects.[34] Although long-term safety data are unavailable, findings of studies in which NAPQI metabolic pathways were evaluated do not suggest patients with compensated cirrhosis are at increased risk of toxicity.[34] On the basis of this information, multiple experts suggest short-term use of 3 to 4 g/d appears to be safe, but a reduced maximum of 2 to 3 g/d is recommended for patients in decompensated hepatic states when there are additional risk factors for hepatotoxicity or when used for longer than 14 days.[35-37]

When using APAP for analgesia, especially in an ICU population with elevated risk factors for infection and hemodynamic instability, consideration should be given to APAP's effects on thermoregulation and hemodynamics. In healthy volunteers with endotoxin-induced fever, a single dose of intravenously administered APAP demonstrated rapid antipyretic activity, detectable 30 minutes after start of the infusion, that persisted throughout a 6-hour study and increased from 10% to 40% the percentage of volunteers with a temperature less than 38.0 °C at any time.[38] This effect is clinically concerning; when used continually for pain, APAP may mask fever and delay discovery of early infection. Intravenously administered APAP also significantly reduces blood pressure and heart rate in critically ill patients, some to a degree that is clinically important.[39]

Nonsteroidal Anti-Inflammatory Drugs

Mechanism of Action. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a group of therapeutically similar medications with analgesic, anti-inflammatory, and antipyretic activity. Therapeutic effects are due to decreased prostaglandin synthesis through inhibition of COX-1 and COX-2 enzymes. The COX-1 enzyme is constitutively expressed in many tissues, producing prostaglandins in stomach epithelial and smooth muscle cells that protect against mucosal injury, in platelets that promote aggregation, and at several sites in the kidney to maintain hemodynamic regulation and glomerular filtration.[40,41] The COX-2 enzyme is found constitutively in fewer tissues, but production increases 20-fold in the presence of inflammatory stimuli.[41] Cyclooxygenase-2 produces prostaglandins that cause fever, increase sensitivity to pain, and contribute to acute inflammation.[40]

Individual NSAIDs have varying degrees of activity at the 2 enzymes. Aspirin is relatively selective for COX-1 and is the only NSAID that causes irreversible enzyme inactivation.[40] Ketorolac inhibits both enzymes but has higher selectivity for COX-1.[41] Ibuprofen, diclofenac, and naproxen inhibit both enzymes to a similar degree, and meloxicam inhibits COX-2 to a greater extent, with a relative ratio of COX-2 to COX-1 activity of 25:1.[40,41] Celecoxib has a COX-2 selectivity ratio greater than 155:1 and is the only COX-2 inhibitor currently on the market.[40]

Medication Use and Characteristics. Nonsteroidal anti-inflammatory drugs are potent analgesics with an established role in treatment of mild to severe pain, especially when due to inflammation, injury from trauma, or invasive procedures. Nonsteroidal anti-inflammatory drugs are recommended in conjunction with APAP as part of a multimodal regimen for the treatment of postoperative pain in patients without contraindications.[17] Although select patient groups in ICU settings may benefit from NSAIDs, COX-2 inhibitors have not been studied in this population, to our knowledge, and routine use of nonselective NSAIDs is not recommended, because of a lack of clinically significant benefit and because of concerns for adverse renal and hematologic effects.[18] A 400-mg dose of ibuprofen has similar analgesic efficacy to 10 mg of intramuscular morphine.[42] After major surgery, nonselective NSAIDs and COX-2 inhibitors were shown to decrease opioid consumption, and nonselective NSAIDs also reduced nausea and vomiting.[43] Dual treatment with APAP and an NSAID provides more effective postoperative analgesia than either alone.[44]

Nonsteroidal anti-inflammatory drug formulations include tablets, capsules, and suspensions to allow for oral and feeding-tube administration and parenteral solutions for intravenous or intramuscular injection. Nonsteroidal anti-inflammatory drugs have an analgesic ceiling; doses exceeding 400 mg of orally administered ibuprofen and 10 mg of intravenously administered ketorolac do not provide enhanced analgesia, but their anti-inflammatory properties increase up to the maximum doses limited by safety.[45,46]

Nonsteroidal anti-inflammatory drugs have many pharmacokinetic similarities, including

Table 2: Selected Nonsteroidal Anti-Inflammatory Drug Dosing for Adults[a]

Population	Dosing Schedule	Maximum Single Dose	Maximum Daily Dose
Ibuprofen			
Adults	400 to 800 mg IV every 6 h	800 mg	3200 mg
	400 mg orally every 4-6 h	800 mg	2400 mg
Ketorolac			
Patients <65 years of age	30 mg IM/IV every 6 h, not to exceed 5 days of treatment	60 mg IM 30 mg IV	120 mg
Patients ≥65 years of age, renally impaired and/or weight <50 kg	15 mg IM/IV every 6 h, not to exceed 5 days of treatment	30 mg IM 15 mg IV	60 mg

Abbreviations: IM, intramuscular; IV, intravenous.

[a]Data were derived from Woolf and Salter[5] and the ketorolac prescribing information.[47]

that most are well absorbed from the gastrointestinal tract. Some NSAIDs, such as naproxen, celecoxib, and meloxicam, have a prolonged half-life, allowing for once or twice daily dosing, whereas others, such as ibuprofen, diclofenac, and ketorolac, are more rapidly eliminated, requiring shorter dosing intervals. Most NSAIDs are extensively hepatically metabolized, with the exception of ketorolac, of which 60% is excreted in the urine as unchanged drug and requires dose reduction or avoidance in patients with renal dysfunction.[47] Suggested dosing regimens for ibuprofen and ketorolac are listed in Table 2.

Adverse Effects. Adverse effects of NSAIDs are dose related and reflect physiologic consequences of prostaglandin inhibition based on selectivity for the COX-1 or 2 enzymes. Cyclooxygenase-1 inhibition can cause platelet dysfunction, increase the risk of bleeding and adverse gastrointestinal effects, reduce renal blood flow, and increase the risk of acute kidney injury.[48] Cyclooxygenase-2 inhibition can increase the risk of atherothrombosis and decrease cardiomyocyte protection against arrhythmias and oxidative injury—increasing the risk of heart failure.[48] Cyclooxygenase-2 inhibition can also decrease renal blood flow, cause sodium and water retention, vasoconstriction, and elevated blood pressure, thus increasing long-term risk of cardiovascular disease and progression of chronic kidney disease.[48] Increased risks of surgical-related bleeding compared with placebo (2.4% vs 0.4%) and anastomotic leak after colorectal surgery (odds ratio, 1.79, 95% confidence interval, 1.47-2.18) were observed with nonselective NSAIDs, but not COX-2 inhibitors.[49,50]

Considerations for Use in Select Populations. Safe use of NSAIDs in critically ill trauma patients will depend on individualized assessment of a patient's risk of gastrointestinal hemorrhage, platelet dysfunction, and renal injury in the context of other risk factors, injuries, surgeries, and premorbid disease states. Nonsteroidal anti-inflammatory drugs should generally be avoided in patients with significant or acute renal dysfunction, history of or multiple risk factors for gastrointestinal bleeding, hypocoagulable states, surgeries with high risk of bleeding, uncontrolled blood pressure, congestive heart failure, cirrhosis, or asthma.[51] Celecoxib may be safer in patients with asthma; however, initiation and ongoing treatment should be monitored because case reports exist of increased exacerbations.[52] Use of celecoxib or coadministration of nonselective NSAIDs with a proton pump inhibitor or high-dose histamine-2 receptor antagonist can reduce the risk of NSAID-related duodenal and gastric ulcers.[53,54] After a fracture, COX-2 mediates local release of prostaglandins that promote bone healing.[55] In the setting of fracture, high-quality and consistent evidence regarding the impact of NSAIDs on bone healing is lacking. Although NSAID exposure has been associated with delayed or nonunion bone healing, subgroup analysis suggests short courses or low doses mitigate this risk.[56]

Gabapentinoids

Mechanism of Action. Gabapentin and pregabalin are gabapentinoids that are structurally similar γ-aminobutyric acid analogues with antiepileptic, analgesic, and anxiolytic

effects.[57,58] Although the mechanism is not fully understood, gabapentinoids do not bind to γ-aminobutyric acid receptors, nor do they increase γ-aminobutyric acid.[58] Analgesia is mediated primarily through signal interruption in the spinal cord by gabapentinoids' binding to the α_2-δ subunit of calcium channels in the central nervous system, preventing release of pronociceptive neurotransmitters. Gabapentinoids may also act on descending noradrenergic and serotonergic pathways to modulate transmission of pain signals in the spinal cord.[58-60] Analgesia in the perioperative setting may result from reduction in pronociceptive neurotransmitters that mitigate some of the neuronal hyperexcitability induced by trauma.[61]

Medication Use and Characteristics. Gabapentinoids have an established role in neuropathic pain and are recommended for use in patients with conditions causing this pain who are critically ill.[18] Gabapentin reduces pain and improves sleep in patients with traumatic nerve injury pain.[62] Their role in treatment of acute perioperative pain has been increasing in recent years and current guidelines recommend clinicians consider gabapentinoid use in this setting.[17] Several meta-analyses have demonstrated that preoperative administration of gabapentinoids may reduce opioid consumption and reduce pain scores.[63] Larger preoperative doses (≥150 mg of pregabalin and ≥600-900 mg of gabapentin) may be more effective in this setting, but they also carry higher risks of adverse effects.[64,65] Decreased opioid consumption and pain scores have also been observed with postoperative administration of gabapentinoids, but their benefit as a component of ongoing multimodal analgesia has not been seen in the absence of neuropathic pain.[66-68]

Gabapentin and pregabalin have pharmacokinetic similarities but also important differences. Gabapentinoids are only available in dosage forms for oral or feeding-tube administration. Gabapentin absorption is slow and limited to the small intestine, with a peak concentration at 3 hours. Gabapentin exhibits saturable absorption, with somewhat unpredictable bioavailability that decreases from 80% after a 100-mg dose to 27% after 1600 mg.[69] Pregabalin is absorbed from the small intestine and proximal colon with 90% bioavailability; peak plasma concentrations occur 1.5 hours post dose and demonstrate a linear increase as the dose increases.[60]

Adverse Effects and Considerations for Use in Select Populations. Both gabapentin and pregabalin are extensively cleared by the kidney, necessitating dose reduction in patients with renal dysfunction. Adverse effects are usually dose-related, including dizziness, drowsiness, and respiratory depression. Abrupt discontinuation can result in withdrawal symptoms, including seizure.[51]

Ketamine

Mechanism of Action. Ketamine is a phencyclidine derivative that exerts dose-related analgesic and dissociative anesthetic effects by preventing amplification of pain signals, development of central sensitization, and opioid tolerance. Whereas at low doses ketamine primarily acts as an *N*-methyl-D-aspartate antagonist, at higher doses it has activity at several other sites, including acetylcholine, opioid, serotonin, dopamine, and norepinephrine receptors, as well as voltage-sensitive sodium channels.[70] Ketamine also acts as an anti-inflammatory agent by reducing the production of excess proinflammatory cytokines.[71]

Medication Use and Characteristics. Ketamine is recommended by current guidelines for management of acute pain in critically ill postsurgical patients as an adjunct to opioid therapy and in acute postoperative pain as part of a multimodal regimen.[17,18] Available literature to guide use in critically ill trauma patients comes from single-center retrospective trials. In a trauma ICU population with a high rate of substance abuse, the addition of ketamine as an adjunct for sedation and analgesia resulted in significantly reduced cumulative opioid and propofol doses but increased administration of ziprasidone and dexmedetomidine.[72] In a mixed medical-surgical ICU, the addition of a low-dose ketamine infusion decreased delirium but did not change opiate consumption or ICU length of stay.[73] In trauma ICU patients with rib fractures, low-dose ketamine infusion (0.1 mg/kg per hour) reduced pain scores and opioid requirements but not length of stay.[74] In adult and elderly patients with multiple rib fractures, low-dose ketamine infusion (2-2.5 μg/kg per minute) decreased opioid consumption in patients with an Injury Severity Score greater than 15 but did not decrease pain scores overall.[75,76]

Ketamine is available as a solution for injection that can be given as an intravenous push, infusion, or intramuscular injection. Onset is

within 1 minute for intravenous administration and approximately 10 minutes for intramuscular administration. Given as an intravenously administered bolus, low-dose ketamine (0.3 mg/kg) induces a significant analgesic effect within 5 minutes and provides a moderate reduction in pain for 2 hours.[77] Ketamine is metabolized by the liver to norketamine, an active metabolite with approximately one-third of ketamine's potency.[78]

Adverse Effects. Adverse effects of ketamine include excess salivation, dose-dependent cardiovascular effects (eg, hypertension, tachycardia, arrhythmia) that can be severe, and psychiatric effects such as emergence reactions and hallucinations.[78] Although data are lacking regarding the incidence and management of emergence phenomena in critically ill patients administered ketamine, emergence reactions have been suggested to occur with a reduced frequency with subanesthetic analgesic doses and have been successfully treated by administration of benzodiazepines in chronic pain and procedural sedation settings.[79-81] Ketamine should be avoided in patients who cannot tolerate elevations in blood pressure or heart rate, based on medical history, physiologic findings, or disease processes.

Central α_2 Agonists

Mechanism of Action. Clonidine and dexmedetomidine are α_2 agonists that act on presynaptic receptors in the central nervous system to produce sympatholysis, sedation, and analgesia. Analgesia is thought to be mediated through agonism of receptors located in the dorsal horn of the spinal column that reduce pain signaling and substance P release.[82] Dexmedetomidine is more selective than clonidine, with relative receptor specificity of 1620:1 and 200:1, respectively, for α_2 to α_1.[83] The α_2 agonists lack respiratory depressive and amnestic properties.

Medication Use and Characteristics. Central α_2 agonists are used as adjuncts in the management of perioperative pain. In surgical patients, both clonidine and dexmetatomidine are opioid sparing, reduce early nausea, and decrease pain intensity at 24 hours, but these medications also increase the risk of bradycardia and hypotension.[84] As part of a sedation regimen for patients in the ICU, dexmedetomidine reduced opioids by more than 50% and increased bradycardia but not cardiovascular adverse events.[85]

The most commonly used dosage forms of clonidine are a tablet and patch. The tablets are almost completely absorbed with peak concentrations at 2 to 5 hours post dose with a half-life of approximately 16 hours. The patch has approximately 60% bioavailability and produces therapeutic plasma levels 48 to 72 hours after application that persist for 8 hours after removal and then slowly decline over several days.[86] Dexmedetomidine is administered by continuous intravenous infusion, with or without an initial bolus, because of its rapid onset and short half-life.

Adverse Effects. Adverse effects are dose dependent and, as noted, include bradycardia and hypotension. In patients who are volume depleted, hemodynamically unstable, or have a history of bradyarrhythmia, α_2 agonists should be avoided or used cautiously. Rapid withdrawal after prolonged administration, especially of high doses, can result in significant tachycardia and hypertension. Strategies to mitigate the development of and to manage dexmetatomidine dependence include using the lowest adequate dose for the shortest time necessary, gradual dose reductions, and use of clonidine to wean.[87]

Lidocaine

Mechanism of Action. Lidocaine, an aminoamide anesthetic and a class 1b antiarrhythmic agent, acts as an antagonist at voltage-gated sodium channels that enable initiation and transmission of action potentials in excitable membranes involved in both neuropathic and inflammatory pain. Intravenously administered lidocaine suppresses ectopic action potentials in damaged nerves at a dose lower than that required to inhibit impulses of those that are not injured.[88] It also reduces levels of circulating anti-inflammatory cytokines. Lidocaine has become a common component of perioperative pain control regimens, most commonly in the form of patches but also as an intravenously administered bolus followed by infusion for select patients.

Medication Use and Characteristics. The role of lidocaine in management of acute pain in the ICU has not been established. Intravenously administered lidocaine is not routinely recommended as an adjunct to opioid therapy for analgesia in critically ill adults because of concerns that risks of toxicity outweigh potential benefits in this population.[18] A small study to evaluate its safety and efficacy as an analgesia

adjunct in the ICU demonstrated a reduction in pain scores of 20% from baseline in 3.3 hours (no loading dose was administered) and a decrease in opioid need by approximately two-thirds after initiation of the lidocaine infusion.[89] Another small placebo-controlled study of patients admitted to the ICU after cardiac surgery demonstrated that a bolus and 48-hour lidocaine infusion did not affect self-reported pain scores, time to extubation, cumulative postoperative opioid or sedative dose, or length of ICU or hospital stay.[90] Lidocaine patches may be considered for neuropathic or well-localized pain. In hospitalized trauma patients with rib fractures, lidocaine 5% patches decreased pain scores when compared with no patch but not when compared with a placebo patch; lidocaine 5% patches have not been shown to reduce opioid use or time to return to baseline activity.[91,92]

Lidocaine is available in many dosage forms. For acute pain in hospitalized patients, it is most commonly administered intravenously as a bolus or infusion and as patches for topical application. In healthy adults, application of up to 4 lidocaine 5% patches results in peak drug concentrations between 6 and 10 hours and, even when left in place for 24 hours, drug concentrations average less than 200 ng/mL, which is significantly below thresholds for toxicity or antiarrhythmic efficacy.[93] The onset of analgesia for intravenously administered lidocaine is within 2 minutes, and the drug has a half-life of 1.5 to 2 hours in healthy adults but is prolonged in patients with congestive heart failure, liver disease, shock states, severe renal disease, or concomitant treatment with medications that inhibit metabolism through cytochrome P450 1A2 or 3A4.[94]

Less than 10% of lidocaine is excreted unchanged in the urine and is otherwise extensively metabolized by the liver to active metabolites that are renally cleared. Lidocaine and its active metabolites can accumulate in the setting of prolonged intravenous administration, higher doses, or organ dysfunction. Administration for longer than 24 hours can decrease the clearance rate of lidocaine; dose reduction, if continued beyond 24 hours, is recommended to avoid toxicity.[95] Lidocaine patches can be cut to a smaller size as needed but should not be applied to broken or inflamed skin.[96]

Adverse Effects. Although the patches are generally well tolerated, they can cause transient local application site reactions. Adverse effects of intravenously administered lidocaine range from mild to severe and include neurologic (eg, perioral tingling, nystagmus, confusion, agitation, drowsiness, seizure) and cardiovascular (eg, heart block, dysrhythmias, cardiovascular collapse) effects, especially when plasma levels exceed 5 to 6 μg/mL.[94] Because of the complexities of dosing and severe implications of toxicity, use of intravenously administered lidocaine for acute pain should not be routine in critically ill trauma patients. Lidocaine is contraindicated in patients with Adam-Stokes and Wolff-Parkinson-White syndromes and severe heart block without a functioning pacemaker.

Complementary Therapies for Pain Management

Complementary therapies can be considered part of a multimodal strategy to effectively manage pain in select patients on acute and critical care trauma units. There is an increased demand for complementary therapies for pain management by health care professionals and patients.[97] Acupuncture, virtual reality (VR), and mirror therapy (MT) are examples of complementary therapies that may be implemented in addition to the pharmacologic interventions for treatment of acute and postoperative pain in appropriate patients on critical care and intermediate care trauma units.

Acupuncture

Acupuncture is an ancient Chinese medicine technique in which hair-thin needles are inserted into distinct points on the body, and the needles are then manipulated at acupoints or meridian points.[97] The goal is to achieve balance in *qi*—the body's energy force.[97,98] The *qi* travels along meridian points or channels between organs, and the appropriate amount and quality of energy must be provided for health to remain balanced.[97,98] In addition, electrical stimulation of the needles, known as electroacupuncture, can be used.[97] It is thought that analgesic properties of acupuncture involve stimulation of endogenous opioids such as endorphins and enkephalins.[98]

Acupuncture Support From Postoperative Pain Studies. A systematic review of 15 randomized control trials (RCTs) showed that patients who received acupuncture, compared with sham acupuncture, had significantly less postoperative pain, measured with a visual analog scale at 8 and 72 hours. There also

was a significant decrease in opioid use among patients who received acupuncture when compared with the control group at 8, 24, and 72 hours postoperatively.[99] Furthermore, the group treated with acupuncture was associated with fewer opioid-related adverse effects (ie, nausea, pruritus, dizziness, sedation, urine retention).[99]

The efficacy of acupuncture was analyzed in a systematic review and meta-analysis. The authors found that postoperative patients who received acupuncture (ie, traditional, electroacupuncture, or transcutaneous electric acupoint stimulation) had less pain and decreased opioid use 1 day after surgery compared with patients in the control group. Subgroup analysis indicated treatment with conventional acupuncture was associated with less pain on postoperative day 1 compared with pain reported in a control group, yet similar amounts of opioids were used by both groups. Those who received electroacupuncture had no significant difference in pain scores or in the cumulative amount of opioids used on postoperative day 1 compared with those in the control group.[100] Multiple systematic reviews with meta-analyses have shown acupuncture to be effective for decreasing postoperative pain, which is advantageous because many trauma patients will require surgery.[99-102] In a meta-analysis of 39 RCTs (n = 2391 patients), moderate-certainty evidence demonstrated that acupuncture significantly delayed opioid use, and low-certainty evidence showed that acupuncture reduced pain for patients after knee arthroplasty.[102] Although the evidence reviewed was not specific to trauma patients, the potential benefits of decreased pain, opioid use, and opioid-related side effects (eg, nausea, dizziness, pruritis, sedation) suggest acupuncture may be an effective complementary therapy for those with injury, although strong supporting research is needed.

Acupuncture Support in Traumatic Injuries. Somatic pain in trauma patients often occurs from a fracture or musculoskeletal injury, is well localized, and is often described as aching, sharp, or stabbing.[103] Pain from rib fractures remains difficult to treat, and techniques such as regional or neuraxial analgesia are not always feasible because of additional injuries, anticoagulants, or hemodynamic instability. An RCT was performed to evaluate the efficacy and efficiency of acupuncture for relieving acute pain in patients hospitalized with rib fractures. Those treated with acupuncture using filiform needles, in addition to receiving conventional analgesics, reported less pain intensity, which lasted over 6 hours in most patients during coughing, deep breathing, and turning, than did the control group treated with thumbtack intradermal needles and identical analgesics doses ($P < .05$).[104]

Patients with traumatic brain injury commonly report headaches; among military personnel, the prevalence of recurrent or chronic headaches is 80%.[105] When veterans with mild to moderate traumatic brain injury in outpatient settings were randomly assigned to receive traditional Chinese acupuncture, auricular acupuncture, or usual care, there was a significant decrease in mean Headache Impact Test scores from baseline to week 6 in those treated with acupuncture compared with a slight increase in the usual care group.[105] In addition, using a numeric rating scale, pain scores significantly decreased from baseline to week 6 in those treated with traditional Chinese acupuncture or auricular acupuncture when compared with usual care.[105] The traditional Chinese acupuncture and the auricular acupuncture groups demonstrated greater improvement in headache-related quality of life than those treated with usual care.[105] With such positive results, studies evaluating use of acupuncture for treatment of acute headache pain in hospitalized patients with traumatic brain injury should be considered.

Acupuncture Support in the ICU. A feasibility and acceptability study for use of acupuncture to relieve pain (and nausea) in a 20-bed, medical-surgical ICU showed favorable outcomes although 32% of the 576 patients admitted to the ICU were deemed eligible for the treatment and only 42% of those eligible (8% of total) received at least 1 acupuncture session. Average self-reported pain scores after acupuncture treatment decreased from scores obtained just before treatment by 2.56 points on day 1, 2.36 points on day 2, and 1.98 points on day 3 ($P < .05$). Furthermore, there was a decrease in the mean morphine dose measured 4 hours post treatment on days 1 through 3 ($P < .05$). No adverse events occurred during treatment, but 2 patients did experience side effects (ie, pain at needle insertion site, agitation during treatment).[106]

Potential side effects of acupuncture include pruritis at the insertion site, needling pain, hematoma, and bleeding.[107] Serious adverse events of acupuncture are infection, acute

hypertensive or hypotensive crisis, erysipelas, asthma attack, aggravation of suicidal thoughts, and pneumothorax.[99,107] The rate of adverse events for acupuncture is typically low when training is appropriate and substantially lower than for many drugs or procedures used to treat pain. However, acute and critically ill trauma patients may be coagulopathic; therefore, it is important to understand the risks, know when therapy might be contraindicated, and continuously assess for these complications if acupuncture is provided.

Although many practitioners may support the use of acupuncture in the hospital setting, evidence on the use of acupuncture for treating pain in the acute and critically ill trauma patient is limited. Thus more research from large, well-powered RCTs is needed to validate the benefits of acupuncture for this population.

Virtual Reality

Distraction and immersion techniques for acute pain management include VR, music therapy, movies, and video games. For almost 2 decades, VR has provided immersive, multisensory distraction for hospitalized patients with acute pain.[108] Virtual reality is thought to alleviate pain by diverting conscious attention and enabling immersion into the computer-generated world, thereby making less attention available for incoming pain signals.[109] Thus, this nonpharmacologic therapy modifies the individual's visual, auditory, and proprioception senses by limiting the nociceptive stimuli reception.[110] As technology continues to evolve, VR has become portable, with less expensive hardware and software; likewise, there is more digital content, which may increase the use of VR as an adjunct or complementary therapy for pain relief.[111] Virtual reality has been widely used for pain control in burn and postoperative patients and in various other patient populations for the treatment of anxiety, pain control, and rehabilitation support.[110,112-114]

In a case report, researchers evaluated VR's effect on procedural pain during physical therapy for a 32-year-old man with upper and lower extremity injuries who was hospitalized after being hit as a pedestrian by a semitruck.[115] The patient received 10 minutes of passive range of motion exercises by nursing staff with no distraction and 10 minutes of passive range of motion exercises with VR. On a 0-to-10 pain scale, there was a decrease from a mean pain score of 8.5 (severe pain) during passive range of motion exercises without distraction to a mean score of 4 (mild/moderate pain) during such exercises with VR.[115]

Researchers at Cedars-Sinai Medical Center compared the effects on pain in hospitalized patients of viewing a 3-dimensional passive range-of-motion exercises experience with a headset with those of viewing a 2-dimensional distraction video. Although both groups (n = 50 patients each) had a significant drop in postintervention pain scores (VR group: pre-VR and post-VR pain scores, 5.4 and 4.1, respectively; $P < .001$; video group: preintervention and postintervention pain scores, 5.4 and 4.8, respectively; $P < .001$), the VR group had a 24% reduction in pain compared with 13.2% in the video group.[110] Mean pain reduction was significantly greater in the VR group than in the control video cohort ($P = .008$), and a greater proportion of patients achieved a pain response in the VR cohort (65%) compared with the control group (40%; $P < .01$; number needed to treat = 4). No adverse events were reported with use of VR.[110] Although this study lacked randomization, the researchers still demonstrated benefits of VR as a safe and effective adjunctive therapy for pain management within a diverse group of patients hospitalized in an acute setting. In a follow-up study, researchers conducted a prospective, randomized, comparative effectiveness trial (N = 120) to compare pain scores of hospitalized patients who received VR administered with a headset with pain scores of patients who received a control intervention (ie, viewing in-room health and wellness television programs). Again, results showed that compared with patients in the television control group, patients in the VR group experienced a significant decrease in pain scores ($P < .04$). In a subgroup with severe pain at baseline, the effect of VR was more pronounced than in the control group. Despite beneficial effects of VR in reducing pain scores, there was no difference in the amount of opioids used between the 2 groups before or after interventions. Patients who received VR were significantly more satisfied with their audiovisual experience than those who viewed the television programs.[116]

Results of studies in hospitalized patients suggest VR is a safe adjunctive therapy for managing pain in acute inpatient settings, although consideration should be given to potential adverse effects.[110,116] Potential side

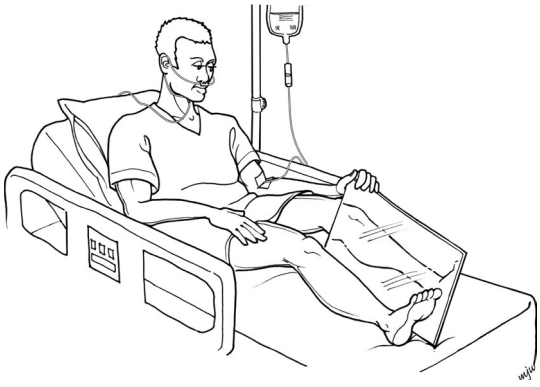

Figure: Mirror therapy for a patient with a left leg below-the-knee amputation. The reflection of his left leg (which looks like his right leg) is viewed in the mirror. Illustrated by Mark J. Wieber, MA, RN, CNOR. Reprinted with permission.

effects of VR include dizziness, nausea, vomiting, and motion sickness. Likewise, patients with a history of motion sickness, vertigo, dementia, stroke, and epilepsy should not receive VR. Although study authors suggest VR can be an effective adjunct in managing pain, more research is needed to validate effectiveness of VR as a complementary therapy for trauma patients in ICU and IMCU settings.

Mirror Therapy

In the United States, the majority of amputations are due to nontraumatic causes like diabetes, peripheral artery disease, and cancer. Meanwhile, almost half of amputations result from trauma, with traumatic limb loss occurring most commonly from industrial incidents, vehicular crashes, and gun violence.[117] Patients are at risk for development of postamputation pain that includes residual limb pain and phantom limb pain (PLP). Postamputation pain is defined as acute if it resolves in 2 months and chronic if it persists for longer than 3 months. Residual limb pain is pain at the stump site, surgical site, or proximal extremity; occurs most commonly in the acute postoperative setting; and tends to improve over time.[118] Phantom limb pain will develop in approximately 50% and up to 80% of amputees, and it can occur up to 6 months after amputation and last for several years.[119,120] Although PLP is usually localized and distal to the amputation site, it has a later onset and typically becomes chronic. Phantom sensations are nonpainful perceptions that the amputated limb is still intact and phantom limb movement is the nonpainful feeling of the amputated limb in motion. The aforementioned pain and sensory perceptions are common among patients with limb loss and can occur simultaneously or independent of each other. Patients can experience all, some, or none of these phenomena. Phantom pain and sensations are described by patients as burning, aching, stabbing, tingling, cramping, itching, vice-like, electric shocks, and warm or cold.[118,121] It is hypothesized that reorganization of the somatosensory cortex is what causes PLP and sensations to be stimulated.[118]

Mirror therapy is another complementary therapy that can be used by amputees to reduce or eliminate pain due to traumatic limb loss. Mirror therapy is performed by placing a mirror parasagitally on the affected side, allowing the intact limb to be viewed in the reflection of the mirror (Figure). While visualizing the movement of the intact limb in the mirror, the patient perceives the amputated limb as being intact and able to obey commands from the brain.[121] Hence, it is postulated that MT reverses the maladaptive plasticity within the sensorimotor cortex and reduces pain by improving the mobility of the phantom limb.[122,123] Magnetic resonance imaging has been used to show the correlation of phantom pain with the degree of maladaptive reorganization of somatosensory pathways and the ability of MT to reverse the reorganization with a consequent pain reduction.[119]

Ramachandran[124] first used MT in 1993 for a patient with upper limb amputation and continuous PLP for the preceding 11 years, who, after treatment, had almost complete resolution of pain. In 1996 Ramachandran and Rogers-Ramachandran[125] were the first to investigate the use of VR mirror box treatments for PLP so patients could have control over limb paralysis (learned paralysis) and spasm sensation (learned pain). By using visual feedback with MT, patients gained more control over phantom limb paralysis and spasms. In a case report, a 28-year-old woman involved in a motor vehicle crash sustained a traumatic transhumeral amputation of her dominant right arm and began experiencing PLP.[121] Three and half months after the injury, the patient received instruction on MT and was provided online counseling and support for 28 days to treat persistent PLP.[121] The patient kept a diary and recorded

pain intensity; the diary showed her average pain score decreased by 1.15 points on a numeric pain scale (4.57 to 3.42) after the second week of MT use and by 1.57 points in the third and the fourth weeks after the treatment. Similarly, in a literature review on use of MT to treat PLP, significant improvements in visual analog scale scores after MT were reported in multiple studies.[122] Likewise, Chan et al[126] reported similar findings when they assigned patients with amputations at a military medical center to 1 of 3 treatment groups (MT vs covered mirror vs mental visualization). The MT group was the only group to have 100% of patients report decreased pain after 4 weeks of treatment. Authors of a systematic review found that the current level of evidence cannot justify MT as first-line treatment for PLP, and they suggested additional research should consist of RCTs to analyze MT effects on pain alleviation and on integration of prosthetic limb use.[127] Also, large, high-powered RCTs are needed to evaluate the efficacy of MT as a complementary therapy in IMCU and ICU settings and determine which patients benefit most from the intervention.

Potential barriers to MT may include a patient's inability or unwillingness to acknowledge limb loss/amputation and participate in nonpharmacological interventions to alleviate PLP.[128,129] Sometimes MT has been reported to worsen PLP or phantom sensations. Performing MT may aggravate a depressive syndrome or trigger feelings of grief, guilt, anxiety, or posttraumatic stress disorder; thus, providing emotional support via counseling, support groups, family, and/or friends may be helpful. Although MT is safe, economical, practical, and easy for nurses to teach, studies done in high-acuity units are lacking and needed to verify the effectiveness of this complementary therapy in high-acuity trauma settings.[126]

Importance of Pain Assessment

To determine the need for analgesia and to evaluate the effectiveness of any intervention to treat pain, a valid and reliable measure of pain should be used in all acute and critically ill trauma patients.[97,130] The recommendation of the Society for Critical Care Medicine is that patients who are able to communicate should self-report their pain using a verbal or visual 0-to-10 numeric rating scale.[6] When unable to obtain a patient's self-report, a valid and reliable observational behavioral and physiological pain assessment should be performed and 2 tools—the Behavioral Pain Scale and the Critical-Care Pain Observation Tool—are currently recommended for use in critically ill adults.[6] The Behavioral Pain Scale consists of 3 subscales that are assessed and scored by nurses: facial expression, movement of the upper limbs, and compliance with mechanical ventilatory support.[130] The Critical-Care Pain Observation Tool is used to assess and score observed behaviors in 4 subscales: facial expression, body movements, muscle tension, and either compliance with mechanical ventilatory support or vocalization for extubated patients.[131,132] When adequate pain assessments are not performed in critically ill patients, pain management is adversely affected.[133] Once identified, pain in trauma patients should be managed using a multimodal approach consisting of pharmacologic and nonpharmacologic interventions aligned to improve physical healing and well-being.

Multimodal Analgesic Practices in Acute and Critical Care

Multimodal analgesia combines opioid and nonopioid drugs, as well as complementary therapy, with different mechanisms of action that work synergistically to treat pain. The goal of multimodal analgesia is to limit opioid exposure and risks without sacrificing patient comfort or rehabilitation.[10,134] This strategy is particularly useful for patients who are opioid dependent and/or opioid tolerant. Multimodal analgesic regimens should be individualized to the patient and the type of pain; mechanism of pain (inflammatory or neuropathic); type of injury; and any surgical procedure, location of pain, expected duration of pain, and abilities and preferences of the patient should be considered.[134] The American Pain Society published guidelines in 2016 for the management of postoperative pain and recommended administering around-the-clock nonopioid analgesics and nonpharmacologic therapies.[17] Guidelines from the Society for Critical Care Medicine for the prevention and management of pain in the ICU acknowledge that opioids are the mainstay for pain management in most ICU settings, but a multimodal analgesia approach is supported that minimizes opioids and sedatives while optimizing pain control. Consideration should be given to drug effectiveness, dose, and duration when multimodal strategies are being evaluated.[6]

Additional interventions that can be considered in a multimodal pain management plan may include patient-controlled analgesia, regional nerve blocks, and epidural-administered analgesia, which are beyond the scope of this article.[135] Last, clinicians may opt to add complementary therapy to a multimodal regimen, considering patient preferences for nonpharmacologic treatment, patients' ability to tolerate and participate in the treatment, and potential safety considerations and risks associated with treatment.

Summary

Pain management in acute and critically ill trauma patients is challenging. Consistent pain assessments using valid and reliable tools are essential to identify pain and evaluate effectiveness of analgesic interventions in acute and critically ill trauma patients. A multimodal analgesic regimen is encouraged to effectively treat pain. In this article, we have provided a review of nonopioid pharmacologic medications and examples of complementary therapies that can be considered in addition to opioids for pain management in trauma patients. Integrating nonopioid drugs and complementary therapies may not only aid in achieving pain relief but can help minimize the use and potential complications of opioids.

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