The evolution of pain management in the critically ill trauma patient: Emerging concepts from the global war on terrorism

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Background: **The evolution of military medical care to manage polytrauma, critically ill-wounded warriors from the greater war on terrorism has been accompanied by significant changes in the diagnosis, management, and modulation of acute and chronic trauma-related pain. A paradigm shift in pain management includes early treatment of pain at the point of injury and throughout the continuum of care with a combination of standard and novel therapeutic interventions. These concepts are important for all critical care providers because they translate to most critically ill patients, including those resulting from natural disasters. Previous authors have reported a high incidence of moderate to severe pain and poor analgesia in intensive care units associated with sleep disturbances, tachycardia, pulmonary complications, increased stress response with thromboembolic incidents, and immunosuppression, increased intensive care unit and hospital stays, and needless suffering. Although opioids have traditionally been the cornerstone of acute pain management, they have potential negative effects ranging from sedation, confusion, respiratory depression, nausea, ileus, constipation, tolerance, opioid-induced hyperalgesia as well as potential for immunosuppression. Alternatively, multimodal therapy is increasingly recognized as a critical pain management approach, especially when combined with early nutrition and ambulation, designed to improve functional recovery and decrease chronic pain conditions.**

Discussion: **Multimodal therapy encompasses a wide range of procedures and medications, including regional analgesia with continuous epidural or peripheral nerve block infusions, judicious opioids, acetaminophen, anti-inflammatory agents, anticonvulsants, ketamine, clonidine, mexiletine, antidepressants, and anxiolytics as options to treat or modulate pain at various sites of action.**

Summary: **With a more aggressive acute pain management strategy, the military has decreased acute and chronic pain conditions, which may have application in the civilian sector as well. (Crit Care Med 2008; 36[Suppl.]:S346–S357)**

KEY WORDS: acute pain management; multimodal analgesia; regional analgesia; regional anesthesia; critical care analgesia

Trauma-related pain is a natural consequence of injury and the subsequent surgical management of combat-related injuries. The global war on terrorism (GWOT) has resulted in severe polytrauma injuries ranging from traumatic brain injury, pulmonary contusion, multiple amputations, oral maxillofacial fractures, soft tissue destruction, multiple long bone fractures, and vascular injuries. Despite the profound degree of injury, the U.S. military has developed improvements in combat casualty care that have improved the percentage of immediate deaths among all seriously injured, the killed-in-action rate, to an unprecedented 14% (1). Increased numbers of critically injured patients are surviving to reach definitive medical care, which may explain why the died-of-wounds rate, the percentage of deaths after admission to a medical treatment facility among all seriously injured, has increased slightly compared with historic averages. The evolution of military medical care to manage these severely injured cases has also been accompanied by significant changes in the diagnosis, management, and modulation of both acute and chronic trauma-related pain.

Changes in pain management include the articulation of the importance of pain management, specifically to decrease or modulate the potent inflammatory response resulting in hypercoagulability, multiorgan dysfunction, systemic inflammatory response, acute lung injury, traumatic brain injury, depression, and posttraumatic stress disorder. It is important to note that the stress response after trauma is greater than the stress response after elective surgery (2–4). A paradigm shift in pain management includes early treatment of pain at the point of injury (even in the austere environment) and throughout the continuum of care with both combinations of standard and novel therapeutic interventions. This article outlines the emerging experience, concepts, importance, and rationale for the identification and treatment of acute pain from trauma as well as detailing evolving thoughts on the therapeutic techniques to treat pain and improve outcomes in critically ill patients. These concepts are potentially valuable for all critical care providers because they not only translate to other critically ill patients, but they are also tools that may be necessary to manage critically ill trauma patients in national disasters. In general, the principles of pain control in a challenging environment are similar to medical care in other challenging environments. Standard care is maintained (for example, hand hygiene, head of bed ele-

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Dr. Malchow has received a consultancy fee from SonoSite Inc. (Bothell, WA) and meeting travel costs from Sorenson Medical (West Jordan, UT). Dr. Black has not disclosed any potential conflicts of interest.

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DOI: 10.1097/CCM.0b013e31817e2fc9

vation, patient-controlled analgesia [PCA]), whereas advanced techniques are moved as close to the front lines as possible (for example, advanced ventilators, peripheral nerve catheters) and innovation is used wherever possible.

Background

The Society of Critical Care Medicine has published clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult (5). In addition to the obvious beneficence and nonmaleficence that mandate pain control, there is a multitude of physiological and psychologic reasons to provide analgesia to critically ill patients. The same rationale applies to military trauma and critical care systems, although the logistic challenges, the severity of injuries, and some of the solutions used by the military differ from their civilian counterparts. The casualties in the GWOT have highlighted the deficits in the pain management of combat-related trauma and the lack of standard approaches for pain management of the critically ill. For example, one author noted that over 80% of American casualties were transported from Baghdad to Germany with uncontrolled pain defined by a numeric rating score >5 (C. Buckenmaier, personal communication, 2006). This severity of the problem was recognized by the passage of the Veterans Pain Act of 2007, whereby Congress found pain a leading cause of short-term and long-term disability among veterans. At one hospital, 89% of returning veterans who had sustained polytrauma injuries experienced pain with a mean numeric rating score pain score of 4.6 (6). Interestingly, despite the austere nature of combat trauma, several authors have noted similar deficits in pain control nationally and in state-of-the-art intensive care units (ICUs). Other studies also highlight the high incidence of pain in the ICU setting (7) and the inadequate attention given to ameliorating pain (7, 8). Rotondi et al. reported that 87% of postventilated patients recalled moderate to extreme levels of pain (9). Whipple reported 74% of multitrauma patients in intensive care units received poor analgesia and rated their pain intensity as moderate to severe (10). Pain from routine care, including turning, wound care, and tracheal suctioning, also was a significant source of pain (11). Even when pain is treated in the ICU, analgesia is administered without adequate assessment. In one recent study, 90% of ICU patients were treated with opioids, whereas only 42% were assessed for pain (12). In addition, procedural analgesics and nonopioid adjuncts were only used approximately one third of the time (12).

Despite the high degree of pain encountered in the ICU, the reluctance to treat pain is understandable and multifactorial. Intensivists receive little training in acute pain management despite the American Council on Graduate Medical Education mandating that during fellowship there be a multidisciplinary educational experience in pain management. However, this training is variable and rarely occurs formally. Additionally, analgesia is commonly (and in some cases erroneously) associated with adverse effects, including hypotension, respiratory depression, ileus, delayed ventilator weaning, increased mechanical ventilator days, increased ICU length of stay, and depressed neurologic status. There are even some data that the focus on pain control may contribute to preventable deaths from overdoses of pain medications (13).

Benefits of Acute Pain Management

Studies demonstrate that adequate analgesia is associated with improved outcomes, whereas inadequate analgesia is associated with adverse outcomes. Unfortunately, randomized, controlled studies with long-term outcomes are lacking (14–18). Table 1 outlines the adverse outcomes associated with inadequate pain control, including strong associations with thromboembolic incidents (19, 20), pulmonary complications (21), increased ICU or hospital time (22), and needless suffering. Improved analgesia is also associated with less agitation, sedation, and mechanical ventilation in the ICU (23, 24). Other adverse outcomes associated with poor pain control include the development of chronic pain and posttraumatic stress disorder (PTSD) (15, 25).

The mechanisms purported to result in adverse outcomes from pain include stimulation of catabolic stress responses (26, 27). Adverse effects of this stress response include a catabolic state with resultant tachycardia, increased oxygen consumption, hypercoagulability, and immunosuppression (28, 29). The clinical impact of this catabolic state is not fully understood, but appears to have an overall negative impact. Moreover, researchers have demonstrated increased levels of inflammatory mediators during acute pain. The effect of pain-related changes from both the pro- and anti-inflammatory cascade are also not well understood, but these cascades provide potential therapeutic targets to improve morbidity and mortality in addition to simply providing analgesia. Although pain induces a catabolic response, it also appears that the corollary is true, that analgesia attenuates the catabolic response. The protein-sparing effect of neuraxial blockade after abdominal and lower extremity surgery has been well demonstrated (30, 31). In addition to protein-sparing, there is a reduction in cortisol with a subsequent reduction in hyperglycemia, (30) and an improvement in postoperative lymphocytic immune function (32). Analgesic choice may also contribute to the amount of fluid resuscitation in the critically ill patients (33).

Table 1. Negative outcomes associated with inadequate analgesia

	Outcome
Thromboembolic events	++
Increased agitation	++
Pulmonary complications	++
Catabolic stress response	++
Immunosuppression	++
Needless suffering	++
Posttraumatic stress disorder	+
Chronic pain	+
Increased length of stay	+
Increased mortality	+

+, moderate correlation; ++, good correlation.

Interestingly, standard approaches to the treatment of pain can also have negative effects. For example, opioids, independent of their analgesic qualities, inhibit humoral and cellular immunity (34, 35). Sacerdote et al. noted that morphine, when compared with tramadol in equianalgesic quantities, worsened immune function (36). Researchers have found an increased rate of infectious disease among opioid abusers not solely explained by confounding variables such as poor nutrition and hygiene (for example, nonsterile needles). In these studies, opioid exposure proved to be an independent risk factor for immune dysfunction (37, 38).

Conversely, classes of other analgesics demonstrate survival benefits in animal models. Ketamine, for example, markedly improved survival when administered to rats with burns or severe septic shock

(39, 40). Furthermore, studies have demonstrated suppression of the production of proinflammatory cytokines (for example, interleukin-6, tumor necrosis factor-α) by ketamine using human blood *ex vivo* (41, 42). Ketamine additionally reduces both the activation of leukocytes as well as the adherence and migration of leukocytes to the endothelium (43).

There is evidence that pain control offers an effective secondary prevention strategy for PTSD (44), especially relevant to the military population; approximately 17% of all returning soldiers in this present conflict experience PTSD, whereas the prevalence is even higher among injured soldiers (45). The literature of seriously injured trauma patients reports a wide range developing PTSD (46). PTSD is independently associated with functional impairments and diminished quality of life beyond the impact of injury severity and other medical comorbidities (47–49). In the largest U.S. study to date, examining almost 3000 patients, pain at 3 months postinjury was associated with a significantly increased risk of symptoms consistent with PTSD (25). What remains unclear is whether better pain control or the choice of analgesia reduces the incidence of PTSD. In one recent paper describing U.S. service members with burns, the use of ketamine during the perioperative period was associated with a reduction in PTSD symptoms (27% versus 46%, $p = .04$) (50).

Other analgesics and biologic markers are also associated with improved outcomes in the critically ill patient. Clonidine, which acts as both a sedative and an opioid adjunct, has been shown to reduce 1-yr surgical mortality (51). The efficacy of clonidine is similar to that of perioperative β blockers (52). Although clonidine is associated with a higher incidence of hypotension, it is also associated with a lower incidence of myocardial ischemia. Oral clonidine is particularly suited to the austere environment.

Therefore, although all anesthetic drugs and techniques carry a risk and cost, it appears that optimal treatment of pain offers outcome benefits to the critically ill trauma patient ranging from metabolic to physiological.

Multimodal Pain Control

The rationale for multimodal therapy is to capitalize on the synergistic action between pharmacologic agents and different techniques. For example, ketamine, an N-methyl-D-aspartic acid (NMDA) receptor antagonist, and clonidine, an alpha-2 agonist, act synergistically with opioids through action at different receptors (53–55). Other opioid adjuvants and techniques have also shown benefit in acute and chronic pain (56, 57). In addition to drugs and techniques, multimodal therapy includes optimal timing of these interventions. Interestingly, the use of multimodal pain therapy is not a new idea. In the 17th century, Severino applied ice to injured areas to reduce pain, but the technique was limited by frostbite, slow onset, painful administration, and limited depth of analgesia. Even after Serturner extracted morphine from the opium plant in 1803, physicians continued to use other nonopioid analgesics. In the early 1900s, Cushing furthered the use of cocainization of nerve trunks before amputation as a means to block neural fibers, which were felt to cause shock and hemorrhage.

Pre-emptive analgesia, the reduction of the inciting nociceptive afferent impulse before injury, is often not possible in trauma but remains viable for posttrauma surgery. However, preventive analgesia, reducing nociceptive inputs throughout the entire hospital stay, is far more feasible in trauma and surgical patients. Although pre-emptive and preventive analgesia have conflicting data regarding their efficacy, it appears that preventive analgesia may reduce both acute as well as chronic pain by reducing both the peripheral sensitization from the injury and the central sensitization with its subsequent windup (15, 56, 57).

Multimodal therapy helps avoid the complications of opioid-centered analgesia, which include physical dependence, addiction, ileus, postoperative respiratory depression, and opioid-induced hyperalgesia (58, 59). These problems with opioid-centered postoperative pain management occur regardless of the opioid used (for example, fentanyl versus morphine) or the route of administration (for example, intermittent dosing vs. PCA) (60).

In the broadest sense, multimodal therapy even encompasses the approach in which analgesia is delivered. The American Society of Anesthesiologists guidelines suggest that interdisciplinary perioperative analgesic programs with a dedicated acute pain service and 24-hr anesthesiologist availability enhance patient comfort and prevent analgesic gaps (61). The U.S. Army has recently used this model at Brooke Army Medical Center by expanding its existing Acute Pain Service (APS). A dedicated APS anesthesiologist has been complemented with assigned housestaff to provide a comprehensive, round-the-clock APS with plans to incorporate physician extenders and psychologists. The Army has moved dedicated APSs farther forward to augment its other providers. An APS was established in Landstuhl, Germany, early in the war; because of its success, another APS team may move into Iraq in 2008.

The Army is collecting longitudinal data to see what, if any, impact these modalities had on the development of chronic pain. Although there is not yet enough data to comprehensively comment on the Army's experience, anecdotally, it appears that an APS improves outcome and reduces pain ratings (62). In addition to the effectiveness of the advanced techniques used by APSs, they do not seem to confer additional risk. Werner et al. looked at over 84,000 patients and found that regardless of the route of opioid administration (intravenous, PCA, epidural), the rate of serious respiratory depression was similar (62).

Regional Analgesia

There are significant benefits to the use of regional analgesia, epidural analgesia, or continuous peripheral nerve blocks (CPNB) in the polytrauma patient (63, 64). Regional analgesia can provide improved analgesia, improved outcomes, and lead to higher patient satisfaction (65). Ideally, regional analgesia techniques should cover the entire initiation phase during the initial inflammatory response lasting days or perhaps weeks in the case of polytrauma. This may require multiple sequential catheters to provide optimal long-lasting analgesia (66, 67). This strategy of preventive analgesia is thought to be more beneficial than the disappointing human data with preemptive analgesia. In the current military conflict, these continuous regional analgesic techniques have been successfully placed in both the combat theater and Europe at the earliest opportunity typically with pumps that accompany the service member back to the United States.

Benefits. Many studies report improved postoperative analgesia with fewer adverse side effects with regional analgesia (68–71). Grass reported less sedation with sufentanil patient-controlled epidural analgesia compared with morphine PCA and intramuscular opioids (68).

Salomaki et al. showed decreased nausea and vomiting with epidural fentanyl (20%) compared with intravenous fentanyl (65%) (72). Patients treated with regional analgesia had less nausea and vomiting, required less supplemental oxygen, and had less postoperative ileus resulting from minimizing opioid use and the sympathectomy that accompanies epidural analgesia (73, 74). Peripheral nerve blocks also decrease pruritus, urinary retention, hypotension, difficulty with ambulation, and respiratory depression (68).

Several studies have shown improved patient outcome with perioperative continuous regional analgesia, including: decreased ICU stay (19, 75), decreased hospital stay (71, 75), decreased cardiac morbidity (19, 75–77), decreased pulmonary dysfunction (69–72), earlier return of bowel function (71, 73), decreased neuroendocrine stress (75), decreased infections (75), and decreased mortality (16, 18). In 1987, Yeager examined 53 patients after abdominal, thoracic, and vascular surgery (75), whereas Tuman et al. examined 80 major vascular patients in 1991 (19). Both studies reported decreased ICU stays with epidural analgesia versus systemic narcotics. In addition, Yeager's epidural group had a 14% incidence of cardiac morbidity (myocardial infarction, congestive heart failure, angina, or arrhythmia) compared with 52% in the systemic narcotic group; Tuman et al. also demonstrated a significant difference in cardiac events with 10% versus 27%. Blomberg and others in a series of studies demonstrated a favorable myocardial oxygen supply versus demand balance with a decrease in heart rate, contractility, preload, and afterload accompanied by an increased coronary blood flow to the endocardium during thoracic epidural blockade. Furthermore, coronary perfusion pressure was maintained and stenotic but not nonstenotic coronary vessels became dilated (76, 78, 79). In a recent meta-analysis by Liu et al., minimal benefit was seen in cardiac surgery when a neuraxial technique was used, although pulmonary benefits were demonstrated (80). In particular, fewer pulmonary complications were shown, including less atelectasis, infiltrates, and cough in the epidural group when compared with a systemic narcotic group. Furthermore, Boylan et al. demonstrated earlier tracheal extubation in the epidural group when compared with the control group (70, 71). Liu et al. examined various analgesic techniques on recovery of bowel function and found a local anesthetic plus opioid combination to provide the optimal result, especially compared with systemic opioids (22). Epidural opioids have been shown to decrease the stress response compared with systemic opioids, specifically free cortisol levels (81). Yeager et al. showed a 7% incidence of major infections (pneumonia, sepsis) in the epidural analgesia group compared with 40% in the systemic narcotic group (75). Regional analgesia can also decrease thromboembolic complication (82); Tuman et al. showed a decrease in the alpha angle and maximal amplitude value on postoperative thromboelastogram as well as fewer arterial occlusions in the epidural group when compared with the systemic narcotic group (19).

Wu and colleagues reported analysis of a Medicare claims database in 2004 and 2006 and showed a significantly lower odds of death at 7 and 30 days postoperatively for those patients who had postoperative epidural analgesia (16, 83). Unfortunately, to date, no prospective, randomized study has shown a clear survival benefit.

Both epidural and CPNBs have been shown to decrease pain scores, increase range of motion exercises, decrease hospital stay, and decrease rehabilitation time compared with intravenous–PCA analgesia, although CPNB had fewer side effects compared with epidural analgesia (84, 85). Meta-analyses have shown improvement inpatient satisfaction when regional analgesia is used. Borgeat et al. demonstrated greater patient satisfaction with postoperative interscalene analgesia, a form of CPNB, compared with intravenous–PCA for shoulder analgesia (86). Wu and colleagues in 2001 reviewed 18 previous trials that examined patient satisfaction with regional anesthesia and reported that over 70% of these studies demonstrated improved patient satisfaction (87).

Risks. Although regional analgesia offers many benefits, it also introduces risks. The major risks associated with regional analgesia are local anesthetic toxicity and nerve injury (88). Pneumothorax, phrenic nerve blockade, inadvertent epidural or subarachnoid spread, hematoma, and infection are other risks to be considered. These risks have largely been described in the outpatient surgery population and may be greater in the critically ill patient (88, 89). In addition, although there has been concern in the military community about regional analgesia masking compartment syndrome, there are no reports of this phenomenon in the military's experience of over 600 regional techniques. Communication among the surgeon, anesthesiologist, and intensivist is essential; frequent examinations, low concentrations of infusions, and delay of regional analgesia until the patient is stabilized and oriented have all likely contributed to the safety record of regional analgesia of the patients wounded in the GWOT.

Local anesthetic toxicity resulting in either seizures and/or cardiac arrest can be a devastating complication with which all pain providers must be concerned. With peripheral nerve blockade, the incidence of seizures is roughly one in 1,000, whereas the incidence with epidural anesthesia is roughly one in 8,000 (88, 90). The incidence of cardiac arrest for epidural anesthesia and peripheral nerve blockade is approximately one in 10,000 and one in 7,000, respectively (5, 88). Prevention of local anesthesia toxicity relies on using the lowest effective dose, frequent aspiration, intermittent boluses, the use of a vascular marker, and avoiding agents with a low therapeutic index. Treatment should focus on airway management, control of seizures with a sedative, treatment of dysrhythmias, and control of cardiac toxicity with immediate administration of intralipid therapy. Recently, the successful resuscitations from local anesthetic toxicity in humans have been reported with intralipid therapy (91, 92) making intralipid availability a critical component of every location where regional anesthesia is performed.

As a result of an unclear definition, the incidence of nerve injury varies widely between studies ranging from 0.2% to 2% (93, 94). Auroy et al. reported an incidence of one in 5000 for both epidural and peripheral nerve blockade (88). Although the number of patients with persistent neural deficits was small, all patients in the epidural and peripheral nerve block groups had either paresthesia during block placement or pain on injection. The incidence appears to decrease with time, because Borgeat et al. found that although 14% had persistent sensory deficits on the tenth postoperative day, the number had decreased to 0.2% at 9 months (95). Bergman et al. showed that continuous techniques in over 400 axillary catheters did not increase the risk of neural injury when compared with single injections (96).

Mechanisms of nerve injury include trauma, toxicity, ischemia, or, more fre-

quently, a combination of these mechanisms (93). Neural trauma may result from the needle, intraneural injection, compression, or stretch. Although high concentrations of the local anesthetics can be neurotoxic, concentrations used at clinical concentrations are considered safe. Intra- or extraneural compression, edema, and vasoconstrictors could result in neural ischemia. Prevention of neural injury involves minimizing sedation to obtain feedback during a test dose and avoiding high concentrations of epinephrine and local anesthetics. Treatment begins with a focused history and physical and development of a differential diagnosis, including pre-existing nerve injury, prolonged use or high pressures of the tourniquet, surgical trauma, local edema and swelling, patient position, tight splints or casts, and/or regional anesthesia. Workup may include imaging studies to evaluate for hematoma and possible nerve conduction studies to record baseline function. Treatment should focus on reversible causes (for example, hematoma, casts), therapy for neuropathic pain, and reassurance, because most neural injuries improve with time.

Pneumothorax is primarily a risk with supraclavicular brachial plexus block and thoracic paravertebral block (PVB), but has also been seen with other blocks. Although the risk of pneumothorax during supraclavicular blockade has been reported from <0.1% to 5%, the incidence of pneumothorax with thoracic PVB is roughly one in 300 (97, 98). The risk is highly dependent on patient factors such as the presence of scoliosis as well as provider experience (99).

Other risks associated with regional analgesia include phrenic blockade, inadvertent epidural or subarachnoid spread, hematoma, and infection. Phrenic blockade occurs with virtually all interscalene blocks as well as 40% of supraclavicular blocks, although it is typically well tolerated in patients without significant pulmonary disease. Inadvertent epidural spread occurs frequently with PVBs, occasionally with lumbar plexus blockade (up to 10%), and rarely with interscalene and deep cervical plexus block. Inadvertent intrathecal anesthesia, possibly resulting in total spinal anesthesia, can occur during lumbar plexus block, PVB, interscalene block, and epidural anesthesia through inadvertent dural sleeve puncture.

Hematoma formation is a well-known complication of neuraxial anesthesia with an incidence between one in 5,000 to one in 150,000 depending on the presence of anticoagulation and needle size (100). The American Society of Regional Anesthesia has specific guidelines on their web site (www.asra.com) that pertain to neuraxial blockade in the presence of anticoagulants. Particularly concerning is the recent relatively high rate of epidural hematoma formation with high-risk dosing of low-molecular-weight heparin. Hematoma has also been associated with peripheral nerve blockade in the presence of anticoagulation, namely lumbar plexus block with Lovenox (Sanofi-Aventis, Bridgewater, NJ) (101).

Finally, infection may result from indwelling catheter techniques, varying from one in 10,000 with epidural catheters to as high as 1% with CPNB catheters (96). Risk factors associated with catheter infections include immunocompromised patients, diabetes, traumatic placement, duration of catheter, frequent dressing changes, and lack of systemic antibiotics. Additionally, type and concentration of local anesthesia may affect the risk of infection (102, 103). In a series of deep CPNB stimulating-catheter infections, patients noted primarily pain deep to the catheter site in the absence of erythema, induration, or purulent drainage (Lai I, Kaderbek E, Jones B, et al, unpublished observations, 2007).

Technique. Epidural catheters should be placed at the dermatomal epicenter of the injury or incision to optimize segmental analgesia, thereby targeting only those nerve roots requiring blockade. For example, a standard thoracotomy incision at T6 should have a T6 epidural catheter. In addition to these risks and benefits, epidural analgesia can result in hypotension in up to 30% of cases, particularly with larger boluses of high-concentration local anesthesia in hypovolemic patients. However, establishment of blockade after volume resuscitation in a stable patient with dilute solutions can provide excellent analgesia while maintaining stable hemodynamics (104).

Compared with epidural analgesia, CPNB offers an attractive alternative that may avoid hypotension, respiratory depression, urinary retention, and difficulty with ambulation. Peripheral nerve blocks include upper and lower extremity blocks as well as PVBs. Common upper extremity blocks include interscalene, supraclavicular, infraclavicular, and axillary approaches to the brachial plexus, whereas common lower extremity approaches include lumbar plexus, sciatic, femoral, popliteal, and ankle blocks. Paravertebral blockade can be performed at either the thoracic or lumbar region resulting in excellent unilateral blockade of nerve roots with minimal risk for hypotension, bradycardia, or respiratory depression. CPNB offers better analgesia than single-shot nerve blocks by virtue of longer duration, decreased local anesthetic toxicity risk by avoiding large concentrated boluses, and decreased motor blockade. Occasionally, dual catheters may be required in a single patient to achieve adequate analgesia in multiple areas. Ganesh and Cucchiaro reported a study in which adolescents were discharged 24 hrs after extremity surgery with dual CPNBs with good to excellent analgesia (105). This practice will likely become more common because it potentially reduces hospital stay, economic impact, opioid use, and opioid side effects. Ropivacaine may be preferred for its greater safety margin in cases when multiple infusions are used.

Pharmacologic Agents

Opioids. Traditionally, opioids form the cornerstone of acute pain management; however, they are often overused. Opioids notably bind with opioid receptors peripherally and centrally, providing analgesia without loss of touch, proprioception, or consciousness. Peripherally, they reduce neurotransmitter release and nociceptor sensitization, particularly in inflammatory tissue, whereas centrally they modulate afferent input in the substantia gelatinosa of the dorsal horn lamina where C fibers terminate as well as cortical areas to blunt perception of pain. Acute pain providers currently are armed with a wide range of opiate choices, including (in increasing potency) meperidine, morphine, methadone, hydromorphone, and fentanyl with various routes of administration, including intravenous, intravenous–PCA, intramuscular, oral, transmucosal, transdermal, subcutaneous, epidural, intrathecal, and intra-articular. There is little empiric evidence that any of the opioids have a better balance between effect and adverse effect for a particular patient in any clinically relevant manner (106). Morphine's active metabolite, morphine 6 glucuronide, can accumulate in the presence of renal insufficiency (107).

Methadone, however, is a unique opioid with NMDA antagonism and serotonin reuptake inhibition and can be chal-

lenging to manipulate with its long half-life. There is a danger that the effects of methadone accumulation, leading to delayed onset of adverse effects, can occur with patients first beginning therapy. This danger is reflected in a national report that shows a significant increase in methadone mortality in the last few years (108, 109) and a Food and Drug Administration health alert. Intensivists must use caution prescribing methadone in opioid-naïve patients because plasma levels and risk of death peak 5 days after starting the medication. Patients have often been transferred to the floor at the time of greatest risk where there is less monitoring (109). In addition to dosing concerns with methadone, there is prolongation of the QTc in 16% of patients (110). Although methadone has a long history of safety, it does appear that rare patients will develop torsades de pointes (110).

Transdermal fentanyl, another long-acting opioid, is only approved for chronic pain management, not for acute pain management, and has also been involved in several negative outcomes and a Food and Drug Administration health alert. The transdermal fentanyl patch is not to be confused with a novel-transdermal fentanyl PCA, which is approved for acute pain management. IONSYS (ALZA Corporation, Mountain View, CA) uses an iontophoretic transdermal system in which a small current is applied to a reservoir of fentanyl allowing a 40-μg dose to move effectively across the dermis to be readily absorbed through cutaneous capillaries. The system has a built-in 10-min lockout and requires replacement after 80 doses or 24 hrs, whichever occurs first, and reduces both nursing and pharmacy workload (111, 112).

PCAs offer a perceived advantage over nurse-administered opioids by empowering the patient to self-administer analgesia as needed, thereby decreasing analgesia gaps, decreasing excess opioid dosing, which could result in excess sedation, and a potential for respiratory depression. However, providers should be aware that PCAs have contradictory results regarding their safety and efficacy compared with other routes of opioid administration (113–115). Overall, it appears that patients prefer these devices (113, 116). It also appears that there is an underappreciated risk of catastrophic respiratory complications with these devices (114, 115, 117). Table 2 lists various PCA options. Expanding the PCA arsenal to include various agents (for example, morphine, hydromorphone, and fentanyl) at equianalgesic doses allows ability to change opioids easily as a result of side effects or ineffectiveness. Brooke Army Medical Center has made all opioid solutions equipotent to lessen the risk of a programming error.

Table 2. Patient-controlled analgesia modalities

Drug	<> (mg/ml)	Basal (mg/hr)	Patient-controlled analgesia dose (mg)	Lockout (min)	Load (mg)
Morphine	1	0, 1	1, 2, 3	6–12	5–10
Meperidine	10	0, 10	10, 20, 30	6–10	50–100
Hydromorphone	0.2	0, 0.2	0.2, 0.4, 0.6	6–10	1–2
Fentanyl (mg)	25	0, 25	20, 25, 30	6–10	100–200

Oral opioid choices include short-acting agents such as Percocet (oxycodone/acetaminophen; Endo Pharmaceuticals, Chadds Ford, PA), Vicodin (hydrocodone/acetaminophen; Abbotts Pharmaceuticals, North Chicago, IL), or hydromorphone as well as long-acting agents, including methadone, morphine sustained release, and oxycodone sustained release (OxyContin, Purdue Pharma LLP, Stamford, CT). When changing the opiate or the route of administration, the provider must use care in converting the dose (see Table 3). Once a new 24-hr dose is calculated based on a different medication or route, half the calculated dose is given in divided doses to allow for varying pharmacodynamics and pharmacokinetics. In addition, multimodal therapy with adjunctive agents requires reduced dosing as well.

Table 3. Narcotic conversion chart

Narcotic	Intravenous dose (mg)	By mouth Dose (mg)
Morphine	10	30–60
Hydromorphone	2	10
Methadone	10	20
Oxycontin	15	30

Despite their popularity, opioids cause both short-term and long-term sequelae, which are particularly problematic in the trauma patient (118). These sequelae are excess sedation, a potential for respiratory depression, ineffectiveness in dynamic pain, nausea, vomiting, constipation, ileus, urinary retention, and pruritus. Long-term consequences include possible immunosuppression of B and T cell function, opioid tolerance, opioid-induced hyperalgesia (OIH), and the potential for opioid addiction in susceptible patients. OIH can occur even after short-term administration and results in a paradoxic decrease in a patient's pain threshold such that they are more sensitive to pain. The mechanism of OIH appears to include enhanced NMDA activity, increased levels of the pronociceptive spinal dynorphin, and increased excitatory pathways from the rostral ventromedial medulla to the dorsal horn. "Rekindling" of OIH may occur after resolution of OIH and subsequent administration of a small dose of opioid (58, 119, 120).

Acetaminophen. Although acetaminophen is a relatively weak analgesic, it is attractive as part of a multimodal pain regimen because acetaminophen is void of platelet dysfunction, gastritis, significant renal toxicity, bone-healing concerns, or associated nausea and vomiting. The mechanism of action is reported to function at a central cyclo-oxygenase (COX)-3 receptor-producing analgesia. Numerous studies have demonstrated synergy with other analgesics with at least 20% opioid-sparing as well as decreased nausea and vomiting and sedation using up to 4000 mg daily in divided doses (121, 122). Naturally, care must be taken with alcoholic patients or patients with hepatic dysfunction.

Nonsteroidal Anti-inflammatory Drugs. Nonsteroidal anti-inflammatory drugs (NSAIDs) also play a potentially critical role in multimodal therapy, although with notable limitations. Traditional NSAIDs inhibit both COX-1 and COX-2 receptors, thereby decreasing the production of prostaglandins and thromboxane, causing decreased nociception. Traditional NSAIDs bind receptors only peripherally, whereas the newer COX-2 agents work both peripherally and centrally, thereby decreasing both peripheral and central sensitivity (123). Their use is associated with many benefits, including decreased opioid requirements, decreased pain scores, decreased nausea and vomiting, decreased constipation, decreased sedation, and finally decreased heterotopic ossification, a complication frequently associated with the polytrauma patient. Traditional NSAIDs are limited by poten-

tial adverse effects such as platelet dysfunction, gastritis, renal impairment, and impaired bone healing, most of which are dose-dependent. Oral COX-2 agents, currently only celecoxib, may be an attractive alternative because they lack platelet dysfunction and have decreased gastritis risk, although the renal impairment risk and bone-healing concern is similar to traditional NSAIDs. Unfortunately, the COX-2 inhibitors have been associated with increased thromboembolic events, including myocardial infarction as well as higher rates of congestive heart failure and hypertension and, most recently, some of the traditional NSAIDs have also been associated with an increased thromboembolic risk (124, 125). However, in select patients after a discussion with the primary trauma team, traditional NSAIDs, including ketorolac for up to 5 days, and COX-2 inhibitors can be quite helpful in achieving greater analgesia, particularly for dynamic type pain and as part of a multimodal regimen (56, 126).

Anticonvulsants. Anticonvulsants have long played a role in the treatment of neuropathic chronic pain conditions, including peripheral diabetic neuropathy, postherpetic neuralgia, causalgia, and reflex sympathetic dystrophy (now chronic regional pain syndrome). Gabapentin and pregabalin are structural analogs of gamma-amino-butyric acid; as such, they reduce calcium influx at the calcium channel and activate spinal noradrenergic activity, thereby reducing spinal cord excitatory amino acids, glutamate, and aspartate (127). Pregabalin, a newer agent, is more expensive but has a more favorable pharmacokinetic profile. This profile allows for more rapid titration as well as twice-daily dosing. More commonly, gabapentin is used at Brooke Army Medical Center as a result of pharmacy restrictions. Gabapentin is initiated at 300 mg three times daily, then increased by 300 mg per dose every 3 days to a maximum daily dose of 3,600 mg. The most frequent side effects are dizziness and drowsiness in 10% of patients, yet both drugs are well tolerated in most patients. Gabapentin was used in several studies in the treatment of phantom limb pain; its benefits included improved analgesia, an average decrease of 50% less opioids, decreased OIH, decreased anxiety, decreased chronic pain, and increased patient satisfaction (128–130).

Ketamine. Historically, ketamine has played a central role in anesthesia for the trauma patient as a result of the profound analgesia and hemodynamic stability it provides. Increasingly, ketamine has been used for postoperative analgesia and acute pain management in the trauma patient; the Army has for years been interested in developing a nasal formulation of ketamine specifically for acute pain. The Army has accrued significant experience in low-dose ketamine in both acute and chronic pain. Even at subanalgesic doses, it appears to improve fentanyl's efficacy in certain pain domains (54, 131).

The most publicized adverse effect of ketamine has been its psychotomimetic effects. Combining ketamine with other agents, such as benzodiazepines or propofol, has been found to attenuate and often abolish the psychotomimetic side effects (132, 133). A series by Friedberg evaluated the use of ketamine, combined with propofol, in 1264 patients premedicated with benzodiazepines and reported no emergence dreams or hallucinations (134). Several studies demonstrate the occurrence of psychotomimetic effects with ketamine is directly related to plasma concentrations of the drug (135, 136). Analgesic plasma concentrations are lower than the plasma concentrations seen with psychotomimetic effects (54, 131).

Long-lasting psychiatric effects have also been a concern surrounding ketamine use. Previous Air Force policy stated that ketamine administration was a nonwaiverable event for flying status. Hersack, in 1994, reviewed the literature for the incidence of long-term side effects and found ketamine had no long-term psychologic effects (137). The only serious sequelae were four cases of psychologic effects lasting up to 3 wks with subsequent resolution. Henceforth, the Air Force changed its policy on ketamine, shortening restricted flying status for the first 3 wks after ketamine administration (137).

A second factor impeding the use of ketamine is purported increases in intracranial pressure (ICP). However, studies supporting this hypothesis were performed in spontaneously ventilating subjects in which the $Paco_2$ was not controlled (138, 139). Research performed in subjects administered ketamine under controlled ventilation demonstrated no evidence of increases in cerebral blood flow or intracranial pressure when CO_2 was held constant (140, 141).

Another proposed mechanism of increased ICP secondary to ketamine was a postulated direct dilatory effect on cerebral vasculature (142). Schwedler et al. injected ketamine directly into the cerebral circulation and failed to produce significant change in cerebral blood flow (141). Nonetheless, the current teaching is that ketamine should be avoided in patients with intracranial pathology because it may elevate ICP. When multiple studies enrolling patients with increased ICP were performed, ketamine demonstrated an attenuation of further increases in ICP when administered in combination with a benzodiazepine (143, 144). Patients with traumatic brain injury were also studied, and ketamine demonstrated no adverse effects on cerebral hemodynamics; in fact, decreased ICP was observed in the ketamine group (145).

Another criticism of ketamine is its alleged depressant actions on myocardial tissue, thereby decreasing its use in the patient with a catecholamine-depleted state. This misconception is derived from a study of *in vitro* canine atrial tissue, which demonstrated negative inotropic actions at high plasma concentrations of ketamine (10–300 μg/mL) (146). However, clinically used ketamine levels, in the same study (less than 3 μg/mL), displayed positive inotropic effects. These early studies also failed to adequately evaluate ketamine's cardiovascular action *in vivo* on human subjects at clinically used levels. Many intravenous anesthetics evaluated in human myocardial tissue, including etomidate, propofol, thiopental, and midazolam, found ketamine to be the least depressant on myocardial tissue (147). Ketamine was found to have less negative inotropic effect on the myocardium than etomidate, a widely accepted induction agent for patients with cardiovascular failure. Ketamine is thought to act as a cardiac stimulant through sympathetic-mediated mechanisms.

Cardiac stimulation, however, is not always desired, especially in patients with increased myocardial oxygen demand and limited supply such as those with coronary artery disease. Premedication, especially with benzodiazepines, has been found to reliably attenuate the stimulating cardiovascular effects of ketamine (148). Interestingly, a recent study comparing ketamine with an inhalational/opioid technique in coronary artery surgery found ketamine use decreased the need for inotropes after surgery and reduced the incidence of myocardial infarctions (149).

Ketamine's use throughout the "inflammatory period" of injury may result

in decreased central hypersensitivity resulting from the continual C fiber windup phenomenon in the polytrauma patient. Ketamine binds noncompetitively to the phencyclidine site of the NMDA receptor as well as sigma opioid receptor resulting in intense analgesia; other benefits include prevention of OIH, decreased opioid tolerance, decreased opioid requirements, increased sense of well-being and patient satisfaction, decreased risk of respiratory depression, and decreased chronic pain. Although anesthetic doses may be associated with secretions as well as agitation and hallucinations, subanesthetic doses are tolerated extremely well with the addition of a benzodiazepine if necessary. The combination of ketamine and morphine in low PCA doses (1 mg morphine and 1 mg ketamine) has been shown to be beneficial with few side effects (150). Ketamine infusions below 2.5 μg/kg/min have also shown similar benefits in reducing opioid consumption and having few side effects (131, 151).

Clonidine. Clonidine is an α-2 agonist acting at the locus ceruleus and in the dorsal horn of the spinal cord at 2A antinociceptive receptors, causing analgesia, sedation, and anxiolysis from a supraspinal, spinal, and peripheral site of action. Decreased pain scores, decreased opioid requirements, decreased OIH, and prolonged nerve blocks have been shown with all routes of administration, especially from the regional anesthesia literature (56).

The use of systemic clonidine has been shown to reduce opioid consumption (152–154). This same opioid-sparing effect is seen with dexmedetomidine (155, 156). In Germany, over 50% of ICUs use clonidine as an analgesic and sedative adjunct (157). In a hemodynamically stable patient, clonidine is initiated at 0.1 mg by mouth twice daily increasing to a maximum of 0.2 mg three times daily. Hypotension and bradycardia can be observed, although typically there is no increase in respiratory complications.

Lidocaine/Mexiletine. The local anesthetic lidocaine and the oral analog mexiletine, Class IB antiarrhythmics, provide analgesia separate from their direct local anesthetic properties. Administered systemically, local anesthetics can decrease pain and opioid requirements possibly through decreasing ectopic afferent neural activity at the NMDA receptor within the dorsal horn. The combination of clonidine and mexiletine appears particularly beneficial in difficult, central-mediated pain syndromes such as phantom limb pain ([159]; Malchow RM, unpublished observations, 2007; [160]). Intravenous lidocaine continuous infusion (1–2 mg/min) as well as topical lidocaine has been shown to decrease pain in the burn patient (4). Mexiletine beginning at 150 mg twice daily can be administered empirically or after a positive intravenous lidocaine test, after documenting the absence of conduction abnormalities on a 12-lead electrocardiogram. Mexiletine is increased by 150 mg every 3 days to a maximum of 900 mg daily, although nausea and vomiting may limit dose escalation.

Tricyclic Antidepressants. Tertiary amines, most notably amitriptyline, as well as secondary amines such as nortriptyline and desipramine are effective in neuropathic and central hypersensitivity conditions primarily by blocking norepinephrine and serotonin reuptake in the dorsal horn. Their limitations result from a broad side effect profile, including antihistamine, anticholinergic, and antiadrenergic effects, which together frequently cause sedation, dry mouth, constipation, and possible tachycardia and orthostasis. Although amitriptyline has been most studied, the secondary amines may be equally effective with fewer side effects. After ruling out significant cardiac contraindications by history, physical, and electrocardiogram, amitriptyline can be started at 10 to 25 mg every evening, increasing to 50 mg after 1 wk of therapy, although their analgesic properties may take 3 to 4 wks (56, 126) In postamputee patients naïve to pharmacologic therapy, over 80% of patients had relief with an average of 56 mg amitriptyline per day (159).

Benzodiazepines. Many trauma patients exhibit significant anxiety, anger, frustration, and stress as a result of their injuries and resulting profound global impact on their lives and families. The addition of a scheduled benzodiazepine can significantly calm the polytrauma patient and simultaneously decrease pain scores. This effect is distinct from the sedation and anxiolysis that benzodiazepine provide. This nocebo hyperalgesia, in which the anticipatory expectation of pain worsens pain, has just recently been appreciated (160). The "nocebo effect" is the functional opposite to the placebo effect. Brain scans have shown that the perceived intensity of a painful stimulus after negative expectations is higher than without the negative expectation (162). Unfortunately, benzodiazepines have been associated with worsened outcomes, including increased delirium in the ICU setting (162, 163). Patients getting repeated procedures may benefit from anxiolysis. After the acute setting, benzodiazepine can be weaned by first discontinuing daytime administration followed by evening doses.

CONCLUSION

Ongoing improvements in pain management have included better education, training, research, and availability of "state-of-the-art" medications and techniques. Multimodal analgesia has improved the ability of the military's healthcare providers to provide safe and effective analgesia in critically ill patients at all points in the evacuation chain. As the rationale for pain control and specific therapies and agents evolves, pain control has continued to improve. There is a growing recognition that pain is a problem that negatively affects outcomes and therefore requires greater attention in the critically ill trauma patient. Finally, trauma providers are recognizing that how we treat pain may be as important as the decision to treat pain; needless to say, pain management remains a priority for the U.S. military.

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