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Management of Analgesia Through Multiple Phases of Trauma

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Abstract Managing the pain in a patient with traumatic injuries can be a delicate and difficult task. In the acute phase the options for pain control are often limited to opioids, which must be administered cautiously as to not further disrupt the homeostasis of an already fragile patient. Careful management of sedation during this period is also crucial to patient comfort and stability. In the recovery phase, a multimodal approach to pain control is preferred, utilizing opioid and non-opioid medications, regional and neuraxial blocks if appropriate, and other treatments to help limit the patient's discomfort. Multimodal therapy may also more effectively prevent long-term sequelae including conversion to a chronic pain syndrome and opioid dependence and abuse.

Keywords Pain · Trauma · Multimodal · Analgesia · Regional · Opioid-sparing

Introduction

Significant barriers to treating the pain of a polytrauma patient exist at all stages of injury recovery. In the immediate/resuscitative stage there is concern for worsening hemodynamic instability, respiratory depression, and cognitive impairment. Intravenous administration is often the only practical route, limiting the number of analgesics from which to choose. Furthermore, it is difficult for severely injured patients to communicate levels of distress or pain. Many of these concerns may continue to affect how treatment is provided in the ICU or the floor. As recovery progresses, however, new barriers arise, many of which revolve around the use of opioid analgesics. Concerns for facilitating addiction, dependence, and opioid-induced hyperalgesia often frustrate the patient–practitioner relationship and can hinder the ability to effectively manage pain. *This paper reviews the current evidence regarding pain management for polytrauma patients, specifically the role of multimodal, multidisciplinary therapies that are opioid-sparing. It also provides a brief overview on various sedation strategies that may be employed in the ICU.*

Unfortunately, there is a paucity of data regarding the topic of analgesia and sedation focusing specifically on the polytrauma patient [1]. Therefore, this review will also draw from evidence regarding postsurgical pain, which can serve as a surrogate for studying trauma-induced pain. Additional insight has been gleaned from the recent military conflicts in Iraq and Afghanistan. Improved protective outfitting has increased the survivability of many injuries, and as a result, more injured personnel are needing to receive treatment in the field. The austere and often dangerous environment of military medicine has prompted practitioners to implement creative strategies, particularly involving regional anesthesia, that treat severe pain without impairing cognition or hemodynamic stability. Techniques to more aggressively manage post-trauma pain that have proven effective within the military should be borrowed and adapted by the civilian community in order to continue improving patient care [2].

This article is part of the Topical Collection on *Anesthesia for Trauma*.

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Epidemiology

Inadequate acute pain management for the trauma patient has been recognized. One study evaluating polytrauma patients in the ICU found that almost 75 % of patients rated their pain as either moderate or severe [3]. More recently, a survey of 110 soldiers injured in the battlefield revealed that even after being admitted to a fully equipped medical care facility the average worst pain score was greater than 7/10 [4]. These findings are comparable to what has been found for patients undergoing elective surgical procedures. Apfelbaum et al. surveyed 250 adults who had undergone surgery, both inpatient and outpatient. Approximately 80 % of the respondents reported they had experienced acute pain in the post-procedural time period, and most reported the severity of pain as being moderate, severe, or extreme [5]. Interestingly, the number of patients reporting extreme pain had actually increased when compared to a similar study performed a decade earlier [6].

Evidence also suggests that patients who experience a traumatic injury are likely to develop chronic pain. Macrae et al. in a survey of 10 pain clinics throughout North Britain, reported that trauma was the third most common source of pain [7]. The prevalence of continued pain found from a survey of 3047 patients 12 months following trauma was 62.7 %. Joints and extremities (44.3 %), back (26.2 %), head (11.5 %), neck (6.9 %), abdomen (4.4 %), chest (3.8 %), and face (2.8 %) were listed as the most common regions of pain [8]. Similar to another study that evaluated patients for chronic pain seven years following traumatic lower extremity injury, untreated depression and poorer socioeconomic status were risk factors for ongoing pain. In Castillo et al., high reported pain intensity and sleep dysfunction 3 months following the injury were also risk factors for developing chronic pain [9].

Morbidity of Pain

The endocrine, metabolic, and inflammatory responses to traumatic injury augment physiological responses to nociceptive stimuli worsening pain. Furthermore, spino-bulbo-spinal pathways involving higher brain regions including the parabrachial nucleus, periaqueductal gray, nucleus tractus solitarius, insular cortex, anterior cingulate cortex, amygdala, and hypothalamus establish a bidirectional relationship allowing nociception, in turn, to influence autonomic and endocrine systems [10]. Inadequate pain control in the perioperative period has been linked to many adverse events including myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, impaired immune function, and anxiety [11]. Unrelieved pain also affects patient recovery, prolongs hospital stay, and adds to overall health care costs [12].

For a significant number of trauma patients, acute pain will ultimately transition into a chronic pain state. The process by which this occurs is complicated and incompletely understood. Most theories are based on the nervous system's ability to alter how it responds to stimuli, a property termed neuronal plasticity. Inflammatory mediators from tissue trauma sensitize nociceptors resulting in peripheral sensitization. The resulting nociceptive signaling barrage that is then relayed to the dorsal horn initiates a more widespread cascade of neuroplastic changes including NMDA-receptor wind-up, long-term potentiation, and central sensitization [13]. Changes at the level of the brainstem and cortex also occur that alter how ascending nociceptive signals are processed, becoming more facilitative rather than inhibitory [14].

Psychologically, acute pain worsens anxiety and increases the risk of developing post-traumatic stress disorder (PTSD) [15]. In the setting of prolonged unrelieved pain, hopelessness and depression may develop. Patients living with chronic pain are more prone to social withdrawal, loss of function, loss of income, and reliance upon social security disability than the general population [16].

Role of Multimodal Analgesia

With the large number of ligands, receptors, and neural pathways involved in the pain signaling cascade, it is reasonable to infer that interference of multiple parts of the process is more likely to produce greater pain relief. The practice of multimodal analgesia hinges on this concept and can be defined as the "administration of two or more drugs that act by different mechanisms to provide analgesia" [17]. In addition to traditional pain medications such as NSAIDs, acetaminophen, and opioids, multimodal analgesic regimens also utilize a variety of medications, termed as adjuvant analgesics, which were not initially intended to be used for analgesic purposes. Examples of adjuvant analgesics include gabapentinoids, antidepressants, and alpha-2 agonists.

For many years, it was hypothesized that administration of an analgesic prior to the onset of nociception was superior to the same dose delivered afterwards. This concept was based on animal studies which suggested that such preemptive analgesia could more effectively blunt the central sensitization that occurs following tissue injury [18]. Clinical studies, however, have not supported this theory [19]. Lack of supportive clinical findings may in part be due to flaws in study design wherein only one single-dose medication delivered pre-incision versus post-incision was expected to significantly reduce overall pain scores. Given the complexity of nociceptive processing, it is not surprising that such a minor intervention would fail.

The model of preemptive analgesia has subsequently evolved into one of the preventive analgesia in which a more comprehensive multimodal regimen is provided to the patient throughout the entire perioperative period. The goal is to achieve a more complete blockade of the pain signaling cascade. In the setting of trauma, where preemptive analgesia is impossible, preventive analgesia is the only option. While earlier administration may remain important, success is no longer solely predicated on preincision delivery but instead on a more complete interruption of the process. Indeed, some evidence suggests the model of preventive analgesia may not only reduce acute pain more effectively but also decrease the incidence of chronic postsurgical pain [20].

Acetaminophen

Acetaminophen is one of the most commonly used antipyretic and analgesic medications in the world. Despite its popularity, its mechanism of action is still unknown. Theories include centrally mediated cyclooxygenase (COX) inhibition, its properties as a peroxidase, inhibition of nitric oxide synthase, and interactions involving cannabinoid and serotonergic systems. Acetaminophen does not exhibit significant anti-inflammatory action, interfere with platelet function, or alter renal blood flow which distinguishes it from non-steroidal anti-inflammatories (NSAIDs). Because of its significant hepatic metabolism, acute liver toxicity is possible following large doses. For patients with known liver disease, history of alcoholism, or injury affecting liver function acetaminophen should be dosed carefully or avoided [21].

Acetaminophen is relatively lipophilic molecule that is absorbed almost entirely in the small intestine. Opioids and surgery have been shown to significantly decrease bioavailability secondary to delayed gastric emptying [22]. Despite this finding, single-dose acetaminophen still seems to be beneficial in the management of acute postoperative pain [23]. Intravenous delivery of acetaminophen is available and provides a much more reliable plasma concentration of the drug; however, its formulation is more costly. Furthermore, the increased plasma concentrations obtained from intravenous dosing preoperatively have not translated into increased clinical effectiveness over the oral route, but this comparison has not been looked at for the trauma population [24]. Gastric emptying is known to be extremely delayed in critically ill trauma patients compared to healthy individuals, a fact that might reduce the effectiveness of orally administered acetaminophen [25]. Acetaminophen should be included within a multimodal analgesic plan whenever possible. For critically ill trauma patients, especially those who are unable to receive any form on enteral medication, intravenous acetaminophen should be considered.

Non-steroidal Anti-inflammatories

In the presence of tissue injury, increased production of pro-inflammatory prostaglandins results induces a hyperalgesic state. Non-steroidal anti-inflammatories (NSAIDs) work by inhibiting cyclooxygenase (COX), an enzyme involved in prostaglandin production pathway. Two types of COX enzymes exist. The COX 1 enzymes are constitutively expressed by a variety of cell types. COX 2 enzymes maintain a low basilar level of expression until they are upregulated in the presence of inflammation and tissue injury. NSAIDs can be categorized based on their respective COX 1/COX 2 selectiveness. Traditional NSAIDs are fairly nonselective, significantly inhibiting both COX 1 and COX 2 enzymes. A newer group of NSAIDs, the coxibs, are much more selective for COX 2. Both traditional NSAIDS as well as the coxibs have been shown to reduce pain scores, opioid consumption, and nausea in the postsurgical setting [26, 27].

Because of the broad range of functions COX enzymes serve, NSAIDs have numerous side effects that prescribers should consider prior to initiating. The introduction of the coxibs has mollified the side effect profile to an extent, but not completely. The coxibs have reduced the risk of bleeding related to gastrointestinal ulceration and platelet dysfunction [28]. There is further evidence that the currently available coxibs are associated with reduced risks of renal toxicity compared to traditional NSAIDs [29]. However, for patients with orthopedic injuries, any benefit coxibs offer over traditional NSAIDs with regard to an increased incidence of fracture malunion is unclear. Finally, there is no clear advantage of coxibs over traditional NSAIDs regarding increased risk of cardiovascular disease. Although incompletely understood, the most likely hypothesis involves NSAID-induced hypertension. In particular, diclofenac has been associated with worse cardiovascular outcomes even compared to other NSAIDs; therefore, an alternative choice might be reasonable for patients with preexisting cardiovascular disease [30]. Ultimately, it is probably best to limit the use of any NSAID to as short a duration as possible [31, 32].

Opioid

Opioids remain the mainstay of pain treatment for the injured patient. They are a key component of the analgesic regimen in the acute care and prehospital setting. As part of a multimodal regimen they are often continued throughout

the hospitalization and even after discharge during the weeks and months of recovery.

Opioids, which include all substances with opium-like effects, bind to specific receptors in the central nervous system, peripheral nervous system, and along the GI tract. The effect of this binding is dependent upon the receptor that is bound and whether the opioid is an agonist or antagonist at that receptor site. Binding of mu, kappa, and delta receptors by opioid agonists can result in a multitude of effects including analgesia, respiratory depression, miosis, reduced bowel motility, vasodilation, euphoria/dysphoria, sedation, and physical dependence.

Opioids are indicated for the acute relief of moderate to severe pain. The risks and side effects must be considered in the context of the patient with one or multiple injuries. For example, the desire to keep the patient comfortable must be weighed against the need to obtain serial mental status exams or prevent hypercarbia and increased cerebral blood flow in a head-injured patient.

Opioid-induced hyperalgesia (OIH), a paradoxical response whereby a patient receiving opioids for the treatment of pain becomes more sensitive to painful stimuli, is well-established in the literature for chronic opioid use [33]. There are now a small number of published studies that have looked at the development of OIH in the setting of acute perioperative opioid exposure. Guinard et al. demonstrated increasing postoperative requirements of morphine in patients who were administered a remifentanil infusion in the operative room [34]. A similar response of increasing pain and opioid requirements were reported by Chia et al. when high-dose fentanyl was administered in the operating room [35].

These reports are in contrast with several other studies that demonstrated no signs of OIH in patients that received intraoperative opioids. Further investigation is needed to help clarify these mixed findings and to better guide clinical practice.

There is an epidemic of opioid use and misuse in the United States. Accordingly, there is increasing state and federal oversight of prescribing practices and a de facto limiting of qualified prescribers. In addition, although there is a strong indication for the prescribing of opioids in the acute setting there is much more debate on the role of chronic opioids in noncancer pain. For these reasons, it is important to use a multimodal approach to the treatment of pain in the injured patient and to continue to work towards weaning the patient from opioid medications as clinical improvement occurs.

During the early phase of trauma, when patients are often hemodynamically unstable and require further resuscitation, opioids may exacerbate lability. In several animal models of hypovolemic shock, opiate antagonists have been found to decrease the hemodynamic response to volume loss. Potential mechanisms include reduction of the normal sympathetic response to injury and volume loss, parasympathetic stimulation via vagus nerve, and direct myocardial depression [36•]. Although human studies are limited, one meta-analysis concluded that use of naloxone improved the mean arterial pressure (MAP) of patients in shock [37].

Peripheral Nerve Blocks

Over 50 % of patients presenting with an Injury Severity Score (ISS) >16 will have an accompanying peripheral extremity injury [38]. Regional anesthesia is able to provide the patient with superior analgesia while avoiding many of the systemic side effects associated with other analgesics, particularly opioids. A complete list of the potential benefits of regional anesthesia is found in Table 1 [39, 40]. The advent of ultrasound-guided techniques has allowed many more practitioners to gain confidence in their ability to successfully and safely employ this modality [41]. As the availability of ultrasound continues to increase, use of regional anesthesia has also expanded from the perioperative arena to the ICU, ER, and even the field of combat.

Continuous catheters allow for analgesia beyond the 12–18 h provided by most single injection techniques. Ropivicaine, with its reduced cardiotoxicity compared to bupivacaine, is the local anesthetic most often used. If needed, temporary administration of a higher concentration through the catheter will provide a denser blockade allowing for certain procedures (e.g., debridement, grafting, fracture fixation…) to be performed without the need for a general anesthetic.

Buckenmaier et al. reported on peripheral nerve catheters used for 187 combat-related injured military personnel. Catheters remained in place for a median of 8 days (range 1–33 days). Complications were identified in only 7 patients (3.7 %) and included two catheter malfunction-kinking, catheter tip dislodgement in situ, two superficial catheter site infections, and two catheter dislocations [42].

Table 1 Potential benefits of regional anesthesia

Avoidance of a difficult airway/ability to maintain protective airway reflexes
Avoidance of the need for heavy sedation/general anesthesia
Reduced postoperative pain scores
Opioid-sparing/reduced opioid-related adverse events
Reduced time in postanesthesia care unit (PACU)
Decreased hospital length of stay
Reduced postoperative bleeding
Decreased incidence of deep vein thrombosis (DVT)
Increased range of motion/decreased rehabilitation time
Increased patient satisfaction

No adverse events related to bleeding were identified despite these patients being concurrently treated with enoxaparin 30 mg BID for DVT prophylaxis.

In addition to demonstrating how regional anesthesia may be better integrated into care pathways for trauma patients, the study by Buckenmaier et al. also discussed the appropriateness of regional anesthesia in the setting of anti-coagulation and coagulopathy. According to the current ASRA guidelines, some of the deeper peripheral nerve blocks (paravertebral, sympathetic, lumbar plexus, and deep sciatic) are considered by the authors to be of high enough risk that they be treated with the same precautions as neuraxial procedures; however, this inclusion has generated controversy [43, 44]. It may be most prudent to adhere as closely as possible to the ASRA guidelines while simultaneously recognizing that they are not intended to be a "cookbook" for patient care.

Buckenmaier et al. reported that 1 % incidence of catheter site infection falls within the consistently reported range of 0–3 %. Catheter duration beyond 48 h is the greatest independently associated risk factor for catheter-related infection. Other identified risk factors include patients located in the ICU, trauma patients, catheter insertion at femoral or axillary sites, and lack of antibiotic prophylaxis [45].

In certain cases, patients may benefit from two or more continuous catheter placements. Examples include patients who have sustained injury to multiple extremities, simultaneous blockade of the femoral and sciatic components of an injured lower extremity, or the use of bilateral paravertebral catheters for rib fractures. Although local-anesthetic systemic toxicity (LAST) is rare, it is a life-threatening complication and must be taken seriously. In an American Society Anesthesiology (ASA) Closed Claim Analysis, LAST was associated with 7 of 19 claims involving death or brain damage [46]. Bleckner et al. evaluated serum ropivicaine concentrations in patients receiving long-term continuous peripheral nerve block catheter infusions and found the median ropivicaine blood concentration to be 0.11 mg/L [47]. Of note, two patients had isolated serum ropivicaine levels of 0.63 mg/L and 0.59 mg/L. Both of these measurements were obtained 24 h following a procedure during which the patients each had their catheters bolused with a total of 60 ml of 0.5 % ropivicaine. Neither of the patients demonstrated signs or symptoms of LAST. In a study involving healthy volunteers, a mean free plasma concentration of 0.6 mg/L was related to the onset of CNS toxicity [48•]. Strategies to reduce the risk of toxicity associated with multiple catheters include reducing the concentration of infused ropivicaine (e.g., 0.1 or 0.15 %) and to transition from a continuous infusion to an intermittent bolus delivery [40].

One major concern regarding the use of regional anesthesia in the setting of trauma is compartment syndrome (CS). CS is a serious complication that occurs when the interstitial pressure within an osteofascial compartment increases to such a point that blood flow is impeded resulting in tissue ischemia and, if left untreated, tissue necrosis. Although CS usually occurs as the result of a high energy injury, other reported causes include crush or reperfusion injury, exercise, arterial puncture, tight dressings and casts, burn, and snake bites. The two most common sites affected are the lower leg related to tibial fractures and the forearm. Hesitation to place peripheral nerve blocks in trauma patients stems from concern that the block might mask the symptoms of disproportional pain and paresthesia that are classically associated with CS. However, the clinical signs and symptoms are routinely unreliable. Furthermore, many case reports have noted that the use of regional anesthesia facilitated earlier detection due to patients complaining of breakthrough pain despite a previously functioning continuous catheter [40]. A recent systematic review (Driscoll et al. unpublished) evaluated 28 case reports and 6 research articles stating that a reliable conclusion regarding appropriate practice could not be made based on the current evidence. For patients at risk of CS who also have continuous catheters, it is probably prudent to infuse a more dilute concentration of local anesthetic in order to reduce the likelihood of masking symptoms.

Central Neuraxial Techniques

Increased risk limits use of central neuraxial techniques such as epidural analgesia in the polytrauma population. Contraindications including hypovolemia, hypotension, coagulopathy, head or spinal injury, and sepsis are all relatively common among this patient population. Furthermore, as these patients often have an altered level of consciousness that limits their ability to provide reliable neurological feedback, many practitioners are unwilling to attempt placement out of concern for unrecognized spinal cord or nerve root injury [49].

The most common application of epidural analgesia in the setting of trauma is for management of pain related to rib fractures. Evidence suggests that number of rib fractures are directly related to increased morbidity and mortality in both young and elderly patients [50, 51]. Adequate pain management is a central tenant in the care of these patients in order to achieve increased pulmonary excursion and improved clearance of secretions. A recent systematic review of the use of thoracic epidural analgesia for traumatic rib fracture failed to identify benefits toward mortality, ICU length of stay (LOS), and hospital LOS over other analgesic techniques. Although several studies evaluated in the review did indicate superior pain control, this finding was unable to be assessed in the pooled analysis

due to missing information. Epidural catheters infused with local-anesthetic-only solutions were found to significantly reduce the duration of mechanical ventilation. Given the lack of substantial benefit and the potentially increased risk of placement in this population due to altered mental status hindering adequate neurological assessment, the authors were unable to recommend the routine use of epidural analgesia for patients with rib fractures [52]. Paravertebral catheters are considered by many to be safer alternatives regarding the risks of bleeding, infection, and neurological injury in the trauma population. For this reason, their use in the management of rib fracture pain has become the treatment modality of choice by many experts [53].

Gabapentinoids

The gabapentinoids, gabapentin, and pregabalin, have been utilized in the treatment of neuropathic pain conditions such as post-herpetic neuralgia and diabetic neuropathy for many years. Their potential benefits when combined with their relatively benign risk profiles have resulted in increased use of these medications for more widespread pain conditions such as fibromyalgia. More recently there has been growing interest in the efficacy of these medications in the reduction of acute postsurgical pain and, potentially, the development of more chronic postsurgical pain states.

Gabapentinoids are believed to exert their analgesic mechanism of action at the level of the dorsal horn by inhibiting $\alpha 2 - \delta 1$ calcium channels at the presynaptic membrane. The subsequent reduction of the influx of calcium presynaptically upon depolarization limits the release of excitatory neurotransmitters into the synaptic cleft blunting the synaptic transmission of nociceptive signals. Such reduction in neuronal excitability may help prevent central sensitization and the development of hyperalgesia and allodynia. Indeed, gabapentin and pregabalin have both been found to reduce postoperative pain; incidence of chronic postsurgical pain has also been found in a combined systematic review and meta-analysis of the literature [54].

It is worth noting that gabapentin and pregabalin have both been shown to be effective in the management of several types of post-traumatic neuropathic pain in randomized controlled trials [55, 56]. A recent systematic review found gabapentin and pregabalin to exhibit some efficacy in the management of neuropathic pain following SCI [57]. Gabapentin also may reduce phantom limb pain in the intermediate period following amputation [58]. Pruritus, which is an almost universal complaint during the acute phases of healing following burn injury, has also been found to respond well to the gabapentinoids [59].

Most patients who receive gabapentinoids (around 80 %) report side effects including dizziness, somnolence, peripheral edema, gait or balance disturbance, and tremor. However, serious adverse events are much less common (around 8 % or lower) and are not significantly higher than placebo [60]. Caution may be indicated regarding the use of these medications in patients with heart failure [61]. Because they are eliminated through the kidneys, the dose must be adjusted for patients with renal insufficiency.

Antidepressants

Antidepressants are commonly used in the treatment of chronic pain, but their usefulness in acute pain has not been thoroughly reviewed. In their systematic review, Wong et al. concluded that although there is insufficient evidence to support widespread use of antidepressants in acute pain, there may be specific clinical conditions in which they are indicated [62]. For the management of postmastectomy pain, venlafaxine 37.5 mg ER was compared to placebo and found to reduce the analgesic requirements in the postoperative period, with exception for the first postoperative day. Furthermore, at 6 months there was a clinically and statistically significant reduction in regards to the neuropathic pain symptoms of burning, stabbing, and pricking compared to placebo [63]. Although the role of antidepressants in post-trauma pain has not been studied, this reduction in neuropathic pain may prove beneficial and future investigation would be useful.

NMDA-Receptor Antagonists

N-methyl-D-aspartic (NMDA) receptors are a subclass of glutamate receptors that upon activation allows positively charged ions (Na^+, Ca^{2+}, K^+) to travel through the cell membrane. Under normal conditions, this receptor is tonically blocked by magnesium ions; however, when prolonged depolarization occurs, such as in the setting of trauma-induced nociceptive afferent barrage, calcium displacement of magnesium allows the ion channel to open. The NMDA receptor is believed to be involved in the processes of central sensitization, opioid tolerance, opioid-induced hyperalgesia [64].

Ketamine, which was first described in the literature in 1965, was initially anticipated to be used as a sole anesthetic or induction agent. However, investigation of its efficacy as an analgesic has since become a key topic of interest for many investigators. Ketamine's most studied mechanism of action involves inhibition of the NMDA receptor. However, interaction with other receptors including opioid, sigma, nicotinic, and serotonergic has also been recognized and postulated to contribute to its analgesic efficacy. Ketamine also suppresses the synthesis of pro-inflammatory cytokines

TNF-α and IL-6 which may contribute to longer-lasting analgesic potential [65].

As an induction agent ketamine has many advantages. It is rapid in onset. Spontaneous respiratory effort and protective reflexes of the airway are maintained. Although ketamine is a direct myocardial depressant, in the setting of trauma its sympathomimetic effects typically preserve hemodynamic stability [66]. In fact, one study noted that fentanyl was required in most patients to blunt any unwanted hypertensive response to intubation [67]. Unlike etomidate, ketamine does not cause adrenal suppression. Previous concerns regarding the use of ketamine in patients with traumatic brain injury are no longer supported in the literature [68]. Especially with larger doses, psychotomimetic effects may occur; however, the incidence and severity of this adverse effect can be significantly reduced with co-administration of a benzodiazepine. Although further study is warranted regarding effectiveness, use of ketamine as an induction agent allows for early initiation of an opioid-sparing multimodal regimen in a patient population for which alternative options are often limited.

A Cochrane Analysis concluded that perioperative ketamine reduced opioid consumption and postoperative nausea and vomiting during the first 24 h. In their discussion, the authors identified patients who were opioid tolerant and those who were more prone to experience opioid-related adverse events such as the elderly might benefit the most [69]. A review by De Kock et al. concluded that low doses of ketamine (<1 mg/kg) not only demonstrated some minor analgesic effects but, perhaps more importantly, reduced the amount of hyperalgesia that developed from surgical incision and opioid analgesia [70].

Infusion of magnesium, the natural inhibitor of the NMDA receptor, has been shown to reduce pain and opioid requirements for up to 48 h following surgery [71]. Furthermore, there is some evidence in the setting of spinal surgery that magnesium and ketamine infusions may be synergistic [72].

Other medications including dextromethorphan, memantine, and amantadine also possess NMDA-receptor antagonist properties. Dextromethorphan is probably the most studied. A systematic review of 28 studies concluded that analgesic and opioid-sparing benefits were too inconsistently found for any recommendations to be made [73]. Carlsson et al. found that dextromethorphan produced clinically significant analgesia for patients suffering from neuropathic pain following traumatic injury; however, the required doses were too large for many to tolerate due to side effects and the study size was small [74]. A review by Collins et al. was unable to offer any conclusions regarding the effectiveness of any of the NMDA antagonists for neuropathic pain [75].

α2 Agonists

α2 agonists exhibit analgesic and sedative properties that could prove to be beneficial in the trauma setting. α2 agonists are believed to exert most of their analgesic actions at the level of the dorsal horn through inhibition of nociceptive signaling at the level of the synapse; however, other peripheral and supraspinal mechanisms of action may also exist [76, 77]. Their ability to induce sedation is thought to result from reduced norepinephrine release from the locus ceruleus creating a hypnotic state that resembles sleep [78].

There is very little evidence regarding the efficacy of these medications for the trauma population. Indeed, with the two most common side effects of this class being hypotension and bradycardia, this is not surprising; however, in adequately resuscitated and hemodynamically stable patients these medications offer the potential for opioid-sparing analgesia. In a meta-analysis of 1792 patients, use of perioperative systemic α2 agonists provided superior analgesia while reducing opioid consumption and incidence of postoperative nausea and vomiting [79]. These medications can be continued as part of a multimodal opioid-sparing analgesic regimen well into the recovery period. Clonidine is available in both oral and transdermal forms. Although the evidence is mixed, it may be an effective long-term analgesic for some patients [80]. Tizanidine may also be an appropriate choice for patients with ongoing pain needs, especially those suffering from spasticity due to traumatic brain or spinal cord injury [81].

Lidocaine Infusions and Mexiletine

Lidocaine and the oral analog mexiletine can be administered systemically and have been shown to decrease pain and opioid requirements [82••]. IV and topical lidocaine improved pain control in burn patients. Mexiletine, in conjunction with clonidine, was shown to improve pain control in patients with phantom limb pain. Intravenous lidocaine with or without ketamine did not improve functional recovery, pain scores, or opioid consumption in patients recovering from open abdominal hysterectomy [83]. These mixed results may be related to the underlying mechanisms of the pain, neuropathic or nociceptive, and their relative contributions to the patient's pain experience.

Alternative and Complimentary Modalities

Alternative and complimentary modalities may help reduce the experience of pain and associated anxiety in the acutely injured trauma patient. According to Matsota et al., music

may provide some anxiolysis but is not effective when pain is severe [84]. They do note, however, given that it is inexpensive and lacking in side effects it may be useful in individual patients. A randomized control trial of 58 inpatients with rib fractures demonstrated a statistically significant improvement in cough, deep breathing, and turning over in the acupuncture group, with the effect lasting at least 6 h in most patients [85]. The military has begun to utilize techniques such as acupuncture, virtual reality, and yoga to assist the pain management of wounded soldiers [86]. Neurofeedback has been demonstrated to be effective in the treatment of both chronic as well as acute pain [87].

Sedation in the ICU

Sedation of trauma patients in the ICU is a topic that is beyond the scope of this article. However, several of the analgesics discussed above are often incorporated into various sedation techniques. Opioids are frequently chosen because of their duel analgesic and anxiolytic properties. All opioids have the downside of respiratory depression, sedation that precludes accurate neurological exam, and precipitation of withdrawal if suddenly discontinued. Fentanyl is widely preferred because of its perceived short half-life offering faster wake up times. In reality, though, because of factors such as high protein binding, large volume of distribution, and reliance on hepatic metabolism, its context-sensitive half-life can range from 3 to 25 h. Remifentanil, because it is metabolized by non-specific tissue and plasma esterases, maintains its half-life of 4 min despite prolonged infusion, but there are concerns that it may cause opioid-induced hyperalgesia to an extent that is greater than other opioids. One study that compared fentanyl to remifentanil for sedation of mechanically ventilated patients found no differences in outcome between the two [88].

Ketamine has the potential to serve as a useful adjunct in sedation regimens in order to capitalize on its opioid-sparing effects; however, studies are needed. It has also been used as a sole agent, especially for patients who were hemodynamically unstable or in status asthmaticus [89]. A systematic review noted that ketamine's more favorable hemodynamic profile may make it preferable for more unstable patients but that further investigation was warranted [90].

Dexmedetomidine, with its analgesic and anxiolytic properties that are not γ-aminobutyric receptor mediated, may allow it to help to avoid the withdrawal and emergence delirium associated with some of the more traditional agents used for sedation such as opioids and benzodiazepines [91]. In a study of 342 mechanically ventilated patients in the neurointensive care unit, dexmedetomidine was found to have a similar incidence of hypotension and bradycardia when compared to propofol [92]. However, concerns regarding adverse effects of tachyphylaxis and complications of respiratory failure, acute respiratory distress syndrome, and agitation have prompted to the United States Federal Drug Administration to approve its use only for 24 h [93].

Ultimately, no sedation agent has been found to be clearly superior, and instead sedation technique may play a more important role in determining outcome. Repeated studies have demonstrated that minimizing sedation for patients in the ICU provides clinical benefit. Lighter sedation is associated with decreased length of mechanical ventilation, length of ICU stay, morbidity, and mortality. For a more complete review of the topic please refer to Reade et al. [94].

Conclusion

Effective pain control is essential in the care and recovery of the trauma patient. Inadequate pain treatment can contribute to an increase in complications, prolonged recovery, and even death. In addition, there is increasing evidence that it may contribute to the development of chronic pain and disability. Most pain practitioners favor the use of multimodal therapy in the treatment of pain in the injured patient to improve patient comfort and to limit development of these acute and chronic sequelae.

Compliance with Ethics Guidelines

Conflict of Interest Roland Short and Ryan Almeida declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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