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PAIN MANAGEMENT IN TRAUMA (MR HOFFMAN, SECTION EDITOR)

Pain Management in the Unstable Trauma Patient

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Abstract

Purpose of Review Review the current literature regarding the optimal approach to pain control in unstable trauma patients, specifically focusing on the initial management of pain and rapid transition to multi-modal agents.

Recent Findings There is a clear benefit to multi-modal analgesia instituted as rapidly as possible in trauma patients. While early management of pain depends upon the use of short-acting IV opioids, the rapid transition to adjunctive pain control strategies is optimal. The benefits include not only improved patient experience but also improved physiologic parameters and lower long-term risk of chronic pain and disability.

Summary The initial management of pain in unstable trauma patients is focused on titrating short-acting IV opioids to effect. Rapid institutions of multi-modal pain control, however, can improve short-term pain management while reducing the physiologic load imposed by uncontrolled pain and reduce the risk of long-term chronic pain and opioid misuse.

Keywords Multi-modal analgesia · Pain management in unstable trauma patients · Benefits of early analgesia

Introduction

The management of the unstable trauma patient is a time pressured and difficult undertaking with multiple competing concerns. A key paradigm shift in civilian and military trauma management has been the early treatment of pain, starting at the injury scene and continuing throughout the continuum of care [1]. While physiologic management is directed towards the primary survey, it is important to remember that injured patients are in pain and management of pain is an essential component of their care [2].

The etiologies of pain in the acutely injured trauma patient are myriad, stemming not only from their injury patterns but also from the pain triggered by therapeutic interventions and exacerbated by psychological distress, anxiety, intoxication, and delirium. The assessment of pain is made more difficult because of alterations in the level of consciousness, traumatic brain injury, alcohol, or other drug intoxications. A patient's satisfaction regarding their pain control can be remarkably unreliable as pain control satisfaction has been reported as high, despite moderate to high levels of reported pain [3].

In this review, we will focus on the management of acute pain in the unstable trauma patient. We will review the long-term benefits of aggressive early pain control. While we will not discuss the pathophysiology of nociceptive and neuropathic pain, we will discuss the pharmacology and potential utility of a variety of analgesic agents and provide recommendations for the management of pain in the pre-operative setting. We will conclude by reviewing recommendations for management in hemodynamically abnormal trauma patients, patients with hepatic and renal dysfunction, patients with pre-existing opioid use disorders, and those on pre-injury opioid blockers. We will additionally briefly review methamphetamine co-intoxication, management of pain in the geriatric patient, and management of pain in a patient with severe brain injury.

Benefits of Early Analgesia

An essential part of the practice of medicine is the control of pain symptoms and, as such, early analgesia is a moral

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imperative. Pain should be routinely assessed and documented to allow for individualized dosing of analgesics [4••]. This individualized approach to pain control allows for improved pain outcomes and achieves the primary goal of improved patient comfort, a key compassionate goal of medicine [5, 6]. In addition to the moral imperative to control the subjective pain in the injured patient and the importance of analgesia/sedation in an intubated patient, there is evidence that early and aggressive pain control may blunt the physiologic response to pain and limit hypermetabolism, hypercoagulability, and immunologic alterations that can be seen with a profound pain response as well as limit ICU and hospital stays lengths [1, 7•, 8•]. Untreated pain can also compromise the already impaired physiologic processes after injury—compromising pulmonary function, intracranial pressure, gastrointestinal function, and ability to participate in rehabilitation [9].

An early aggressive approach to pain control can limit the development of chronic debilitation and facilitate a more rapid return to function [1, 10]. Pain is not a homogeneous experience and typically consists of physiologic, inflammatory, and neuropathic pain—the physiologic components being the most critical early in injury [11]. Activation-dependent neural plasticity is a characteristic that can also be described as autosensitization where repeated activation of a nociceptor terminal can decrease the activation threshold, resulting in a greater subjective pain response for similar stimuli. This can manifest as either allodynia or hyperalgesia and highlights the importance of early pain control to limit the potential for these adverse sequelae development [11].

Acute pain places patients at risk for complex chronic pain, and early interventions to mitigate the subjective experience of pain may help limit the risks of chronic pain syndromes [12•, 13, 14]. Early assessment of a patient's pain level is necessary as extrapolations from the peri-operative pain literature suggest there may be a critical period in which the secondary effects of pain can be modified to help avoid the complex sequelae later [10]. A critical finding to consider is that the patient's experience of pain can be highly discordant from physician or nurse assessment of their pain [15].

Unfortunately, opioid use in the acute setting is a risk factor for opioid use in the chronic setting, and a greater amount of early opioid used increases the risk of long-term use, abuse, and overdose [16, 17]. While opioids are a mainstay of early analgesia in trauma, strategies to reduce the risks of high-dose opioid exposure early, through multi-modal approaches, can set the stage for success in late pain management. Early, appropriate goal setting with patients is essential to further these goals. While pain "free" is not a goal, management of pain to a tolerable level that allows patient comfort in the acute setting and facilitates mobility and rehabilitation in the sub-acute setting is essential.

Selection of Agents

Pain management in the unstable trauma patient should be optimized for each patient and scenario and multi-modal pain medication is recommended. The following section briefly outlines options for pain management with potential risks of different classes of analgesics. Opioids remain a mainstay of pain control, with choice of agent, dose, and route to be tailored to patient-specific concerns. Multi-modal pain control should be employed whenever possible. Acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), topical products such as lidocaine patches and diclofenac gel, and neuropathic pain medications should be considered for appropriateness in all patients. Regional anesthesia, including epidural pain relief and local blocks, can be a source of great pain relief depending on the injury pattern. Ketamine is an important adjunct to pain control regimens, especially in unstable patients due to its favorable hemodynamic profile.

Opioids in the Opioid-Naïve Patient

Opioid therapy remains the backbone of acute pain relief in unstable trauma patients due their potent efficacy and should be employed in the lowest effective dose for the shortest duration that is possible. The diversity of dosing strategies and timing is outlined in Table 1. Opioids all act upon the mu pain receptor both in the brain and the dorsal horn of the spinal cord and the intestines. There are many routes in which to administer opioids, including intravenous, intraosseous, intramuscular and subcutaneous, intranasal, enteral, and rectal. The more lipid soluble the compound, the faster it will act after administration due to an increased rate of absorption from the tissue and entry into the central nervous system (CNS) [18]. An important consideration is that longer term use and higher doses are associated with a greater risk of long-term misuse and overdose [16, 17]. While this is an important consideration, this concern is often tabled for urgent pain management needs of the acutely injured trauma patient.

When choosing a frequency and route of administration, consider the following points.

- Enteral absorption during the resuscitation phase may be limited; therefore, intravenous should be preferred until resuscitation is nearing completion.
- Bolus dosing should be utilized to limit the amount of opioid administered, unless this results in ineffective pain control or is associated with transient hypotension.
- While bolus dosing of agents with a short half-life such as fentanyl is effective for some patients, the short duration of action often necessitates a continuous infusion for adequate pain relief.

Table 1 Common dosing and infusion rates for frequently used opiate medications. An original table

Drug	Oral dose	Parenteral dose	Infusion rate	Dosing interval
Hydromorphone	6 mg	1.5 mg	0.1–0.2 mg/h	3–4 h
Hydrocodone	30 mg	Not available	Not available	3–4 h
Oxycodone	20 mg	Not available	Not available	3–4 h
Morphine*	30 mg*	10 mg*	Not recommended	3–4 h
Fentanyl	Not available	100 mcg	25–100 mcg/h	1 h
Sufentanil	Not available	Not recommended	10–60 mcg/h	Infusion

*Morphine is not recommended for use in unstable trauma patients due to the risk of worsening hypotension, bronchoconstriction, and neurotoxic adverse events

- Once enteral opioids are deemed appropriate, short-acting formulations are preferred over extended release formulations to allow for rapid titration.

Fentanyl and sufentanil are very potent synthetic opioids with a fast onset and relatively short duration of action. They are therefore typically administered via continuous infusion for longer term pain needs or as bolus doses for acute and uncontrolled post-traumatic pain [18]. These agents are highly lipophilic and easily cross the blood-brain barrier. Fentanyl and sufentanil undergo hepatic metabolism and renal excretion, without clinically important metabolites—making their safety in hepatic and renal failure an important factor in their use. With high doses or prolonged exposure from continuous infusions, these drugs can accumulate, resulting in a prolonged duration of action. A noted adverse effect of fentanyl includes muscle rigidity with high-dose boluses, which can transiently impair ventilation due to chest wall rigidity [18]. Even with these limitations, fentanyl is a common first-line medication for the management of acute traumatic pain in the pre-hospital setting, the trauma bay, and the intensive care unit.

Morphine is the quintessential opioid, although it is problematic and should be generally avoided in the unstable trauma patient. Morphine causes histamine release, resulting in hypotension and bronchoconstriction, an effect that is compounded by the hypovolemia common in bleeding trauma patients. In addition, the two main metabolites of morphine, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), can compound management. In a patient with renal dysfunction, M6G can accumulate, leading to a prolonged duration of action [18]. More concerning, M3G has a low affinity for opioid receptors and lacks analgesic activity but is associated with neurotoxic adverse effects such as hyperalgesia, allodynia, and myoclonus [18, 19]. These pharmacologic factors preclude use in unstable trauma patients in all but the most unique circumstances. Widely available opioids that are much more commonly used include hydromorphone, oxycodone, hydrocodone, fentanyl, and sufentanil.

Hydromorphone is a synthetic derivative of morphine and is commonly available for intravenous and enteral use and can be given by almost any available route. Hydromorphone has higher lipid solubility than morphine allowing for a more rapid onset of action. Hepatic metabolism creates hydromorphone-3-glucuronide (H3G) and has been shown to have neurotoxic side effects, but the clinical significance remains unclear [18, 20]. This is an excellent option for unstable patients who are in need of somewhat longer acting pain medication.

Oxycodone is a semisynthetic opioid available in oral formulations. Hydrocodone is synthesized from codeine and is also available in oral formulations, typically combined with acetaminophen, and has approximately equal potency to oxycodone [18]. While both agents are excellent oral pain medications that are commonly used in the sub-acute setting, as they are limited to oral formulations, they have a limited role in the unstable trauma patient where the rapid onset and easy titration of intravenous opioids is typically preferred.

Opioids in the Chronic Opioid User

Chronic prior to admission opioid use should be considered and accounted for in pain regimens. Maintenance opioids should not be expected to adequately treat new, acute post-traumatic pain. While opioids are available in a multitude of extended duration dosage forms for chronic pain, the use of these formulations should be avoided in the unstable trauma patient. Transdermal fentanyl patches are especially ill suited for this population. Hypotension, alterations in body temperature, and fluctuations in fluid status result in variable transcutaneous absorption and thus an unpredictable therapeutic and side effect profile. In addition, the onset of pain control takes up to 12 h to develop and up to 16 h to see the full clinical effect [18]. Once removed, the plasma half-life is 17 h, so if excess sedation or respiratory depression occurs, prolonged corrective therapies such as naloxone may be required [18].

While pain management in the chronic opioid user should be individualized, the following guidelines provide a starting point for management:

- If transdermal fentanyl patches are present upon arrival, remove the patch and replace it with an equivalent opioid

intravenously or enterally until the patient is hemodynamically normalized.

- Patients on chronic methadone therapy should have their regimens confirmed and restarted as soon as clinically feasible to avoid undertreatment of pain or iatrogenic withdrawal syndromes [18]. Intravenous methadone formulations are available if enteral access is limited, but oral doses should be halved when given intravenously.
- Buprenorphine poses a unique problem in trauma patients. As a partial mu agonist, buprenorphine binds strongly to the mu receptor. When another opioid is administered, buprenorphine can block its analgesic effect while occupying the mu receptor. Opioids should still be administered and titrated to effect, recognizing that elevated doses may be required. Once the patient has stabilized, reinducing the patient onto buprenorphine therapy will require mild or moderate opioid withdrawal, which should be discussed with the patient and planned carefully for [21]. Whenever possible, attempt to continue buprenorphine therapy to avoid this withdrawal syndrome that may trigger relapse in patients with opioid use disorders [21].
- Long-acting, injectable naltrexone is an opioid antagonist that will complicate acute pain regimens. The amount of opioid administered will likely be greater than usual, and the resulting respiratory depression may be prolonged. Titration of a short-acting opioid analgesic to the needs of the patient is suggested. Non-opioid pain management strategies should be optimized.

Non-opioid Analgesics

Acetaminophen (paracetamol) is recommended in all patients who do not have an allergy or other contraindication to this therapy. In addition to decreasing pain intensity, acetaminophen has been shown to decrease opioid consumption and has little to no effect on platelet function [4••, 20]. The clearest data supporting widespread acetaminophen use comes from the intravenous formulation, but all formulations are considered comparably effective [4••]. Of note, the intravenous formulation of acetaminophen has been linked to clinically relevant hypotension [22]. Scheduled, divided dosing of acetaminophen 4000 mg daily should be considered in all patients. Dose limitations of 2000 mg daily should be considered in severe or decompensated liver impairment, especially if patients are also malnourished or cachectic at baseline [23]. While clearly not sufficient for the management of severe post-traumatic pain, acetaminophen is an essential part of multi-modal pain control and should be introduced as soon as clinically reasonable.

Ketamine is a *N*-methyl-D-aspartate (NMDA) receptor antagonist that offers many advantageous properties in the unstable trauma patient [4••]. It is a dissociative anesthetic that provides analgesia when used at lower doses than are used for anesthesia induction or procedural pain relief. Low-dose ketamine has been shown to improve pain relief while reducing opioid requirements [4••]. Current guidelines recommend a 0.5 mg/kg bolus followed by an infusion of 1–2 mcg/kg/min for 24–48 h as an adjunct to opioid therapy [4••]. With a favorable risk/benefit profile, a rapid onset of action, and the potential to be used as both an adjunctive analgesic and a conscious sedation medication, ketamine is increasingly being used in the trauma bay and during initial resuscitation phases. Ketamine administration increases blood pressure, heart rate, and cardiac output, likely via inhibition of catecholamine reuptake, which is desired in hypotensive patients [18]. In patients at risk of myocardial ischemia, the corresponding increases in myocardial oxygen consumption due to increasing cardiac output is not ideal [18]. Other adverse events include diplopia, nystagmus, sedation, and psychological effects [24••]. Psychomimetic adverse event rates vary from undetected to 16%, but these events typically respond to benzodiazepines or simple cessation of the infusion [24, 25]. It may be prudent to avoid in patients with acute psychiatric illness. Intracranial hypertension is not considered an adverse effect of ketamine, except in the setting of hydrocephalus or other cerebrospinal fluid flow obstruction [26••, 27]. Indeed, ketamine has been shown to decrease intracranial pressure in traumatic brain injury [27]. The synergistic effect of ketamine with short-acting intravenous opioids, paired with a minimal impact on hemodynamics, make it an ideal adjunctive medication in the unstable trauma patient [25].

NSAIDs are generally not recommended in unstable patients due to gastrointestinal, renal, and bleeding adverse events with limited pain reduction [4••]. Gastrointestinal adverse event risk is particularly high in patients with concomitant *Helicobacter pylori* infection, heavy alcohol consumption, corticosteroid use, and advanced age [18]. Renal adverse events may be compounded by hypotension and therefore, NSAIDs should be avoided in hemodynamic instability which essentially precluded their use in the unstable trauma patient. NSAIDs are known to inhibit platelet activation, leading to an increased risk of hemorrhage and platelet dysfunction [18]. Should NSAID therapy be employed, patients should be hemodynamically stable without acute kidney injury. To minimize the potential adverse effects, use the lowest effective dose for limited durations of time.

The topical application of analgesic and anti-inflammatory medications offer benefits of lowered systemic drug exposure and local pain relief. Unfortunately, in the unstable trauma patient, risk and efficacy are unclear. Lidocaine patches have strong safety and tolerability profile; however, the efficacy of these patches for rib fracture pain remains controversial [28–30]. Topical NSAIDs, specifically diclofenac gel, have been extensively studied in soft tissue injury showing

efficacious pain relief with few adverse events. Systemic absorption is only a fraction of systemic dosing, with serum concentrations less than 10% of orally administered drugs [31]. A trial of topical analgesic therapy is reasonable but should be discontinued if no benefit is seen or reported. As with acetaminophen, these adjunctive medications are likely insufficient to manage acute post-traumatic pain in an unstable trauma patient by them but are an essential part of multi-modal pain control and should be introduced as rapidly as possible.

Regional Anesthesia

Regional anesthesia offers many advantages in trauma patients but has notable limitations in the unstable trauma patient related to the logistics of placing these catheters. Regional anesthesia can provide acute pain relief and dense anesthesia to specific areas of the body, and is often more effective than systemic opioids and sedatives with a more favorable side effect profile. The limitations of regional anesthesia outweigh the benefit in most unstable trauma patients. These limitations include the inability of the patient to consent, interact, and position for catheter placement that coagulation status must be known and coagulopathy must be corrected prior to placement and the sympathectomy associated with a local anesthetic that is unacceptable in hemodynamically unstable patients [32].

Regional peripheral blocks may be more feasible but also have notable limitations. Injuries may complicate tissue plane identification, dense anesthesia can mask symptoms of compartment syndrome, positioning needed for placement may be problematic, and the efficacy data in the trauma population is limited [33]. Additionally, nerve injury should be considered prior to placement as it can be masked after nerve block [32].

Gabapentinoids

Neuropathic pain medications should be considered in patients experiencing neuropathic pain, although this is uncommon in the acutely injured, unstable trauma patient. Available medications include gabapentin, carbamazepine, and pregabalin. These medications are an important adjunct to pain management in neuropathic pain and after hemodynamic stability has been achieved and an oral diet is being started, they can be started at low doses and titrated to efficacy, tolerability, and side effect profile.

Case Scenarios with Specific Recommendations

With this general information in mind, we will now turn to several specifically challenging scenarios to outline at least an initial approach to complex pain management in the unstable trauma patient. It is important to note that there is no such thing as a uniform approach to pain management and these suggestions exist primarily as suggestions for a starting point and an approach to pain management.

1) The hemodynamically abnormal pre-hospital patient
    a. Management of pain in the pre-hospital setting can be particularly complex as there are competing demands for rapid transport, initial diagnosis, and lifesaving procedures. In these settings, IV fentanyl bolus dosing is typically the pre-hospital drug of choice [34]. The rapid onset and relatively short half-life of fentanyl in bolus dose format allow titration to an individual patient's needs. While longer transport times will frequently necessitate repeat dosing of fentanyl, it is still preferred over longer acting opioid due to the ability to titrate and match a patient's pain.
2) Chronic alcohol use
    i) There may be a degree of cross tolerance between alcohol and opioids. In patients with prior alcohol histories who are currently sober, increased opioid dosing may be required. In the acute setting, this can be accounted for with repeat intravenous bolus dosing of fentanyl or hydromorphone. In a patient with advanced liver disease, we advise starting at the lowest effective dose and titrating up slowly to match pain needs as altered pharmacokinetics in the cirrhotic liver can make a response to opioid therapy difficult to predict. In the acutely intoxicated patient, the additive effect of increasing opiate doses and alcohol can result in an increased risk of respiratory depression, so dose titration should be done cautiously [35].
3) Pre-injury chronic opioid use
    a. The combination of increasing opioid use for chronic pain and opioid use disorders results in the increasing likelihood of encountering an unstable trauma patient with a very high opioid tolerance. The cross tolerance between opioids typically results in patients with pre-injury opioid use needing significantly higher doses for equi-analgesic effect. While not necessarily an issue in the acute setting, chronic opioid dosing should be replaced as soon as is feasible and acute pain needs to be treated in addition to this chronic opioid therapy. In the acute setting, titrating fentanyl or hydromorphone to effect remains an acceptable strategy and ketamine can be used in very difficult situations for adjunctive effect.
4) Pre-injury buprenorphine use
    a. The increasing use of the antagonist/agonist buprenorphine for the treatment of opioid use

disorders does complicate pain management. The initial management of pain, again, relies upon titrating dose of fentanyl and hydromorphone to effect, although the doses needed may be very high. These are patients where ketamine can be an excellent adjunct for pain control and the importance of multimodal pain control with regional blocks is amplified. If possible, subspecialty pain and addiction medicine physicians should be involved early as the transition off and back on to buprenorphine can be difficult and nuanced.

5) Geriatric patients

   a. The management of pain remains important, regardless of a patient's age. Older patients clearly feel pain, although their ability to verbalize and manifest that pain may be filtered through superimposed layers of stoicism, delirium, dementia, and depression. Optimal pain control is essential as both uncontrolled pain and opioid overdoses are associated with delirium and an increased risk of a poor outcome. In the acute and unstable setting, as is the theme, small doses of short active opioids are a reasonable starting point, although the rapid transition to a multi-modal approach almost universally results in better pain and cognitive outcome. If possible, involving a geriatric medicine consult service in the care of these complex patients is advisable as the interplay of underlying neurocognitive disorders, pain, and the sedating effects of opioids can be complex.

6) Patient unable to communicate

   a. There are myriad reasons why acutely unstable trauma patients may be unable to communicate. This ranges from intoxicants to severe traumatic brain injury to chemical neuromuscular blockade. The pain management of these patients is eased somewhat as they typically have a controlled airway and thus, the respiratory side effects of opioids are of lesser significance. Regardless of a patient's ability to communicate or mental status, they can and do feel pain. It remains critically important to continue to manage their acute traumatic pain, regardless of their ability to communicate. As visual and verbal scales are unhelpful in the obtunded patient, observation tools—such as the Critical-Care Pain Observation Tool (CPOT) can be very helpful [36, 37•]. While somewhat outside the scope of this article, it is important to note that if the neuromuscular blockade is being considered for the management of acute respiratory distress syndrome, the analgesic strategy that is in place at the initiation of neuromuscular blockade must be a fixed dose with proven efficacy as any and all bolus doses based on observed factors will be unreliable.

Conclusion

The management of acute pain is an essential part of trauma care. This starts in the pre-hospital setting and continues through the trauma bay, the operating room, and the intensive care unit. As a general rule in unstable trauma patients, start with small doses of a rapidly titratable opioid such as fentanyl or hydromorphone, and then, adjust dose frequency and dose amount to effect. While opioids remain the mainstay of treatment given their rapid onset and efficacy, multi-modal pain control that includes regional analgesia should be initiated as soon as the initial resuscitation phase is over. Ketamine can be very helpful in the acute setting, both at analgesic and sedation dosing, for patients with difficult to control pain, active buprenorphine use, or pre-existing opioid tolerance. There is a clear benefit to early pain control, both from an acute physiologic response to injury perspective as well as a long-term neurocognitive recovery perspective. While no pain is not a feasible goal, the compassionate treatment of trauma patients must include a careful eye towards pain control during initial resuscitation.

Compliance with Ethical Standards

Conflict of Interest Drs. Cook and Barton both declare nothing to disclose.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors were performed in accordance with all applicable ethical standards including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines.

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37.• Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. Am J Crit Care. 2006;15(4):420–7 **Pain control is essential, even if patients are not able to interact. The CPOT score is a validated tool to allow the ICU staff to score patients pain and thus titrate analgesics to effect**.