Chapter 25

PREHOSPITAL ANALGESIA

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INTRODUCTION

Historically, analgesic interventions in the prehospital environment were of secondary importance in the management of trauma patients. Aggressive pain control was even considered detrimental to injury diagnosis on arrival to the hospital. An introduction to a 1981 paper on prehospital analgesia stated, "Any agent that interferes with the patient's normal pain response may frustrate the physician attempting to make a diagnosis," and "a suitable agent . . . should be quick-acting and short-lived in order to preserve the pain response for diagnostic purposes in the ED."[1] Compounding this deemphasis on pain control was a prevailing belief that seriously injured casualties suffered little, as the oft-quoted statement by Dr Henry K Beecher suggested: "severe wounds in soldiers are often associated with surprisingly little pain."[2] As a US Army physician serving overseas during World War II, Beecher reported that up to 75% of battle-wounded soldiers deferred analgesia.

Fortunately, medical thinking in both regards is moving beyond these antiquated paradigms. Little controversy now remains that point-of-injury treatment of pain, before transfer to a definitive care facility, is a desirable and in fact medically beneficial goal. Holbrook et al, for example, found that use of morphine in US military personnel immediately after combat-related trauma was associated with lower rates of posttraumatic stress disorder (PTSD).[3] What remains undecided is the ideal analgesic regimen for trauma patients, a medical demographic largely defined by their heterogeneous and complex afflictions. A standardized pain regimen may aid one patient immensely while resulting in catastrophic complications for another. Therefore, valid concerns about the potential for adverse reactions to medications in this vulnerable population do exist and bear consideration. Both objectives of blunting nociception and avoiding exacerbation of the physiologic insults of trauma thus shape the development of any widely applied prehospital pain control algorithm.

AN IDEAL BATTLEFIELD ANALGESIC

Treatment of pain in the battlefield setting involves unique and demanding circumstances unlike any other medical scenario. Environmental challenges of heat, cold, aridity, moisture, dust, and sunlight exposure threaten the stability of medical materials. Various routes of medication administration must be available because victims of polytrauma may have multiple traumatically amputated limbs or severe hemorrhagic shock; either situation confounds intravenous (IV) access. Traumatically disrupted gastrointestinal organs make oral administration ineffective at best, life-threatening at worst. Intraosseous (IO) access, especially by sterno-manubrial approach, is thus experiencing heightened interest for its availability in even critically wounded patients. Methods of delivery should be as straightforward as possible because all friendly forces in combat are potential caregivers. In a tactical setting, medical care may be administered by the casualties themselves, a medically naive service member, a trained medic, or even a credentialed independent provider.

Once suitable for the demands of the battlefield, an analgesic intervention for traumatic injury must produce a clinically significant reduction in pain, proportionate to the severity of wounds sustained. Pain relief should have a rapid onset, measurable in minutes, with a rarity of adverse effect at clinically efficacious doses. Hemodynamic stability should be maintained, if not augmented, given the threat of hypovolemic or obstructive shock. Optimally, medications would not impair airway reflexes or minute ventilation, although a reduction in respiratory rate and tidal volume is consistent with adequate pain control. Besides preservation of cardiopulmonary function, medications given for combat analgesia should have minimal deleterious side effects, such as excessively altered mental status, disabling motor block, platelet inhibition, emetogenic potential, increased intracranial pressure (ICP), allergic reaction, or interference with expected effect of other medications. Other desirable qualities include a large therapeutic index, low interpatient pharmacokinetic variability, and arguably an amnestic effect.

Exclusive to military operations is the need to preserve the fighting force even in the face of excruciating pain. If adequate pain control for wounds will impair a service member's operation of a critical weapon system or fighting position, the analgesia could be withheld for the survivability of the unit. Therefore, analgesics that will not remove an otherwise mission-ready service member from the fight should be in the provider's armamentarium.

MODALITIES

In the search for the optimal pain intervention regimen on the battlefield, evidence in the form of randomized clinical trials is lacking. Best practice must be extrapolated from retrospective or observational

studies, established civilian trauma pain management, and other data not wholly representative of the combat trauma population.

Narcotics

Narcotics have been in use for military pain management since the American Civil War, testimony to their effectiveness in treating acute pain. Once available only at the field hospital, single-use morphine "syrettes" were developed by the US Navy for use by individual service members; their use was reported by Major Charles Wilson as early as 1941.[4] Intramuscular (IM) morphine has since been the historical "gold standard" in battlefield analgesia, but IV, intranasal (IN), and transmucosal preparations of various opioids have been explored in recent years. Smith et al studied 204 trauma patients given IV morphine or IV fentanyl during helicopter evacuation.[5] The medications were equally effective, with both groups achieving a decrease in mean pain scores from 80 mm to approximately 55 mm on the visual analog scale (VAS), which uses a 100-mm line to score pain. Neither group achieved pain scores below 40 mm, which is considered mild pain. Doses used in this study were 4 mg IV morphine and 50 μg IV fentanyl, with an average of two subsequent doses during transport to the hospital. No statistically significant difference in adverse effects was identified.

In a double-blinded, randomized, but small clinical trial, Galinski et al compared prehospital administration of IV morphine and IV fentanyl, at doses of 0.1 mg/kg and 1 μg /kg, respectively. Both treatments were effective at reducing pain by approximately 40 mm on the VAS, and there was no significant difference in pain relief or incidence of side effects.[6] Bounes et al conducted a randomized, double-blind, out-of-hospital trial comparing strict sufentanil or morphine regimens for adult patients with severe traumatic acute pain. While pain control in the sufentanil group was superior at 9 minutes after institution of treatment, the difference was negligible at 15 minutes.[7] Overall, administration of IV narcotics for patients in the prehospital setting suffering from moderate to severe pain appears safe and effective in studied dosing schemes.[8–11] No IV formulation of narcotic, however, holds the distinction as the "best" IV opioid for acute trauma patients.

For patients in whom IV access is impractical or impossible, alternative routes of administration are an option. Rickard et al found no significant difference between prehospital use of IN and IV fentanyl.[12] IN fentanyl was dosed at 180 μg, with subsequent doses of 60 μg, while IV morphine was given in 2.5-mg to 5-mg doses. Each reduced verbal rating scores (VRS) of pain by approximately 4 points on a scale of 0 to 10. Karlsen et al evaluated 903 patients who received IN fentanyl in a prospective observational study, noting a median pain score reduction of 3 points, with no serious side effects or naloxone requirement.[13] Both studies involved patients with nontraumatic, presumed cardiac pain, confounding their application to battlefield settings, but they illustrate that IN administration is a viable option when necessary. More proven in the operational environment is oral transmucosal fentanyl citrate (OTFC), which is formulated as a "lollipop" for placement on oral mucosa for absorption and systemic effect. Buccal absorption produces quick onset of analgesia, while gastric and intestinal absorption afford sustained analgesia. OTFC use in 286 military casualties over 7 years demonstrates satisfactory reduction in verbal-numeric rating scale scores, averaging a 4.8-point reduction in 15 to 30 minutes.[14] Only one patient in this series required naloxone due to hypoventilation, and that was after receiving 3,200 μg of oral fentanyl and 20 mg of morphine.

In 2010, Park et al reviewed 21 studies encompassing 6,212 patients who received various forms of prehospital analgesia, with most data focused on the use of opioids, specifically morphine, fentanyl, alfentanil, and tramadol. These studies represented a mixture of patient populations, such as civilians with traumatic injuries and acute medical patients; three studies specifically examined military injuries. Park et al concluded that opioids overall achieved satisfactory pain levels (defined as less than or equal to 30 mm on the VAS) in approximately 35% of patients by 10 minutes, and 70% by 40 minutes. No patients in this systematic review required ventilatory support, only two required naloxone, and cardiovascular instability related to opioid administration was uncommon.[15]

This review succinctly concludes that narcotics of various formulations have an acceptable efficacy and safety record when used for traumatically injured patients at the studied doses. Any attempt to improve upon opioid analgesia onset and intensity must be balanced against the very real untoward effects of narcotics. Concerns about aggravating hypovolemic shock or hypercarbia resulting in intracranial hypertension are well founded, especially in the deployed combat scenario. In any setting, use of narcotics for severe pain assumes the risk of potentially life-threatening respiratory depression.

Nonsteroidal Antiinflammatory Drugs

Although not the mainstay treatment for management of severe traumatic pain, nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen serve important roles in battlefield pain management. They

supplement the analgesia of narcotics without contributing to the risks of respiratory depression or hypotension, and may be readily dispersed to nonmedical personnel. The risks of NSAID-related gastrointestinal bleeding or acute renal injury are remote in the typical healthy service member, and acetaminophen has a minimal side effect profile in appropriate doses.[16] Furthermore, NSAIDs and acetaminophen are ideal sole agents to address minor ailments that could otherwise impact a soldier's mission-readiness.

Data is absent concerning acetaminophen or NSAID effectiveness for prehospital treatment of combat-injured patients; rather, most studies address orthopedic ailments in the emergency department setting. Viallon et al administered 1,000 mg of oral acetaminophen to 571 emergency department patients with musculoskeletal injuries, ranging from sprains to dislocations to fractures, showing that pain scores improved on average by 27/100 mm on the VAS after 1 hour.[17] Impressively, 1,000 mg IV acetaminophen demonstrated equivalent analgesia to 10 mg IV morphine in a randomized, double-blind study of adult patients with isolated limb traumatic injury.[18] Ibuprofen, ubiquitous in the military world, and acetaminophen were both found to reduce VAS scores by a mean of 20/100 mm within 1 hour in the emergency department when administered for acute musculoskeletal pain, but the two drugs did not show synergistic analgesia when given together.[19]

In contrast, a Cochrane database systematic review of ibuprofen and acetaminophen administration for postoperative pain management found the combination of an NSAID and acetaminophen to be more effective than ibuprofen alone. Groups compared included patients experiencing acute perioperative pain or migraine. Higher dosing strategies of ibuprofen plus acetaminophen (versus placebo or ibuprofen alone) increased the percentage of patients achieving 50% of maximal pain control at 6 hours and significantly lengthened the amount of time until further rescue medication was needed.[20] In postoperative pain control and acute musculoskeletal injuries, ketorolac and diclofenac have demonstrated analgesia comparable to weaker opioids.[16] Proving efficacy of NSAIDs or acetaminophen for combat injuries will be challenging even if such as study is attempted, but the paucity of side effects and the likelihood of some analgesic benefit make these medications attractive in polytrauma patients.

Inhalational Analgesia

Volatile anesthetics have known analgesic effect, a quality exploited by several countries in the prehospital setting and emergency department. The United Kingdom readily employs Entonox (BOC Healthcare, Worsley Manchester, United Kingdom), a 50/50 mixture of oxygen and nitrous oxide, for administration by emergency medical technicians before the patient arrives at the hospital. A randomized clinical trial conducted by Ducassé and colleagues compared Entonox to an oxygen placebo during ambulance administration.[21] The study enrolled adult patients with moderate acute traumatic pain, a demographic resembling a typical military trauma patient. After 15 minutes of inhalation, Entonox successfully decreased initial pain scores from a median of 6 to 3 or below on a numeric rating scale in 67% of patients.

Although inexpensive and hemodynamically benign, nitrous oxide has several contraindications that restrict its widespread application in the traumatically injured patient population. It is well known to complicate certain traumatic injuries, such as pneumothorax or air emboli, due to its relatively high solubility coefficient when compared to nitrogen.

Methoxyflurane, a halogenated ether, was removed from the US and Canadian markets for unacceptable risk of hepatotoxicity and dose-dependent nephrotoxicity when used at general anesthetic doses. In low concentrations of up to 0.5%, however, patients may enjoy the benefit of pain relief with minimal risk of hepatic or renal damage. Buntine et al showed a mean reduction in VRS scales of 2.47 in 83 patients receiving methoxyflurane during ambulance transport, with 72.3% of patients reporting satisfaction with the level of pain control.[22]

Middleton et al reviewed the prehospital pain regimens for 52,046 patients to compare IV morphine, IN fentanyl, and inhaled methoxyflurane.[23] Only 59.1% of patients who received methoxyflurane had a 30% or greater reduction in their pain, as measured on a 0 to 10 verbal-numeric rating scale. This analgesic efficacy was statistically inferior to the respective 81.8% and 80.0% of patients receiving IV morphine or IN fentanyl with the same threshold of pain relief. With IM, IN, and transmucosal preparations of other medications answering the need for analgesia when IV access is not available, the expansion of inhaled halogenated ether use in a prehospital setting is unlikely.

Ketamine

The *N*-methyl-D-aspartate (NMDA) antagonist ketamine was first synthesized in the 1960s from phencyclidine in an attempt to decrease incidence of delirium while retaining the dissociative anesthetic quality.[24] The potential for battlefield pain management was quickly recognized, and ketamine came into use

by the US military during the Vietnam War. Ketamine is now experiencing a resurgence of interest for analgesia on the modern battlefield thanks to a deeper understanding of its favorable hemodynamic effects in the trauma patients, relative preservation of airway reflexes and the carbon dioxide response curve, and multiple available routes of administration.

The historically cited adverse effects of ketamine in the traumatically injured patient must be addressed in the context of recent academic skepticism, these concerns being increased ICP, increased intraocular pressure (IOP), and distressing psychotic symptoms. The former was addressed in a review of five randomized prospective studies, including patients with traumatic brain injuries, in which ketamine infusions for sedation showed no statistically significant increase in ICP and possibly an increase in cerebral perfusion pressure.[25] Halstead et al challenged the second concern by measuring IOP in otherwise healthy children without ocular injury who received ketamine for procedural sedation in the emergency department. IOP was not statistically increased after giving ketamine in average doses of 1.6 mg/kg.[26] Lastly, ketamine use was associated with a decrease in PTSD in burned active duty service members despite more extensive burns and longer stays in the intensive care unit in the ketamine-treated group.[27]

Barring these specific controversies, IV and IM ketamine has an excellent safety record when used outside a medical facility. Bredmose et al found no episodes of hypoxia or loss of airway patency related to ketamine administration in 1,030 prehospital clinical encounters.[28] A systematic review by Jennings et al evaluated six studies, finding that ketamine delivered effective relief for acute traumatic pain in the prehospital setting, either as monotherapy or by reduction in morphine requirement.[29] When compared directly against the "gold standard" of morphine in a prehospital prospective study, ketamine delivered equivalent reductions in VAS pain scores as morphine, lower rates of emesis, but increased risk of hallucinations and agitation.[30] Also, 57 of 169 patients with head trauma who received ketamine in this series suffered no demonstrable declines in mental status. If both drugs are available for point-of-injury care, some data supports superior analgesia with coadministration of ketamine and morphine over morphine alone, with mean VRS reductions of 5.6 versus 3.2, respectively.[31] The ability to administer ketamine via the IN route needs further exploration, but preliminary investigation in nine patients suggests efficacy for point-of-injury use.[32] While it is premature to conclude that ketamine should completely replace narcotics as the foundation of moderate to severe combat trauma pain management, its theoretical and proven qualities appear closely suited to the needs of today's battlefield medicine.

CURRENT MILITARY PRACTICE

The US military has widely adopted the Tactical Combat Casualty Care (TCCC) model for training its service members to prevent battlefield deaths with simple, life-saving procedures. The guidelines are regularly reviewed and updated as new data are published, most recently on 28 October 2013 (http://www.usaisr.amedd.army.mil/assets/pdfs/TCCC_Guidelines_131028.pdf). While TCCC recommendations cast a wide net over battlefield medical care, only the pain management aspects will be summarized in this discussion. Casualties are quickly dichotomized into mission-capable and disabled patients by the attendant medical provider. Personnel with minor wounds who are able to meaningfully contribute to combat operations are administered 1,300 mg oral acetaminophen every 8 hours and 15 mg oral meloxicam once daily. Meloxicam was selected for its relative cyclooxygenase-2 selectivity.[33] Ideally, all service members carry these medications as part of their issued first aid kits and may self-administer them when hurt.

Seriously injured trauma casualties may receive acetaminophen and meloxicam if they can tolerate oral medications, but the TCCC algorithm then stresses escalation to narcotics and ketamine. Patients with moderate to severe pain, not suffering from hemodynamic shock, and without evidence of respiratory depression, receive an 800 μg OTFC lozenge/lollipop. TCCC guidelines suggest taping the OTFC lozenge-on-a-stick to the patient's finger, so that if the patient becomes excessively sedated, the drooping arm will pull the lozenge from the mouth and prevent further narcotization. A second lozenge may be used directly following the first in the event of inadequate analgesia.

If a patient is suffering moderate to severe pain and is at risk for hemodynamic or pulmonary instability, ketamine is the first-line treatment. When IV or IO access is available, the qualified medical provider on scene administers 20 mg of ketamine every 20 minutes. Alternatively, ketamine may be injected IM in 50-mg aliquots or sprayed IN as a 50-mg dose every 30 minutes. Ketamine dosing is halted upon attaining satisfactory analgesia, or in the event of nystagmus, ventilatory compromise, or agitation. TCCC allows for ketamine dosing for patients with ophthalmic injuries or significant traumatic brain injury, acknowledging the controversy over increased IOP and ICP, respectively.

IV or IO morphine remains on the algorithm as an alternative to OTFC, given in 5-mg doses every 10 minutes, titrated to pain control, with monitoring of respiratory depression. The availability of naloxone is strongly encouraged when administering any narcotic, however, and use of ketamine and narcotics is reserved for combat medics or paramedics, the latter being members of the special operations community who have received advanced medical training.

SUMMARY

Even in the 21st century modernized battlefield, the optimal pain regimen for military trauma victims is unclear. While randomized clinical trials and certainly placebo controls are impractical for research in a combat zone, higher quality data elucidating best care practices for this particular population are needed. There remains a paucity of information, and what is available is complicated by wide variation in the patient, provider, and environment. The combat medical provider is strongly encouraged to utilize current guidelines pursuant to their level of expertise, but critically apply them as each unique trauma scenario dictates. Potential side effects must be recognized and averted if possible. Treatment algorithms should be routinely scrutinized for updates based on new evidence and shifting paradigms. No service member should suffer unnecessarily after injury, but control of pain must never take priority over life-saving interventions, which are paramount in combat casualty care.

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