Analgesia and Sedation in the Prehospital Setting

A Critical Care Viewpoint

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ABSTRACT

Pain is one of the most common complaints of battlefield casualties, and unique considerations apply in the tactical environment when managing the pain of wounded service members. The resource constraints commonly experienced in an operational setting, plus the likelihood of prolonged casualty care by medics or corpsmen on future battlefields, necessitates a review of analgesia and sedation in the prehospital setting. Four clinical scenarios highlight the spectrum of analgesia and sedation that may be necessary in this prehospital and/or austere environment.

KEYWORDS: *pain; analgesia; sedation; ketamine; opioids; fentanyl; guideline; military; operational; deployed; battlefield; prehospital*

Introduction

Pain is one of the most common complaints of battlefield casualties, and analgesia (i.e., pain management) has been an integral part of war for thousands of years. From the Romans' use of cool water, mandrake, and other natural remedies to the United States' cutting-edge pharmacologic therapy, multiple modalities and treatments have accompanied prehospital care.[1] Adequate pain control decreases deleterious outcomes, such as chronic pain and posttraumatic stress disorder.[2,3] Analgesia should be given when feasible after injury or as soon as possible after the management of MARCH (i.e., massive hemorrhage, airway, respiration, circulation, hypothermia prevention). This must be appropriately documented, including all details of the specific medication, dose, route, and time. Also, there may be tactical factors for delaying pain management (e.g., the need for the individual to maintain a weapon or security). The goal is to provide appropriate pain management while simultaneously protecting the patient's hemodynamic status, as well as operational safety and feasibility.

A second goal of the practitioner may then be acute or prolonged sedation. Sedation and analgesia are separate treatments with different therapeutic goals. Analgesia is the decreased sensation of pain, and treatment has been simplified over time by use of the Tactical Combat Casualty Care (TCCC) guidelines to allow for the safe administration of medications without the need for advanced monitoring for pain control only.[4] Sedation is a drug-induced decreased level of consciousness, the depth or degree of which ranges from anxiolysis to deep sedation, per the American Society of Anesthesiologists.[5] Relevant to this guideline are moderate sedation, which is a one-time event typically done to assist a procedure; dissociative sedation, which is achieved through the administration of ketamine; and deep sedation, which is typically performed over a prolonged period for critically ill or injured patients. In most cases, sedation does not typically provide analgesia, and additional pain medication is required.

The *JSOM* Critical Care Supplement is intended to address appropriate pain control and sedation in the prehospital/prolonged casualty care setting across a variety of skill levels and severities of injury. This guide is meant to promote treatment appropriate to the degree of injury, emphasizing expedient return to duty. However, for those too severely wounded to contribute to the fighting force, aggressive pain control and even total sedation might be appropriate. Because the possibility of near-peer conflict arises in situations where air superiority may not be the reality, prolonged care for casualties may become standard in prehospital or Role 1 care. Therefore, this supplement will also address the critical aspects of longer-term pain control, sedation, and necessary monitoring across all spectrums of injury.

Cases

Four Joint Services casualties are brought to a Role 1 facility. They were injured after an improvised explosive device detonated as they were exiting their vehicle during a joint exercise. The medical team, of which you are part, has the typical Role 1 capabilities, primarily immediate life-saving supplies. As a Role 1 provider, you may expect to hold casualties up to 72 hours. This is particularly likely given that your unit does not always have the ability to undertake expedient evacuations because of the near-peer environment in which you are now operating. Additionally, you may be responsible for transporting these casualties when evacuation does arrive, which could take more than 16 hours. Your team has had inconsistent communication over the last few days, and you know there may be options for air drops (e.g., equipment, medication) that may include medication outside traditional TCCC guidelines—for example, other parenteral (intramuscular [IM], intranasal

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[IN], intraosseous [IO], and intravenous [IV]) and oral medications. You are initially tasked with pulling medications while the rest of your team works to specifically address your patients' pain needs. Your patients are as follows:

Patient 1. A 26-year-old man with a 5-in laceration to the face. Bleeding is controlled, and he currently rates his pain at 4/10. He is hemodynamically normal. Treatment prior to arrival: bandage.

Patient 2. A 23-year-old woman with an open fracture of the upper right arm, no numbness or paresthesia. She has a present ipsilateral radial pulse and currently rates her pain at 6/10. She is hemodynamically stable. Treatment prior to arrival: bandage, SAM (structural aluminum malleable) splint, and sling without reduction of the fracture.

Patient 3. A 32-year-old man with an open femur fracture of the right leg and below-the-knee blast injury with partial amputation of the lower left leg. He complains of 10/10 pain. He is hemodynamically abnormal, with a pulse of 110 beats per minute (bpm) and blood pressure level of 90/60mmHg. Treatment prior to arrival: tourniquet on the upper left leg (bleeding is controlled) with a bulky dressing, as well as a second dressing covering the open femur fracture, with two pieces of wood used to make a makeshift splint. There is no distal pulse (i.e., dorsalis pedis and posterior tibialis) on the right leg, and he complains of paresthesia.

Patient 4. A 24-year-old man with penetrating facial and chest injuries and a suspected moderate to severe traumatic brain injury (TBI). The patient is combative, with a Glasgow Coma Scale score of 10 (range, 3–15). He is hemodynamically abnormal, with a pulse of 120 bpm and a blood pressure measurement of 88/58mmHg. Treatment prior to arrival: cricothyroidotomy, three chest seals, and two needle thoracostomies. He has a patent IO device in place.

Based on the current TCCC guidelines, these patients could receive the following medications for initial pain control[4]:

Patient 1. TCCC combat wound medication pack (CWMP; acetaminophen and meloxicam).

Patient 2. CWMP *plus* oral transmucosal fentanyl citrate (OTFC) 800µg *or* fentanyl 50µg IV *or* fentanyl 100µg IN. If hemodynamically normal, consider an additional dose of fentanyl via desired route *or* ketamine 20–30mg (or 0.2–0.3mg/kg) IV or IO *or* ketamine 50–100mg (or 0.5–1mg/kg) IM or IN prior to reduction of fracture.

Patient 3. Ketamine 20–30mg (or 0.2–0.3mg/kg) IV/IO *or* ketamine 50–100mg (or 0.5–1mg/kg) IM or IN. Consider an additional dose of ketamine via the desired route prior to reduction of open fracture.

Patient 4. Ketamine 1–2mg/kg IV/IO slow push *or* ketamine 100mg IM (2–3mg/kg) to the end point of dissociative anesthesia. Consider additional ketamine via slow IV infusion of 0.3mg/kg in 100mg normal saline over 10 minutes, with repeated doses every 45 minutes for continued dissociative moderate sedation, given the degree of injury as well as the threat to the patient's and the team's safety.

Additional medications may be available outside the recommended TCCC guidelines; these may include morphine, hydromorphone, sufentanil, ketorolac, benzodiazepines (specifically midazolam), dexmedetomidine, propofol, etomidate, and anesthetic gases.

Discussion

The four cases discussed above represent the spectrum of analgesia that can be provided in the prehospital or prolonged casualty care environment. However, several caveats exist for each situation. It is first important to discuss the new TCCC pain and analgesia guidelines, updated within the last calendar year to include expanded use of both fentanyl (IV and IN) and ketamine (IV, IO, IN, and IM) in both solitary and prolonged sedation dosing[4] (Table 1).

It is important to note that ketamine is unique in that it can be both an analgesic and a sedative; this is the only medication discussed in this article that has both abilities. At a lower dosing of 0.1–0.4mg/kg, ketamine acts primarily as a pain-control medication. It generally does not produce an altered or dissociative state when given slowly (over minutes) at this dose.[6] At higher doses of 1–5mg/kg, a dissociative state predominates in addition to pain control, and patients typically enter a moderate to deep sedation state (referred to as dissociative sedation when specifically discussing ketamine).[5] Ketamine is generally safe even in overdose and has shown success when administered in a military setting by a field provider, with accidental doses of > 5mg/kg resulting in a dose-dependent prolonged state of stupor instead of death.[7,8] The lethal dose determined by Gable[9] was a median dose of 11.3mg/kg for a human, 10 times the typical sedation dose, versus fentanyl, which can produce deadly respiratory depression at high-normal typical doses.[7,10] This useful dual anesthetic-sedative nature of ketamine, in addition to its easy portability, makes it ideal in austere environments where multiple medications are too heavy or bulky to carry otherwise.

TCCC analgesia medications and guidelines should be used whenever possible. However, we recognize that these medications and delivery modalities may not always be available when others are, and in prolonged casualty-care scenarios where longer-term pain management and sedation are required, other medications may be better suited. Additionally, in higher acuity settings, such as an intensive care unit with continuous monitoring, these alternatives may be the better option, given the indication, availability, and experience of each provider. Regardless, it is essential that each provider be appropriately trained in the correct use and administration prior to use on patients. Tables 2 and 3 illustrate a nonexhaustive list of other commonly available analgesics and sedatives often found in a critical care environment. Appendix 1 also provides additional detail on peak serum concentration, peak effect, and duration of effect of all medications discussed in this article.

Although morphine has been a staple of combat care as far back as 1804, its side-effect profile, as well as its inferior pain control compared with that of other synthetic opioid analogs, should cause it to be the last option considered.[11] There should now be a concerted effort to utilize options such as fentanyl, hydromorphone, and perhaps even sufentanil once more widely available. Also, midazolam is a common benzodiazepine often seen in an operational setting because it does not require refrigeration, unlike other benzodiazepines.

TABLE 1 *Medications Recommended in the TCCC Pain and Analgesia Guidelines*

Medication	Dose(s)	Action(s)	Contraindications	Side Effects
Acetaminophen (Paracetamol, Tylenol)	Two 500mg tablets (1000mg total) by mouth every 8 h	Antipyretic, analgesic via unknown mechanism	Liver failure patients, unable to tolerate PO medication, known allergy	No major side effects
Meloxicam (Mobic)	15mg tablet by mouth 24 h	NSAID	Renal injury/failure, severe life-threatening bleeding, unable to tolerate PO, known allergy	Increased bleeding
Fentanyl OTFC*	800µg transmucosal, repeat × 1 in 15 min if pain is uncontrolled	Opiate mu-agonist, OTFC dose made to drop from casualty's mouth when altered	Significant facial wounds, hemodynamic instability, opioid allergy, significantly altered mental status	Increased altered mental status, respiratory depression, potential drop in hemodynamic status
Fentanyl*	50µg (0.5–1µg/kg) IV/IO *or* 100µg IN; repeat every 30 min as needed	Opiate mu-agonist, redistributes in adipose tissue and multiple doses can "stack" with increased effect/side effects	Hemodynamic instability, opioid allergy, significantly altered mental status	Increased altered mental status, respiratory depression, potential drop in hemodynamic status
Ketamine* (ANALGESIA)	20–30mg (0.2–0.3mg/kg) slow IV/IO, repeat every 20 min as needed *or* 50–100mg (0.5–1mg/kg) IM/IN, repeat every 20–30 min, as needed	NMDA and glutamate receptor antagonist, dissociative anesthetic, partial opiate mu agonist	History of laryngospasm, prior ketamine hypersensitivity or allergy, schizophrenia or active psychosis	Nausea, vomiting, diplopia, drowsiness, dysphoria, confusion, emergence reactions, increased secretions, laryngospasm, tachycardia, increased blood pressure, enhanced skeletal muscle tone
Ketamine Infusion* (SEDATION)	Initial dose: 1–2mg/kg slow IV/IO until dissociation *then* Maintenance: 0.3 mg/kg in 100mL 0.9% NS over 5–15 min, repeat every 45 min as needed	Same as above	Same as above	Same as above, though slower RATE of administration has been shown to decrease many side effects

*Providers should have appropriate reversal agents (naloxone for all opioids) as well as all components of MSMAID to address any negative side effects of these medications.

IN = intranasal; IO = intraosseous; IV = intravenous; MSMAID = monitor, suction, machine [ventilatory support], airway, IV/IO, drugs; NMDA = *N*-methyl-D-aspartate; NS = normal saline; NSAID = nonsteroidal anti-inflammatory drug; OTFC = oral transmucosal fentanyl citrate; PO = by mouth; TCCC = Tactical Combat Casualty Care.

Sedation

Many of these medications may be used in sedation, whether for moderate sedation for simple procedural tasks or for longer-term sedation, as might be needed in a severely injured, intubated, or critically ill patient awaiting definitive transportation. Regardless of the drug chosen, there must be special preparation and monitoring throughout all sedations. Medics should use the MSMAID (monitor, suction, machine [ventilatory support], airway, IV/IO, drugs) mnemonic when building medical kits, from an assault aid bag to an aid station. Any level of sedation requires at a minimum good patient positioning to maintain the patient's airway, as well as continuous pulse oximetry, frequent blood pressure assessment, and end tidal CO_2 ($ETCO_2$) detection, known as capnography. $ETCO_2$ has been shown to detect a lack of respiratory effort minutes before pulse oximetry values decrease.[12]

Not all procedures require moderate sedation; however, there are certain circumstances where it should be considered. The most recent 2021 TCCC guidelines offer the following list of potentially appropriate environments: during transportation, when sedation by infusion is a safer option versus multiple boluses of one-time medications; when either the mission itself or transportation options are space-limited and movement must be kept to a minimum; when mission-critical interventions occur that cannot be disrupted (e.g., cricothyrotomies) and prolonged analgesia is required for safety; when an evacuation may be prolonged and a longer duration of pain control is required; and when operational tempo necessitates.[4]

Moderate Sedation

Once the practitioner has ensured a safe environment with the appropriate monitoring available for moderate sedation, multiple drug choice options exist. Ketamine is an excellent single agent and should be the first choice, given its inclusion in the 2021 TCCC guidelines. Ketamine is ideal for both a hemodynamically stable as well as unstable patient, although thought should be given to whether a patient with instability should ever be sedated prior to appropriate resuscitation. Ketamine has less effect on hemodynamic status compared with opioids, etomidate, benzodiazepines, and propofol.[13–16] Effects of a 1mg/kg IV dose peak within 1 minute should be expected to last approximately 10 minutes.[13] Emergence reactions and dysphoria are often cited as the greatest factors barring successful ketamine use; however, evidence shows these perceptions are rare at lower doses and can be diminished by slowing the rate of administration of ketamine.[6] If a patient has a significant emergence reaction, either more ketamine or a one-time small dose of benzodiazepine can be administered for safety purposes.

Alternative single agents for sedation include propofol and etomidate. Propofol is a commonly available agent; however,

TABLE 2 *Analgesia Alternatives When TCCC Care Cannot Be Met and Environment Allows*

ANALGESICS				
Medication	**Dose**	**Action(s)**	**Contraindication(s)**	**Side Effects**
Morphine	1–10mg IV loading dose, may be followed by additional 1–4mg IV; also may be given subcutaneously	Opiate mu-agonist	Contraindicated in TCCC guidelines due to side effects, opioid allergy	Itching, nausea, respiratory depression, circulatory depression, tachyphylaxis (drug tolerance)
Hydromorphone (Dilaudid)	0.2–1mg IV every 1 to 3 h as needed; may be used as sedation in drip as well at 0.5–2 mg/h	Synthetic opiate mu-agonist	Opioid allergy, any existing respiratory depression, acute or severe bronchial asthma, severe gastrointestinal obstruction	Respiratory depression, circulatory depression, constipation, tachyphylaxis (drug tolerance)
Sufentanil	30μg transmucosal tablet, can be repeated once after 1 h sublingually for a maximum dose of 360μg in 24 h	Synthetic opiate mu-agonist	Opioid allergy, any existing respiratory depression, severe bronchial asthma, gastrointestinal obstruction, evidence of hemorrhage or shock	Respiratory depression, serotonin syndrome, hypotension, depressed mental status
Oral Hydrocodone, Oxycodone, Morphine, etc.	Dosage varies and can be in immediate or extended-release options	Synthetic opiate mu-agonist in both immediate and extended release	Patient must be able to tolerate medication PO and be hemodynamically stable	See above mu-agonist side effects
Gabapentin*	100–900mg PO every 8 h (must titrate up)	GABA analog: nerve cell inhibitor	Acute pain, non-nerve pain, renal impairment, seizure disorders, substance abuse	Depressed mental state, dizziness, respiratory depression, restlessness
Muscle Relaxants* (cyclobenzaprine, metaxalone, methocarbamol, tizanidine, etc.)	Dosage and duration of action vary	Skeletal muscle relaxant; central alpha-2 adrenergic receptor agonist; acetylcholine agonist	Existing tricyclic antidepressant use, hyperthyroidism, heart failure, urinary retention, liver impairment	Anticholinergic toxicity, dizziness, drowsiness, confusion, constipation, urinary retention, serotonin syndrome
Ketorolac (Toradol)	10–30 mg IV every 6 h; 30–60 mg IM every 6 h	NSAID	Hypersensitivity to aspirin or other NSAIDs, peptic ulcer disease, severe hemorrhage, renal failure	Increased bleeding, peptic ulcers, GI bleeding, can worsen existing kidney injury

*Most evidence signals that these medications are not useful in an acute pain control setting; however, they can be used as adjuncts to other methods if alternative options fail.

GABA = gamma-aminobutyric acid; GI = gastrointestinal; IV = intravenous; NSAID = nonsteroidal anti-inflammatory drug; PO = by mouth; TCCC = Tactical Combat Casualty Care.

it has marked hemodynamic effects and often leads to profound hypotension. When given at 1–2mg/kg dosing, peak effects occur within 0.5–3 minutes and last 3–5 minutes.[17] This is a poor drug choice in any patient with hemodynamic compromise. Additionally, propofol should be avoided in any patient with a TBI because even a single episode of hypotension with a TBI is associated with worse neurologic outcomes.[18] Etomidate has less hypotension associated with its administration, with rapid onset within 1 minute and a duration of action of 3–5 minutes at typical dosing.[19] Although it is associated with transient adrenal suppression, no data show statistical significance between the drug and death related to this suppression.[20]

Benzodiazepines can be given alongside other medications; however, there is a strong recommendation against polypharmacy because it increases the likelihood of respiratory depression and death; there have been deaths in an operational setting from the combination of opioids and benzodiazepines (reference 21 and Frank Butler, e-mail to author, February 28, 2020). These authors do not recommend using benzodiazepines with opioids for moderate sedation in the operational setting. However, 0.5–2.0mg of midazolam IV can be used when managing emergence reactions.[22,23]

Prolonged Sedation

Situations may arise in prolonged casualty care, delayed evacuation, or austere environments in which prolonged sedation is required in intubated and critically ill or injured patients. The 2021 TCCC guidelines recommend a ketamine drip as the primary and sole agent. When ketamine is not available, alternative agents can be used. It is assumed in these cases that the patient has a secured airway and is undergoing continuous monitoring of both blood pressure and pulse oximetry.

Propofol is common but can cause the same dose-dependent hypotension in drip form as it does when used in moderate sedation. Patients also require intubation to be on propofol because it can severely affect respiratory drive, and the airway must be protected. Often, propofol is used in a smaller dose for sedation, and a second agent, such as ketamine or fentanyl, is added for pain control. This is important to note because propofol alone offers no pain control, and a second agent is necessary for analgesia.

Dexmedetomidine (Precedex) is also a commonly used adjunct in sedation. For many patients, it is inadequate as a single agent and is often used in conjunction with other sedatives in a critical care setting. Significant bradycardia is associated with this drug, often prohibiting its use. This drug is unique in that, unlike the situation with propofol or benzodiazepines, the patient does not need to be intubated because they retain their own respiratory drive.

Benzodiazepines are now seen rarely as single agents and are associated with higher mortality across multiple critically ill patient populations compared with other sedatives and therefore should be used only when no other alternative exists.[24,25]

TABLE 3 *Sedation Alternatives When TCCC Care Cannot Be Met and Environment Allows*

SEDATIVES				
Medication	**Dose**	**Action(s)**	**Contraindication(s)**	**Side-Effects**
Benzodiazepine* (diazepam, midazolam, lorazepam, alprazolam, clonazepam, etc.)	Dosage varies as well as duration of action; lorazepam, midazolam, diazepam most used sedatives in drip form	GABA agonist: anxiolytic, sedative, muscle relaxant, anticonvulsant, amnesic	Renal or hepatic impairment, elderly or critically ill patients, delirious patients, substance abuse	Respiratory depression, depressed mental status, hypotension, paradoxical reactions, tachyphylaxis (drug tolerance)
Etomidate	0.1–0.3 mg/kg IV for one time dose; no longer recommended for sedation due to adrenal suppression	GABA agonist, general anesthetic, sedative hypnotic	Adrenal suppression, critical illness, requirement for prolonged sedation	Myoclonus, adrenal suppression, nausea, apnea
Propofol*	0.5–2mg/kg IV initial dose; 5–60μg/kg per min in prolonged sedation	GABA agonist, general anesthetic	Hypertriglyceridemia, bradycardia, hypotension, severe TBI	Bradycardia, QT interval prolongation, profound hypotension, propofol infusion syndrome
Dexmedetomidine (Precedex)	1μg/kg IV over 10 min followed by 0.2–1.5μg/kg/h infusion for sedation	Alpha-2 adrenergic agonist	Cardiac injury, existing bradycardia, hypotension	Hypotension, bradycardia, tachyphylaxis (drug tolerance),
Anesthetic Gases* (nitrous oxide, halothane, isoflurane, desflurane, sevoflurane)	Dosage varies as well as duration of action	Mechanism remains mostly unknown	Vary to include lack of appropriate monitoring devices, those with severe asthma, hepatic failure, renal dysfunction, heart failure	Malignant hyperthermia, nausea and vomiting, carbon monoxide poisoning

*Patients *must* have a protected airway when receiving these medications for deep sedation.
GABA = gamma-aminobutyric acid; IV = intravenous; TBI = traumatic brain injury.

Finally, etomidate is now no longer used for long-term sedation and should not be considered. Anesthetic gases are also only appropriate for operating room environments, and they should not be used for long-term sedation, especially in a combat environment.

Overdose Treatment

The administration of opiates can and often does lead to numerous side effects in casualties, including altered mental status, hypoventilation, apnea, and sometimes even death. Naloxone hydrochloride (Narcan) is the opiate antagonist used to treat overdoses. Providers should be comfortable administering naloxone in multiple forms, including IM, IN, and IV. Although a 2 to 4mg IN/IV/IO bolus can be used to treat acute overdose, the immediate and sudden reversal of pain treatment can often lead to combative patients. Therefore, multiple sources recommend incremental doses of 0.2–0.4mg in IM or IV dosing, meanwhile assessing response to each dose prior to administering another.[26] The end goal is to improve the respiratory rate while not fully reversing the pain control of the opioid medication itself. Even smaller doses (e.g., 40μg) can be used in nonemergency settings, and these "micro bumps" allow the provider even more control in increasing the respiratory rate. The use of either capnometry or capnography to follow $ETCO_2$ allows the provider to determine an accurate respiratory rate. To make "micro bumps," the medic dilutes the typical 0.4mg amount in 1mL inside 9mL of saline (prefilled 10mL syringes/vials work very well). This creates a 400μg/10mL, or 40μg/mL, dose and can be delivered 1mL at a time.

Conclusion

Many analgesia and sedation drug options exist, requiring the front-line provider to have experience with and understanding of different options to be best prepared for critically ill or injured patients. Although TCCC recommendations should be adhered to whenever possible, because prolonged casualty care or medication shortages are potentially part of our operational future, flexibility in care is essential to mission success. Understanding the strengths and limitations of the medications a medic decides to carry is a must, and being comfortable in the administration of these medications is necessary. Proper planning for managing the analgesia and sedation of combat casualties in the evolving operational environment may include bringing more medication than previously carried in an assault aid bag or layering additional medication from the point-of-injury through the evacuation process to ensure proper management until transfer to a higher level of care. With the information presented in this article, the reader may gain an increased, nuanced appreciation of the four initial case studies given here.

Patient 1. This case represents a patient who is hemodynamically stable with mild injuries only. The CWMP will likely provide sufficient pain control and is simple to dose, with synergistic pain control between the two medications.[27] However, the patient may also benefit from an alternative NSAID, such as ketorolac, if available. Use of oral opioid medications is not recommended for minimal injury because the potential for addiction exists even with minimal dosing.

Patient 2. This case represents a patient who is hemodynamically stable with a moderate injury that will also require a procedure (i.e., fracture reduction). Although administering OTFC is simple and straightforward, other options may be considered, such as alternative opioids (IV or PO), as well as NSAIDs, such as ketorolac. If the practitioner chooses to undergo moderate sedation for fracture reduction, then ketamine, propofol, and etomidate would all be reasonable choices given her appropriate heart rate, blood pressure level, and lack of TBI.

Patient 3. This case represents a patient who is hemodynamically unstable with significant injury, requiring procedural sedation and long-term pain control. Use of OTFC, other opioids, propofol, and most benzodiazepines will risk further hypotension in a patient who already has low blood pressure and

so are not the best choices. Ketamine can be used for pain control as well as moderate sedation for this patient. If he requires prolonged sedation and does not have a definitive airway, then ketamine and/or dexmedetomidine can be an alternative. If the patient develops bradycardia in response to dexmedetomidine, then the use of dexmedetomidine must immediately be stopped. This is also a patient who, after appropriate resuscitation, stabilization, and monitoring, may benefit from multimodal oral pain medications, such as gabapentin (for nerve pain), muscle relaxants, and oral opioids.

Patient 4. This case represents a hemodynamically unstable, severely injured patient with a TBI and a definitive airway. Cricothyrotomies are generally more comfortable for such patients than endotracheal tubes and should not always require ongoing sedation. However, this patient has multiple injuries and is a danger to himself and others. For safety, he should be fully sedated while he is evaluated and treated. Ketamine again represents the best option because it has been shown to be protective in TBIs and does not increase mortality, as was previously thought.[28,29] Again, medications that could worsen hypotension should not be used. The only exception may be fentanyl; previously thought to help with cerebral vascular flow, a recent 2020 meta-analysis shows no response to this medication, and it should be used with absolute caution.[30] Overall, a significant gap exists in knowledge as to which sedatives are best in TBIs. Normal hemodynamics should be prioritized regardless of medication choice.

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TTD, BA, and RAC conceived the review. TTD primarily wrote the manuscript, and all authors assisted with further writing and substantial editing

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APPENDIX 1 *Dosing Details for Common Analgesics and Sedatives*

ANALGESIA						
Class	**Medication**	**Onset (minutes)**	**Peak Effect (minutes)**	**Serum Half-Life (hours)**	**Duration of Effect (hours)**	**Duration of Intermittent Dose (hours)**
Non-NSAID	Acetaminophen (PO)	30–60	30–60	2–3	4–6	4–6
NSAID	Ibuprofen (PO)	30	60	2–2.5	4–6	4–6
	Ketorolac (Toradol) (IV)	30	120–180	5	4–6	6–8
	Meloxicam (Mobic) (PO)	120	240+	20	24	24
NMDA Receptor Antagonist	Ketamine (IV/IO) (single dose)	0.5	1–5	2–4	Variable	(10–15 min)
	Ketamine (IM) (single dose)	3–4	15	2–4	Variable	(15–30 min)
Opioid	Fentanyl (IV/IO/IM)	1–2	2–5	7–12	0.5–1	0.5–1
	Fentanyl (OTFC)	5–10	30	3–14	2–3	1–3
	Morphine (IV)	1–2	5–15	2–3	4–5	4–5
	Hydromorphone (Dilaudid) (IV)	1–2	8–20	2–3	3–4	4–5
	Sufentanil (ODT)	6	60	2.5	3	1
	Hydrocodone (PO)	30	60	3–4	4–8	4–6
	Oxycodone (IR) (PO)	15	60–120	2–3	3–6	4–6
	Tramadol (PO)	60	120+	6–9	4–6	4–6
GABA	Gabapentin (PO)	Variable	120+++	5–7	Variable	8
Muscle Relaxant	Cyclobenzaprine (Flexeril) (PO)	60	240+++	18–32	12–24	8
SEDATIVES						
Class	**Medication**	**Onset (minutes)**	**Peak Effect (minutes)**	**Serum Half-Life (hours)**	**Duration of Effect (hours)**	**Duration of Intermittent Dose (minutes)**
NMDA Receptor Antagonist	Ketamine (IV/IO) Anesthetic (single dose)	0.5	1–5	2–4	(5–10 min)	10–15
	Ketamine (IM) Anesthetic (single dose)	3–4	15	2–4	(15–30 min)	15–30
Benzodiazepines	Midazolam (IV)	2–5	3–5	3	<2	30+
	Lorazepam (IV)	1–5	15–20	14	12–24	360+
	Diazepam (IV)	2–5	1	33–45	Variable	20+
General Anesthetic	Etomidate (IV) (single dose)	<1	1	3	(2–5 min)	Not recommended
	Propofol (IV) (single dose)	<1	1	(40 min)	(3–10 min)	3–10
Central Alpha-2-Agonist	Dexmedetomidine (Precedex) (IV) (single dose)	5–10	15–30	Distribution (6 min) / Terminal 3 hr	1–2	60–120

IM – intramuscular; IR = immediate release; IV – intravenous; PO = oral; ODT = oral dissolvable tablet; OTFC = oral transmucosal fentanyl citrate.

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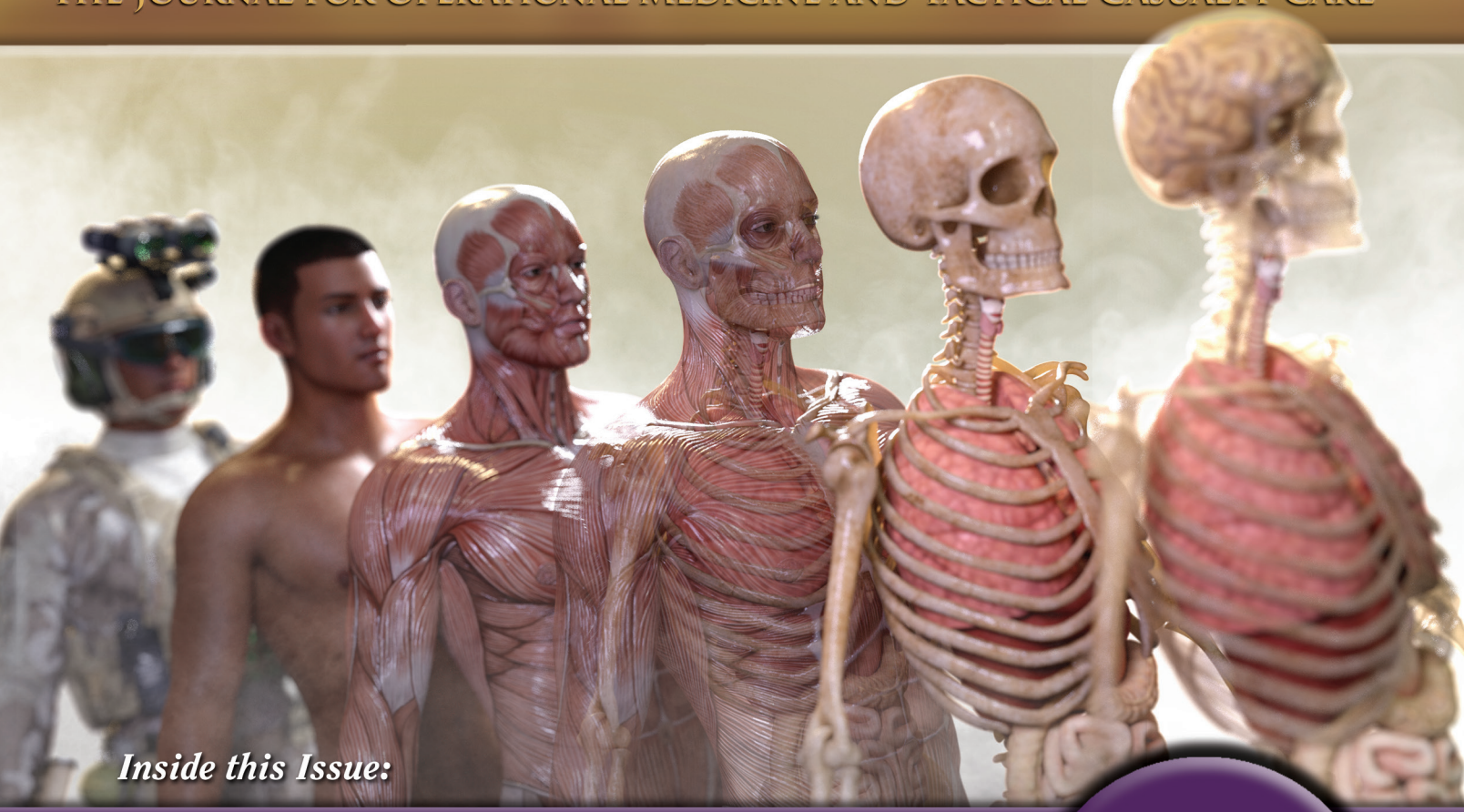

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