

A Triple-Option Analgesia Plan for Tactical Combat Casualty Care: TCCC Guidelines Change 13-04

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ABSTRACT

Although the majority of potentially preventable fatalities among U.S. combat forces serving in Afghanistan and Iraq have died from hemorrhagic shock, the majority of U.S. medics carry morphine autoinjectors for prehospital battlefield analgesia. Morphine given intramuscularly has a delayed onset of action and, like all opioids, may worsen hemorrhagic shock. Additionally, on a recent assessment of prehospital care in Afghanistan, combat medical personnel noted that Tactical Combat Casualty Care (TCCC) battlefield analgesia recommendations need to be simplified—there are too many options and not enough clear guidance on which medication to use in specific situations. They also reported that ketamine is presently being used as a battlefield analgesic by some medics in theater with good results. This report proposes that battlefield analgesia be achieved using one or more of three options: (1) the meloxicam and Tylenol in the TCCC Combat Pill Pack for casualties with relatively minor pain who are still able to function as effective combatants; (2) oral transmucosal fentanyl citrate (OTFC) for casualties who have moderate to severe pain, but who are not in hemorrhagic shock or respiratory distress and are not at significant risk for developing either condition; or (3) ketamine for casualties who have moderate to severe pain but who are in hemorrhagic shock or respiratory distress or are at significant risk for developing either condition. Ketamine may also be used to increase analgesic effect for casualties who have previously been given opioids (morphine or fentanyl.)

KEYWORDS: *battlefield analgesia, fentanyl, ketamine, morphine*

Proximate Cause for the Proposed Change

1. Eastridge et al noted in their review of 4,596 U.S. military combat fatalities from the conflicts in Afghanistan and Iraq: “Recent emphasis in battlefield trauma care has focused on reducing death from noncompressible hemorrhage through the use of tranexamic acid, controlling junctional hemorrhage with the Combat Ready

Clamp, providing fluid resuscitation that minimizes dilutional coagulopathy *and providing a battlefield analgesia option that does not cause respiratory depression or exacerbate hemorrhagic shock*” (italics added).¹

2. Despite the awareness that opioids may contribute to preventable combat deaths, many combat units at present carry only intramuscular (IM) morphine for battlefield analgesia. Joint Trauma System weekly teleconferences reveal that opioids are still regularly being used on casualties who are in hemorrhagic shock. Opioid analgesics are contraindicated in these casualties.²⁻⁴

3. On a recent assessment of prehospital care in Afghanistan, two important observations regarding pain medications were recorded from deployed physicians and physician assistants as well as combat medics, corpsmen, and paramedics (PJs): (1) the TCCC battlefield analgesia recommendations need to be simplified—there are too many options and not enough clear guidance on which to use; and (2) ketamine is presently being used by medics in theater as a battlefield analgesic with excellent results.⁵

Background

Morphine was first prepared by Wilhelm Sertürner in 1804. This new (at the time) agent, together with Alexander Wood’s development of the syringe and needle for subcutaneous injection, profoundly altered the management of pain on the battlefield.⁶ Opioids (such as morphine and fentanyl) are associated with serious side-effects, including respiratory depression, circulatory depression, hypotension, and shock.⁷ Opioid analgesia, although effective, can be fatal when used for individuals wounded in combat who go into hemorrhagic shock.⁸ Hemorrhagic shock is the leading cause of potentially preventable death in U.S. combat casualties.¹

“The first population-based studies on battlefield pain were not conducted until World War II. These studies were in reaction to a growing number of Soldiers

suffering from opioid overdose received for pain that resulted in death in many cases. Interestingly, little research on pain issues in wounded Soldiers has been conducted since. Notwithstanding the paucity of evidence, opioids have remained the cornerstone of battlefield pain management.”⁹ Beecher noted that morphine poisoning was a significant problem in World War II. Soldiers received multiple doses of morphine on the battlefield (reportedly subcutaneous at the time). Absorption and the onset of analgesia were delayed when casualties were cold or when they were volume depleted. The morphine overdose became apparent when the casualties were rewarmed and their intravascular volume restored.¹⁰ Beecher also noted that the intravenous (IV) route was the preferred way to deliver morphine, but that battlefield conditions made IV administration of morphine impractical.

Despite the reports of morphine overdose from World War II, little changed in the U.S. military until the present conflicts in Afghanistan and Iraq.¹¹ Although medical personnel supporting U.S. combat operations now have a number of newer and more advantageous analgesic options, much of the U.S. military is still using IM morphine as the primary medication for battlefield analgesia over 150 years after its inception.

The original 1996 TCCC paper noted that IV morphine when feasible was preferable to IM morphine because of the more rapid onset of action when the medication is given IV, thus providing faster relief of pain and decreasing the chance of an overdose.¹² Intraosseous techniques adopted for battlefield use now also offer fast and reliable access when IV access is difficult to obtain. The use of morphine as the primary battlefield analgesic has persisted in the U.S. military despite the potentially life-threatening side-effects of opioids. In 2009, the Army Surgeon General called for a reevaluation of pain management in combat casualties.⁸ The Army Surgeon General’s Task Force on Pain Management noted that current practice in pain management is often based on local tradition or provider experience and beliefs rather than by evidence-based practices.⁸

In 2004, oral transmucosal fentanyl citrate (OTFC) was added as an option for battlefield analgesia in the TCCC Guidelines. The study published by Kotwal and O’Connor and their colleagues documented that OTFC was safe and effective for use in the tactical environment.¹³ Although there is an FDA “Black-Box” warning regarding the use of this medication in opioid-naïve individuals, there are multiple reports of OTFC being used safely for acute pain in opioid-naïve individuals, as will be discussed later in the paper. OTFC offers excellent analgesia and a very rapid onset of action combined with ease of administration, since IV access is not required.¹³

The use of this medication in Afghanistan and Iraq was largely confined to Special Operations medics, corpsmen, and PJs until 2011, when the Commander of Regional Command (South) approved OTFC for use by Navy corpsmen supporting USMC operations in that region.¹⁴ The U.S. Central Command Surgeon also removed the “SOF-Only” restriction for OTFC that was previously CENTCOM policy, thus opening its use to conventional medics (COL Erin Edgar, personal communication).

Ketamine was added to the CoTCCC-recommended battlefield analgesic options in 2011 following a proposed change to the TCCC Guidelines made by Dr. John Gandy. Ketamine is safe and effective and offers potent analgesia without the cardiorespiratory depressant side-effects of opioids. This recommendation was subsequently approved by the Defense Health Board.¹⁵

Discussion

As a point of emphasis, this proposed change to the TCCC Guidelines does not add any new analgesic medications to those previously recommended by the Committee on Tactical Combat Casualty Care (CoTCCC). Rather, it contains improved guidance to combat medical providers to help them choose the right analgesic for specific types of casualties.

The Combatant Command responsible for oversight of U.S. forces in the conflicts in Afghanistan and Iraq is the U.S. Central Command (USCENTCOM). The lead agent in the U.S. Department of Defense for developing best-practice trauma care guidelines is the Joint Trauma System (JTS), an organization which has recently been designated as the Defense Center of Excellence for Trauma by the Assistant Secretary of Defense for Health Affairs. The following observations were obtained in Afghanistan in November of 2012 during a USCENTCOM/JTS assessment of battlefield trauma care in that country¹⁶:

“34. The experience with ketamine as a battlefield analgesic has been very good to date. (Salerno Role I – 101st; BAF Role I – CJSOTF, BAF Role I – Shadow DUSTOFF, Tarin Kowt Role I – NSW) Ketamine does not cause cardiorespiratory depression as opioids do and is, therefore, well-suited for casualties in pain who are also in shock or at risk for going into shock. (CoTCCC Chairman) From August 2011 to August 2012, the DoD Trauma Registry recorded 93 administrations of ketamine to combat casualties in the pre-hospital battlefield environment with no complications noted. (JTS Trauma Care Delivery Director)

39. The TCCC battlefield analgesia options should be simplified. Consider reducing the pre-hospital pain management protocol to three treatment options: 1)

Able to fight – Mobic and Tylenol, 2) Unable to fight and in no risk of shock – OTFC 800mcg, 3) Unable to fight and in or at risk of shock – Ketamine 50mg IM. (BAF Role I – CJSOTF; BAF Role I – 1st Infantry Division)

65. The weekly JTS trauma teleconferences on occasion note that casualties who are given opioids are either in shock when the medication is administered or become hypotensive subsequently. No studies have been published from the current conflict that review outcomes in combat casualties as a function of the type and route of analgesia used in combat casualties as well as the type and severity of wounds sustained, and physiologic parameters indicative of circulatory or respiratory status. (CoTCCC Chairman)

74. The USAF Pedro & Guardian Angel Team primarily provides Combat Search and Rescue (CSAR) support and secondarily provides casualty evacuation (CASEVAC) support. . . . Medical equipment includes Propaq electronic monitors, Golden Hour boxes, 2 “D” cylinders of oxygen, blood components or Hextend (no LR or NS); hypothermia prevention through Ranger Rescue Wrap (heavy sleeping bag, 360 degree access, active heating pads) and wool blanket; they use ketamine liberally and consider it the best option for analgesia in combat casualties. (Bastion Role I – USAF Pararescue)

88. There are meetings with USA MEDEVAC personnel and USAF CASEVAC personnel every other Friday . . . Both systems are using and like ketamine. There have been no known adverse effects from pre-hospital ketamine in the KAF AO. (KAF Role III – Intensivist)

202. The impact of pre-hospital opioid analgesia on casualty outcomes has not been well-documented. (CoTCCC Chairman)

204. There is a moral obligation to treat pain. Effective analgesia also helps to decrease the risk of PTSD. Opioids are overused at present. Ketamine is not really a new option, but there is relatively little ketamine use in theater at present. The use ratio of ketamine as compared to opioids is about 1:25. This ratio should approximate 1:1. From 1mg to 3mg of midazolam is useful for ketamine side-effects. Ketamine should not be given IV push, but injected over 1 minute. (Theater Trauma Conference – V Corps Command Surgeon)

205. TF Med A theater clinical operations has been tasked to obtain single dose vials of ketamine (currently only available in very concentrated multi dose vials) and a ketamine auto-injector. (Theater Trauma Conference – TF Med A Commander)

238. There was unanimous agreement among the USMC/USN physicians and corpsmen interviewed that having a ketamine auto-injector would be a very desirable addition to battlefield analgesia options. (Bastion Role I – USMC/USN physicians and corpsmen)

253. Each SEAL Operator carries a morphine 10mg IM auto-injector for battlefield analgesia. SEAL medics

noted that OTFC works better than IM morphine and is often given in conjunction with IM morphine. SEAL medics do not routinely carry ketamine. (Tarin Kowt Role I – NSW)

Recommendations for Military Research and Development Commanders included:

3. As nausea and emesis can occur with opiate administration, develop an oral transmucosal fentanyl citrate lozenge with ondansetron (“fentanyl-ondansetron swirl lollipop”).

4. Develop an oral transmucosal ketamine lozenge product (“ketamine lollipop”).

5. Similar to the IM auto-injector used for morphine, develop a ketamine 50mg IM auto-injector for pre-hospital trauma care. Explore other potential routes of ketamine administration to include intranasal and transcutaneous.

16. Conduct a retrospective study of combat casualty outcomes in the DoD Trauma Registry as a function of the type and route of pre-hospital analgesia used as well as the type and severity of wounds sustained and physiologic parameters indicative of circulatory or respiratory status.

Recommendations for the U.S. Central Command included:

10. Explore all options to enable intranasal ketamine for pre-hospital analgesia in combat casualties.”⁵

Prehospital care reports from the point of injury are often lacking and, even when present, rarely include any reports whatsoever of administration of analgesics prior to aeromedical evacuation. The availability and administration of analgesics in this phase of care is, for all intents and purposes, unknown (Col Jeff Bailey, JTTS Director, personal communication, 2013).

Morphine Sulfate

The narcotic most frequently used for prehospital analgesia on the battlefield during the past century has been morphine.¹⁷ After morphine was discovered in 1804, it was used liberally during the Civil War, resulting in such a significant incidence of opioid dependency that this became known as the “Soldier’s disease.” During World War II, morphine use was associated with overdoses and, in many cases, death.^{6,10} Morphine has been the most widely used opioid analgesic because of its familiarity and its simplicity.¹⁸

Opioids are contraindicated in patients and casualties with hypotension²⁻⁴ but are still being given to casualties who are either in hemorrhagic shock or who subsequently become hypotensive.⁵ No studies were found during this review that examined the safety and efficacy of IM morphine use during the past 12 years of conflict

in Afghanistan and Iraq; thus, the impact of IM morphine administration on outcomes for casualties in or at risk of hemorrhagic shock or respiratory distress is unknown. Likewise, the potential adverse effects of IM morphine when used for casualties with TBI have not been studied in these conflicts.

Morphine administration in an animal model of hemorrhagic shock was shown to increase mortality in a dose-dependent manner. Thirteen animals in shock treated with low-dose morphine had a 15% survival rate compared to 60% survival rate in the control animals that were given saline. None of the 10 animals treated with high-dose morphine survived.¹⁹

The position paper of the National Association of EMS Physicians in 2003 noted that: "In many systems morphine is the analgesic of choice for ischemic chest pain that is not relieved by administration of nitrates. Its use for noncardiac pain has been limited due to exaggerated fears of side-effects such as respiratory depression and hypotension. Morphine can be titrated via the IV route to produce safe and effective analgesia."²⁰ The use of IM morphine was not even brought up as an option worthy of consideration in this study. Other studies of prehospital analgesia in civilian settings also describe the use of IV morphine without mentioning IM morphine as an option worthy of consideration.^{4,21}

In addition to the potentially lethal potentiation of hemorrhagic shock, administering morphine via the IM route results in an unnecessary delay in obtaining adequate pain relief for the casualty. Wedmore and colleagues noted that: "Intramuscular morphine has a delayed onset of pain relief that is suboptimal and difficult to titrate."¹⁷ The 2012 Defense Health Board memo on ketamine observed that morphine has historically been administered on the battlefield as an IM injection, and that this limits its analgesic effectiveness due to morphine's delayed onset of action when given IM.¹⁵ IV morphine was recommended in the original TCCC report¹² and is still recommended as an option in the TCCC Guidelines.³ This option typically provides effective analgesia, but entails the time and logistics required to start an IV line; to draw up the medication; to infuse the recommended 5mg initial dose; and then to maintain IV access for the casualty in anticipation of possible additional doses if needed.

In a survey of combat medical personnel conducted by the Naval Medical Lessons Learned Center, respondents indicated that IM morphine is the most commonly used but least efficacious battlefield analgesic. It was rated below IV morphine, OTFC, and ketamine in providing rapid and effective relief of pain from combat wounds.²² This reported prevalence of IM morphine is

largely because OTFC and ketamine use has been confined primarily to Special Operations combat medical personnel, and, more recently, Navy corpsmen supporting USMC combat operations. OTFC and ketamine are not routinely given to Army medics, who thus have no options for potent analgesia other than IM morphine auto-injectors.

In Holbrook's study of the impact of analgesia for the pain stemming from combat injuries and subsequent development of PTSD, morphine administration occurred during care provided at a medical treatment facility (not at the point of injury) and was IV (not IM) in 98% of casualties.²³ This observation leads one to ask why effective analgesia was not achieved earlier in the continuum of care and why this aspect of care was not discussed in the report. Published commentary on the Holbrook report also noted the lack of reporting of any adverse effects that may have been associated with morphine administration.²⁴

USCENTCOM Joint Theater Trauma System personnel have noted that pain medication for combat casualties is being withheld from some casualties because the medics have no analgesic options other than IM morphine and they know that opioids are contraindicated in casualties who are in hemorrhagic shock or respiratory distress, or are at significant risk for either condition (Col Jeff Bailey/LTC Jim Geracci, personal communications, 2013).

Oral Transmucosal Fentanyl Citrate (OTFC)

Following the addition of OTFC to the TCCC Guidelines based on the recommendations of Kotwal and O'Connor and their colleagues, this agent has become widely used in Special Operations units and, more recently, in USMC units.^{14,16}

Aronoff and colleagues found that ". . . 800µg OTFC and 10mg IV morphine produced similar durations of analgesia; the mean time until additional analgesia was requested was approximately 3.5 hours (220 minutes vs 210 minutes, respectively). The duration of analgesia for the 800µg OTFC and 10mg IV morphine were significantly longer ($p < .04$) than the duration of analgesia for the 200µg OTFC and 2mg IV morphine (159 minutes vs 153 minutes, respectively) . . . Mean time to onset of meaningful pain relief was similar in all patient groups—about 5 minutes—and was less than 10 minutes in approximately 80% of all patients."⁷ Another study also found that 800µg of OTFC produced relief of pain within 5 minutes and that both the analgesic effect and duration were similar to that produced by 10mg of IV morphine.²⁵

The pharmacodynamics of OTFC are similar to those of IV morphine but have the advantage of not requiring

IV access, thus allowing for increased ease and speed of administration.⁷ OTFC lozenges should not be chewed. OTFC is rapidly absorbed through the oral mucosa when the lozenge is placed between the cheek and the gum. This transmucosal absorption accounts for OTFC's rapid onset of analgesia. The portion of the medication that is swallowed and absorbed through the gastrointestinal tract is more slowly absorbed and accounts for the duration of the analgesic effect.¹³ Although OTFC is labeled by the FDA for breakthrough cancer pain in opioid-tolerant patients, it has been used to relieve acute pain in opioid-naïve individuals with a variety of non-cancer clinical conditions with excellent results and an acceptable side-effect profile.^{7,26-30}

OTFC has been used extensively in the 75th Ranger Regiment throughout the conflicts in Afghanistan and Iraq. This unit reported the lowest incidence of preventable deaths ever experienced by a large unit throughout a major conflict.³¹ The primary reason for the elimination of preventable prehospital combat fatalities in this study was likely better control of external hemorrhage through the use of tourniquets and hemostatic agents, but an additional factor may have been the reduced reliance on IM morphine for battlefield analgesia by the 75th Ranger Regiment. Kotwal's 2011 report of 419 battle injury casualties from the 75th Ranger Regiment noted that "81 self-administered oral combat wound pill packs consisting of a fluoroquinolone and two analgesics (acetaminophen and either celecoxib or meloxicam)." Additionally, "a total of 146 casualties received prehospital analgesics other than combat wound pill packs. These include: 82 casualties who were administered oral transmucosal fentanyl citrate, 23 who received morphine sulfate, 27 who received both, and 14 who received other analgesics (hydromorphone hydrochloride, hydrocodone bitartrate, ketorolac tromethamine, or ibuprofen). Of the 50 casualties who were administered morphine, 30 (60%) received it intravenously and 20 (40%) intramuscularly." OTFC was therefore the most commonly administered analgesic in the 75th Ranger Regiment.³¹

Kacprowicz notes that "fentanyl has been extensively studied in the medical literature, and both the oral lozenge form and intravenous forms have been well documented to relieve pain with few adverse effects in both the adult and pediatric patient populations."³² He and his colleagues noted further that OTFC was ". . . uniquely suited for the management of pain in the combat setting."³² The Army Surgeon General's Dismounted Complex Blast Injury Task Force recommended increased use of OTFC as a battlefield analgesic because of its faster onset of analgesia with resulting increased ease of titration as well as the ease of administering OTFC compared to IM morphine.³³

In the largest study on battlefield analgesics to be published from Afghanistan and Iraq, Wedmore and his colleagues reported OTFC use in 286 casualties. They found that OTFC provided statistically significant pain relief, with the numeric rating scale (NRS) decreasing from 8.0 to 3.2 within 30 minutes after the first dose of OTFC. Nausea was the most frequent adverse effect with an incidence of 12.7%. The single incident of a major adverse effect occurred in a casualty who received 3200µg of OTFC and 20mg of morphine. This casualty experienced hypoventilation and a hemoglobin oxygen saturation of less than 90%. The respiratory depression responded well to naloxone. The study concluded that OTFC is "a rapid and noninvasive pain management strategy that provides safe and effective analgesia in the prehospital battlefield setting."¹⁷

OTFC has also been recommended as a good choice for analgesia in wilderness environments.³⁴

Ketamine

Although ketamine in the past has been used as a dissociative anesthetic, it is also an effective analgesic and may be used for this purpose in lower doses that avoid many of the side-effects noted to occur with the higher anesthetic dose.^{15,35} Ketamine is highly lipid soluble, so clinical effects are seen within 1 minute of administration when ketamine is given IV and within 5 minutes when given IM.²⁰ Other authors have also noted that ketamine has a rapid (within approximately 5 minutes) onset of action when administered IM.^{15,35}

Ketamine produces a mild to moderate increase in heart rate and blood pressure. It is also a bronchodilator.²⁰ This mild sympathetic response is due to direct stimulation of the brain stem, which results in catecholamine release as well as an inhibition of norepinephrine reuptake. This produces the observed mild increase in heart rate and stroke volume. Respirations are not normally affected and blood pressure is generally normal or slightly increased.³⁶ Ketamine's positive effect on airway resistance has made it a rescue drug for patients in status asthmaticus who do not respond to standard treatments.³⁷

The only absolute contraindications to ketamine use are age less than 3 years and a history of schizophrenia.³⁸ Neither is a significant problem in deployed combat forces. Green's clinical practice guidelines for the use of ketamine in the emergency department note that head trauma has now been removed as a relative contraindication for the use of this medication.³⁸ The hesitance to use ketamine in traumatic brain injury (TBI) patients was based on older studies from the 1970s that showed elevations in intracranial pressure in patients with abnormal cerebrospinal fluid pathways caused by mass

lesions or aqueductal stenosis.³⁹ More recent studies have not noted the same effect in patients without these conditions.³⁹⁻⁴² Filanovsky noted that, based on its pharmacological properties, ketamine appears to be “the perfect agent for the induction of head-injured patients for intubation.”³⁹

Although the DHB memo on ketamine noted the potential for increased intraocular pressure with ketamine use, two recent studies have reported that ketamine use was not associated with clinically significant elevations in intraocular pressure.^{43,44} There is good evidence that ketamine does not cause dose-related adverse events within the range of clinically administered doses.^{38,45} Black and McManus note that “ketamine has also been utilized successfully as a prehospital analgesic in the combat setting. Ketamine in subanesthetic doses is an almost ideal analgesic because of its profound pain relief, its potentiation of opioids, its role in preventing opioid hyperalgesia, and its large margin of safety.”⁴⁶

IV ketamine, when combined with IV morphine, was found to be safe and effective for adult trauma patients. Adding ketamine produced a reduction of 2.4 points in the verbal numeric rating pain scale compared with IV morphine alone.⁴⁷ Intranasal ketamine produced a significant reduction in pain intensity compared to placebo ($p < .0001$). Pain relief occurred within 10 minutes of ketamine administration and lasted for up to 60 minutes. Of note, there were no patients in the ketamine group who required rescue pain medications, while 7 of 20 (35%) patients in the placebo group did. Ketamine administered intranasally was well tolerated with no serious adverse events reported.⁴⁸

In a 2011 survey of combat medical personnel conducted by the Naval Medical Lessons Learned Center, ketamine’s rating of 4.67 (of a possible 5) as a battlefield analgesic agent was the highest given to any of the prehospital analgesic options; IV morphine was second with 4.48, OTFC third with 4.42, and IM morphine last at 4.13.²² Guldner and colleagues stated that, “Ketamine is a unique agent that can be administered either intravenously or intramuscularly to produce predictable and profound analgesia, with an exceptional safety profile.”⁴⁹ Ketamine has been suggested as a useful field agent for challenging situations such as disasters.²⁰ Ketamine has been the single most popular agent for use in painful emergency department procedures in children for nearly two decades.³⁸ Ketamine may also be useful as an adjunct to reduce the amount of opioid required to provide effective analgesia.⁵⁰ The review by Jennings et al in 2011 found ketamine to be a safe and effective option for prehospital analgesia. Ketamine was noted to be as effective or more effective for this purpose than opioids alone.⁵¹

One impediment to optimal use of ketamine on the battlefield is that drug manufacturers are constrained from marketing an IM auto-injector by Food and Drug Administration regulations. Since analgesia is an off-label use of ketamine, companies are not allowed to commercialize the medication for this use and marketing of a ketamine auto-injector is therefore prohibited. This forces combat medical personnel on the battlefield to spend additional time preparing the medication for injection and introduces the potential for medication errors.

Ketamine may also be delivered via the intranasal route.^{15,48} A pilot project in which 50mg of ketamine is drawn up in syringes with atomizers for intranasal use in the field by medics has been implemented by the Third Infantry Division in Regional Command (South) in Afghanistan (LTC David Cole, division surgeon, and CPT Paul Stringer, division pharmacist, personal communication, 2013).

Selecting the Optimal Agent for Battlefield Analgesia

The simplified triple-option approach to battlefield analgesia has three primary goals:

- To preserve the fighting force
- To achieve rapid and maximal relief of pain from combat wounds
- To minimize the likelihood of adverse effects on the casualty from the analgesic medication used

There are currently four options for battlefield analgesia recommended by the CoTCCC: meloxicam/Tylenol (PO), morphine (IV), fentanyl (OTFC), and ketamine (IM, IV, or IN).

Alonso-Serra and colleagues stated that, “There is insufficient published evidence to decide which is the best agent for prehospital analgesia. The medical director of each EMS system must evaluate different alternatives available on the market and decide which agent or agents are most suitable for the system’s local needs and capabilities.”²⁰ To restate this observation for battlefield analgesia, the optimal analgesic choice for a particular casualty depends on the nature of the casualty’s injuries, his or her level of pain and physiologic condition, as well as the tactical circumstances.

Beecher noted that many combat casualties do not have severe pain.⁵² These casualties may therefore be able to remain engaged as combatants, helping their unit achieve or maintain tactical superiority and accomplish its mission. In this setting, one seeks whatever analgesia can be obtained without administering an agent that may produce an altered sensorium, as both opioids and ketamine

have the potential to do. The analgesic agent chosen should also not impair coagulation, as some nonsteroidal anti-inflammatory medications do. The two oral pain medications in the CoTCCC-recommended Combat Pill Pack (acetaminophen and meloxicam) do not cause either decreased sensorium or altered platelet function.³

OTFC has been recommended as a safe and effective battlefield analgesic and one that does not require IV access.^{6,13,17} OTFC has also been recommended as a good analgesic choice for casualties in austere environments such as mountain rescue in the civilian sector as well.⁵³ OTFC was recommended for use in wilderness medical settings as early as 1999.⁵⁴

Opioid analgesic agents entail the risk of cardiorespiratory depression. This is of particular concern in casualties who may be suffering from hemorrhagic shock and/or respiratory distress.^{2,3,15} Malchow and Black note that, “Although opioids have traditionally been the cornerstone of acute pain management, they have potential negative effects ranging from sedation, confusion, respiratory depression, nausea, ileus, tolerance, opioid-induced hyperalgesia as well as the potential for immunosuppression.”⁵⁵

The U.S. military has historically relied on opioid-based pain management. This strategy may result in potentially lethal side-effects on the battlefield.¹¹ Morphine is contraindicated in patients who have hypotension or impaired respiratory status.^{2,3} The potential for opioid analgesics to exacerbate hypoxia and hypotension and therefore cause secondary brain injury in casualties with moderate-to-severe TBI makes them unsuitable for use in these casualties as well.^{3,56} Since OTFC is also an opioid, the same concerns apply to this agent.⁵⁷ Additionally, opioids should be avoided in patients with injuries that may reasonably be anticipated to result in hemorrhagic shock, such as poorly controlled junctional hemorrhage or penetrating torso trauma. Opioids should also be avoided in casualties with airway injuries, penetrating chest injuries, severe blunt trauma to the chest, or possible pulmonary blast injury – these injuries entail increased risk of respiratory distress or hypoxia.

Mollman noted that “the major advantage of ketamine is that when repeat doses are required, it raises blood pressure, so it is suitable for use in shock.”⁵⁸ The Defense Health Board’s review of ketamine as a battlefield analgesic found that this agent enhances the ability of combat medical personnel to relieve pain in tactical settings without the risk of opioid-induced hypotension and respiratory depression.¹⁵ The report notes that in casualties with polytrauma, relieving the pain from combat injuries with opioids may be lethal as a result of opioid-induced cardiorespiratory depression if the casualty has

noncompressible hemorrhage and/or pulmonary injury. Ketamine has been rated as the most effective battlefield analgesic by combat medical personnel²² and was the preferred analgesic of USAF pararescue personnel in the 2012 survey of battlefield trauma care in Afghanistan.⁵ It does not, however, currently have the ease of administration that OTFC does.

Ketamine is being increasingly used in far-forward casualty scenarios because of its rapid analgesia, reduced nausea and vomiting, and its lack of blood pressure reduction in casualties who may already be hypotensive.¹¹ In a 2012 JTS Performance Improvement project on prehospital analgesics used in Afghanistan from 1 August 2011 to 31 August 2012 and captured in the DoD Trauma Registry, ketamine was found to have been given to 28% (88 of 315) of casualties who received analgesics during initial transport from the point of injury to an MTF, but only 1% (2 of 219) of casualties receiving analgesics at the point of injury (COL Russ Kotwal, unpublished data, presented at the JTTS Trauma Conference, Bagram Airfield, Afghanistan, 9 November 2012). In a 2013 JTS Performance Improvement project on prehospital analgesics provided in Afghanistan from 1 January 2009 to 31 June 2013 and captured in the DoD Trauma Registry, ketamine was found to have been safely administered by prehospital providers 131 times without associated adverse events reported. (COL Russ Kotwal, unpublished data, presented at the JTTS Trauma Conference, Kabul, Afghanistan, 12 August 2013). Additionally, there are anecdotal reports from operational military settings which note that casualties with severe pain that is refractory to morphine may experience rapid relief of pain after administration of ketamine.³⁴

Ketamine has been found to be a safe and effective option for prehospital analgesia.^{36,51} It is an increasingly popular option for use as an analgesic in the prehospital setting.⁵⁹ Ketamine is also used as a chemical restraint to manage patients with “excited delirium” in the prehospital setting at doses up to 500mg – 10 times the IM analgesic dose recommended in this report.⁵⁹ Malchow and Black state that, “Historically, ketamine has played a central role in anesthesia for the trauma patient as a result of the profound analgesia and hemodynamic stability it provides.”⁵⁵ Ketamine has also been used safely by nurse providers for sedation in remote civilian environments.⁶⁰ Both fentanyl and ketamine have been recommended as good options for mountain rescue.⁶¹

Analgesic medications administered during battlefield trauma care should be recorded on the TCCC Casualty Card along with the casualty’s numerical pain rating both before and after the medication is given.^{16,62}

Conclusions

1. The current TCCC Guidelines for battlefield analgesia need to be simplified.
2. There are better choices for battlefield analgesia than IM morphine available in 2013.
3. The optimal analgesic option will vary with the nature of the casualty's injuries, his or her physiologic condition, and the tactical circumstances present in the casualty scenario.
4. The meloxicam and acetaminophen contained in the CoTCCC-recommended Combat Pill Pack provide limited analgesia but avoid unwanted adverse effects. They should be used for casualties whose pain is relatively less severe and who are still able to be effective combatants.
5. If opioids are required and safe to use for a particular casualty, OTFC provides rapid and effective analgesia, equivalent to that obtained with IV morphine. OTFC is also easier and faster to administer than IV morphine or ketamine.
6. Therefore, for casualties with more severe pain in whom relief of pain takes precedence over preserving combat effectiveness, OTFC is the analgesic of choice if the casualty is not in hemorrhagic shock or respiratory distress and is judged to be at low risk for the subsequent development of either condition.
7. Opioid analgesia should be avoided in casualties in shock, in respiratory distress, or at significant risk for developing either condition.
8. Ketamine also provides excellent analgesia. This agent requires slightly more time and expertise to administer than OTFC, but avoids the risk of cardiorespiratory depression. Ketamine may be use IV, IM, or IN.
9. For casualties with more severe pain in whom relief of pain takes precedence over preserving combat effectiveness, ketamine is therefore the analgesic of choice if the casualty is in hemorrhagic shock or respiratory distress or is judged to be at significant risk for the subsequent development of either condition.

Proposed Change to the TCCC Guidelines

Current Wording

Tactical Field Care

13. Provide analgesia as necessary.

*NOTE: Ketamine must not be used if the casualty has suspected penetrating eye injury or significant TBI (evidenced by penetrating brain injury or head injury with altered level of consciousness).

a. Able to fight:

These medications should be carried by the combatant and self-administered as soon as possible after the wound is sustained.

- Mobic, 15mg PO once a day
- Tylenol, 650mg bilayer caplet, 2 PO every 8 hours

b. Unable to fight:

Note: Have naloxone readily available whenever administering opiates.

- Does not otherwise require IV/IO access
- Oral transmucosal fentanyl citrate (OTFC), 800µg transbucally
 - Recommend taping lozenge-on-a-stick to casualty's finger as an added safety measure
 - Reassess in 15 minutes
 - Add second lozenge, in other cheek, as necessary to control severe pain
 - Monitor for respiratory depression

OR

- Ketamine 50–100mg IM
 - Repeat dose every 30 minutes to 1 hour as necessary to control severe pain or until the casualty develops nystagmus (rhythmic eye movement back and forth)

OR

- Ketamine 50mg intranasal (using nasal atomizer device)
 - Repeat dose every 30 minutes to 1 hour as necessary to control severe pain or until the casualty develops nystagmus

IV or IO access obtained:

- Morphine sulfate, 5mg IV/IO
 - Reassess in 10 minutes.
 - Repeat dose every 10 minutes as necessary to control severe pain.
 - Monitor for respiratory depression

OR

- Ketamine 20mg slow IV/IO push over 1 minute
 - Reassess in 5–10 minutes.
 - Repeat dose every 5–10 minutes as necessary to control severe pain or until the casualty develops nystagmus
 - Continue to monitor for respiratory depression and agitation
- Promethazine, 25mg IV/IM/IO every 6 hours as needed for nausea or for synergistic analgesic effect

*Note: Narcotic analgesia should be avoided in casualties with respiratory distress, decreased oxygen saturation, shock, or decreased level of consciousness.

Tactical Evacuation Care

13. Provide analgesia as necessary.

*NOTE: Ketamine must not be used if the casualty has suspected penetrating eye injury or significant TBI (evidenced by penetrating brain injury or head injury with altered level of consciousness).

- a. Able to fight:
These medications should be carried by the combatant and self-administered as soon as possible after the wound is sustained.
 - Mobic, 15mg PO once a day
 - Tylenol, 650mg bilayer caplet, 2 PO every 8 hours
- b. Unable to fight: (Note: Have naloxone readily available whenever administering opiates.)
 - Does not otherwise require IV/IO access
 - Oral transmucosal fentanyl citrate (OTFC), 800µg transbucally
 - Recommend taping lozenge-on-a-stick to casualty's finger as an added safety measure
 - Reassess in 15 minutes
 - Add second lozenge, in other cheek, as necessary to control severe pain
 - Monitor for respiratory depression
 - OR
 - Ketamine 50–100mg IM
 - Repeat dose every 30 minutes to 1 hour as necessary to control severe pain or until the casualty develops nystagmus (rhythmic eye movement back and forth)
 - OR
 - Ketamine 50mg intranasal (using nasal atomizer device)
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IV or IO access obtained:

- Morphine sulfate, 5mg IV/IO
 - Reassess in 10 minutes.
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 - Repeat dose every 5–10 minutes as necessary to control severe pain or until the casualty develops nystagmus
 - Continue to monitor for respiratory depression and agitation
- Promethazine, 25mg IV/IM/IO every 6 hours as needed for nausea or for synergistic analgesic effect

*Note: Narcotic analgesia should be avoided in casualties with respiratory distress, decreased oxygen saturation, shock, or decreased level of consciousness.

Proposed Change

New wording – Red text denotes new material

Tactical Field Care

Analgesia on the battlefield should generally be achieved using one of three options:

1. Mild to Moderate Pain

Casualty is still able to fight

TCCC Combat Pill Pack:

- Tylenol – 650mg bilayer caplet, 2 PO every 8 hours
- Meloxicam – 15mg PO once a day

2. Moderate to Severe Pain

Casualty IS NOT in shock or respiratory distress
AND

Casualty IS NOT at significant risk of developing either condition

- Oral transmucosal fentanyl citrate (OTFC) 800µg
- Place lozenge between the cheek and the gum
- Do not chew the lozenge

3. Moderate to Severe Pain

Casualty IS in hemorrhagic shock or respiratory distress
OR

Casualty IS at significant risk of developing either condition

- Ketamine 50mg IM or IN
OR

- Ketamine 20mg slow IV or IO

*Repeat doses q30min prn for IM or IN

*Repeat doses q20min prn for IV or IO

*End points: Control of pain or development of nystagmus (rhythmic back-and-forth movement of the eyes)

*Analgesia notes

1. Casualties may need to be disarmed after being given OTFC or ketamine.
2. Document a mental status exam using the AVPU method prior to administering opioids or ketamine.
3. For all casualties given opioids or ketamine – monitor airway, breathing, and circulation closely
4. Directions for administering OTFC:
 - Recommend taping lozenge-on-a-stick to casualty's finger as an added safety measure OR utilizing a safety pin and rubber band to attach the lozenge (under tension) to the casualty's uniform or plate carrier.
 - Reassess in 15 minutes
 - Add second lozenge, in other cheek, as necessary to control severe pain
 - Monitor for respiratory depression
5. IV Morphine is an alternative to OTFC if IV access has been obtained
 - 5mg IV/IO
 - Reassess in 10 minutes.
 - Repeat dose every 10 minutes as necessary to control severe pain.
 - Monitor for respiratory depression
6. Naloxone (0.4mg IV/IN/IM) should be available when using opioid analgesics.

7. Both ketamine and OTFC have the potential to worsen severe TBI. The combat medic, corpsman, or PJ must consider this fact in his or her analgesic decision, but if the casualty is able to complain of pain, then the TBI is likely not severe enough to preclude the use of ketamine or OTFC.
8. Eye injury does not preclude the use of ketamine. The risk of additional damage to the eye from using ketamine is low and maximizing the casualty's chance for survival takes precedence if the casualty is in shock or respiratory distress or at significant risk for either.
9. Ketamine may be a useful adjunct to reduce the amount of opioids required to provide effective pain relief. It is safe to give ketamine to a casualty who has previously received morphine or OTFC. IV Ketamine should be given over 1 minute.
10. If respirations are noted to be reduced after using opioids or ketamine, provide ventilatory support with a bag-valve-mask or mouth-to-mask ventilations.
11. Promethazine, 25mg IV/IM/IO every 6 hours may be given as needed for nausea or vomiting.
12. Reassess – reassess – reassess!

Tactical Evacuation Care

Same as above

Vote – The proposed change noted above was approved by the required two-thirds or greater majority of the voting members of the CoTCCC on 30 October 2013.

Level of evidence: Level C (AHA – Tricoci 2009)

Considerations for Further Research and Development

1. Conduct a retrospective study of combat casualty outcomes in the DoD Trauma Registry as a function of the type and route of prehospital analgesia used as well as the type and severity of wounds sustained and physiologic parameters indicative of circulatory or respiratory status.
2. Explore all options to make 50mg intramuscular ketamine auto-injectors available for use by U.S. combat forces.
3. Explore all options to enable intranasal ketamine for prehospital analgesia in combat casualties.
4. As nausea and emesis can occur with opioid administration, explore the feasibility of developing of a combined lozenge product that includes both oral transmucosal fentanyl citrate and an oral transmucosal antiemetic such as promethazine or ondansetron.
5. Explore all options to develop an oral transmucosal ketamine lozenge product to be used for prehospital analgesia in combat casualties.
6. Establish a Military Use Panel as a shared effort between the DoD and the FDA. The purposes of the

panel would be: (1) to evaluate establishment of a military indication for medication which are labeled for other indications, but have applicability for military use. Examples include OTFC, ketamine, and tranexamic acid; and (2) Evaluate products that have been approved for use by NATO allies and have military applications, but which have not been approved by the FDA for use in the United States, such as dried plasma.

7. Continue to develop new drugs being developed for battlefield analgesia such as the sufentanil microtab and conduct the appropriate prehospital studies to evaluate the safety and efficacy of these agents in comparison to the agents recommended above.

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Disclaimers

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense. This recommendation is intended to be a guideline only and is not a substitute for clinical judgment.

Disclosures

The authors have nothing to disclose.

Release

This document was reviewed by the Director of the Joint Trauma System and by the Public Affairs Office and the Operational Security Office at the U.S. Army Institute of Surgical Research. It is approved for unlimited public release.

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