Prehospital Analgesia With Ketamine for Combat Wounds: A Case Series

Autor: Andrew D. Fisher, MPAS, APA-C; Bryan Rippee, SOCM
Zpracoval: Jaroslav Duchoň

Background
No data have been published on the use of ketamine at the point of injury in combat. Objective: To provide adequate pain management for severely injured Rangers, ketamine was chosen for its analgesic and dis- sociative properties. Ketamine was first used in the 75th Ranger Regiment in 2005 but fell out of favor because medical providers had limited experience with its use. In 2009, with new providers and change in medic train- ing at the battalion level, the Regiment implemented a protocol using doses of ketamine that exceed the cur- rent Tactical Combat Casualty Care recommendations. Methods:Medical after-action reports were reviewed for all Ranger casualties who received ketamine at the point of injury for combat wounds from January 2009 to October 2014. Patients and medics were also interviewed. Results: Unit medical protocols authorize ketamine for tourniquet pain, amputations, long-bone fractures, and pain refractory to other agents. Nine of the 11 patients were US Forces; two were local nationals (one female, one male). The average initial dose given intramuscularly was 183mg, about 2 to 3mg/kg and intravenously 65mg, about 1mg/kg. The patients also received an opi- oid, a benzodiazepine, or both. There was one episode of apnea that was corrected quickly with stimulus. Eight of the 11 patients required the application of at least one tourniquet; four patients needed between two and four tourniquets to control hemorrhage. Pain was assessed with a subjective 1–10 scale. Before ketamine, the pain was rated as 9–10, with one patient claiming a pain level of 8. Of the US Forces, seven of the nine had no pain af- ter receiving ketamine and two had a pain level of four. Two of the eight had posttraumatic stress disorder. Conclusions: In this small, retrospective sample of combat casualties, ketamine appeared to be a safe and effective battlefield analgesic.

Introduction
As of January 2014, the Global War on Terror (GWOT) has accounted for 51,359 combat-related in- juries. 1 Patient data and diligent research have led to the adoption of novel trauma management strategies and greatly reduced battlefield mortality. These strate- gies include more liberal tourniquet application, hypo- tensive resuscitation, earlier hypothermia management, and use of hemostatic agents in the field environment.2 Point--of-injury (POI) pain management strategies have also seen advancement. Kotwal et al. were able to show the effectiveness of oral transmucosal fentanyl citrate (OTFC) in an austere combat environment.3 Most of the advances have been made in Special Operations Units. In these units, subanesthetic doses of ketamine are being used as an alternative to various opioids, including morphine, a drug that has been administered to combat casualties since the Civil War.4 Ketamine's safety profile, wide therapeutic margin, and lack of detrimental hemo- dynamic effects in patients who are in shock represent a promising method for controlling moderate to severe pain at the POI. There have been concerns about ket- amine. Historically, there have been concerns about its use in traumatic brain injury (TBI), fears of increased intracranial pressure (ICP) and of increased intraocular pressures in eye injures. In addition there are concerns about laryngospasm with ketamine. Historically, missions conducted by the 75th Ranger Regiment during the GWOT have been point raids lim- ited to a single period of darkness. However, between 2009 and 2011, the 75th Ranger Regiment performed numerous remain-over-day missions, where the assault force would set up a defensive position in a house for a 24-hour period. Typically, there would be several hours of contact with the enemy. Medical evacuation was de- layed for up to 120 minutes. Arduous terrain, time con- straints, and weight of essential combat equipment place limitations on what medical equipment is feasible for ground medical personnel to carry. Equipment is nearly always limited to a single aid bag, and there are seldom more than three medical personnel on any one mission. Drugs are chosen based on ease and route of adminis- tration, efficacy, safety, side effects, contraindications, and packaging. Medics must be capable of administer- ing drugs in dusty, dark, or confined environments with high potential for hostile fire and high levels of combat- associated stress.

Current Guidelines and Information
Ketamine was initially described in 1965 and used in clinical practice in the 1970s. It is classified as a dis- sociative drug, but it has analgesic effects when ad- ministered in subanesthetic doses. Ketamine acts on the cortex and limbic system and blocks glutamate by antagonistically blocking the N-methyl-d-aspartate re- ceptor. Historically, ketamine has been used in the peri- operative and emergency departments of hospitals, with an increase in use in the prehospital setting within the civilian medical system over the last several years. The use of ketamine in the prehospital military setting is also on the rise, with recent additions made to the Tactical Combat Casualty Care (TCCC) guidelines in October 2013. Recently, ketamine has been approved for use by all conventional forces in Afghanistan.

To date, there are no studies that show the use, safety, and effective- ness of ketamine at the POI in the combat setting. A recent study by Grumbo et al. showed that ketamine was effective and safe for medical evacuation flights in Afghanistan.8 Few civilian studies have been published that discuss the use of ketamine for pain management. One study discussed the use of ketamine for chemical restraint, where it was shown to be effective and safe.

Currently, the Committee on Tactical Combat Casualty Care (CoTCCC) recommends lower ketamine dosages than does the 75th Ranger Regiment. If the casualty is unable to remain in the fight, the CoTCCC recommends administering ketamine dosages of either 50–100mg intramuscularly (IM) or 50mg intranasally (IN) via nasal atomizer device. Repeated doses can be given every 30 to 60 minutes as necessary to control severe pain or until the casualty develops nystagmus (Table 1). If IV or intraosseous (IO) access is or can be established, the recommended dosage of ketamine is 20mg slow IV/IO push over 1 minute, then reassess in 5 to 10 minutes. Repeated doses can be given every 5 to 10 minutes as necessary to control severe pain or until the casualty develops nystagmus. CoTCCC also recommends con- tinuous monitoring for respiratory depression and agitation.7 Most recently, there was a recommendation of a triple option analgesia,9 which recommends either IV morphine sulfate, oral transmucosal fentanyl sulfate, or ketamine as the ideal battlefield analgesic agents. The fourth edition of the Ranger Medic Handbook (RMHB) references the use of ketamine in the proce- dural analgesia and pain management protocols.10 The RMHB basic pain-management protocol initially recommends the use of oral transmucosal fentanyl citrate (OTFC) to control severe pain. If OTFC fails to control the pain, the recommendation is to then progress to ei- ther ketamine 250mg IM, morphine sulfate 10mg IV, or hydromorphone 2mg IV (Table 2). The advanced pain- management protocol also recommends OTFC initially for severe pain. If OTFC fails to control pain, then pro- gression to midazolam 2mg IV/IO with either ketamine 75mg IV/IO push followed by 20–25mg increments or ketamine 250–500mg IM is recommended. Hydromorphone is a follow-on option for refractory severe pain.

Methods

This is a retrospective study using the 75th Ranger Regi- ment's Pre-Hospital Trauma Registry (PHTR) to find all uses of ketamine from 2009 to 2014. The amounts of ketamine along with all other pain and/or sedating med- ications were noted and accounted for in each reviewed case. A subjective questionnaire was sent to all available patients who received ketamine at POI (Appendix A). The questionnaire asked about pain prior to and after tourniquet application, and pain before and after ket- amine administration. The questionnaire also asked if the patient recalled any events before, during, or after ketamine administration. There was also an area for any additional subjective comments from the patients. Both 50mg/mL and 100mg/mL vials of ketamine were used. The dosing of ketamine and other pain medications was at the discretion of the medic or medical officer at the POI. The criteria for ketamine were: (1) tourniquet application; (2) long-bone fracture due to penetrating trauma; or (3) extremity amputation.

Along with ketamine, most patients with severe pain received hydromorphone and/or midazolam. The ketamine dose used for these patients differed from case to case. During this time, the 75th Ranger Regiment did not have a standard protocol for ketamine use, and varying doses were given depending on the provider overseeing the medical personnel at the various combat outstations. The discussion among the providers in the 75th Ranger Regiment prior to the release of the RMHB led to a unanimous recommendation of 50–100mg IV, but there were instances where it was given IM in larger amounts.

Results

Of the 11 patients who received ketamine, two were lo- cal nationals who were lost to follow-up. The remaining nine cases were active duty Soldiers assigned to the 75th Ranger Regiment. Although times were recorded in the PHTR, the administration times were not exact due to the difficulty of maintaining precise time during ongo- ing combat operations. It is estimated that the onset of action of IV ketamine was 1 minute or less. Onset of action for IM administration was less than 3 minutes. The average initial dose for ketamine, when given IV was 65mg, when given IM was 183mg, with an average total dose given IV was 97mg and IM was 217mg (Appendix B). All patients who received IV administration of ket- amine received at least two doses. One patient received two 100mg doses IM. Most of the side effects from the administration of ketamine were extremity movements and incoherent speech. The extremity movement made it difficult to move a casualty through heavy brush and the incoherent speech, was above the normal volume of speech, however, it is not known if it caused unnecessary attention from the enemy.

One patient developed a pe- riod of apnea after receiving ketamine and midazolam. This was his second round of receiving ketamine and midazolam, after being moved through a pomegranate orchard. The move was made more difficult by the spo- radic gunfire from the enemy and suppressive fire from attack helicopters; the patient was moving his extremi- ties throughout this time. Once the patient arrived at the helicopter-landing zone, he was given his second round of medication. Within 30–60 seconds of administration of both ketamine and midazolam, he stopped breath- ing. He was observed for 30–45 seconds before being aroused by painful stimuli. The eight patients who responded to the questionnaire, many reported vivid dreams, with one casualty noting an almost out-of-body experience. He reported seeing him- self from above with treatments being performed. He re- ceived midazolam in conjunction with ketamine. Patient 7 received two doses of ketamine as TCCC recommended; prior to ketamine he had received morphine 15mg and midazolam 7.5mg. Even with morphine, midazolam, and low-dose ketamine, he still had significant pain. Tourni- quet pain was, by far, reported as the worst pain. Ampu- tations closely followed. Most long-bone fractures were associated with tourniquet application, usually due to the vascular damage and associated massive hemorrhage.

It was noted by the authors and in personal commu- nication with the treating medics that procedures were easier to perform and it was easier to move patients who had received ketamine. Procedures such as splinting and reduction of fractures, and wound packing and dress- ing were easier to perform with the sedating effects of ketamine. Excessive patient movements, such as moving extremities and talking, were common when using ket- amine alone or with Dilaudid. The authors noted and in personal communication with the treating medics, when using midazolam with ketamine, there was a drastic de- crease in extremity movements and incoherent speech.

Discussion

The doses of ketamine being administered in this patient population appear to be safe and appear to have controlled the pain effectively. This dosing range is still far below the recommended dose for surgery, but enough to cause analgesia and dissociation. The use of midazolam or dilaudid appeared to offer additional sedation and pain management.

In this small study, ketamine appears to have improved pain scores without being associated with significant adverse effects. Unfortunately, because it is an off-label use, many conventional forces providers are hesitant to allow their medics to use it at the POI, with many still relying on the use of morphine. Morphine has sev- eral qualities that are undesirable for trauma patients. It causes hypotension, hypoventilation, and it takes 30 minutes following IM injection to have a therapeu- tic effect. This delay in onset of action not only causes undue suffering from inadequate pain control but also can lead to early administration of additional doses and can increase the chance of overdose. Also, there is a relatively high percentage of patients who experienced nausea, vomiting, itching, and hypotension from hista- mine release associated with morphine administration.11 Conversely, ketamine has a low prevalence of signifi- cant side effects, preserves cardiovascular function due to positive inotropic and chronotropic effects, and is a bronchodilator.5 It has been reported that ketamine can be tolerated up to 100 times the recommended dose in children.12 The current recommended doses of ketamine for anesthesia are 1–4.5mg/kg IV and 6–13.5mg/kg IM; it is not possible to exceed that in its current packaging of 500mg vials. Ketamine has been shown to decrease the dependence on opioids when used intraoperatively The use of ketamine for procedural sedation in the combat setting was used in a single patient to control hemorrhage from facial and right eye injuries. In this same patient, a cricothyroidotomy was contemplated but subsequently aborted secondary to rapid transport time. It was the impression of the treating medic that ketamine would have provided adequate sedation had the procedure been necessary. It may be used more frequently as evacuations become longer in the current combat setting.

As evacuation time and care in the field become pro- longed during future operations, wound care by the medic may be necessary and can be extremely painful. Ketamine is an optimal drug for procedural sedation in the combat setting: its relative short effects, safety pro- file, and wide therapeutic index allow for all necessary procedures and wound management without worry about airway or vascular compromise. Ketamine has been shown to be as effective as other agents for rapid sequence intubation.13 Other options for pain manage- ment include regional blocks, but these are technically challenging in the field setting and have been associated with a risk of systemic toxicity, mostly due to an inad- vertent intravascular injection.14 There is also a small risk of peripheral nerve damage. In addition to the risks of both regional and local anesthesia, another issue is the ability to carry an adequate amount of anesthetic when all medical supplies must be carried on the back of the medic.

Ketamine has long been thought to worsen TBIs, and fears of elevated ICP have limited its use in trauma pa- tients. Many combat trauma patients who suffer pen- etrating trauma from improvised explosive devices also suffer TBI. Three of the patients in this case series were exposed to overpressure that could cause a TBI, yet there were no adverse outcomes from the ketamine ad- ministration. Recent data show that the historical con- traindication for use with TBI seems overreaching and that ketamine decreased ICP in children by 30%.
Increased intraocular pressure (IOP) is another histori- cal concern with the administration of ketamine in the presence of an eye injury, but recent studies have shown that doses less than 4mg/kg are not associated with in- creased IOP when there is no globe injury.17 Although patient 8 had penetrating shrapnel wounds to his eye and TBI, he was administered ketamine with no adverse effects or increased morbidity. Of the concerns regard- ing laryngospasm with ketamine use, there were no re- ported cases in this small group.
A 2006 study showed posttraumatic stress disorder (PTSD) rates for Servicemembers who deployed to Iraq was 16.6% and was significantly higher for wounded Servicemembers, with a rate of 31.8%.18,19 Ketamine is thought to be associated with a decreased prevalence of PTSD. There are no studies that conclude that prehos- pital ketamine can decrease PTSD in severely injured patients, but it has been shown to decrease the amount of PTSD in patients when ketamine is given periopera- tively.20 Another study showed use of an analgesic was as- sociated with a lower incidence of PTSD.21 There is an opinion among military providers that ketamine's rapid onset of effective analgesia in the prehospital setting could help decrease the prevalence of PTSD. Of the nine US Servicemembers who received ketamine at the POI, only two were subsequently diagnosed with PTSD. We compared the injuries and scenarios surrounding the in- juries of nine other Soldiers assigned to the 75th Ranger Regiment with similar injuries. We compared past medi- cal and behavioral health history along with the medi- cal records surrounding the injuries. We were limited to the medical records available in electronic medical record. In that group, six of the nine had PTSD. Even though this was a small group, when compared to other severely injured Soldiers with similar injuries from the 75th Ranger Regiment, ketamine appeared to decrease the incidents of PTSD.

Limitations

Due to the small size of this retrospective study, it is dif- ficult to draw any definitive conclusions about higher doses of ketamine being administered in the prehospital setting. In addition, other narcotic and sedative agents given with ketamine confound results, especially regard- ing ketamine's effectiveness. The data from the patient questionnaire are based on answers given up to 3 years after the injury; recall on pain levels can be skewed in this population. The PHTR is very thorough but reliant on the medic filling out the casualty card and writing the report for input reliably. Certainly, there could be errors on medication doses and the times they were given.

Conclusion

Ketamine has been shown to be a safe and effective drug as a dissociative agent and an analgesic. It has a supe- rior safety profile when used in a combat trauma setting, with none of the undesirable side effects of opioids. Despite the small population of the study, the results are promising. The data show larger doses of ketamine can be tolerated well with few side effects. As with all other controlled substances, clear protocols and proper training at all levels, as outlined in the fourth edition of the RMHB, are the keys to proper and successful use of ketamine. With these promising results, there should be further studies on the use of ketamine at the POI.
Recently, in Afghanistan, ketamine has been available in the atomized form. It is hoped that with a new and easier way to administer ketamine, it will be used more often. It is recommended that the US Food and Drug Administration authorize the use of ketamine for analgesia. Further, it is recommended that the Joint Theater Trauma Registry track and analyze the use of ketamine for future studies. The current recommended doses of 20mg IV and 100mg IM are simply not adequate and have demonstrated an ineffective duration of action. Therefore, the CoTCCC should increase its recommended doses of ketamine to 50–100mg IV and 250mg IM. Midazolam's amnesic and sedation properties work synergistically with ketamine to decrease hallucinations, extremity movement, and incoherent speech, therefore, it is recommended the CoTCCC add the use of mida- zolam in conjunction with ketamine. Further development of auto-injectors could potentially make conventi- onal forces providers more comfortable about administering the medication, allowing less-experienced medics to use it in the prehospital environment. The potential for ketamine to decrease the incidence of PTSD would be substantial during the recovery of the injured Servicemember. Overall, ketamine is an extremely useful analgesic and dissociative. When used at doses of 50–100mg IV, it has been shown effective in the prehospital combat environment.

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Jaroslav Duchoň