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COMPARISON OF THE EFFECTS OF KETAMINE AND MORPHINE ON PERFORMANCE OF REPRESENTATIVE MILITARY TASKS

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□ **Abstract—Background: When providing care under combat or hostile conditions, it may be necessary for a casualty to remain engaged in military tasks after being wounded. Prehospital care under other remote, austere conditions may be similar, whereby an individual may be forced to continue purposeful actions despite traumatic injury. Given the adverse side-effect profile of intramuscular (i.m.) morphine, alternative analgesics and routes of administration are of interest. Ketamine may be of value in this capacity. Objectives: To delineate performance decrements in basic soldier tasks comparing the effects of the standard battlefield analgesic (10 mg i.m. morphine) with 25 mg i.m. ketamine. Methods: Representative military skills and risk propensity were tested in 48 healthy volunteers without pain stimuli in a double-blind, placebo-controlled, crossover design. Results: Overall, participants reported more symptoms associated with ketamine vs. morphine and placebo, chiefly dizziness, poor concentration, and feelings of happiness. Performance decrements on ketamine, when present, manifested as slower performance times rather than procedural errors. Conclusions: Participants were more symptomatic with ketamine, yet the soldier skills were largely resistant to performance decrements, suggesting that a trained task skill (autonomous phase) remains somewhat resilient to the drugged state at this dosage. The performance decrements with ketamine may represent the subjects' adoption of a cautious posture, as suggested by risk propensity testing whereby the subject is aware of impairment, trading speed for preservation of task accuracy. These results will help to inform the casualty care community regarding appropriate use of ketamine as an alternative or opioid-sparing battlefield analgesic. Published by Elsevier Inc.**

□ **Keywords—prehospital care; military medicine; soldier skills**

INTRODUCTION

Tragically, to varying degrees, casualties are virtually inevitable in sustained combat operations. Although lamentable in their own right, casualties can also jeopardize mission completion, reduce combat effectiveness, and increase exposure and danger to others. To this end, the goals of Tactical Combat Casualty Care (TCCC) include treating the casualty, preventing additional casualties, and completing the mission (1). In some instances, the best initial "medicine" during care under fire may dictate that the casualty take cover or remain engaged in other military tasks. Indeed, the extent to which a casualty can remain capable and engaged may prove critical for care under fire, self-evacuation, and safety and effectiveness of the unit. It is with ease that one can make the

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intellectual transition to similarities with prehospital care in other austere environments such as wilderness or expedition medicine. In such cases, treatments and biologics are often limited, and the patient or team member may have to continue on for a period of time with purposeful tasks despite traumatic injury.

Timely and effective analgesia is essential in trauma casualty care. The types of injuries encountered on the modern battlefield resulting from high-energy blast or direct-fire weapons are significant and can cause tremendous pain. It is not suggested or recommended that casualties sustaining significant trauma continue mission-oriented tasks as a matter of convention. However, some situations are conceivable whereby the need is present due to extreme circumstance, there are no good alternatives, and evacuation is not imminent. Since its discovery in the early 19th century and subsequent well-documented military use in the Crimean War and American Civil War, morphine (and its derivatives) has remained the mainstay for acute severe battlefield pain (2). Its perpetuity in this capacity speaks to its strengths and desirable qualities as a potent analgesic. Indeed, the 10-mg intramuscular (i.m.) morphine injector has been the current battlefield standard for acute severe pain for some time. However, morphine can be associated with untoward side effects (including hypotension, sedation, nausea and vomiting, respiratory depression, euphoria/dysphoria, and others), and the military medical community has searched for adjuvants and alternatives to augment or spare morphine use in some instances (3,4).

Morphine can detract from a casualty's ability to "remain capable" on the battlefield if required by the situation, particularly at higher doses. One combat medic field reference, for example, states that the casualty should be considered nonambulatory after administration of morphine (5). TCCC mandates that combatants with altered mental status must be disarmed due to the risk of inappropriate weapon use (1). Furthermore, the commonly used i.m. route is notoriously problematic under conditions of hemorrhage, hypovolemia, and hypothermia whereby absorption is poor, analgesia is unreliable, and overdose remains a concern with subsequent volume resuscitation during later stages of care.

Although morphine is a very good analgesic, there remains interest in potential alternatives, adjuvants, and substitute routes of drug delivery for battlefield pain control. The guidance of "improved drugs to manage pain" is listed specifically as a key technology to be explored and developed as a Health Service Support Force Operating Capability (6). Likewise, pain control research remains a designated program area of the Army's Combat Casualty Care Research Program (CCCRP) with the mission of "fostering the development of biologics, pharmaceuticals, and medical devices that improve the first responder's capability to provide effective treatment more rapidly and as close to the place of the injury as possible" (7). Medics with direct combat experience have also requested improved battlefield analgesia—in particular, seeking alternatives to morphine and alternate routes of administration (Chief of Anesthesia, U.S. Army Institute of Surgical Research, personal communication).

In 2009, the Royal Centre for Defence Medicine (United Kingdom) conducted a study of clinical opinion assessing the effectiveness of current battlefield analgesia and options for improvement (8). Surveying 122 clinicians (emergency physicians and nurses, anesthesiologists, surgeons, intensivists, general practitioners, and combat medical technicians), more than half (52%) disagreed that i.m. morphine had the ideal analgesic properties for the military prehospital arena. The majority of respondents reported simplicity, reliability, and rapid onset of action as having the highest importance. Furthermore, a majority (70%) responded that an analgesic more potent and with a more rapid onset than morphine was desirable. Seventy-four percent reported that a nasal spray was an acceptable delivery method.

The concept of exploiting routes of drug administration other than i.m. is not new (9–11). These may include buccal transmucosal, intranasal aerosol, transdermal, and others (12). Early intravenous access with more precise titration is ideal, but certainly problematic under combat conditions (8,11). Morphine is an excellent, time-tested battlefield analgesic for acute severe pain, but does have some shortcomings. And the i.m. delivery route can be problematic, especially with shock states common with battlefield-type injuries. As part of larger programs to address these issues, this study was sponsored by the Army's CCCRP in support of an Integrated Product Team researching intranasal (i.n.) ketamine as a potential battlefield analgesic.

Although largely used as an anesthetic, use of ketamine as an analgesic is not surprising given the *N*-methyl-D-aspartate receptor's significant role in pain perception. Furthermore, it has been known for over 25 years that ketamine interacts with opioid receptors (13). Other purported receptor interactions include norepinephrine, serotonin, and muscarinic (14). Recommended analgesic dose ranges vary (0.4–1.0 mg/kg i.m. and 0.2–0.5 mg/kg i.v.) and are generally given as lower than that needed for anesthetic purposes (5–10 mg/kg i.m. or 1–2.5 mg/kg i.v.) (15,16). The efficacy and opioid-sparing effects of subanesthetic ketamine for analgesia have been studied previously, as well as experiences in combat and other prehospital care arenas (16–21).

Department of Defense involvement with an intranasal ketamine development effort began in approximately 2000. An analgesic product was envisioned that could provide acute pain relief while preserving the casualty's