Fentanyl Plus Ketamine Versus Fentanyl Alone for Acute Burn Pain

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JHM IRB - eForm A – Protocol

1. Abstract

The proposed research is a triple-blind, placebo–controlled, randomized clinical trial to evaluate the safety, efficacy and opiate-sparing effect of standard of care opiate (fentanyl) augmented with low-dose, slowly infused ketamine for the treatment of pain during acute burn wound care (e.g., twice-daily dressing changes). The standard of care for wound care among adults with acute intermediate and/or deep partial thickness burns involves twice daily wound care. Each wound care sessions, especially during the first week, involves severe pain during dressing removal, debridement, wound cleansing, re-application of topical ointment, and dressing replacement. The standard method for alleviating pain during wound care procedures is through the use of intravenous opiate medications (i.e., fentanyl).

Ketamine has recently emerged as a potentially effective analgesic alternative to narcotics for use in combat associated casualties. Early case reports, post hoc chart reviews and, more recently, small RCTs have consistently shown ketamine to be equal to or, more often, superior to opiate analgesics for treating acute pain in U.S. emergency departments and in combat casualties. There is an urgent need for a well-controlled and rigorously designed study with sufficient power to definitively test the hypothesis that fentanyl when augmented with low-dose, slow-infusion ketamine provides superior analgesia in the acute burn setting. Findings from acute burn centers are likely to generalize to a number of acute trauma settings, including injuries sustained in a battlefield setting.

We propose to enroll 94-104 acute adult burn patients hospitalized in the Johns Hopkins Bayview Medical Center's Johns Hopkins Burn Center (Burn Intensive Care Unit) who have sustained burns ≥2% and ≤40% total body surface area (TBSA ≥2% & ≤40%). Subjects will be randomized to either a fentanyl + saline ("usual care" - UC) condition, or to fentanyl plus ketamine (K + UC) condition. Subjects in the K + UC condition will receive low-dose, slow-infusion ketamine using methodology previously employed in the small clinical trials reviewed in background section (see information below on medications, dosing, timing etc.). Subjects in the UC condition will receive fentanyl plus normal saline whereas those in the study drug arm will receive fentanyl plus ketamine. It is hypothesized that subjects in the K + UC condition will have superior pain relief with reductions in primary and secondary hyperalgesia, as well as reductions in allodynia. It is also hypothesized that adjunctive ketamine will be associated with an opiate sparing effect, reductions in symptoms of acute stress disorder, posttraumatic stress disorder, major depressive disorder and sleep disturbance during the study and for up to one month follow-up in the acute post-burn period.

b. DOSING -

KETAMINE GROUP (Study Drug, Fentanyl PLUS Ketamine, slow infusion):

i. Ketamine Loading Dose (Study Drug, slow infusion via programmed pump): 0.3 mg/kg, initiated approximately 10 minutes prior to wound care and infused over approximately 5 minutes… *THEN*
ii. *Fentanyl Loading Dose via programmed pump = 1 mcg / kg
*This is given to participants in both Group 1 and Group 2 starting at <1 minute before wound care.
iii. Ketamine (Study Drug, Infusion via programmed pump): 2.5 mcg/kg/min, initiated immediately following the Fentanyl Loading Dose and continued for the duration of the session. The EPIC order set specifies that the nurse determines when the session is over, and that the nurse will turn off the infusion at that point.

USUAL CARE GROUP (Fentanyl PLUS Saline)

i. Saline Loading Dose (Placebo, Infusion via programmed pump) = An identical volume of saline as that in 0.3 mg/kg of ketamine. This will be initiated in the Usual Care group approximately 10 minutes before the wound care is set to begin and infused over approximately 5 minutes (i.e., during the same time that the Ketamine Group receives the ketamine loading dose).
ii. *Fentanyl (UC, injection via programmed pump) = 1 mcg / kg IV.
*This is given to participants in both Group 1 and Group 2 initiated < 1 minute prior to wound care.
ii. Saline (Placebo, Infusion via programmed pump) = identical volume of fluid as that in 2.5 mcg/kg/min of ketamine, initiated immediately following the Loading Dose and continued for the duration of the session. . The EPIC order set specifies that the nurse determines when the session is over, and that the nurse will turn off the infusion at that point.

PRN DOSE*

i. PRN Fentanyl PRN (UC, injection) = 1 mcg / kg.

*The PRN is provided to participants in both Group 1 and Group 2 when a participant requires additional pain medication. The criteria for providing PRN fentanyl are based on customary nursing practices, including a self-reported persistent rise in NAS pain ≥2 or a NAS ≥ 7/10 (JCAHO standard) and combined with nursing judgment.

2. Objectives

There are two primary objectives and seven secondary objectives for this proposal. Primary objectives (i.e., Specific Aims #1 and #2) are:

Specific Aim #1: To test the effectiveness of ketamine augmentation to usual care (fentanyl) (K+UC) relative to Usual Care (UC) in reducing the severity of acute nociceptive pain in response to pressure at: a) the burn wound (primary hyperalgesia); b) in body areas adjacent to the burn (secondary hyperalgesia) and; c) body areas distal to the burn (allodynia).

The standard of care for wound care procedures among adults with acute intermediate and/or deep burns involves twice daily wound care procedures. Each wound care procedure, especially during the first week, involves moderate to severe pain during dressing removal, debridement, wound cleansing, re-application of topical ointment, and dressing replacement.

To compare and contrast the K+UC condition relative to the UC condition for reducing acute nociceptive pain, we will measure the following: 1) Self-reported pain and pain unpleasantness; 2) Sympathetic arousal; 3) Time until maximal pain relief; 4) Post-procedure, self-rated recall of average pain and pain unpleasantness following each wound care procedure, and self-rated satisfaction with pain management. Each of these is described below.

1) **Self-reported pain:** Pain is operationally defined as participant self-reported pain severity at the time of assessment, using the Numeric Analogue Scale (NAS) (McCaffrey, Pasero, 1999). NAS

Assessments will be performed within 5 minutes prior to administration of K+UC or UC, at the onset of the wound care procedure, every 10 minutes during each procedure, and at 15, 30, 45 and 60 minutes after the first and second procedures of the day, and, again at 6-hours post-procedure for the 1st wound care session each day.

The protocol standardizes body surface areas (wound, proximal, distal) where pain will be measured in the context of standardized pressure, and the duration and interval before releasing pressure. That is, pressure will be applied to each area, in turn, using standard force and a single fingertip, as when assessing skin blanching. This will be repeated once at each body location (wound, proximal, distal) assessed at the 30 minutes and 1-hour assessments during the first sessions on Day 1 (Session 1), Day 3 (Session 1), Day 5 (Session 1) and Day 7 (Session 1) and again at 1 hour after each of these wound care sessions is completed.

Central Sensitization - The NAS will be rated in regards to each of the following 3 patient-specific areas at each specified time point: a) Within the wound area (primary hyperalgesia); b) Skin proximal to but outside the wound area (secondary hyperalgesia) and c) Generalized pain at skin distal from the wound (allodynia). The repeated assessment of pain severity during the wound care will allow for evaluating increased pain hypersensitivity (hyperalgesia), and the assessment of pain for 1 hour afterwards will enable us to detect enhanced temporal summation of pain as has been observed among combat veterans with PTSD relative to combat veterans without PTSD and non-service members without PTSD (see below, Moeller-Bertram, Strigo, et al., 2016)

2) **Sympathetic arousal:** This will be measured using an Itamar Watch-PAT 200. This is a device that will be worn by all subjects while in the burn unit. In addition to providing measures of sympathetic reactivity prior to, during and after wound care, this device will also provide measures of sleep. A description of this device is provided at: https://www.youtube.com/watch?v=wE4pVhvS5Xg

3) **Time to maximal pain relief and duration of time at maximal pain relief:** These are operationally defined as: time elapsed between the start of wound care and the time at which the lowest pain rating is reported by each participant for each wound care session, and, the number of 10-minute observations where pain is reported at that maximal relief pain score. Thus, the NAS ratings will be used to create change scores (each NAS score subtracted from baseline score) with the largest change from baseline score designated as maximal pain relief. If the maximal pain relief is reflected in more than one rating, the first of these will represent the time to maximal pain relief.

4) **Recall Effect on Pain and Satisfaction With Pain Management:** This is defined as patient recall of average pain, and rating of satisfaction with wound care pain management. Recall of the average pain experienced during each of the 14 procedures will be rated 1-hour after each wound care sessions ends, and 6 hours afterward each AM session ends measured with the same 0-10 point NAS used to rate pain during the wound care procedure. This will allow testing of the well-documented memory effect whereby the worst and the last pain ratings during the procedure will best predict memory for pain afterwards.

Rating of satisfaction with wound care pain management will be measured using a numeric analog scale (ratings 1 to 100, with 1 = totally dissatisfied, and 100 = totally satisfied) at after each wound care sessions ends, and 6 hours afterward each AM session ends. Patient satisfaction is anticipated to be an inverse function of remembered pain, thus, it is expected that it will be inversely related to pain recall, and that the K+UC group will have higher satisfaction with pain management.

Specific Aim #2: To determine whether adjunctive ketamine is associated with opiate sparing.

This will be measured by documenting each participant's number of Requests for Additional Analgesic Medications (i.e., RAAMs) for acute nociceptive pain during each of the 14 wound care procedures from Day 1 to Day 7 of the Trial.

The seven secondary outcome measures of the proposal are: 1) Rates of acute and posttraumatic stress disorder (i.e., ASD and PTSD); 2) Rates of major depressive disorder; 3) Sleep quality and duration; 4) Pain-related anxiety; 5) Catastrophizing; 6) Emotion Regulation and; 7) Trauma resilience.

1) ASD and PTSD will be assessed using the Diagnostic and Statistical Manual of Mental Disorders V- (DSM V). By definition, to meet criteria for PTSD, symptoms must be present for 1 month. As such, prior to the 1-month post-injury time-point, subjects with symptoms consistent with PTSD related to their burn injury will be diagnosed with ASD, rather than PTSD. It is hypothesized that subjects in the K + UC group will have a lower percentage of patients who meet criteria for PTSD, when compared to subjects in the UC group. It is also hypothesized that a number of factors will moderate the presence and severity of ASD and PTSD; these include:

a) Pain, as measured above. Mutual Maintenance Theory: We anticipate that "mean pain" of all 14 sessions (i.e., group average of all observations across all 14 sessions) and the trajectory of pain through the 14 sessions (i.e., group X individual trajectory within session, and, group X individual trajectory across all 14 sessions) will be predictive of PTSD development and PTSD symptom severity at 1-month.

b) Sympathetic reactivity (as measured above). We expect that greater sympathetic reactivity during the wound care procedures will be associated with ASD and PTSD.

c) Depressive symptom severity as measured using the Beck Depression Inventory (BDI-II) during the week of wound care, and at the 1-month time-point.

d) Sleep during the night following wound procedures (measured by both self-report and with the Itamar Watch-PAT200) and at the 1-month time point (self-report).

e) Trauma Resilience (as measured using the Trauma Resilience Scale: Trait- at baseline, and at 1-month time-point).

f) Distress at baseline in reporting the burn event (as measured by self-report and the Itamar Watch-PAT200)

g) Optimism (as measured by the Life Orientation Test: Trait – baseline)

h) Emotion Regulation (as measured by the Emotion Regulation Scale-State: baseline and post-procedure)

2) Major Depressive Disorder: It is hypothesized that subjects in the K + UC group will have significantly lower rates of major depressive disorder, as defined by the DSM V and Beck Depression Inventory-II, than subjects in the UC condition. It is anticipated that the same factors that are hypothesized to moderate ASD and PTSD (see above) will moderate major depressive disorder. Further, we anticipate that severity of ASD and PTSD will be predictive of severity of major depressive disorder.

3) Sleep: Sleep will be assessed by the Itamar Watch-PAT 200, and by self-report (Insomnia Severity Index, and, Sleep-Pain Diary). It is hypothesized that subjects in the K+UC group will have superior sleep to those in the UC group. The same factors that are hypothesized to moderate PTSD and depression are anticipated to moderate sleep quality.

4) Pain Anxiety Symptom Scale-20 (Kleiman, 2011) will be used to test the hypothesis that the K+UC condition, when compared to the UC condition will result in significantly fewer symptoms of pain-related anxiety at 1-month follow-up. Similarly, these measures will be used to test the hypothesis that pain anxiety assessed within 1 hour prior to start of Sessions 1, 5 and 7 will moderate the effect of Study Drug on measures of acute pain. Finally, this measure will be used to test the hypothesis that change in pain anxiety will moderate the effect of study drug on change in PTSD symptoms and PTSD diagnosis.

5) Catastrophizing: Pain-related catastrophizing will be measured using the Pain Catastrophizing Scale (PCS; Sullivan, 1995) which was developed to assess three components of catastrophizing: rumination, magnification, and helplessness. It is hypothesized that the K+UC condition, when compared to the UC condition will result in significantly fewer symptoms of pain-related catastrophizing at 1-month follow-up. It is also hypothesized that pain-related catastrophizing assessed within 1 hour prior to start of Day 1 (Session 1), Day 4 (Session 7) and Day 7 (Session 13) will moderate the effect of Study Drug on measures of acute pain (across all 7 days and 14 sessions, as well as during Sessions 1, 7 and 13 respectively).

6) Emotion Regulation: Emotion regulation will be measured using the Emotion Regulation Scale (ERS: Spaapen, Waters, Brummer, Stopa, Bucks, 2014) and will test the hypothesis that emotion regulation will moderate the effect of pain anxiety and pain catastrophizing on pain, opiate sparing, PTSD, and depression symptom severity at 1-month follow-up.

7) Trauma Resilience: We will use the Connor-Davidson Resilience Scale (CD-RISC: 2007) to measure resilience to test the hypothesis that trauma resilience will moderate the effect of pain anxiety and pain catastrophizing on acute pain, opiate sparing, PTSD, and depression symptom severity at 1-month follow-up.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

There is a need for high-grade evidence supporting the optimal drug, dose, route and duration of analgesia to be used in combat and other austere conditions. The greatest need is to identify medications with superior benefits (rapid onset, adequate pain relief, retained physical and physical function) and fewer side effects (impaired cognition, respiratory suppression, reduced physical function) than are observed with the use of standard opiate-based pain medications.

One unfortunate, yet essential characteristic of wound care for deep burns, as well as for many traumatic injuries, is the debridement / wound cleansing / dressing change procedures that occur 2-times per day until wound closure has been achieved. Burn wound debridement, cleansing, and dressing change procedures involve repeated exposure to acute nociceptive stimuli, often leading to an intensifying sensitivity of nociceptors in the wounded area (primary hyperalgesia), the area surrounding the wounded area (secondary hyperalgesia) (Myer, Ringkamp, Campbell, Raja, 2005), as well as generalized pain in areas that are remote from the wound (allodynia). (Latremoliere, 2009).

The standard practice for analgesia during acute burn care is the use of using either hydromorphone (Dilaudid) or fentanyl – in the BICU, fentanyl is by far the preferred analgesic. The choice of narcotic analgesic is determined by the preference of the Critical Care Medicine team in the Burn Intensive Care Unit. Fentanyl (Siblimaze), opiate analgesics are given intravenously. The onset time for narcotics administered intravenously is within minutes. In addition to concerns related to opiate-induced respiratory suppression, ongoing use of morphine in situations such as sustained daily burn wound care over weeks and sometimes months, can lead to the development of tolerance and opiate-induced hyperalgesia (Gupta, 2015).

Ketamine (2-(O-chlorophenyl)-2-methylamino cyclohexanone) is a non-barbiturate anesthetic/analgesic agent structurally related to phencyclidine and cyclohexamine. Ketamine is the only single-agent anesthetic capable of producing a "dissociative" anesthesia, which has been useful for a variety of outpatient and inpatient surgical procedures. This agent is also known to produce potent

analgesia at sub-anesthetic therapeutic concentrations. The hypothesized opiate sparing effect of ketamine for the treatment of burn-related pain holds significant promise for treating/preventing previously mentioned untoward opiate effects.

Numerous theories have been proposed to explain the effects of ketamine, including use-dependent blockade of N-methyl-d-aspartate (NMDA) receptors in the central nervous system, interactions with opiate receptors at central and spinal sites, and interaction with norepinephrine, serotonin, and muscarinic cholinergic receptors. Data suggest that some effects of ketamine may be mediated via non-opioid mechanisms. Warncke, et al., (1997) interpreted their experimental burn findings in healthy volunteers that the mechanisms underlying secondary hyperalgesia are "mediated by glutamatergic transmission via NMDA receptors." The potential advantages of using ketamine instead of narcotics and benzodiazepine drugs during austere operations include the preservation of muscle tone and protective airway reflexes, reduced risk of respiratory depression, reduced incidence of hemodynamic instability in shock, reduced need for opioids, and decreased nausea and vomiting.

Two recent randomized controlled trials (RCTs) compared the efficacy and features of ketamine versus opiates in treating pain among samples with pain related to minor trauma in an emergency department setting (Motov, 2015; Miller, 2015). Neither study found significant differences between morphine and low-dose intravenous ketamine in pain relief at 30 minutes post-infusion – that is, ketamine and morphine were equi-analgesic (Miller, 2015; Motov, 2015). Motov also noted the groups were similar in the number of patient requests for additional analgesic fentanyl at 30 or 60 minutes. Notably, however, Miller found that the mean time to maximum pain relief was much more rapid following treatment with ketamine (i.e., ketamine = 5 minutes, Morphine = 100 minutes). If this observation of abbreviated elapsed time to achieve maximum pain relief is replicated in the current study of burn wound pain, then ketamine may hold a distinct advantage over opiate medications when pain is severe and time is of the essence (e.g., combat, wound care).

In contrast to studies involving patients with trauma injuries, a recent review of the few RCTs examining ketamine in burn patients (McGuinness, 2011) found that ketamine reduced burn pain (both primary hyperalgesia and secondary hyperalgesia) significantly better than morphine. This differential efficacy of ketamine in burn pain, but not in non-burn traumatic wounds, if validated in well-designed studies among patients with acute burns, may have important implications for managing battlefield trauma- versus battlefield burn- related pain. While ketamine has been a tool in the treatment of burn patients for years, there is a dearth of well-designed trials of the safety and efficacy of ketamine in burn patients. Fewer still have studied optimal dosing, opiate-sparing potential, preferred delivery modality, patient comfort and satisfaction, impact on targets in other systems/syndromes, and mechanism of action. Many of the extant ketamine studies in patients with burn injuries involved case report or case series designs, no blinding or randomization, higher doses of ketamine, only pediatric patients, drug delivery via inhalation versus IV infusion, and small, inadequately characterized samples (McGuinness, 2011). Stated simply, there is insufficient literature to ensure the safety and efficacy to support the use of ketamine as analgesia in combat soldiers with burns, or adult civilians with burn injury sustained in austere conditions.

2. Safety and Efficacy of Low-Dose, Slow Infusion Ketamine (Pourmand, et al, 2017)

The goal of using low-dose ketamine (LDK) is to provide analgesia without producing the adverse effects that occur more frequently at higher doses. LDK has been found to be safe and effective as an analgesic with a favorable adverse effect profile. Within the studies reviewed, 1187 patients received LDK. The most common adverse effects were dizziness, nausea, vomiting, and mild neuropsychological reactions such as hallucinations or agitation (4) [25]. Almost all of these adverse effects resolved spontaneously - emergence phenomenon is unusual when low doses are used and when reported, it is mild and transient.

LDK has been shown to be safe and effective for the treatment of a wide variety of painful conditions in the ED where it is comparable to opioids in reducing pain. Respiratory suppression is less of a risk with ketamine than with high dose of IV opioids and it is effective for the management of pain exacerbations in opioid tolerant patients. Although potential for abuse is present, "ketamine has less potential for addiction or epidemic overuse" than opioids.

Pourmand A, Royall C, Alhawas R, Shesser R. Low dose ketamine use in the emergency department, a new direction in pain management. American Journal of Emergency Medicine 35 (2017) 914–932. http://dx.doi.org/10.1016/j.ajem.2017.03.005

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2. [17] J. Sleigh, M. Harvey, L. Voss, B. Denny. **Ketamine – more mechanisms of action than just NMDA blockade** Trends in Anaesthesia and Critical Care, 4 (2014), pp. 76-78
3. [18] A. Gupta, L.A. Devi, I. Gomes. **Potentiation of μ-opioid receptor-mediated signaling by ketamine** J Neurochem, 119 (2011), pp. 294-302
4. [25] B. Sin, T. Ternas, S.M. Motov. **The use of subdissociative-dose ketamine for acute pain in the emergency department.** Acad Emerg Med, 22 (2015), pp. 251-257

The risk and benefits of LDK, relative to opioid medications, were reviewed by Lee and Lee (2016). The reviewed a total of 6 trials involving 438 patients evaluating LDK in the ED. They reported that "… subgroup analysis of pain reduction indicates that the favorable effects of ketamine were similar or superior to those of placebo or opioids." While the results indicated that low-dose ketamine was associated with a higher risk of neurological (relative risk [RR] = 2.17) and psychological (RR = 13.86) events, the opioid medications had a higher risk of major cardiopulmonary events (RR = 0.22).

Lee EN, Lee JH. The effects of low-dose ketamine on acute pain in emergency setting: A systematic review and Meta-Analysis. *PLoS ONE*, 2016;11(10): e0165461. https://doi.org/10.1371/journal.pone.0165461

3. Cognitive impairment in healthy volunteers and in clinically-defined abusers of ketamine (Liu, Lin, Wu, Zhou, 2016)

Liu, Lin, Wu, and Zhou (2016) reviewed toxic effects of ketamine in "normal" (healthy controls) and clinical samples of ketamine abusers. They describe and discuss the concern that "… the therapeutic value of ketamine to treat psychiatric disorders faces a major challenge that ketamine also owns significant reinforcing and toxic effects." Specifically, they note that "An acute dose of ketamine has been demonstrated to induce cognitive impairments in healthy volunteers and cognitive deficits are also observed in frequent ketamine users (Curran, Morgan, 2000; Liang et al., 2013; Morgan et al., 2010). Liu, et al., (2016) note that ketamine-induced cognitive impairment has been suggested to have therapeutic value in that it has shown to have a rapid effect on explicit and inexplicit suicidal cognition among depressed patients at imminent risk of suicide (Price et al., 2014; Solé et al., 2015).

The neuronal mechanism underlying the cognitive impairment induced by ketamine is only beginning to be understood. Neuroimaging studies revealed that "acute administration of ketamine in healthy volunteers resulted in impaired verbal working and episodic memory, in conjunction with altered activities in cingulate region, striatum and frontal cortex" (Honey et al., 2005; Honey et al., 2004; Northoff et al., 2005; Rowland et al., 2005). This differed from findings in a clinical sample where "decreased posterior cingulate and medial pre-frontal deactivations was evident during a working memory task following ketamine administration" (Anticevic et al., 2012), and pPerceptual distortions and delusional thoughts were correlated with increased BOLD response in the paracentral lobule (Stone et al., 2015). These studies suggest that ketamine effects on specific circuits play a major role in ketamine-induced cognitive impairment and that the involved circuits may differ between healthy volunteers and clinical samples of ketamine abusers.

The measure Side Effect Measure of Opiates and Ketamine was added to the study protocol to evaluate side effects and compare the form and frequency in participants in each group.

Liu Y, Lin D, Wu B, Zhou W. Ketamine abuse potential and use disorder. *Brain Research Bulletin* 126(2016): 68-73. http://dx.doi.org/10.1016/j.brainresbull.2016.05.016

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Curran, Morgan, 2000
Honey et al., 2005
Honey et al., 2004
Liang et al., 2013
Morgan et al., 2010
Price et al., 2014
Solé et al., 2015
Stone et al., 2015

Evidence for ketamine effect in reducing behavioral and physiological aspects of anxiety and depression.

Recently, ketamine has also been shown to hold promise as a cutting edge therapy for chronic, treatment-resistant major depression (Lapidus, 2014) and chronic posttraumatic stress disorder (PTSD; Feder, 2014).

There is a rapidly expanding interest in pharmaceutical interventions alone or in combination with prolonged exposure that may, in the face of acute trauma exposure, facilitate the prevention, resilience or early recovery from symptoms of PTSD and stress-related depression symptoms (Weng, et al, 2013). Although these are not primary outcome measures in the proposed Ketamine for Acute Pain in Burns study, many patients with significant burn injuries develop PTSD and/or depression, in part related to the wound cleansing/debridement process. As such, in addition to evaluating the utility of ketamine as an adjunct to opiates for the purposes of pain management, the current proposal will evaluate its potential effects on psychological and psychiatric outcomes (i.e., stress, mood, PTSD, depression, sleep).

Engin, et al., (2009) note that demonstrating ketamine's effects on depression and anxiety are complicated in human trials because of its' dissociative anesthetic properties "which are obvious to both patients and clinicians" as well as in animal models that are often confounded by "ketamine's side-effects on general activity, which have not been routinely measured or taken into account in experimental studies" (p. 359).

They report on a rigorously designed set of animal experiments wherein ketamine decreased "behavioral despair in the forced swim test, a widely used rat model of antidepressant drug action." This effect was not confounded by side-effects on general activity, and was comparable to that of a standard antidepressant drug, fluoxetine."

Interestingly, ketamine also produced anxiolytic-like effects in the elevated-plus-maze. Importantly, the effective dose of ketamine in the plus-maze did not affect general measures of behavioral activity. Finally, in a neurophysiological model of anxiolytic drug action, ketamine reduced the frequency of reticularly-activated theta oscillations in the hippocampus, and that "This particular neurophysiological signature is common to all known classes of anxiolytic drugs (i.e. benzodiazepines, 5-HT1A agonists, antidepressants) and provides strong converging evidence for the anxiolytic-like effects of ketamine." (p. 359).

Engin E, Treit D, Dickson CT Anxiolytic- and antidepressant- like properties of Ketamine in behavioral and neurophysiological animal models. *Neuroscience* 2009; 161:359-369.

Groeber (et al., 2015) obtained findings in a rat model of PTSD indicating that investigations of the hypothesized salubrious effect of ketamine on acute post-exposure symptoms should take into account reductions in general behavior (unwanted) as well as enhancing extinction of classical conditioned associated between aversive stimuli and neutral cues. They examined the effects of ketamine to determine the potential modulation of the acquisition and extinction of a conditioned fear using a conditioned suppression procedure. First, rats were trained to acquire behaviors associated with food reinforcement. They were then exposed to a model of hopeless, traumatic stressor), "inescapable shock (IES, unconditioned stimulus) paired (×20) with an audio/visual conditioned stimulus (CS) to establish conditioning". Then, ketamine or placebo were administered either after initial conditioning or after each of the subsequent extinction trials. The design then involved administering a series of four ketamine injections 60 min apart (100, 50, 50, 50 mg/kg, respectively) "in order to sustain a ketamine effect for a minimum of 4 hours".

The results were:

1) ketamine produced a general decrease in food-reinforced behavior, however,
2) ketamine did not affect the acquisition of the conditioned fear when the regimen was administered shortly after the initial pairings of IES and CS, and,
3) ketamine did not alter extinction to the conditioned fear when the regimen was administered following each CS presentation following initial conditioning.

The authors conclude that, while ketamine impairs food-reinforced behavior, "it does not, however, appear to directly modulate learning and memory processes associated with conditioned fear." (p. 90)

Groeber Travis CM, Altman DE, Genovese RF. Ketamine administration diminishes operant responding but does not impair conditioned fear. *Pharmacology, Biochemistry and Behavior* 139 (2015) 84–91.

Zarate et al., (2013) responded to criticisms of early interventions using ketamine in trauma-exposed humans. The concern reported in the literature was that since "ketamine induces transient dissociation similar to active PTSD, there is a theoretical risk that ketamine infusion might induce or exacerbate PTSD-like symptoms." Previous studies of ketamine for anesthesia in trauma victims have shown mixed results in terms of producing PTSD symptoms. Two studies by Schonenberg and colleagues demonstrated that a single dose of ketamine in the peritraumatic period ("fractures, contusions, burns, or cuts resulting from household, leisure, or work accidents") significantly increased the likelihood of later PTSD symptoms (1,2). To address these concerns, the authors report on Operation Iraqi Freedom/Operation Enduring Freedom service members with burn injuries who received perioperative ketamine and were shown later to experience fewer PTSD symptoms (McGhee, et al., 2008). (3). They also note that LDK is being examined for its effect on reducing the core symptoms of PTSD (ClinicalTrials.gov identifier: NCT00749203).

To address these concerns and inconsistent evidence the authors cited their own data w in which "We failed to uncover a clinically significant increase in positive symptoms of psychosis, dissociative symptoms, or anxiety between depressed subjects with a history of trauma and/or PTSD for 1 week after a single sub-anesthetic

dose of ketamine. Furthermore, the presence of these variables did not impede the robust and relatively sustained antidepressant effects of ketamine." (p. e37). Limitations in the dataset they report on included: secondary data analysis, and potential lack of statistical power.

Importantly, for the Ketamine in Acute Burn Pain Study, Zarate's group reported that, while "… it is theoretically possible that repeated or larger doses of ketamine could exacerbate PTSD-like dissociation. Nevertheless, the absence of such adverse events in our analyses and the consistent finding of glutamatergic dysfunction in preclinical models of fear conditioning and PTSD (4,5) warrants continued investigation of glutamatergic medications (including ketamine and ifenprodil) in this often chronic and debilitating disorder." (p. e37).

Zeng EC, Niciu MJ, Luckenbaugh DA, Ionescu DF, Mathews DC, Richards EM, Franco-Chaves J, Brutsche NE, Zarate CA, jr. Acute stress disorder symptoms do not worsen in Posttraumatic stress disorder and abuse with a single subanesthetic dose of ketamine. *Biological Psychiatry* 2013; 73:e37–e38. http://dx.doi.org/10.1016/j.biopsych.2012.10.017

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(Zeng, et al., 2013)

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3. McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH (2008): The correlation between ketamine and posttraumatic stress disorder in burned service members. J Trauma 64:S195–198; discussion S7–8.
4. Nair J, Singh Ajit S (2008): The role of the glutamatergic system in posttraumatic stress disorder. CNS Spectr 13:585–591.
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McGowan et al (2017) noted that ketamine has been shown in murine models to be prophylactic against stress-induced depressive-like behavior. Noting the absence of data as to ketamine as a prophylaxis, they administered ketamine 1 month, 1 week and 1 hour before training in Contextual Fear Conditioning (3-shock contextual fear conditioning paradigm; murine model of hopelessness / depression). They also administered ketamine after Contextual Fear Conditioning (i.e., either before extinction, or, before reactivation) in order to in order to determine "when ketamine is most effective at reducing fear expression or preventing fear reactivation".

Results indicated that mice administered prophylactic ketamine 1 week but not 1 month or 24 hours before CFC, exhibited reduced freezing behavior when compared with mice administered saline. The authors concluded that "ketamine can buffer a fear response when given a week before as prophylactic, but not when given immediately before … in order to protect against heightened fear responses to aversive stimuli." (p. 1579).

In contrast, ketamine administration following CFC:

1) before extinction – "did not alter subsequent fear expression",

2) before reinstatement – with *single cue* (1-shock) "increased the number of rearing bouts in an open field, possibly suggesting an increase in attentiveness" however,

3) before reinstatement – with greater aversiveness *triple cue* (3-shock) Of the greatest relevance to this Ketamine for Acute Burn Pain RCT, administering ketamine before a more aversive *triple cue* (3-shock) reinstatement test "buffered fear expression during the first re-exposure and transiently decreased freezing throughout extinction" and the authors concluded that "… *there is a limited time window following reinstatement during which ketamine may be effective in decreasing fear expression*" (p. 1581).

McGowan JC, LaGamma CT, Lim SC, Tsitsiklis M, Neria Y, Brachman RA, Denny CA. Prophylactic Ketamine attenuates learned fear. *Neuropsychopharmacology* (2017) 42, 1577–1589; doi:10.1038/npp.2017.19

Clarke (et al., 2017) tested the effect of repeated ketamine administration during acute stressors in a mouse model of depression-like behavior, biology and brain function. Results indicated that the expected antidepressant effect was achieved and persisted for 8 days after repeated administration, there was dose-response effect of ketamine on depression-like behavior and on the LPS-induced elevation in pro-inflammatory cytokines, IL-1b and TNF-a. The abstract is copied here, and the pdf full text is attached to eFormA.

Considerable recent attention has focused on the rapid antidepressant effects observed in treatment resistant patients produced by the NMDA receptor antagonist, ketamine. Surprisingly, the effects of ketamine in the context of stressor exposure, as well as the consequences of its chronic use are unclear.

Thus, we assessed the impact of acute and repeated ketamine treatment together with acute [restraint or lipopolysaccharide (LPS)] or chronic (unpredictable different psychogenic challenges) stressor exposure. Importantly, acute ketamine treatment did provoke an antidepressant-like effect in a forced swim test (FST) and this effect lasted for 8 days following repeated exposure to the drug. Although acute restraint and LPS individually

provoked the expected elevation of plasma corticosterone and brain-region specific monoamine variations, ketamine had no influence on corticosterone and had, at best, sparse effects on the monoamine changes. Similarly, ketamine did not appreciably influence the stressor induced neurochemical and sucrose preference alterations, it did however, dose-dependently reverse the LPS induced elevation of the pro-inflammatory cytokines, interleukin-1b (IL-1b) and tumor necrosis factor-a (TNF-a). Likewise, repeated ketamine administration increased adult hippocampal neurogenesis.

These data indicate that repeated ketamine administration had greater behavioral consequences than acute treatment and that the drug might be imparting antidepressant effects through its effects on neuroplasticity and inflammatory processes rather than the typical neurochemical/hormonal factors affected by stressors.

Clarke M, Razmjou S., Prowse N, Dwyer Z, Litteljohn D, Pentz R, Anisman H, Hayley S. Ketamine modulates hippocampal neurogenesis and proinflammatory cytokines but not stressor induced neurochemical changes. *Neuropharmacology* 112 (2017) 210e220.
http://dx.doi.org/10.1016/j.neuropharm.2016.04.021

Our group previously conducted analyses of a dataset collected as part of a multicenter, longitudinal burn injury model system to assess the prevalence and characteristics of psychological and psychiatric disorders following burn injury (McKibben, 2008). In addition to finding a very high prevalence and chronicity of ASD/PTSD after burns (McKibben, 2008), we noted significant relationships among pain, posttraumatic stress and disability (Corry, 2009), insomnia (Smith, 2008), depression (Edwards, 2007) and suicidal ideation (Edwards, 2007). Results from these analyses suggested that interventions that can effectively reduce acute burn pain would also be associated with reductions in subsequent psychological/psychiatric distress and disorders. We will test several hypotheses in the current study seeking to establish treatment effects and mechanisms.

Mechanisms of Burn Pain, Ketamine and Morphine

Ketamine mechanism of action and pharmacokinetics (Pourmand, et al, 2017)

Ketamine is a well-known *N*-methyl-D-aspartate (NMDA) receptor antagonist. One of the normal functions of the NMDA receptor is to potentiate painful stimuli, which may lead to a "hyperalgesia" or "central sensitization". Ketamine's analgesic effect has been attributed, in part, to its ability to block this sensitization (1) [16]. Ketamine is a non-competitive NMDA receptor antagonist with a, "slow off rate" causing a prolonged tonic blockade of the receptor contributing to long lasting analgesic effects (2) [17]. Ketamine also has direct effects on the delta opioid receptor and acts to augment opioid mu-receptor function (2) [17]. The way by which ketamine augments opioid receptor function has been attributed to downstream effects involving the extracellular signal-regulated kinase 1/2 (ERK1/2). Ketamine potentiates opioid induced ERK1/2 phosphorylation, requiring lower opioid doses for equal phosphorylation (3) [18]. Ketamine has also been shown to delay desensitization and improve re-sensitization of opioid receptors resulting in prolonged overall effect of opioid stimulation, which may be useful in patients with opioid-related hyperalgesia (3) [18].

Safety and Efficacy of Low-Dose, Slow Infusion Ketamine (Pourmand, et al, 2017)

The goal of using low-dose ketamine (LDK) is to provide analgesia without producing the adverse effects that occur more frequently at higher doses. LDK has been found to be safe and effective as an analgesic with a favorable adverse effect profile. Within the studies reviewed, 1187 patients received LDK. The most common adverse effects were dizziness, nausea, vomiting, and mild neuropsychological reactions such as hallucinations or agitation (4) [25]. Almost all of these adverse effects resolved spontaneously - emergence phenomenon is unusual when low doses are used and when reported, it is mild and transient.

LDK has been shown to be safe and effective for the treatment of a wide variety of painful conditions in the ED where it is comparable to opioids in reducing pain. Respiratory suppression is less of a risk with ketamine than with high dose of IV opioids and it is effective for the management of pain exacerbations in opioid tolerant patients. Although potential for abuse is present, "ketamine has less potential for addiction or epidemic overuse" than opioids.

Pourmand A, Royall C, Alhawas R, Shesser R. Low dose ketamine use in the emergency department, a new direction in pain management. American Journal of Emergency Medicine 35 (2017) 914–932.
http://dx.doi.org/10.1016/j.ajem.2017.03.005

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(linked numbers from original: Pourmand, et al., 2017)

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2. [17] J. Sleigh, M. Harvey, L. Voss, B. Denny. **Ketamine – more mechanisms of action than just NMDA blockade** Trends in Anaesthesia and Critical Care, 4 (2014), pp. 76-78
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McGuinness (1) described burn wounds and pain mechanisms in burns that illuminates the reasons why ketamine plus morphine is such a promising two-pronged approach. They reported that burns damage surface and deep tissues, and that burn-related pain is due to cascades of inflammatory processes and pathways. Activation of NMDA receptors leads to sensitization of A and C fibers, thus leading to hyperalgesia at the wound and secondary hyperalgesia in surrounding, uninjured skin (Meyer, Campbell, 1981; Richardson, Mustard, 2009). Repeated painful episodes of wound care along with the inflammatory processes can result in neuroplastic CNS adaptations (e.g., hyperactivity in the dorsal horn of the spinal cord) (Woolf, Thompson, 1991).

Lee and Lee (2016) noted that opioids inhibit nociception by activating the mu receptor, principally at presynaptic sites, as well as monoaminergic descending spinal pathways. Opioids also activate NMDA receptors thus leading to post-synaptic neuronal hyper-excitability of pain (i.e., central sensitization) causing hyperalgesia (Mao, Price, Mayer, 1995). Lee and Lee (2016) point out that ketamine blocks spinal mu receptors and potentiates mu-opioid receptor-mediated signaling (Gupta, 2011), induces the synthesis and release of nitric oxide (Romero, et al., 2011), and has anti-inflammatory effects (de Kock, 2013).

Ketamine is a well-known NMDA receptor antagonist acting post-synaptically, in contrast to opioids which act pre-synaptically, and thus ketamine reduces hyper-excitability (Dickinson, 1997). It is proposed that by blocking NMDA receptors post-synaptically, ketamine will improve the efficacy of opioids, and will thus have an opiate-sparing effect. Ketamine has also been noted to release adenosine, which then inhibits pro-inflammatory cytokine secretion, and may reduce inflammatory pain (Wang, Liu et al., 2013). Notably, an undesirable effect of Mu receptor activation by opioids is that it increases glutamate synaptic effectiveness at NMDA receptors, thus increasing opioid tolerance and leading to chronic pain (Bredlau, 2013). Lee and Lee suggest that increasing the efficacy of opiates by adding adjunctive low-dose, slow infusion ketamine will likely have downstream effects that "… not only prevent the serious adverse effects of opioids, but also inhibit the chronic pain that develops as a result of opiate tolerance." (2016, p. 11/15).

Evidence Update for Primary Aims: Adjunctive low-dose, slow infusion ketamine, when combined with fentanyl "treatment as usual", will lead to greater reductions in pain and produce an opiate sparing effect, when compared to slow infusion saline, when combined with fentanyl "treatment as usual".

McGuinness (2011) performed a systematic review of 4 RCTs involving acute burns. Their review concluded that: 1) ketamine alone, when compared to placebo, reduces primary hyperalgesia; 2) ketamine alone, compared to opiate alone, reduces secondary hyperalgesia, and; 3) the combination of ketamine plus morphine "abolishes" wind-up pain. They noted that none of the side effects reported in any of the 4 trials reviewed led to a participant's removal from study.

Lee and Lee (2016) conducted a systematic review that included 6 small-sized RCTs contrasting the effect of low-dose ketamine ($\leq$ 0.3 mg/kg) delivered by intravenous bolus, relative to control (placebo or morphine), on acute pain in emergency departments. Acknowledging that the small sizes of the 6 trials limits the strength of conclusions draws, the authors report that:

1) *Pain Severity*: Relative to fentanyl alone, ketamine alone led to reduced average self-reported pain scores 20-30 minutes post infusion;

2) *Opiate Sparing*: ketamine alone, relative to fentanyl alone, required less additional pain medications, on average, when the ketamine dose was 0.3 mg/kg but not when it was 0.15 mg/kg;

3) *Serious Side Effects*: Relative to placebo and to fentanyl groups, ketamine participants were at significantly greater risk for neurological and psychological side effects and minor cardiopulmonary events. In contrast, participants in both the fentanyl group and placebo group who received additional opioids were at greater risk of major cardiopulmonary events. No major cardiopulmonary events were observed in the ketamine group.

Also recently, Wang (2016) conducted a systematic review and meta-analysis of 22 RCTs evaluating the safety and efficacy of ketamine, adjunctive to opiates, in managing post-operative pain, opiate sparing, and reduction in opiate side effects (Wang, Johnston, et al., 2016). The post-operative setting is not closely analogous to the wound care model for severe acute pain in austere conditions which is applied in our design. However, post-operative pain has applications in burn injuries such as with donor site pain that is observed following skin grafting for wound closure. Post-operative pain control also appears to be the most active area of ketamine-research related to pain. Wang et al report that compared to PCA morphine augmented with hydromorphone, the ketamine augmentation resulted in an average reduction in pain of < 1.0 cm on a 10.0 cm visual analog scale (VAS), and, more impressively, reduced cumulative morphine consumption across post-operative days 1-3 (range = 5-20 mg). In the few studies reporting side effects, nausea and vomiting were reduced in the ketamine adjunct groups.

Evidence Update for Secondary Aims: Low-dose, slow infusion ketamine as an adjunct to fentanyl, when compared to slow infusion saline placebo as an adjunct to fentanyl reduce Symptoms of Acute Stress Disorder and provide Evidence of PTSD Prevention Effect.
Evidence from the empirical literature indicates that the Secondary Aims of the Ketamine RCT study will address important objectives with relevance to military operations and personnel.

This brief review presents evidence that acute pain and symptoms of PTSD have been shown to be highly comorbid in many trauma-exposed populations including combat veterans. This first article investigated the hypothesis that combat-exposed veterans with PTSD have distinct responses to painful stimuli indicative of central sensitization. Central sensitization is "plasticity of the somatosensory system" and has been defined as "a heightened response of neurons and circuits in nociceptive pathways as a result of increased excitability and synaptic efficacy or reduced inhibitory modulation" (REFS 31-33). Experimentally induced pain (capsaicin injection) was administered on 2 separate days, as were thermal and mechanical sensitivity stimuli (Quantitative Sensory Testing) in subjects with combat-related PTSD and combat-exposed controls without PTSD (Moeller-Bertram, Strigo, et al., 2016). After the second day of experimental pain, the group with PTSD, relative to the combat control group, showed:

1) Temporal Summation: significantly slower decay over time in mean pain severity ratings (0-10 VAS) and mean pain unpleasantness ratings (0-10 VAS), and,

2) Hyperalgesia: significant "increase in pain intensity rating following repeated application of pressure stimuli…" (P. 767).

This pattern of findings provides evidence for a greater degree of central sensitization to pain among combat veterans with PTSD relative to combat veterans without PTSD.
Indeed, Central Sensitization can manifest as pain hypersensitivity (hyperalgesia) and enhanced temporal summation [31,59–62].

As mentioned in the pain mechanism section above, burn pain as a clinical model of central sensitization bears a very close resemblance to the experimental capsaicin model presented by Moeller-Bertram, et al., (2014). Acute burn care, required from injury event until wound closure, involves twice-daily exposure to painful wound care. Burn pain has been shown to activate NMDA receptors leading to sensitization of A-delta and primary C-fibers, hyperalgesia at the wound, and, secondary hyperalgesia in surrounding, uninjured skin (Meyer, Campbell, 1981; Richardson, Mustard, 2009). Repeated painful episodes of wound care along with the inflammatory processes can result in neuroplastic CNS adaptations (e.g., hyperactivity in the dorsal horn of the spinal cord) (Woolf, Thompson, 1991). Lee and Lee (2016) noted that opioids inhibit nociception by activating the mu receptor at presynaptic sites and monoaminergic descending spinal pathways and activate NMDA receptors thus leading to post-synaptic

neuronal hyper-excitability of pain (i.e., central sensitization) causing hyperalgesia (Mao, Price, Mayer, 1995).

This brief review and discussion presented a literature update focused on the recent evidence for ketamine's efficacy and safety in ED and Post-Operative settings. The review also confirmed convergent and divergent mechanisms for analgesia from opiates and ketamine that may at least partially explain the complementary roles for each in controlling severe pain. Finally, the low-dose, slow infusion of ketamine seems to both produce only occasional, mild side effects and to reduce incidence of opiate side effects.

The second section of this report presents the specific tasks, activities and products that require a Change In Research submission to the IRB for review. They are presented in a separate section of this report to highlight the progress already achieved, the timelines established to complete the rest, culminating in IRB re-approval and submission of all required materials to the USAMRMC for review by the Human Research Protections Office.

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4. Study Procedures

a. Study design:

Patients will be recruited through the population of adults 18-70 years of age admitted with acute burn injuries to the Johns Hopkins Burn Center. The consent designees (fellows, attendings) will approach potential study participants, and using methods documented in the study-specific Manual of Operations and approved by the IRB, describe study goals, aims, and methods to insure that potential subjects have the opportunity to make an informed decision, are aware of alternatives to participation,

etc… Subjects must meet the following inclusion / exclusion criteria:

Inclusion Criteria:

- Acute burn injury with TBSA ≥2% & ≤40%.
- Adults 18-70 years of age admitted to the JHBC with acute burns
- Estimated length of stay on day of admission ~≥5 and, optimally ≥7 days.
- Pain rated NAS ≥5 in Emergency Room during initial wound evaluation / debridement or on admission to the BICU / debridement.

Exclusion Criteria:

- Requiring endotracheal intubation and sedation
- Diminished Level of Consciousness / Cognitive Function: MMSE ≤20.
- Diminished Capacity – Incapable of providing informed consent (reason(s) to be listed).
- PMH: Insensate to pain in burn wound location (e.g., SCI; peripheral neuropathy)
- Safety: Contra-indication (e.g., potential drug interactions, medical comorbidities)

1. Protocol: Study Design, Dosing & Duration:
   a. Design: Triple blind (nurse, patient, RA) Randomized Controlled, parallel group Trial (RCT):
   Group 1: Usual Care plus Saline placebo (IV Fentanyl plus Saline slow infusion administered via programmed pump)
   Group 2: Usual Care plus Ketamine augmentation (IV Fentanyl plus low-dose Ketamine slow infusion administered via programmed pump)

STUDY PROTOCOL: Medications, Dose, Delivery Modality, Timing -

The changes in dosing, described below, are made to more concretely specify the dosing in this trial and to provide ketamine in doses similar to that in other studies that have been conducted using ketamine for acute pain. This level of detail had not been included in the original of this irb-approved protocol, rather, a range of doses was specified.

STUDY DRUG GROUP (Fentanyl PLUS Ketamine):

1. Ketamine Loading Dose (Study Drug, slow infusion) =
   - 0.3 mg/kg, initiated approximately 10 minutes prior to start of wound care with pump set to deliver slowly over approximately 5 minutes… *THEN*,
2. Fentanyl (UC, injection) =
   - 1 mcg / kg. This is given to participants in both Group 1 and Group 2 initiated < 1 minute prior to wound care.
3. Ketamine (Study Drug, Infusion) =
   - 2.5 mcg/kg/min, with the pump set to initiate infusion immediately following the Loading Dose and continued for the duration of the session. The EPIC order set specifies that the nurse determines when the session is over, and that the nurse will turn off the infusion at that point.

USUAL CARE GROUP (Fentanyl PLUS Saline)

1. Saline Loading Dose (Placebo, Infusion) =
   - An identical volume of saline as that in 0.3 mg/kg of ketamine. This will be initiated approximately 10 minutes prior to start of wound care with pump set to deliver saline slowly over approximately 5 minutes (i.e., during the same time and at the same rate that the Ketamine group receives the ketamine loading dose).

2. Fentanyl (UC, injection) =
   - 1 mcg / kg: This is given to participants in both Group 1 and Group 2 initiated < 1 minute prior to wound care.
3. Saline (Placebo, Infusion) =
   - Identical volume of fluid as that in 2.5 mcg/kg/min of ketamine, with the pump set to initiate infusion immediately following the Loading Dose and continued for the duration of the session. The EPIC order set specifies that the nurse determines when the session is over, and that the nurse will turn off the infusion at that point.

PRN DOSE*

PRN Fentanyl PRN (UC, injection) = 1 mcg / kg.

*The PRN is provided to participants in both Group 1 and Group 2 when a participant requires additional pain medication. The criteria for providing PRN fentanyl are based on customary nursing practices, including a self-reported persistent rise in NAS pain > 2/10 or a NAS ≥ 7/10 (JCAHO standard) and combined with nursing judgment.

1. **Protocol Changes and Clarifications Include**:
   a) *Loading Dose Start Time (see Text, below): Previously, the ketamine loading dose had been slated to start 20 minutes prior to the start of wound care, and the placebo "loading dose" was slated to start 10-minutes prior to the start of wound care. Burn, Critical Care and Pharmacy collaborators have subsequently agreed that it is preferable to start the loading doses at the same time for both groups. Thus, loading doses of randomly assigned, ketamine or placebo (saline) will be administered to participants in the Usual Care condition (placebo) and the Usual Care Plus Ketamine Augmentation condition (ketamine), starting at approximately 10-minutes prior to initiation of dressing change/wound care.
2. The protocol now specifies that
   i. the loading dose of ketamine OR saline will be delivered by pump set at approximately 5 minutes by the nurse to deliver the medication at standardized slow rate.
   ii. * Behavioral Equivalence: Administration of loading doses simultaneously, regardless of group assignment, will maintain the naïve / blinding of provider / nurse / participant.
   iii. * Pharmacokinetic Properties: The pharmacokinetics of ketamine (absorption, metabolism, half-life, excretion) are sufficient to allow for ketamine to be administered approximately 10 minutes prior to fentanyl, versus the previously planned 20-minute lag in start times.

   b. PRN Fentanyl Medications: Pain Assessment Before, During and After **Wound Care Session**.

   Criteria for PRN: The study protocol will use the JHBC standard-of-care method for rating pain and the need for additional analgesic medications before, during and following wound care. That is, as part of standard-of-care, pain is routinely assessed before, during and after wound care by the Registered Nurse/Wound Care Tech (RN / Tech) to determine whether there is a need for additional pain medications. This standard-of-care pain rating process will be applied in this study protocol. The RN / Tech will ask participants to rate their pain before the ketamine / placebo loading dose administration approximately 10 minutes prior to the start of each wound care session, during the wound care session when clinical observations suggest pain assessment is indicated, and, after wound care session ends. At each of these times, when the RN / Tech asks participants to rate their present pain intensity (PPI) on Numeric Analogue Scale (NAS: 0-10), those participants who rate their PPI/NAS as ≥7/10, or, whose pain severity has risen ≥2/10, will be asked the following:
   i. The RN / Tech asks the participant "Do you need additional pain medication?"
   ii. If the participant says "Yes" then the PRN medication is administered (1 mcg/kg-based fentanyl, injected).
   iii. If participant says "No" then the PRN medication is not administered.
   iv. The RA will record, on a standard form, the PPI/NAS that the RN was given, whether a PRN was offered (Y/N), whether the participant accepted (Y/N), what drug / dose /

delivery method were utilized, and elapsed time since loading dose or, the previous PRN analgesic administration.

PRN DOSE (Fentanyl)*

PRN Fentanyl PRN (UC, injection) = 1 mcg / kg.

*The PRN is provided to participants in both Group 1 and Group 2 when a participant requires additional pain medication. The criteria for providing PRN fentanyl are described next:

*PRN – Standard of Care: Pain Severity for PRN Administration: The PRN is provided to participants in either Group 1 or Group 2 when a participant requires additional pain medication. In this protocol, the nurse will consider providing PRN fentanyl, if the participant's self-reported absolute pain severity is ≥7/10 (JCAHO), **OR**, there is a persistent rise in pain severity that is ≥2/10 above the most recent NAS rating. This protocol for providing PRN fentanyl takes into consideration both the standard nursing practice (i.e., persistent rise in pain severity ≥2/10) as well as the JCAHO-standard cutoff for treating pain severity (i.e., ≥7/10).

*PRN – Limit before Alternative Approaches are Considered: After each PRN fentanyl injection, no further PRN fentanyl should be given for at least 15minutes to allow time for the medication to have its effect and to prevent over-medication. It is recommended that consideration of alternative approaches be undertaken after 3 PRN fentanyl injections (i.e., three injections of "1 mcg / kg of PRN fentanyl") as described below. It is also recommended that if there is a failure to reduce pain intensity by ≥ 2/10 after at least 15minutes after PRN administration, another PRN or alternative medication be considered.

The maximum number of PRN fentanyl administrations as well as any alternative approaches will be decided at the discretion of the wound care nurse and the provider on the basis of their Best Care Practices and the consideration of each specific participant's circumstances.

*PRN – Nursing / Provider Judgment: Furthermore, when determining the patient's need for additional analgesic or alternative medication, the trained and experienced BICU nurse and provider often employ assessment of factors other than self-reported pain intensity. These additional factors will also be utilized by the wound care nurse and provider in deciding what medication is or is not necessary during this "Ketamine for Acute Pain During Burn Wound Care" protocol.

Summary of Medication Dose, Timing, Method:

a. The Fentanyl loading dose will begin <1 minute prior to each wound care session for both the Usual Care and the Ketamine Augmentation groups.
b. The drug delivery mechanism for the loading dose of ketamine / placebo, as well as all of the continuous infusions, will be via identical masked / nondescript infusion bags. The ketamine / placebo contents will be delivered at identical volumes and continued for the duration of the wound care session - in order to preserve the blind.
c. The blinded infusion bags will be used to deliver both ketamine and saline and will be prepared and provided by the JHBMC pharmacy (Lisa Ruppell, PharmD). The pump will be programmed by the JHBC nurse based on the provider's prescription, the randomization schedule and the EPIC order set (displayed in EPIC and on infusion bag label).
d. Wound Care Protocol and Outcome Protocol Duration:
    i. Study / Follow-up Protocol: Eligibility determination (ED); consent procedures; informed consent signed (as soon as possible post-admission to the BICU); randomization; initial wound care protocol soon after consented, (1st wound care optimal); twice daily (preferred) wound care (potential range 0-2 sessions daily: there may be days on which no wound care is performed for various reasons such as dressing type, post op, etc) protocol for 7 consecutive days (potential range 3-7 days); Follow-up 1 day, 1-week and 1-month after last of the 7-day study protocol for a total of 5 weeks or n= 35 days per participant.

ii. Wound Care Study Protocol: Includes pretest assessment, premedication (loading dose), wound care and interim infusion and assessments, posttest assessments. Each wound care procedure including assessments will take approximately 1-2 hours.

ii. Ketamine for Acute Burn Pain During Burn Wound Care Protocol: Twice daily wound care sessions, estimated length of hospitalization on BICU is ≥5 days (range = 3 - 7 days).

2. Burn Center 5-year Average population meeting Key Inclusion Criteria

Mary Dieter, RN, MSN, Trauma Coordinator, provided the speadsheets with the admissions data. Ms. Dieter is Trauma Coordinator for the trauma and burns at JHBMC and maintains datasets for the Maryland Institute for Emergency Medical Services Systems (MIEMSS) and the American Burn Association (ABA) Registry and has access to all data from the JHBC entered in these systems.

Dr. Psoter used these data to estimate available sample size of eligible admissions (see Table below). The admissions data enable him to render a more accurate and reliable estimate of eligible admissions for the present study. The most accurate predictor for the number of patients that we anticipate will be admitted to the JHBC during the next 12 months comes from the database of JHBC admissions in the past. We selected the past 5 years of admissions data in order to stabilize means and standard deviations of monthly and annual admissions meeting inclusion and exclusion criteria. From these hard numbers, Dr. Psoter employed the means described next to estimate the number of eligible patients who are admitted to the Johns Hopkins Burn Center that will be approached, offered informed written consent, and to initiate the protocol and to complete the 7-day protocol and the 1-week and 1-month outcome assessments.

Patient Admissions 2012 – 2016: BOTH TBSA Between 2% & 40% AND Age ≥18 years old & ≤70 years old						
	2012	2013	2014	2015	2016*	Annual Average
Admits (n) w/ average LOS ≥5.5 Days	140	135	143	116	53	128
Average age w/ LOS ≥5.5 Days, mean (SD)	42.5 (13.25)	43.3 (13.65)	42.8 (13.52)	42.4 (13.17)	38.6 (14.56)	42.4 (13.53)
Average TBSA (2^{nd} + 3^{rd}) w/ LOS ≥5.5 Days, mean (SD)	8.2 (7.05)	8.6 (7.78)	7.8 (6.95)	9.2 (7.38)	7.1 (6.50)	8.3 (7.21)
Admits w/ LOS ≥7 Days, n (%)	91 (25.9%)	80 (22.8%)	81 (23.1%)	74 (21.1%)	23 (6.6%)	74
Average age w/ LOS ≥7 Days, mean (SD)	42.0 (13.29)	45.7 (12.48)	43.9 (13.40)	43.6 (13.27)	40.5 (15.39)	43.6 (13.30)
Average TBSA (2^{nd} + 3^{rd}) w/ LOS ≥7 Days, mean (SD)	8.9 (7.93)	10.0 (9.13)	9.3 (8.14)	10.5 (8.46)	9.0 (8.30)	9.6 (8.36)

Table 1. Inclusion Criteria for past 5 years

*2016 Based on only 6 months of data

The Ketamine team makes eligibility determination, initiates consent procedures, and the Informed Consent is signed (as soon as possible post-admission). The team then proceeds with initial wound care protocol after consented, (1st wound care optimal) and continues twice daily wound care for 7 days and 14 wound care sessions. The scheduled outcome assessments are on 1-day, 1-week and 1-month after the

last study wound care session for a total of 5 weeks or n= 35 days. The actual minimum length of stay may be ≥3 - 5.5 consecutive days and ≥ 6-11 wound care sessions (see Sample Size Calculations – next).

3. Sample Size and Power Estimations – Additional Biostatistics, Epidemiology And Database Resources
Rebeca Rios, PhD, Psychologist, Statistician
Kevin Psoter, PhD, Epidemiologist/Biostatistician, Statistician

Drs. Psoter and Rios participated in planning, executing, interpreting and writing/illustrating the rich analyses of primary (i.e., pain severity, opiate sparing), and secondary (i.e., symptoms of PTSD and depression) aims. The Biostatistics, Epidemiology and Data Management Core (BEAD) is a recognized research Core of the JHU School of Medicine which provides research support services to faculty and trainees. With sponsored funds from the Vice Dean for Research of the Bayview Medical Campus, BEAD Core research support will be available to support this research project. At a minimum, this can include 60 hours of support services to include research support, trainee career development and subsequent grants development activities based on the results of this investigation.

Furthermore, the sponsored research resources of ICTR will stretch the budget and allow the Ketamine Project to optimize the rigor in database design and management, as well as with overall biostatistical guidance leveraging the Core's team of Masters and PhD level biostatisticians and epidemiologists with wide ranging content and methodologic expertise. Engagement of these services will ensure the quality of the data being compiled, integrated and utilized as this is a vital component of the success of the intervention project and the overall objectives of the study through the engagement in the development of the database structure, variable coding, data input, data manipulation and transformations required for the seamless transition for the conduct of analyses.

The sample size estimates described next were generated by Dr. Psoter, BEAD statistician, as Co-Investigator on the project for the role and tasks delineated here. The next two paragraphs describe the methods and conclusions used by Dr. Psoter to Estimate sample sizes for:

1. Sample Size Estimate: 7-day LOS, as originally planned, and
2. Sample Size Estimate/Corrected: 7-Day LOS as corrected to 5.5 Days (11 wound care sessions - see rationale below) due to uncertainties not always evident or predictable on the first day of admission but which may affect/reduce LOS for any given patient.

1. Sample Size Estimate Based on Stay ≥7 days in Burn ICU.

The sample size calculation is based on the primary statistical procedure for this project which will test the difference in mean pain scores, defined as the average self-report of mean pain score, based on the Numeric Analogue Scale (NAS), during each burn wound care procedures, between individuals randomized to usual care plus placebo (fentanyl plus saline) and those randomized to the intervention arm (usual care + ketamine). PASS Sample Size (Version 14) was used to perform all sample size calculations while considering individuals over the one-year study duration randomized to control and intervention arms in a 1:1 fashion.

In the first case, we further assume that each individual, will, on average, have a length of stay of 7 days thus resulting in 14 wound care procedures performed during hospital stay. We determined the minimum sample size for our trial based on 80% power at p = 0.05 to detect a clinically significant difference in mean pain score during the wound care procedure of 2.0 points between the control and intervention arms with a standard deviation of 3.0. In addition, to account for the clustered nature of procedures performed on individuals, we have used a sample size inflator (also termed "design effect") of 10.1 as described by the Cochrane manual@ conservatively using an interclass correlation of effects of 0.7 amongst repeated measures of pain scores within each individual and 14 observations per individual.

The required sample size needed to accept the alternative hypotheses that the mean pain care score in the intervention arm decreased by 2 points compared to the control arm at the 0.05 level would require 27 individuals per arm (54 total), our anticipated population of 74 eligible individuals is adequate to show a clinically significant improvement for both intervention arms.

@http://handbook.cochrane.org/chapter_16/16_3_4_approximate_analyses_of_cluster_randomized_trials_for_a.htm

2. Corrected Sample Size Estimate for Length of Stay on the Burn ICU ≥7 days as **estimated on Admission** but, however, where the **Actual Length of Stay on Burn ICU is ≥5.5 days** because of Factors that either not present or not evident or were difficult to quantify at time of admission and consent of the patient.

This sample size calculation is based on the primary statistical procedure for this project which will test the difference in mean pain scores, defined as the average self-report of mean pain score, based on the NAS, during each burn wound care procedures, between individuals randomized to usual care (fentanyl plus saline) and those randomized to the intervention arm (usual care + ketamine). PASS Sample Size (Version 14) was used to perform all sample size calculations eligible individuals over the one-year study duration randomized to control and intervention arms in a 1:1 fashion.

In this situation, where Length of Stay is less than the initially estimated >7 days, we further assume that each individual, will, on average, have a length of stay of 5.5 days on the Burn ICU thus resulting in 11 wound care procedures

performed during hospital stay on the Burn ICU. We determined the minimum sample size for our trial based on 80% power at p = 0.05 to detect a clinically significant difference in mean pain score during the wound care procedure of 2.0 between the control and intervention arms with a standard deviation of 4.0. In addition, to account for the clustered nature of procedures performed on individuals, we have used a sample size inflator (also termed "design effect") of 8.0 as described by the Cochrane manual@ conservatively using an interclass correlation of effects of 0.7 amongst repeated measures of pain scores within each individual and 11 observations per individual.

The required sample size needed to accept the alternative hypotheses that the mean pain care score in the intervention arm decreased by 2 points compared to the control arm at the 0.05 level would require 47 eligible individuals (94 total), our anticipated population of 128 eligible individuals is adequate to show a clinically significant improvement for both intervention arms.
@http://handbook.cochrane.org/chapter_16/16_3_4_approximate_analyses_of_cluster_randomized_trials_for_a.htm

Further Explanation For Changing the Estimated Length Of Stay, From The Current >/=7 Days To Proposed >/=5.5 Days:
*To Account For Unpredictable Aspects Of Burn Wounds And Behavior Of Patients With Burn Wounds - See Changes Below.
The changes in the next section below are based on the rationale just presented, and are included in the JHU IRB Changes in Research.

Changes Requested:

a. Inclusion and length of stay clarifications:
The length of stay for our protocol had been set at ≥7 days estimated at time of admission to the burn center. However, the number of days a patient remains in the BURN ICU is highly variable, and dictated by factors difficult to accurately quantify when first admitted. For example, patients leave against medical advice, to seek drugs or alcohol, to return to work, or attend to financial matters. For example, some patients may leave the BURN ICU earlier than was originally estimated due to faster wound healing. Others may proceed to the OR for surgical closure of the wounds prior to 7 days, which typically changes the type and duration of wound care for several days after surgery. The length of ICU stay of others may decrease due to an initial overestimate of wound severity and, hence, a reduced need for close ICU monitoring and a reduced likelihood that the patient would remain in the BICU for 7 or more days.

b. Inclusion requirement clarification 1: While retaining the inclusion criteria as estimated LOS ≥7 days at time of admission, we request a Change in Research such that the actual minimum number of days spent on the BICU be changed to achieve an average LOS of ≥5.5 days. The actual number of wound care sessions is to range from 3-7 days and the range in sessions to be from 3 (1/day for 3 day length of stay) to 14 (2/day days at 2 sessions/day plus 1 session on last day), respectively.

These two ranges (i.e., average LOS ≥7 days, average LOS ≥5.5 days) were used in estimating two sets of power estimates, sample size and in participant accrual. However, data will be considered on an intent to treat basis for those participants with less than 7 treatment days and less than 14 wound care sessions due to abbreviated stay on ICU, surgery for wound closure that obviates further wound care, or who are discharged early.

C. Inclusion requirement clarification 2: Similarly, there are some patients who are ordered to receive only one dressing change per day rather than the usual two per day, while, rarely, some may be scheduled for 3 wound care sessions on certain days. Data on any participants who are otherwise eligible for the Ketamine Trial but who are ordered to have daily wound care procedures ≥2/day or ≤ 2/day will be considered on an intent to treat basis.

Statistical and Database Management Resource: The ICTR is highly regarded for database development incorporating multiple layers of protection. The Director of the ICTR, Scott Carey, trained and supervised the Ketamine Team in developing the REDCap database to enter, save, protect and prepare to export for analysis, the data generated in this project. The benefits of the REDCap database include: firewall behind the existing JHU firewall, establishing restricted and unrestricted accessibility modes to ensure IRB protected data remain accessible only to individuals listed on the IRB, compartmentalizing tasks, and running the latest antiviral and anti-hacking software. Data integrity is assured using multiple methods, including utilizing variable definitions and data dictionary (item name and definition, scale, range, out of range and multiple key hit detectors). The complexity of this database is necessitated by the elegant and rigorous study design with 14 repeated measures over 7 consecutive days, which will entail multilevel analysis of time varying and time invariant data. Each variable is coded by day (1-7) and session (1-14), as well as data input quality such as double entry, blinded data collection and data entry, automated checks, auto scoring programs, time lapse between recording and entry, standardized data collection forms, and, enhanced study-specific Manual of Operations for the Safety, Efficacy and Opiate-Sparing Effects of Ketamine for Acute Burn Wound Care Pain in a Setting Analogous to Austere Battlefield Conditions (IRB00089761). The Manual was adapted from a previously developed Manual that was successfully utilized by Dr. Fauerbach and his team for Management, Operations, and Evaluating Progress towards Goals. It contains a wealth of detailed information that identify topics covered, specificity of instructions for involved personnel, roles, tasks, timelines, procedures and to ensure adequacy of documentation.

Procedure for Obtaining Informed Consent

Obtaining Consent:

- The patient will be directly admitted from the Emergency Department to the Burn ICU which precludes potential participants from receiving the consent form in advance.

  Once the patient is admitted to the Burn ICU, stabilized and oriented to the unit, then the consent designee will approach the eligible participant to obtain his/her consent.

- To identify and confirm the patient's understanding of the study, the "Teach Back Method" will be used and, therefore, will be consistent with JHBMC's patient education policy. Using the Teach Back Method as verification of understanding the consent, ensures that the consent designees will have spent the appropriate amount of time explaining and discussing the study with the patient.

- Unfortunately, those eligible participants who are non-English speaking, have a language barrier, and/or who have a severe hearing impairment, will be unable to enroll in the study despite JHBMC's translator services which are available 24/7. The reason for this is that not all the research tools to be used are available in foreign languages. Valid / reliable translation of standardized psychometric tools is an iterative process that goes well beyond the use of an individual translator. In addition, there may also be policies or sensitivities among some translators that render the burn wound care setting difficult.

- Eligible patients who agree to participate will be registered with the study coordinator once an informed consent form is signed. After eligibility is established, and consent obtained, the study coordinator will assign a *study number* – the study number is a sequential number beginning with "1001". Subjects will not begin protocol-specified treatment until eligibility is confirmed and the patient is assigned a study number.

Tracking eligible-consenting and eligible-not-consenting patients:

Subjects who sign a consent form, but do not initiate protocol treatment for any reason (i.e., subjects who are screen failures), will have study data removed from the database and will not count towards completing our accrual goal of 74-94 subjects. The study coordinator will generate a list - that does not contain PHI - of all burn and age eligible admissions in order to maintain a minimal dataset of variables necessary to characterize the group of study eligible participants who consent with those who do not consent. These data will be used to test the representativeness of the obtained sample with the population of eligible burn admissions who do not consent. These data will enable quantitative statement of generalizability of study findings and to ascertain whether any pertinent subject study characteristic contributed.

Randomization: Group assignment of consecutively admitted and eligible patients providing informed consent will be made according to an a priori, randomly generated, list of 4-digit numbers (numbers will account for non-completers, lost to follow-up, side effects, etc). Participants will be allocated to condition on a random basis in randomly stratified blocks of 2, 4, and 6 to ensure that near-equal group numbers are assigned to each condition at key point throughout the study timeline. Those participants assigned an odd number will be allocated to Group 1 (e.g., Usual Care Plus Saline), and participants assigned an even number will be allocated to Group 2 (e.g., Usual Care Plus Ketamine).

Group assignment will be based on serial admissions meeting study inclusion / exclusion criteria. Randomization as described above is expected to achieve group equivalence in: 1) the first pain severity score obtained using the Numeric Analogue Scale measured during the1st exam prior to the first wound care session in the Burn Center; 2) the TBSA; 3) the need for surgery; 4) the average length of wound care procedures and; 5) "other" variables, including the distribution of baseline symptom severity of acute stress disorder,

depression, anxiety, and insomnia (which will all be assessed at study enrollment before the first target dressing change). Baseline data on participants will be recorded, and comparability between study groups will be examined at 25% (n= ~19-24/group) and 50% (n= ~37-47/group) of study completion to assess presence of balancing issues. These same data will also be examined upon study completion (n= 74-94), and their relationship with core outcome targets will be examined. If necessary, their effect will be taken into consideration in planned analyses.

It is anticipated that, given the large sample size, the process of random assignment will ensure adequate balancing across study conditions (Usual Care Condition, Usual Care PLUS Ketamine Augmentation Condition) of potentially confounding variables. That is, for example, participants differing by clinically important variables such as smaller versus larger burns should be equally represented in both groups. The large sample size and the process of random assignment are deemed more than adequate to ensure representation across the two study arms for the differences in important but extraneous variables such as procedure duration and other aspects of wound care, rehabilitation and surgery.

4. **Real-Time Data Collection: In-Person And Telephone**:

a) Standard Assessment Approach: There will be an assigned RA for each participant enrolled in this study (primary RA). The primary RA will meet the participant in person, at a minimum, prior to each wound care session to establish comfort and rapport and to address and concerns. Typically, the primary RA will conduct the data collection in person, in the wound care area and in view of the participant to facilitate ongoing rapport, and to clearly demonstrate professional and mutual commitment to patient/participant concerns and contributions.

b) Problem: There are several circumstances that will routinely arise in the course of this study that make it nearly impossible to arrange for all assessments to be conducted by the primary RA in the room of the participant. Such circumstances include external factors (e.g., inclement weather, illness) and multiple personal obligations (work/school/family/other responsibilities). There are also study-specific logistic (split shift, Day shift: ~9AM-1PM, and, Evening shift: ~9PM-1AM; weekend shifts) and design requirements (repeated measures: 7 days, twice-daily wound care) that obviate expectations for the primary RA to be present in-hospital, in wound care for each participant.

c) Back-Up Approach and Evidence: Review of the literature indicates that there is substantial consensus for comparable precision, validity and reliability of standardized measures collected via telephone administration, in-person administration and self-completed / mailed-in (Improved Outcome Methods in Longitudinal Studies of Acute Lung Injury; Burn Model Systems; Bellamy, Campbell, Hill, Band, 2002).

d) Solution: The equivalence of results in studies contrasting in-person versus telephone administration of assessment provides sufficient rationale for the Ketamine RCT's utilization of telephone data collection by trained RAs using structured, psychometrically sound measurement tools.
Bellamy N, Campbell J, Hill J, Band P. A comparative study of telephone versus onsite completion of the WOMAC 3.0 osteoarthritis index. *Journal of Rheumatology*. 2002 Apr;29(4):783-786.

e) In order to ensure privacy in data collection, and security in data entry, the following specifications are included in the procedure for remote data collection. The RA, when remotely assessing participants via telephone, they will wear headphones, and will call in from a sound-isolated, disruption free, and locked work space, where neither the inquiries made by the RA, nor the responses made by the participants will be audible to anyone else. The data will be directly entered into REDCap using a Hopkins IT-prepared device. This enters data directly into the REDCap server and does not require nor allow for data recording on personal devices according to the senior software engineer at the SOM ICTR at JHB: Scott Carey (scarey@jhmi.edu, cc'ed).

Concomitant and Supportive Therapy:

The administration of any other therapies intended to treat pain during and between the targeted dressing changes will be permitted, as determined by the provider, and will be reported to and recorded by the study coordinator. Similarly, the use of other concurrent investigational drugs is allowed and is to be reported and recorded by the study coordinator.

Supportive Care Guidelines:

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the subject are allowed, provided their use is documented in the medical records.

b. Study Duration

The time commitment to study participants is approximately 1.25 months. This includes the 1-day pretest baseline, 7 days of twice daily interventions during wound care procedures, and follow-up at 1 day, 1 week and 1 month after the 14th wound care procedure on study day 7. Duration of individual subject treatment will depend on individual response and tolerance.

c. Blinding

The Safety, Efficacy and Opiate-Sparing Effects of Ketamine for Acute Burn Wound Care Pain in a Setting Analogous to Austere Battlefield Conditions (IRB00089761) provides for 3-levels of blind: nurse at bedside, patient-participant, and research assistant with the following methods:

The investigational pharmacy will provide blinded medications (i.e., usual care with normal saline or usual care with ketamine augmentation) for this study (for details, see above). The provider will order the medications, the pharmacy will fill the order in identical delivery systems and deliver it to Pyxis in the BICU, thus resulting in blinding to the content of the injections and infusions for the nurse who administers these medications, the research assistant and the patient. This is necessary to ensure fidelity of procedures and validity of findings, responses, observations and data collection. This procedure reduces the possibility that preconceived notions could influence clinical or research personnel or participant in the study.

d. Justification of why participants will not receive routine care or will have current therapy stopped. N/A

e. Justification for inclusion of a placebo or non-treatment group. (see above background and design for purpose of saline placebo and blinding, respectively). There is no "non-treatment group" - both groups receive usual care - fentanyl. Blinding by pharmacy preparation of the drug and delivery system in identical, nondescript pump formats for both groups is standard in drug trials in order to prevent bias to confound prescription, observations, data recording, etc. There are actually 3-levels of blind in this project: Nurse at bedside, Patient/participant, and, research assistant.

f. Definition of treatment failure or participant removal criteria. Should a patient decide to withdraw, all efforts will be made to complete and report the observations as thoroughly as possible. Reasons for premature withdrawal may include:

- Disease progression
- Unacceptable adverse events.
- Intercurrent illness that prevents further administration of treatment or would affect assessment of clinical status to a significant degree.
- Initiation of non-protocol therapy for the disease under study.
- Non-compliance with protocol or treatment.
- Subject becomes pregnant.

g. What happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely

When the study ends or when a participant's participation ends prematurely, he/she will continue to receive usual care treatment.

5. Inclusion/Exclusion Criteria (see above) See Item #4 Study Procedures

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used. (see discussion in item #3 Background. Ketamine is being administered in accordance with the FDA guidelines for this medication as an analgesic medication for acute pain.

7. Study Statistics

a. Primary outcome variable. Described above (Outcomes)
b. Secondary outcome variables. Described above (Outcomes)
c. Statistical plan including sample size justification and interim data analysis. Described above

Statistical consultation and initial power estimation were obtained from the Johns Hopkins Biostatistics, Epidemiology, and Database program (BEAD). The Johns Hopkins Institute for Clinical and Translational Research (ICTR) worked with the Ketamine Team to develop the randomization model and the REDCap Database and will continue to serve as consultants throughout the duration of the study. The ICTR expertise will be of particular importance when managing issues such as data cleaning and preparation, preparing interim reports, and in designing and conducting both preliminary and final statistical analyses. Using standard methods, the BEAD suggested that a total sample size of 74-94 participants (n= 37-47 per Condition) should be sufficient to provide a power of .85 to detect a statistically significant difference at $p < 0.05$. This study team has discussed this issue of power and decided to be conservative and enhance the opportunity of making a definitive statement regarding study objectives and secondary questions. Therefore, the total target sample size will be increased to n= 100. One clarification is important: Funding is for a 1-year period. Should funding end before 94 participants are enrolled the study will have more than sufficient power to address the primary objectives (n=74).

Data Analysis Plan

Dr. Psoter, a professional biostatistician from the JH BEAD program specializing in clinical trials and longitudinal data analysis, had assisted Drs. Gerold and Fauerbach in conducting the statistical analyses in consultation with Going forward, this role will be assumed by biostatisticians at the JHU-ICTR.

The primary data analyses (Pain variables) will be conducted using analysis of covariance, or, longitudinal growth modeling (if normality assumptions are met) to examine group differences both in cross-section and longitudinally. If normality assumptions are violated then appropriate nonparametric tests will be utilized (e.g., Wald statistic). These methods allow for statistical controlling multiple potential confounding baseline variables and are robust against dropout - expected to be minimal. Data from the following study were used to generate this power estimate (Beaudoin, 2014).

Prior to study start-up, it is anticipated that, since ANCOVA is the recommended procedure for analyzing pre- to post- treatment change scores, that is the test that will be utilized for the primary aim, because: it is more powerful than t-test and Mann-Whitney; it can adjust for baseline group differences; it can be adjusted for baseline randomization strata; and, it can be utilized in analyzing repeated measures such as in the present study.

Prior to testing hypotheses, univariate distributions of variables will be inspected to assess normality, identify outliers, skewness or other abnormalities in distribution, determine appropriate summaries of location and spread and the need for transformation or nonparametric analysis. Preliminary analyses will determine whether the data meet basic assumptions for parametric tests. If relevant covariates are not balanced by the randomization, or confounds are distributed unevenly across groups, they will be included in the models as covariates.

If Pain Intensity is substantially associated with non-study factors (e.g., age, gender, TBSA) these variables will be statistically controlled as indicated in analyses.

The data on average (or summed) Opiate Sparing Effects from baseline to post-treatment, and within group and between group changes over time are likely not to meet criteria for parametric analysis, that is, they are expected to be non-normally distributed and thus inappropriate for Analysis of Covariance (ANCOVA).

It is anticipated that the data on Opiate Sparing (i.e., requested additional dose of analgesic medication) will be non-normal and will be analyzed using Mann-Whitney or other nonparametric method as appropriate. Prior to testing hypotheses, univariate distributions of variables will be inspected to assess normality, identify outliers, skewness or other abnormalities in distribution, determine appropriate summaries of location and spread and the need for transformation or nonparametric analysis. Preliminary analyses will determine whether the data meet basic assumptions for parametric tests. If relevant covariates are not balanced by the randomization, or confounds are distributed unevenly across groups, they will be included in the models as covariates. If Opiate Sparing is substantially associated with non-study factors (e.g., age, gender, TBSA) these variables will be statistically controlled as indicated in analyses.

Trajectory, and, Mediator / Moderator Analyses

Finally, analyses will be conducted that take into account the variability of participant's responses over time. It is anticipated that these analyses may yield significant insight into patterns of Time and Time-by-Group responses that are not easily disentangled using traditional statistical methods. Thus, statistical analyses will include methods (e.g., latent growth mixture modeling, latent class growth curve analysis) to identify classes of patients with similar trajectories and mediator/moderator variables that effect outcome (e.g., stability, resilience, impairment). It is anticipated that these methods will enable identification of participants at greater or lesser risk for chronic pain and ongoing psychological distress. The potential impact on the quality of care, soldier safety and comfort, and early identification and risk stratification – possibly under austere battlefield conditions during the first painful procedures – cannot be over-estimated.

Participant Dropout

Dropouts and participants whose wound care ends or changes substantially prior to the anticipated 7-day study period will be handled on an intent-to-treat manner in all key analyses with the last data obtained treated as the endpoint for that participant. Reasons for dropout will be recorded and contrasted across group.

d. Early stopping rules.

See "Definition of treatment failure or participant removal criteria", above.

8. Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

Ketamine: The risks of low-dose, slow infusion ketamine have recently been reported in several ED Trials reviewed in updated risk / benefit sections above and in summary of changes made. The major disadvantages to using ketamine as a single agent in small or large doses, or when administered rapidly (<1 minute) are altered perceptions occurring commonly and characterized as floating sensations, vivid dreams, hallucinations and delirium. The consequence of these untoward side effects in a combat theater of operations is currently undefined.

One recent retrospective review of ~400 patients (patients 30% acute pain, 70% post-op) found significant drop in pain but also a significant increase in hypertension and hypotension in patients provided ketamine plus opiate analgesia (Kator, 2013).

Procedural Risks: The twice daily wound care involve debridement of necrotic tissue, cleansing raw wounds and related activities and tasks. The risks of pain, infection and distress associated

with these procedures will not differ among participants assigned to either group – prior to the first study procedure. The study aims involve testing whether the study drug reduces pain and distress during the procedures as a direct effect of the study drug. The study inclusion criteria require that a certain moderate-severe pain be present prior to study onset in order to be able to discern differential efficacy in pain reduction across study conditions. There is no risk of greater pain, rather, it is anticipated that the usual care group runs the risk of experiencing less pain relief than the study drug group. It is not being evaluated, but it is not anticipated that there will be differences between consented participants and eligible but non-consenting participants.

All patients enrolled in the study will be patients at the Burn Intensive Care Unit (BICU) and will be under the ongoing care of the Burn Surgery and Critical Care Medicine Services. All patients in the BICU are at risk for delirium from multiple sources and are assessed and monitored for this condition as part of regular nursing and physician assessments of the patient's mental status. However, to address the question regarding the possibility that subjects who receive Ketamine will have a higher incidence of hallucinations/delusions, we will keep a daily tally of such experiences in subjects' research charts (i.e., the presence or absence of hallucinations/delirium in addition to the severity of these symptoms, should they exist) using the Side Effect Measure of Opiates and Ketamine (see Measures) as well as a list of other potential causes of the delirium / hallucinations (e.g., benzodiazepines, alcohol withdrawal). We will conduct post hoc analyses to address the relative frequency and severity of these phenomena in the ketamine versus usual care "control" arms of the study.

b. Steps taken to minimize the risks.

Assessments: Twice during each shift, all patients on the BICU are scored using the nurse-administered CAM-ICU and the RASS. These are recorded in EPIC and changes reported to providers and to the following shift. The study team will assess potential side effects using the patented Side Effect Measure for Opiate and Ketamine (SEM-OK; Janssen). The SEM-OK will be administered prior to day 1, session 1, and after session 1 on days 3, 5 and 7. The RA and the Co-Investigator provider present will rate the SEM-OK.

Low-Dose, Slow Infusion Ketamine: In order to minimize the psycho-mimetic risks, the ketamine+UC will be delivered in a sub-anesthetic, low dose, slow infusion preparation (see above). The dose, route, duration time of infusion have been established per study protocol and as prescribed by and monitored by the study Co-PI (Dr. Gerold, CCAM), the JHBMC Pharmacist (Dr. Lisa Ruppel), Burn Center anesthesiologist (Dr. Asad Latif, CCAM), Burn Center attending surgeon (Dr. Caffrey, Burns & Plastic Surgery), or, under the direct, supervisory and evaluative authority of these physicians, the Burn Fellows, or the burn center mid-level providers (PA, NP) and as monitored by the professional nursing staff of the Johns Hopkins Burn Center. The psycho-mimetic risks will be monitored as noted above using the Side Effect Measure of Opiates and Ketamine (see Measures).

3. Pharmacy's role in policy decision-making with JHBMC Pharmacy and Therapeutics as well as in preparing the drug and delivery system.

i. JHB Pharmacy and Therapeutics Policy - discussed ketamine for research purposes in clinical setting, arrived at definitive decision in consultation with research pharmacist Lisa Ruppel, PharmD at JHBMC and the results of her discussion with Jim Monolakis, PharmD, Director of Interventional Research Pharmacology at JHBMC.

ii. The Ketamine Project team is adding Dr. Lisa Ruppel as Co-Investigator on the project for the role and tasks delineated here.

Lisa Ruppel, PharmD has completed the "Drug Build" for the project. Specifics will be provided. She and Mr. Edwards (see next) collaborate on the "Order Build" and "Drug Build" to ensure the accurate and timely delivery of study drug to study participants. The study drugs (Ketamine as well fentanyl and saline) will be delivered in plain, nondescript identical delivery system for both study drug and usual care preparations. This allows blinding of provider/prescriber, nurse and patient.

iii. The IRB-approved protocol was presented by Dr. Ruppel at the January 2017

JHMBC Pharmacy & Therapeutics Committee (P&T) meeting for approved use in hospitalized patients. The process for approval of clinical policy versus IRB-approved protocols are through the same committee. Full approval was given at the next P&T Committee meeting by all necessary governing bodies for the use of ketamine in this IRB-approved protocol. The pharmacy and Dr. Ruppel in particular, will continue to work with the Ketamine study team to coordinate provision of study materials in a blinded fashion as described next.

iv. Once the Ketamine Project Management Team identifies and consents a participant, the pharmacist will then randomize the subject based on the schema provided by the ICTR database and statistician as described above. Based on group assignment, the pharmacy will prepare the appropriate medication / placebo / study drug, deliver this to the BICU in identical bags labeled in a blinded fashion. Despite being blinded, the label will include all elements required by law.

Lisa Ruppel, PharmD
Clinical Research Pharmacist
Johns Hopkins Bayview Medical Center
(410) 550 – 0958

Tad Edwards has begun the "Order Build" for the order set to be entered in the BICU EPIC.
Tad Edwards, Application Coordinator III
Johns Hopkins Health Systems
(410) 986-2511; IT@jh EPIC

5. Training House Staff and Nursing on Ketamine Protocol
KELLY KROUT, DNP: Nurse Manager for the JHBMC Johns Hopkins Burn Center and the Surgical Intensive Care Unit.
Scheduled Dates of Training Completion –

Overview and Discussion: Monthly Nursing Staff Meeting - 30 February 2017
Didactics & Hands-On: Monthly Nursing Staff Meeting - 29 March February 2017
See Powerpoint Education Tool – attached.

Dr. Krout approved the involvement of nursing personnel in the following aspects of the Ketamine Trial. She described the manner in which the training in the protocol would be best conducted initially on 2/30/17 at the regularly scheduled nursing team meeting (handouts, posters using graphic and verbal modalities) to provide an overview of study aims, background mechanisms and rationale for the study and to address any questions. A more detailed and hands on training covering the specific steps of nursing involvement that is scheduled for nursing staff at subsequent meeting. Follow-up discussions will be conducted at the next nursing staff meeting to discuss individual nurse experiences with the study and to address any questions or concerns that may have arisen in the course of study start-up.
JHBMC Nursing Policy for Ketamine (sub-anesthetic, slow infusion, analgesia for severe, acute burn pain during wound care):

- The Ketamine for Managing Acute Wound Care Pain study stipulates that the RNs will hang and initiate the infusion of the ketamine at rates pre-programmed into the infusion pump.
- As described above, the study drug will be prepared by the pharmacy at JHBMC when the provider orders it for a study participant. The container for delivery of the infusion will be identical for ketamine and saline preparations and, thus, will allow for a triple-blinded (provider, nurse, patient, RA) and randomized manner. All participants will receive usual care fentanyl, while half of the participants will receive saline infusion and the other half of the participant sample will receive ketamine – both as described above. Under the study design, the provider, nursing staff, study staff, and participants will not know which participants receive "ketamine + UC / fentanyl" or "UC / fentanyl + saline".
- RNs will not administer or adjust loading dose or infusion rate - these will be preset by pharmacy in nondescript delivery mechanisms. Infusion pumps for both the Usual Care Group (Saline infusion) and the Usual Care Plus Ketamine Augmentation Group (Ketamine infusion) will be programmed to administer a Loading Dose/infusion of saline for the usual care condition and a Loading dose/infusion of ketamine in the Usual Care PLUS Ketamine condition at 10 minutes prior to onset of wound care. Both conditions will receive usual care fentanyl at < 1 minute prior to wound care onset. Then, the Usual Care Condition will receive a slow infusion of saline beginning after the saline loading dose

infusion ends throughout the wound care until the session ends, and the ketamine plus usual care condition will receive a slow infusion of low dose ketamine starting after the loading dose ketamine ends and continuing on through until the end of the session. These are described in Table 1 and in the text following Table 1, above.

- The ketamine loading dose and the session length infusion will deliver a sub-anesthetic/low dose at a slow rate and neither are expected to cause significant changes in vital signs, including respirations.
- RNs will not titrate or adjust the dose of ketamine (or saline placebo) as all doses are preset as determined under the study protocol and the delivery pump is preprogrammed by the study pharmacist and delivered to the burn center where it will be administered to the participant. The prescribing provider, RA, the nurse, and the patient will be naïve to the contents of the pump being administered.
- RNs will monitor participants as per standard of care and closely monitor them for the effects of the drugs administered as per standard of care for all patients in the BICU (i.e., each patient is rated twice per shift using the CAM-ICU and RASS).
- RNs are expected to administer PRN doses of fentanyl titrated to the patient's perception of pain consistent with their usual practices for wound care. In the case of this Trial, pain rated by the patient as low moderate "despite routine treatment" (Lee and Lee, 2016). The PRN is the BICU standard of care fentanyl PRN Dose = 1 mcg / kg (0.07 mg in a 70 kg individual). This criteria for providing PRN fentanyl is within the range of customary/usual care BICU nursing practice and is provided to participants in either Group 1 or Group 2 when a participant requires additional pain medication as described here and above.

    a. As above, all subjects will be under the ongoing care of the Critical Care Medicine and Burn Surgery Services. In the unlikely a patient becomes hemodynamically unstable during the study, the CCM and/or the Burn Surgical Services would immediately note the alarm and they would initiate an emergency response. The study investigators would be notified in a timely manner regarding any such occurrences and this would be evaluated and reported to the IRB, DoD HRPO and to the NTI.
    b. Our intention is not to exclude participants with hypo- or hypertensive co-morbidities as in order to potentially decrease this risk. Ketamine has been long regarded for its superior hemodynamic stability as compared to other analgesic/sedative medications and such crises are unlikely. Furthermore, the Ketamine for Acute Burn Pain study will employ low doses of ketamine and infused it so slowly that it is unlikely to induce hemodynamic instability.
    c. Of note, the clinical experience of the attending surgeon and critical care / anesthesiology attendings using low dose ketamine in burn patients also indicate that ketamine is not associated with hemodynamic instability. All prospective patients will have sustained serious burn wounds requiring ongoing wound care. This wound care requires sedative/analgesic medications for pain management. One intention of the current study is to demonstrate the efficacy in providing analgesia during the ongoing wound care; this hypothesizes that the adjunctive use of ketamine will afford less hemodynamic instability and fewer adverse events or drug side effects compared with conventional sedative/analgesic regimens.

Most licensed staff of the Johns Hopkins Burn Center are trained in Advanced Burn Life Support (ABLS)

Cardiac and pulmonary safety, efficacy and side effects of Ketamine + Usual Care and the Usual Care regimens will be digitally monitored with alarm set, as well as monitored by the Nurse performing the procedure, the Physician Assistant and/or Nurse Practitioner and Burn Fellow assigned to the Burn Intensive Care Unit.

The Confusion Assessment Method for the ICU (CAM – ICU) and the Richmond Agitation and Sedation Scale (RASS) will be used twice during each shift within one hour after dressing change for assessing the arousal, confusion and agitation, which is consistent with current Burn Unit protocol. The Side Effect Measure for Opiates and Ketamine will be scored once per session for each day shift by the RA and provider at hand.

a. Plan for reporting unanticipated problems or study deviations. All unanticipated problems or study deviations will be reported to the IRB. Furthermore, Dr. Bradford Winters will serve as the Independent Medical Monitor for the Ketamine study. He has agreed to serve in this capacity.
   As the independent medical monitor he will have the specific power to do the following:
   - Stop this research study in progress
   - Remove individual from this study
   - Take any steps to protect the safety and well-being of participants until the IRB can assess the problem or event

a. Legal risks such as the risks that would be associated with breach of confidentiality. Minimal. Subjects will all be patients at the BICU
b. Financial risks to the participants. None

9. Benefits

Description of the probable benefits for the participant and for society.

- The direct costs of acute pain in burn care and emergency care are quite high. The indirect costs are potentially of even greater impact on the individual and society in terms of professional time, facilities, psychological distress, tolerance, potential for tolerance transitioning to addiction, potential for acute pain transitioning to chronic pain, and disability.

- The potential advantages of using ketamine with fewer narcotics and benzodiazepine drugs during austere operations include the preservation of muscle tone and protective airway reflexes, reduced risk of respiratory depression, reduced incidence of hemodynamic instability in shock, reduced need for opioids, and decreased nausea and vomiting.

- The potential benefit for active duty personnel wounded in combat and to civilians in emergency and critical care settings include reduced pain, reduced narcotic use and therefore tolerance, and reduced medical risks such as those listed here. These benefits are especially salient when emergent analgesia is required in combat settings and other austere conditions where loss of airway reflexes, respiratory depression, reduced muscle tone and hemodynamic shock could easily prove fatal.

10. Payment and Remuneration

Detail compensation for participants: Participants will receive $10 after the 1st and 2nd session on each of the first 7 days that they are involved in the study (Total = ($70). They will also be provided a stipend of $10 after the assessments on 1 day, 1 week and 1 month after the last session (i.e., $30, with a study total = $100). All payments will be made in cash after completion of each day (1st week) and after each assessment (1 day, 1 week and 1 month after Study Day #7).

11. Costs

There are no additional costs to the participant associated with the study procedures, drug(s) or personnel. The costs of wound care procedures, pharmaceutical administration, nursing care, and unit charges are the same, on average, for those participating as they are for non-participants who have the same injury and comorbid factors, pre-injury medical history and patient variables. Similarly, there are no added costs between those allocated to K+UC versus those allocated to UC conditions, or between those allocated to these medications as part of the study protocol or those prescribed one of these medications as part of routine burn center pain management

12. Department of Defense, Human Research Protection Office

DoD & HRPO phrases to be added to the protocol and the Consent Form:
Add the following underlined verbiage to the JHU IRB Consent Form as required on all DoD – funded research Consent Forms.
(5) USAMRMC Required Protocol and Consent Form Language;
The following must appear in the consent form:
• A statement that the DoD or a DoD organization is funding the study.
Version: 15 April 2013 Page 5 of 7
(5) USAMRMC Required Protocol and Consent Form Language; Version: 15 April 2013 Page 5 of 7
The following are listed in the revised eFormA, and the revised Consent Form:
Funding:
The Safety and Efficacy of Ketamine for Acute Pain in Burn Wound care As Analogue to Analgesia in Austere Conditions is funded by the United States Department of Defense. The project is funded through a sub-award from the National Trauma Institute.
Authorized to Review Protected Health Information (PHI):
Representatives of the United States Department of Defense are authorized to review Protected Health Information and research records. The investigators have appointed Dr. Bradfield Winter as the Independent Medical Monitor of this project to provide oversight and safety, Dr. Winter, as the Independent Medical Monitor of the study, has also been added to the HIPAA authorization section of the consent form as one of the parties to whom PHI may be disclosed.