The Intraoperative Administration of Ketamine to Burned U.S. Service Members Does Not Increase the Incidence of Post-Traumatic Stress Disorder

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ABSTRACT Aim: Patients with severe burns typically undergo multiple surgeries, and ketamine is often used as part of the multimodal anesthetic regimen during such surgeries. The anesthetic ketamine is an *N*-methyl-D-aspartate receptor antagonist that also provides analgesia at subanesthetic doses, but the psychoactive side effects of ketamine have caused concern about its potential psychological effects on a combat-wounded population. Post-traumatic stress disorder (PTSD) affects approximately 30% of burned U.S. service members injured in Operation Iraqi Freedom/ Operation Enduring Freedom. A preliminary analysis by our research group reported that patients who received perioperative ketamine had a significantly lower prevalence of PTSD than those injured service members who did not receive ketamine. We have now expanded this research to examine the relationship between ketamine and PTSD development in a much larger population. Methods: A retrospective analysis on data from service members being treated for burns at the San Antonio Military Medical Center was conducted. Collected data included drugs received, injury severity score (ISS), total body surface area (TBSA) burned, length of hospital stay (LOS), number of intensive care unit days, number of surgeries, and PTSD Checklist-Military (PCL-M) scores and administration dates. Subjects were grouped based on intraoperative receipt of ketamine, and the groups were compared. The groups were binary for ketamine (yes or no), and dose of ketamine administered was not included in data analyses. Propensity score matching based on ISS and TBSA was performed to control for individual differences in burn severity. Results: Two hundred eighty-nine burned U.S. service members received the PCL-M at least 30 days after injury. Of these subjects, 189 received intraoperative ketamine, and 100 did not. Despite significantly greater injuries, as evidenced by significantly higher TBSA burned and ISS ($p < 0.01$), patients who received ketamine did not screen positive for PTSD at a different rate than those patients who did not (24% vs. 26.98%, $p = 0.582$). Patients receiving intraoperative ketamine also underwent a significantly greater number of surgeries, spent more time in the hospital, spent more days in the ICU, and received more morphine equivalent units ($p < 0.0001$). Propensity score matching based on ISS and TBSA resulted in a total subject number of 130. In the matched samples, subjects who received ketamine still underwent significantly more surgeries and experienced longer hospital stays ($p < 0.0001$). Again, there was no statistically significant difference in the incidence of a positive screen for PTSD based upon the receipt of ketamine (28% vs. 26.15%, $p = 0.843$). Conclusions: Ketamine is often used in burn patients to reduce opioid usage and decrease the hemodynamic and respiratory side effects. Although this study does not show a benefit of ketamine on PTSD development that was identified in previous work with a smaller sample number, it does support the conclusion that ketamine does not increase PTSD development in burned service members.

INTRODUCTION

Pain is a significant problem in the military, from basic training to the battlefield and home again.[1] The most common medications given for severe pain, both on the battlefield and in definitive care facilities, are opioids. However, the widespread use of opioids had led to significant problems in the health system. First, initial use of intramuscular morphine on the battlefield is not very effective at providing analgesia.[2] Although opioids are the most commonly prescribed medication for severe pain, there are numerous side effects that must be considered when administering these drugs. Opioids can cause nausea, vomiting, constipation, respiratory depression, sedation, hemodynamic depression, and itching.[3,4] Additionally, opioids carry the risk of tolerance, dependence, addiction, and opioid-induced hyperalgesia.[5,6] Other alternatives to pain management must be considered.

Pain is a particularly challenging problem in burn patients.[7–9] These patients are already severely injured because of the significant tissue damage produced by a burn; a severe burn can also alter coagulation, inflammation, and metabolic pathways.[10] These alterations to normal physiology have to be considered when medications are being administered, particularly those that can negatively affect hemodynamic stability. The burn also impacts peripheral neurons that send pain signals to the central nervous system. Burn pain has multiple components, making it especially hard to treat.[11] Burn patients

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frequently suffer from unrelieved pain and receive a complex pharmacopeia to attempt to control the pain.[9,12] The basis of pain management is opioids, which have the aforementioned side effects.

Ketamine is an *N*-methyl-D-aspartate receptor antagonist that is commonly used as part of balanced anesthesia, particularly in burn and pediatric patients. Ketamine has a rapid onset of action and allows for stable cardiovascular and respiratory physiology. It produces sedation, analgesia, and dissociative anesthesia, but is also capable of producing profound analgesia even at subanesthetic doses.[13–15] However, ketamine is associated with the psychomimetic effects, including emergence delirium and hallucinations.[16] These negative side effects can be mitigated through benzodiazepine coadministration and pretreatment counseling. However, these dissociative properties of ketamine raised the concern that ketamine may increase the prevalence of post-traumatic stress disorder (PTSD) or other mental health sequelae[17] in combat-wounded service members.

PTSD is a psychological disorder characterized by recurrent flashbacks, nightmares, emotional disturbances, social withdrawal, and forgetfulness.[18] It often arises after a traumatic experience where the participant is threatened with harm and/or death. Experiencing a traumatic event, threat of injury or death, and threat to one's physical integrity, such as untreated pain are predisposing factors for PTSD. PTSD affects almost one-third of the burn patient population, with civilian burn centers reporting a prevalence of 8% to 45%.[19–22]

PTSD is a concern for U.S. service members returning from theater. Approximately 20% of returning injured Operation Iraqi Freedom/Operation Enduring Freedom Service members reported symptoms consistent with PTSD.[23] Pain is a stressor that may contribute to PTSD development and frequently, pain is comorbid with PTSD in veterans.[19,24,25] A previous study conducted at our facility suggested that ketamine administration in the operating room did not increase the risk of PTSD in burned service members; indeed, there was a statistically significant decrease in the prevalence of PTSD among the cohort that received ketamine as compared to those that did not receive ketamine.[26] However, there were a very small number of subjects, particularly in the no ketamine group, and there was an extremely high prevalence of positive screens for PTSD in the no ketamine group. Therefore, this retrospective study revisits the relationship between PTSD and ketamine in population of burned U.S. service members. We compared the prevalence of PTSD in patients who received intraoperative ketamine versus those that did not.

MATERIALS AND METHODS

This retrospective chart review study was conducted under a protocol reviewed and approved by the U.S. Army Brook Army Medical Center Institutional Review Board, and in accordance with the approved protocol. The population analyzed was burned U.S. service members treated at the U.S. Army Institute of Surgical Research (USAISR) burn unit between 2004 and 2011. Inclusion criteria were any active duty service member admitted to the USAISR burn unit who completed the PCL-M screening tool for PTSD. Only those subjects who received screening for PTSD at least 30 days after the burn were included in this study.

Data on age, date of injury, intraoperative medications, opioids received, Injury Severity Score (ISS), percent total body surface area burned (% TBSA), length of hospital stay (LOS), number of days spent in the intensive care unit (ICU days), and number of surgeries were collected from patient charts. Chart data from all military patients admitted to the USAISR burn unit was extracted to a password-protected Microsoft Excel database stored on in-house servers; data included patient demographics, drugs administered, and PTSD Checklist-Military (PCL-M) scores. Morphine equivalent units (MEUs, mg/day) were calculated by adding opioid dosages received both intraoperatively and on the wards and dividing by the LOS. Opioid dosages were converted to intravenous morphine equivalents using standard conversion tables.[27–29] The most recent PCL-M screening results were also collected for each subject. The variability in time frame of when the patient received the PCL-M, postburn, was not analyzed, nor were other drugs or treatments administered. We also did not evaluate subjects based upon the presence of additional mental health disorders.

Multiple screening tools for assessing PTSD are available and are currently used in civilian trauma centers. However, the PCL-M is a screening tool for PTSD that is authorized for use by the U.S. military. It consists of 17 questions rated on a scale of 1 to 5, indicating the presence, frequency, and severity of PTSD symptoms. A score of 44 or higher yields a diagnostic efficiency of 0.900,[30] and thus was the cutoff used for a positive screen in this study. The complete diagnostic criteria for PTSD are described in the "Diagnostic and Statistical Manual of Mental Disorders," third (1980) and fourth (1994) editions.[18] All subjects received the PCL-M immediately before discharge from the USAISR burn unit.

Subjects were stratified into two groups. One group received intraoperative ketamine during their initial operations, and the other group did not receive intraoperative ketamine during their initial operations. The groups were binary for ketamine (yes or no), and dose of ketamine administered was not included in data analyses. The two groups were then compared to determine if there was a difference in incidence of a positive screen on the PCL-M or on frequency/severity of PTSD symptoms, as indicated by the PCL-M Score.

Continuous data was tested for normality and a Student's *t*-test and Wilcoxon two-sample test was performed accordingly. Categorical data was tested using a χ^2 test. Propensity score matching based on ISS and TBSA was performed to control for individual differences in burn severity. A logistic regression was conducted using ketamine as the dependent variable and ISS and TBSA as the independent variables. The

probability index generated from the Logistic Regression was used by a matching algorithm to pair ketamine (yes/no). ISS and TBSA with then compared by univariate analysis to ensure there was no statistical difference between the groups (ketamine yes/no) on these variables after matching. A p value of $p < 0.05$ was considered significant in this study.

RESULTS

Between 2004 and 2011, 785 burned service members were treated at the USAISR burn unit. Of these, 290 received the PCL-M at least 30 days after injury. Of these subjects, 189 received intraoperative ketamine, and 100 did not (Fig. 1). Because inclusion criteria required PCL-M data from at least 30 days after injury, no subjects were lost to follow-up.

Analysis of patient demographics demonstrated that the subjects in both groups were similar in age (Table I). However, those patients who received intraoperative ketamine had significantly higher ISS, %TBSA, and number of surgeries ($p < 0.0001$). Patients receiving intraoperative ketamine also spent more days in the ICU, had longer overall hospital stays, and received more opioids than those patients who did not receive intraoperative ketamine ($p < 0.0001$, Table II). Despite these significantly greater injuries, patients who received ketamine did not screen positive for PTSD at a different rate than those patients who did not ($p = 0.582$, Table II). Patients who received ketamine also did not exhibit increased PTSD symptoms and had similar PCL-M scores to those patients that did not receive ketamine ($p = 0.370$). Because the comparison could be confounded by the significantly greater injuries received by those patients who were administered intraoperative ketamine (Table I), propensity score matching based on ISS and TBSA was done, resulting in a total subject number of 130, 65 in each group. Table III shows the demographics of the patients in the matched groups. The matched groups were similar in age, ISS, % TBSA, days spent in the ICU, and opioids received (Table III). Those patients who received intraoperative ketamine still spent more time in the hospital and experienced more surgeries than those patients who did not receive intraoperative ketamine ($p < 0.0001$, Table III). Again, there was no statistically significant difference in the incidence of a positive screen for PTSD based upon the receipt of ketamine ($p = 0.843$, Table IV). There was also no difference between

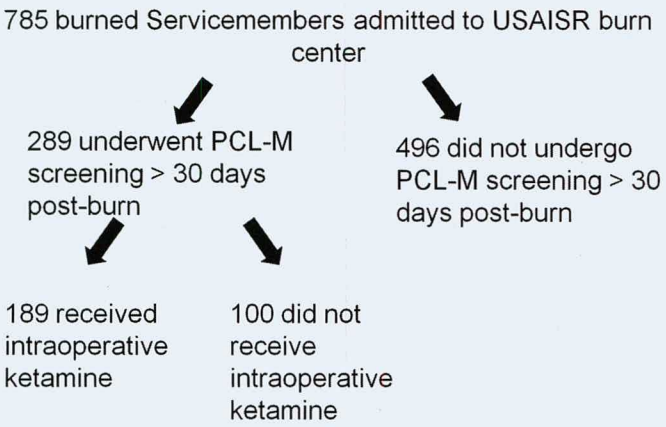

FIGURE 1. Patient population. Between 2004 and 2010, the U.S. Army Institute of Surgical Research admitted 785 burned service members. Of these, 289 received PTSD screening at least 30 days after their injury. One hundred eighty-nine of these subjects received intraoperative ketamine, and 100 did not receive intraoperative ketamine.

TABLE I. Patient Demographics, Injury Severity Parameters, and Intravenous Morphine Equivalents Received

After Matching	No Intraoperative Ketamine ($n = 65$)	Intraoperative Ketamine ($n = 65$)	p Value
Age	24.97 ± 6.35	25.67 ± 6.40	0.577
ISS	9.51 ± 7.01	9.51 ± 7.01	1
Percent TBSA	11.30 ± 10.94	13.09 ± 12.09	0.218
Number of Surgeries	0.95 ± 1.68	3.38 ± 4.35	<0.0001
ICU Days	1.85 ± 4.58	5.55 ± 15.31	0.033
Length of Stay	15.96 ± 22.34	22.05 ± 21.13	<0.0001
MEQ (mg/day)	91.52 ± 107.60	89.26 ± 74.45	0.645

Subjects receiving intraoperative ketamine had greater ISS, higher percent TBSA burned, underwent more surgeries, spent more time in the ICU and in the hospital, and received more intravenous morphine equivalents per inpatient day (MEQ [mg/day]). There was no difference in age between the two groups.

TABLE II. The Relationship Between Intraoperative Ketamine Receipt and PTSD

	No Intraoperative Ketamine ($n = 100$)	Intraoperative Ketamine ($n = 189$)	p Value
PCLM Score	32.98 ± 15.62	34.57 ± 15.64	0.37
PTSD Prevalence	24%	26.98%	0.582

There is no difference between PCL-M scores and PTSD incidence in patients that received intraoperative ketamine versus those that did not.

TABLE III. Propensity Score-Matched Patient Demographics, Injury Severity Parameters, and Intravenous Morphine Equivalents Received

	No Intraoperative Ketamine ($n = 65$)	Intraoperative Ketamine ($n = 65$)	p Value
PCLM Score	33.98 ± 16.10	35.06 ± 15.91	0.663
PTSD Prevalence	28%	26.15%	0.843

After propensity score matching based upon percent TBSA burned and ISS scores, subjects receiving intraoperative ketamine experienced a greater number of surgeries and spent more time in the hospital. There was no significant difference between the two groups in age, ISS, % TBSA, days spent in the ICU, or intravenous morphine equivalents received per day (MEQ [mg/day]).

TABLE IV. Propensity Score-Matched Analysis of the Relationship Between Intraoperative Ketamine and PTSD

Before Matching	No Intraoperative Ketamine (n = 100)	Intraoperative Ketamine (n = 189)	p Value
Age	25.41 ± 6.72	25.65 ± 5.73	0.495
ISS	6.82 ± 6.87	20.66 ± 13.12	<0.0001
Percent TBSA	9.03 ± 9.52	26.57 ± 20.26	<0.0001
Number of Surgeries	0.71 ± 1.52	5.53 ± 5.71	<0.0001
ICU Days	1.33 ± 3.86	18.99 ± 30.24	<0.0001
Length of Stay	12.06 ± 19.03	49.54 ± 57.14	<0.0001
MEQ (mg/day)	80.04 ± 96.59	115.67 ± 116.87	<0.0001

Following propensity score matching based on % TBSA and ISS. There is no difference between PCL-M scores and PTSD incidence in patients that received intraoperative ketamine versus those that did not.

the groups in the incidence/severity of PTSD symptoms as determined by PCL-M scores (p = 0.663, Table IV).

DISCUSSION

Pain is a common and often severe problem for burn patients. Providers balance the impact of pain compared to the potential side effects of anesthetic and analgesic agents.[8] Although opioids are the most common analgesic and anesthetic agents, they have significant risk for respiratory depression, hemodynamic depression, decreased cardiac output, suppression of the immune system, and constipation.[3] These side effects are particularly alarming for burned patients who already suffer from alterations in coagulation, immune suppression, and are at significant risk for multiorgan failure. Effective alternatives to opioids are few, but include ketamine. Ketamine is an effective anesthetic and analgesic agent.[14,15,31,32] However, there are concerns that ketamine might increase psychological problems. However, we found no evidence for an association between ketamine and increased PTSD. For this study, the prevalence of PTSD in 289 burned soldiers (26.1%) is similar to the prevalence found in civilian burn populations (8% to 45%). Our data indicate that intraoperative ketamine administration does not affect the rate of PTSD in burned U.S. service members. These findings identified that ketamine does not increase the prevalence of PTSD.

Ketamine is used as part of a multimodal anesthetic plan that usually includes an opioid component. Ketamine is a multifunctional drug affecting multiple receptors including N-methyl-D-aspartate receptors and opioid receptors.[13,33–35] Ketamine is a potent analgesic, which has opioid sparing properties.[14,36,37] It is used in total intravenous anesthesia where it functions as both an analgesic and anesthetic depending on plasma concentration.[38,39] Our data suggest that intraoperative ketamine can be used in burned service members without affecting the prevalence of PTSD in this population. These data do not provide evidence that ketamine might be effective for the treatment for PTSD. Previous studies by our group found an association between ketamine and decreased PTSD development in service members.[26] However, this study did not find a similar association.

To date, there are no consistent correlations between PTSD in a combat-wounded population and medications received on the battlefield or in the hospital. Multiple retrospective studies have identified correlations between individual drugs and the subsequent development of PTSD. For example, a study of Marines showed that those subjects who received the most morphine within 24 hours following injury had a decreased incidence of PTSD in comparison to those Marines who did not receive morphine. This suggests that morphine reduces PTSD incidence, but does not address the possibility that the decreased PTSD development may be related to effective pain control, or to effects on memory, rather than to an intrinsic property of the drug.[40]

Limitations

This is a retrospective study with significant limitations. The study has a small sample size, and subjects were evaluated over a 7-year period. Many changes in practice and personnel likely occurred over this time frame and may contribute to differences in individual subjects or subsets of subjects that we were unable to identify when grouping all subjects together in this study. To qualify for inclusion in the study, the subject must have been screened for PTSD at least 30 days after burn; this would eliminate many patients with less severe burns as they may not have been available for in-person evaluation and PCL-M screening. There was little consistency in the time postburn at which the patient was screened using the PCL-M, leading to the possibility of underreporting the incidence of PTSD in patients who may have been successfully treated for PTSD before their final PCL-M screen. The presence of other mental health disorders that may contribute to PTSD or be associated with PTSD were not evaluated, and other medications or treatments that may affect PTSD or the manifestation of PTSD symptoms were not included in this study. Each patient also received multiple other drugs and treatments during their hospital stays that may have affected their outcomes. Additionally, there is limited applicability of these findings from an active duty military population, most of whom were burned in a combat zone, to the civilian burn population. Finally, and importantly, the dose of ketamine each patient received was not included in the analysis. Thus, the effects of ketamine were likely not completely explained when evaluated on a binary, yes/no basis.

CONCLUSION

Ketamine is often used in burn patients to reduce opioid usage and decrease the hemodynamic and respiratory side effects of such usage. These data suggest that ketamine administration does not affect PTSD development in burned service members. However, those patients who received

intraoperative ketamine also spent longer in the hospital, underwent more procedures, received more MEUs, and were more severely injured. It is likely that these sicker patients required a more aggressive and comprehensive pain management strategy and thus were more likely to receive ketamine in addition to opioids. Although this study does not show a benefit of ketamine on PTSD development that was identified in previous work with a smaller sample number, it does support the conclusion that ketamine does not increase PTSD development in burned service members. There was no statistical difference in PTSD prevalence in patients that received ketamine versus those that did not. Data from this study and others support the conclusion that ketamine remains a good option for use in a balanced anesthesia regimen the severely burned population.

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