The Correlation Between Ketamine and Posttraumatic Stress Disorder in Burned Service Members

Laura L. McGhee, PhD, Christopher V. Maani, MD, Thomas H. Garza, BS, Kathryn M. Gaylord, PhD, and Ian H. Black, MD

Background: Predisposing factors for posttraumatic stress disorder (PTSD) include experiencing a traumatic event, threat of injury or death, and untreated pain. Ketamine, an anesthetic, is used at low doses as part of a multimodal anesthetic regimen. However, since ketamine is associated with psychosomatic effects, there is a concern that ketamine may increase the risk of developing PTSD. This study investigated the prevalence of PTSD in Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) service members who were treated for burns in a military treatment center.

Methods: The PTSD Checklist-Military (PCL-M) is a 17-question screening tool for PTSD used by the military. A score of 44 or higher is a positive screen for PTSD. The charts of all OIF/OEF soldiers with burns who completed the PCL-M screening tool (2002–2007) were reviewed to determine the number of surgeries received, the anesthetic regimen used, including amounts given, the total body surface area burned, and injury severity score. Morphine equivalent units were calculated using standard dosage conversion factors.

Results: The prevalence of PTSD in patients receiving ketamine during their operation(s) was compared with patients not receiving ketamine. Of the 25,000 soldiers injured in OIF/OEF, United States Army Institute of Surgical Research received 603 burned casualties, of which 241 completed the PCL-M. Of those, 147 soldiers underwent at least one operation. Among 119 patients who received ketamine during surgery and 28 who did not; the prevalence of PTSD was 27% (32 of 119) versus 46% (13 of 28), respectively (p = 0.044).

Conclusions: Contrary to expectations, patients receiving perioperative ketamine had a lower prevalence of PTSD than soldiers receiving no ketamine during their surgeries despite having larger burns, higher injury severity score, undergoing more operations, and spending more time in the ICU.

Key Words: Ketamine, PTSD, PCL-M.

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The ketamine receiving population (ketamine) and the non-ICU, and had more surgical procedures. The demographics of larger burns, more severe injuries, spent more time in the test) (Table 2). Patients receiving ketamine on average had more operations (Table 3). Using SPSS correlation software to determine the Spearman coefficient, it was shown that PTSD correlated with ketamine, but did not correlate with morphine equivalent units during the surgical procedures were statistically significant. There were no statistical differences in the age of ketamine and nonketamine patients or in the amount of morphine per surgical procedure.

PTSD correlated with ketamine during surgical procedures (Table 3). Using SPSS correlation software to determine the Spearman coefficient, it was shown that PTSD correlated with ketamine, but did not correlate with morphine equivalent units during operations, size of the burn, severity of injury, days spent in ICU, or number of operations. The correlation coefficient is -0.166, meaning that ketamine usage was correlated with decreased PTSD. However, although PTSD correlated with ketamine, the correlation was weak.

RESULTS

Of approximately 25,000 soldiers injured in OIF/OEF, 603 were burn victims treated at the USAISR Burn Center. Two hundred forty-one of these burn patients completed the PCL-M from years 2002 through 2007. After IRB approval, charts were reviewed to determine percent TBSA, injury severity score (ISS), total number of surgeries at the USAISR Burn Unit and the anesthetic regimen used, including amounts given. Using a standard opioid conversion calculator, narcotic medications were converted to IV morphine equivalents. Statistical analysis included the Mann-Whitney test for nonparametric data sets, the Spearman correlation test to determine the relationship between PTSD and other factors, and ROC analysis.

Table 1 Patient Demographics

<table>
<thead>
<tr>
<th>Gender (female/male)</th>
<th>Ketamine</th>
<th>No Ketamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>26 ± 6.0</td>
<td>25.1 ± 5.9</td>
</tr>
<tr>
<td>TBSA</td>
<td>21.43 ± 18.34*</td>
<td>10.22 ± 13.18*</td>
</tr>
<tr>
<td>ISS</td>
<td>16.94 ± 12.01*</td>
<td>8.5 ± 8.57*</td>
</tr>
<tr>
<td>ICU days</td>
<td>21.14 ± 36.76*</td>
<td>11.67 ± 38.8*</td>
</tr>
<tr>
<td>Number of operations</td>
<td>2.55 ± 2.52*</td>
<td>1.07 ± 0.26*</td>
</tr>
<tr>
<td>Morphine equivalent units per operation</td>
<td>76.1 ± 65.7</td>
<td>59 ± 58.1</td>
</tr>
<tr>
<td>Total morphine equivalent units in OR</td>
<td>219.7 ± 305.6*</td>
<td>66.8 ± 71.29*</td>
</tr>
</tbody>
</table>

*p > 0.05.

Table 2 Prevalence of PTSD

<table>
<thead>
<tr>
<th>Number of patients with PTSD</th>
<th>Ketamine n = 119</th>
<th>No Ketamine n = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of PTSD (%)</td>
<td>26.89*</td>
<td>46.42*</td>
</tr>
</tbody>
</table>

*p = 0.044.
patients with burns less than 20% TBSA (Fig. 2), the PTSD diagnosis (1 yes, 0 no) (data not shown), and the PCL-M score (data not shown). Best fit lines were determined and showed no significant change in slope across the spectrum of TBSA burn. This indicated that there was no standard sized burn that can be used to successfully predict PTSD development in this population.

### DISCUSSION

Mechanisms to predict PTSD development are not well-developed. Initially, physical injury (burn size) was identified as a potential indicator of PTSD development. Recent studies have shown that PTSD does not correlate with burn size.\(^{10,14}\) This study confirms that PTSD does not correlate with burn size in OIF/OEF soldiers and suggests that burn size is not a good marker for PTSD development in these patients.

The PCL-M is a 17-question screening tool for PTSD recommended for assessment of PTSD in military populations. A score of 44 or higher is considered a positive screen for PTSD and was used in this study.\(^{13}\) The prevalence of PTSD in all 241 burned soldiers screened for PTSD (28%) is similar to the prevalence found in civilian burn populations (8%–45%).\(^{9–12}\)

Ketamine is used as part of a multimodal anesthetic plan that usually includes an opioid component. Ketamine decreases the amount of opioid needed to effectively control pain. Ketamine is a multifunctional drug affecting multiple receptors including NMDA receptors, opioid receptors, and monoaminergic receptors.\(^ {15}\) It is used in total intravenous anesthesia where it functions as both an analgesic and an anesthetic depending on plasma concentration.\(^ {15}\) Ketamine acts as a profound analgesic at low doses by itself, as well as potentiating the effects of opioids. Ketamine is a non-competitive inhibitor of NMDA receptors that block Ca\(^ {2+}\) channels.\(^ {16–18}\) With ketamine exposure, the NMDA receptor is not activated and does not initiate downstream signaling. Ketamine alters Ca\(^ {2+}\), cAMP, protein kinase C, and mitogen activated protein kinase signaling.\(^ {21}\)

Although ketamine is used in a multimodal anesthetic regime, it is associated with dissociative, psychotic, and psychodystheletic effects similar to those associated with PTSD. PTSD is characterized by over-stimulated brain activity. Contrary to concerns about additive effects upon brain activity and PTSD development, in this study the patients receiving ketamine during operative procedures had a lower prevalence of PTSD than soldiers receiving no ketamine during their surgeries despite having larger burns, more severe injuries based on higher ISS, undergoing more operations, and spending more time in the ICU. Soldiers receiving ketamine perioperatively also received more morphine equivalent units. However, the morphine equivalent units did not correlate with PTSD development. Our findings suggest that ketamine does not increase the prevalence of PTSD and may even decrease it. This allows ketamine to be added to the arsenal for effective pain relief.

The mediating effects of ketamine need to be examined further with known correlates of PTSD. Although traditional thinking has been to associate ketamine administration with increased incidence of PTSD, these results question that re-

### Table 3 PTSD Correlation Coefficients for Operative Patients

<table>
<thead>
<tr>
<th></th>
<th>PTSD</th>
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</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>( r = -0.166^\text{a} (p = 0.044) )</td>
</tr>
<tr>
<td>TBSA</td>
<td>( r = -0.085 (p = 0.308) )</td>
</tr>
<tr>
<td>ISS</td>
<td>( r = -0.092 (p = 0.266) )</td>
</tr>
<tr>
<td>ICU days</td>
<td>( r = 0.087 (p = 0.295) )</td>
</tr>
<tr>
<td>Morphine equivalents/operation</td>
<td>( r = -0.049 (p = 0.555) )</td>
</tr>
<tr>
<td>Total morphine equivalents in OR</td>
<td>( r = 0.046 (p = 0.584) )</td>
</tr>
<tr>
<td>Number of operations</td>
<td>( r = -0.045 (p = 0.588) )</td>
</tr>
</tbody>
</table>

\(^{a} p < 0.05.\)

With a receiver operating characteristic (ROC) curve of 0.569. Multiple factors other than ketamine will be required to reliably predict PTSD.

In this study population, burn size did not seem predictive of PTSD prevalence. Using the data from 241 soldiers admitted to the USAISR who completed the PCL-M, the prevalence of PTSD in the soldiers with burns less than 20% TBSA was 49 of 180 (27%), whereas soldiers with burns 20% or greater had a prevalence of PTSD of 17 of 61 (27.8%) (Table 4). This is despite the fact that 20% is the medically accepted standard size of burn that produces maximal response of inflammation and the maximal hyperbolic response.

However, to determine whether there is a percent TBSA burned that would be useful to predict PTSD development, the percent TBSA burned was plotted against the prevalence of PTSD (Fig. 2), the PTSD diagnosis (1 yes, 0 no) (data not shown), and the PCL-M score (data not shown). Best fit lines were determined and showed no significant change in

### Table 4 TBSA is Not Predictor of PTSD

<table>
<thead>
<tr>
<th></th>
<th>Burns Less Than 20%</th>
<th>Burns 20% or Greater</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with PTSD</td>
<td>( n = 180 )</td>
<td>( n = 61 )</td>
</tr>
<tr>
<td>Prevalence of PTSD (%)</td>
<td>27.2</td>
<td>27.87</td>
</tr>
</tbody>
</table>

\( r = 0.0679 x + 22.208 \)

\( * p < 0.05.\)
relationship. In fact, it seems that ketamine may decrease the prevalence of PTSD in the combat burned patient. Potential explanations of this finding could include better pain management for patients receiving ketamine, neuronal protection by ketamine, and/or antagonism of the N-methyl-D-aspartate (NMDA) receptor by ketamine. Further research studies into the role of ketamine and individual anesthetic agents as well as various anesthetic techniques may help elucidate practical perioperative approaches in decreasing the prevalence of PTSD in the combat wounded as well as the civilian population who are at risk for this devastating disorder.

CONCLUSION

Perioperative low-dose ketamine use in burned soldiers undergoing surgery seems to decrease the prevalence of PTSD. The mechanism of this is unclear but could result from better pain control, neuronal protection by ketamine, and antagonism of the NMDA receptor. Further studies are necessary that determine the mechanisms of action and additional factors that will correlate with ketamine to predict PTSD outcome.

REFERENCES


DISCUSSION

Dr. Carl Andrew Castro (Walter Reed Army Medical Center, Washington, DC): Ketamine is a nonspecific, NMDA receptor antagonist that is widely used in low doses to control pain. Because ketamine is psychoactive and has been linked to increases in psychosomatic and psychotic symptoms, McGhee et al. predicted that burn patients who received ketamine would be at greater risk for screening positive for posttraumatic stress disorder (PTSD) than burn patients who did not receive ketamine. Contrary to expectations, only 26% of burn patients who received ketamine screened positive for PTSD, compared with 46% of burn patients who did not receive ketamine, despite the fact that those patients who received ketamine had larger burns, more severe injuries, spent more time in the intensive care unit and underwent more surgical procedures. McGhee et al. postulate that these findings might best be explained as a result of ketamine providing better pain control, neuronal protection, and antagonism of the NMDA receptor.

McGhee’s findings remind me of one of my favorite movies, Total Recall, starring Arnold Swarzenegger. In this futuristic movie, we have developed the scientific and technical expertise to both erase someone’s memory, as well as implant “false” memories. Let us consider for a moment the ability to erase memories. It is well established that antagonism of the NMDA receptor is also known to disrupt memory. Thus, an intriguing explanation for the findings reported by McGhee et al. is that ketamine reduces the prevalence of PTSD in burn patients by disrupting (or erasing) the memories of the unpleasant events associated with burn treatment and surgeries. It is also possible that ketamine might be disrupting or “erasing” the memories of the combat events or experiences directly. Indeed, research clinicians working with patients who have been diagnosed with PTSD have proposed using pharmacologic interventions to disrupt the memories of unpleasant events associated with PTSD. The idea would be
to reactivate the memory of the unpleasant combat experience in a clinical setting and then disrupt or “erase” that memory using a psychoactive drug that interferes with either memory consolidation, memory retrieval, or both. Such experiments have already been successfully conducted in studies with animals. Some investigators have even suggested giving pharmacologic agents as mental health prophylactics to Soldiers/Marines immediately after combat to inhibit the initial memory consolidation of unpleasant combat events that might lead to the development of PTSD.

Obviously much more research is needed to determine whether it is possible to specifically target unpleasant memories that can lead to debilitating illnesses such as PTSD and then “erase” these memories pharmacologically. One must also consider the ethical and moral issues surrounding “erasing” someone’s memory, even if it is done to help them. Whether it is desirable or not to erase someone’s memory, the findings of McGhee et al. provide some evidence, although admittedly only suggestive, that memory “erasing” just might be doable. But let’s not forget one of the key lessons from the movie I mentioned earlier. Although erasing someone’s memory was possible, it was also possible for there to be total recall at any time. Just like in real life, even in the future there are no simple solutions.

**Dr. Laura McGhee** (US Army Institute of Surgical Research, Fort Sam Houston, TX): Thank you very much, Dr. Castro, for your comments and insights. This was a retrospective study. We don’t know the mechanism of ketamine action on PTSD prevalence. You mentioned possible mechanism of better pain control, neuronal protection, and antagonism of the NMDA receptor. Other possible mechanisms include interplay with other anesthetic medications and regimens: does the data suggest ketamine is protective or does it expose potential deleterious effects of other drugs such as opioids and volatile or inhalational agents. Future studies need to be done to identify the mechanism. The idea to reactivate the memory of combat in a clinical setting and disrupt it is a great point. This is indeed likely given conversations with many clinicians about patient reactions in the perioperative setting. The idea of giving pharmacologic agents as mental health prophylactics is good. Typically benzodiazepines are given but they are associated with a detrimental change in hemodynamic parameter that would be deleterious in the severely injured patients. Our data does not address the issue of memory erasing. Our data suggests that ketamine given during operative procedures does not increase PTSD prevalence and may even decrease it.