Acute traumatic pain treatment with ketamine decreased PTSD and anxiety symptoms 6 months post hospital discharge

Colleen McCarthy Trevino, PhD, AGACNP, FNP, Thomas Carver, MD, Carissa Tomas, PhD, Christine Larson, PhD, Margo Mantz-Wichman, BS, RN, William J. Peppard, PharmD, BCPS, FCCM, *and* **Terri deRoon-Cassini, PhD**, *Milwaukee, Wisconsin*

BACKGROUND: Chronic pain, anxiety, depression, and posttraumatic stress disorder (PTSD) are frequently seen after traumatic injury. Ketamine infusions used to treat acute pain may decrease the risk of chronic pain and improve psychological outcomes of injured patients. We hypothesized patients receiving ketamine would have a lower incidence of chronic pain, anxiety, depression, and PTSD.

METHODS: A prospective, randomized, double-blind placebo-controlled trial of severely injured (Injury Severity Score ≥15) adult patients (age, 18–64 years) admitted to a Level 1 trauma center was conducted. Exclusion criteria included pregnancy and chronic opiate use. All patients were prescribed a patient-controlled analgesia and randomized to either adjustable dose ketamine (ADK) starting at 3 μg/kg/min or an equivalent rate of 0.9% normal saline. Quality of life (QoL) outcomes were measured using Depression and Anxiety (Depression Anxiety Stress Scales 21), PTSD (PTSD Checklist for Diagnostic and Statistical Manual of Mental Disorders-5), Trauma quality of life (TQOL), and pain (Brief Pain Inventory-Short Form) questionnaires at hospitalization, and 1, 3, and 6 months postdischarge. Linear regression analysis evaluated the relationship between groups and baseline pain and mental health outcomes at each follow-up.

RESULTS: Forty-four of 82 patients (54%) were randomized to ADK. Both groups were similar in demographics, injury mechanisms/severity, and baseline QOL measures. Patients in the ketamine group had significantly less anxiety symptom severity ($p < 0.05$) and PTSD ($p < 0.05$), with significantly less re-experiencing symptoms (subscale of PTSD) at 3 and 6 months ($p < 0.05$).

CONCLUSION: Ketamine infusion for acute pain treatment in severe traumatic injury may significantly reduce anxiety and PTSD 6 months after injury. This effect may be specific to the memory processes responsible for re-experiencing symptoms. Further research should explore the effects of acute ketamine administration on the neurobiological mechanisms implicated in the development of PTSD, as this could be a novel preventative intervention to improve QoL for injured patients.

LEVEL OF EVIDENCE/STUDY TYPE: Level 1, Therapeutic/Care Management (*J Trauma Acute Care Surg.* 2025;00: 00–00. Copyright © 2025 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Ketamine; posttraumatic distress syndrome; anxiety.

Poor long-term pain and psychological outcomes are debilitating consequences of traumatic injury. The incidence of chronic pain after injury is as high as 79%.[1] Depression, anxiety, and posttraumatic stress disorder (PTSD) are highly comorbid with chronic pain after injury.[2] Yet, those who develop chronic pain and continue to use opioids after injury, have significantly more depression, and anxiety without significant improvement in their pain, suggesting that there is an intricate relationship between pain and psychological distress.[3] Therefore, interventions to prevent the development of chronic pain and mental health disorders are needed to improve long-term quality of life outcomes in the traumatically injured.

Ketamine in Acute and Chronic Pain

Significant reduction in acute pain after trauma has been shown with the utilization of ketamine in prehospital,[4] emergency department,[5] intensive care unit (ICU)[6] and in hospital settings with severely injured patients.[7] However, this finding of reduced acute pain was not found in our institution specifically with traumatically injured patients with rib fractures, but a reduction in oral morphine equivalents (OME) was noted early in hospitalization.[8,9]

A comprehensive Cochrane review evaluated all pharmacological interventions to prevent chronic post-surgical pain and

Submitted: August 2, 2025, Revised: October 1, 2025, Accepted: October 14, 2025, Published online: December 17, 2025.

From the Division of Trauma and Acute Care Surgery, Department of Surgery (C.M.T., T.C., M.M-W., W.J.P., T.d-C.),

Division of Epidemiology and Social Sciences, Institute for Health and Humanity (C.T.), Medical College of Wisconsin; and

Department of Psychological and Brain Sciences (C.L), University of Wisconsin-Milwaukee, Milwaukee, WI.

This study was presented as an oral presentation at the 84th Annual Meeting of AAST and Clinical Congress of Acute Care Surgery on September 10th, 2025, in Boston, MA.

Funding: This study was partially funded by the Comprehensive Injury Center pilot grant at the Medical College of Wisconsin.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for correspondence: Colleen McCarthy Trevino PhD, AGACNP, FNP, Medical College of Wisconsin Department of Surgery, Division of Trauma and Acute Care Surgery, 8701 Watertown Plank Rd. Milwaukee, WI 53226; email; ctrevino@mcw.edu

DOI: 10.1097/TA.0000000000004835

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

found that only parenteral ketamine administration had overall effectiveness on all pain at 6 months follow-up.[10] Other single center studies have contradicted this finding, including the study by Jennings et al.[11] which demonstrated that the broader concept of quality of life (QoL) 6 months after injury was not affected by ketamine use in the pre-hospital setting. In another pilot study, there were no differences in 6-month numeric pain scores and adverse side effect rates were similar between ketamine and placebo.[12] Therefore, the effect ketamine has on both acute and chronic pain remains unclear.

Ketamine and PTSD

PTSD is a neuropsychiatric condition that occurs in approximately 20% to 40% of injury survivors and is highly comorbid with poor quality of life.[13] Early preventative care of PTSD is of interest to trauma centers, as the American College of Surgeons Committee on Trauma requires screening and referral to treatment for injured patients. Ketamine's theoretical benefit is believed to be due to its action as an *N*-methyl-D-aspartate (NMDA) antagonist. NMDA binding results in a neuroexcitatory state that can affect glutamine receptor binding, impacting learning and memory involved in fear conditioning.[14–16] When administered in the acute aftermath of trauma, ketamine could facilitate fear extinction by blocking the NMDA receptors, thus minimizing risk for developing chronic PTSD, as well as potentially mitigating glutamate-induced hippocampal damage seen in chronic PTSD.[17,18] Researchers have proposed a role for agents impacting glutamate transmission during therapy sessions aimed at reducing conditioned fears and traumatic memories.[19,20] There is some randomized controlled trial (RCT) evidence for rapid reduction in PTSD symptom severity following ketamine infusion in patients with chronic PTSD.[21,22] In another study looking at veterans with burns, those who received ketamine during surgery had a prevalence of PTSD of 46% versus 27% in who did not ($p = 0.04$), suggesting that ketamine may reduce PTSD.[23] However, in a meta-analysis on injured soldiers, early ketamine treatment did not decrease the incidence of PTSD nor early PTSD symptoms, but late ketamine treatment did show improvement in chronic PTSD symptoms.[24] Therefore, there is some contradictory evidence regarding the use of ketamine in PTSD treatment and prevention.

Ketamine and Mood

Glutamate systems have been directly or indirectly implicated in mood disorders such as depression and anxiety, schizophrenia, and substance abuse.[25] For this reason, ketamine has been studied in patients with depression and has been associated with significant antidepressant effects, particularly in patients with chronic pain.[26–28] However, it is unknown if early ketamine administration after injury has a long term impact on mood, including post-traumatic stress symptoms, depression and anxiety, with or without benefit to pain.

Given the gaps and inconsistencies in the literature related to ketamine and quality of life benefits, we performed a randomized, placebo-controlled trial to assess the effect of ketamine on acute pain following severe trauma. Our second aim was to evaluate whether ketamine would have any benefit on long-term patient reported outcomes following injury. We hypothesized that ketamine would improve QoL after trauma by reducing long-term chronic pain, depression, anxiety, and PTSD 6 months after severe traumatic injury.

METHODS

Study Design

This study was the second aim of a prospective, randomized, double-blind, placebo-controlled trial utilizing adjustable dose ketamine (ADK) infusions in severely injured adults (Injury Severity Score [ISS], >15).[29] In addition to a multimodal pain management standard of care, ketamine (or placebo) infusions were started within 24 hours of injury and continued for 48 hours as an analgesic adjunct at a Level I trauma center from January 2021 to February 2024. As described in the first paper, all adult (18–64 years of age) trauma patients were screened for eligibility in this study.[29] To be included, the patient had to be within 24-hours of arrival, admitted to the Trauma Service, and had to have an estimated ISS of >15. Consent, randomization, study protocol, and safety/monitoring protocol are described in detail in the Ketamine Infusion Study (Consort Diagram in Supplemental Digital Content 1, http://links.lww.com/TA/E954).[29] This study was registered with clinicaltrials.gov (NCT no. 04274361) and funded through an institutional grant (Comprehensive Injury Center Award). The institutional review board reviewed and approved the study design (IRB000317017) and patients were randomized using a web-based generator following informed consent and followed by both the Trauma Service and the Regional Anesthesia and Acute Pain Service who assessed the patient for adverse events related to the infusion or PCA.[29] Patients were assessed for nausea, pruritus, respiratory depression, sedation level, and presence of disturbing dreams or hallucinations.[29] Initial study design called for randomization within 12 hours of arrival to the institution, but because of difficulty in enrollment, this was amended to 24 hours after arrival.[29] A power analysis was completed based upon the primary outcome of reducing oral morphine equivalents recommending 119 subjects. However, based on an interim analysis at 92 patients, the study was terminated due to meeting the threshold for futility.[29] In addition to the drug intervention, questionnaires regarding the traumatic injury and patient reported quality of life were obtained at baseline hospitalization and at 1 month, 3 months, and 6 months post injury. This study used the Consolidated Standards of Reporting Trials reporting guidelines for reporting parallel group randomized trials (Supplemental Digital Content 2, http://links.lww.com/TA/E955).

Baseline Study Procedure

The patient's electronic health record was accessed to collect information related to their demographics and injuries. In addition to the measures listed below, the Injured Trauma Survivor Screen (ITSS) was administered at the bedside during hospitalization prior to discharge. The ITSS is the standard of care screener for PTSD and depression risk for hospitalized trauma patients at this institution.[30]

1-Month, 3-Month, and 6-Month Follow-Up Study Procedure

A follow-up interview occurred via a telephone call at 1 month and 3 months post enrollment. During the interview,

© 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

subjects completed the quality of life assessment measures (described below). The 6-month visit was scheduled as an in-person follow-up interview in an institutional clinical research space. If the subject indicated they were unable to come to the research space, the option of a phone interview was offered.

Incentives were offered for participation in the study. At baseline after enrollment the participants received $25 cash; at 1- and 3-month interviews, they received $25 gift cards; and at 6-month interviews, they received a $25 gift card for a phone interview or $50 cash for an in-person interview.

Measures and Analyses

The institution's Trauma Program Registry was accessed for the purpose of data collection of the following variables: ISS, length of stay (LOS), ICU LOS, ventilator days, discharge location, discharge status, Abbreviated Injury Scale, as well as hospitalization, and follow-up clinical characteristics. The following measures were collected at baseline hospitalization, 1 month, 3 months, and 6 months post discharge.

Depression Anxiety Stress Scales 21[31] was used to assess severity of symptoms of depression, anxiety, and stress. This is a self-report scale that measures current state or change over time of depression, anxiety, and stress and can discriminate between these three types of emotional disturbances.[31]

PTSD Checklist for DSM-5[32] was used to assess the 20 symptoms of PTSD listed in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). This measure is used to assess for severity of symptoms and change in symptoms over time, as well as screening and provisional diagnosis of PTSD.[32]

The Trauma Quality of Life (TQoL) measure was used to assess domains unique to quality of life for injured patients, including emotional well-being, functional engagement, recovery and resilience, peritraumatic experience, and physical well-being.[33] This is a 59-item measure that is scored on a Likert scale, with a higher score indicating a higher quality of life.[33]

The Alcohol Use Disorders Identification Test-Concise (AUDIT-C) was used to identify those with active alcohol abuse disorders or those that actively engage in hazardous drinking which may affect clinical outcomes.[34] This is a three-question self-report measure used to screen for drinking behaviors that are potentially or currently harmful to health but does not diagnose alcohol dependence.[34]

The Brief Pain Inventory-Short Form was used to evaluate pain severity and its impact on daily functioning.[35] There are two main components, the pain intensity scale based upon a numerical pain scale 0 to 10 and a pain interference scale that evaluates how pain affects activities of daily living.[35]

The Connor Davidson Resilience Scale (CD-RISC)[36] was used to measure psychological resilience in the face of adversity. This is a 25-item measure that focus on emotional regulation, problem-solving skills, and maintaining a positive outlook under pressure on a scale of 0 to 4, with the higher the score, the greater the resilience.[36]

Life Events Checklist (LEC) was used to tabulate lifetime past (preinjury event) exposure to 17 potentially traumatic events and the degree of that exposure that could lead to PTSD.[37] This measure was used to identify exposure to potentially traumatic events in order to facilitate additional assessment and treatment for PTSD symptoms.[37]

Groups (ketamine vs. placebo) were compared with evaluate demographic differences using t-tests and χ^2 tests where applicable. Linear mixed effects models were used to evaluate group differences of each outcome over time with group time fixed effects and the patient as random effect. Linear regression was used to evaluate the relationship between groups and baseline pain and mental health outcomes at each follow-up.

RESULTS

There were 44 subjects in the ketamine group and 38 in the placebo group at baseline. There were no group differences in age, sex, ISS, mechanism of injury (MOI), risk for depression or PTSD on the ITSS, and trauma exposure (measured via the LEC) at baseline, 1 month, 3 months, or 6 months (Table 1).[38] In addition, the two groups were similarly resilient across all study timepoints (measured by the CD-RISC).

Results of the linear mixed effects models indicated patients in the ketamine group had significantly less overall PTSD symptoms at 6 months ($p < 0.05$) (Fig. 1), specifically reexperiencing symptoms which were significantly less in the ketamine group starting at 3 months ($p < 0.05$) and continuing to 6 months ($p < 0.05$), and significantly less anxiety symptom severity at 6 months ($p < 0.05$) (Fig. 2). Over time, pain severity and pain interference decreased ($p < 0.001$) (Fig. 3) and TQOL subscale scores increased ($p < 0.001$), but were not significantly different between groups (p's > 0.05) (Fig. 4). Finally, there were no interactions of group and baseline pain related to outcomes at follow-up timepoints (p's > 0.05); however, in both groups, baseline pain predicted PTSD symptoms, anxiety, depression, and stress at one month (p's < 0.02) but not at 3 months and 6 months (p's > 0.05).

DISCUSSION

The purpose of this study was to evaluate the efficacy of ketamine versus placebo on patient reported quality of life measures following severe injury in a randomized controlled trial. This is highly relevant in this population, with chronic pain and mental health outcomes impacting quality of life following injury. While utilization of ketamine, as previously reported in our own research,[8,9,29] did not impact acute or chronic pain outcomes in this study, there are surprising results on mental health outcomes. Overall, PTSD and anxiety symptom severity were significantly lower at six months following injury for those in the ketamine group, but ketamine did not impact depression, pain, or overall trauma specific quality of life. This is the first study that has shown promise that early administration of ketamine may work to prevent anxiety-related mental health sequalae following injury.

One of the most prominent models of the development of PTSD is based on conditioned fear learning principles.[39,40] According to this model, first, symptoms of PTSD are developed through fear conditioning as the cues or contexts associated with the trauma lead to a fear response. Second, the conditioned fear response is maintained through difficulties extinguishing this conditioned response or learning that the cues and contexts associated with the traumatic event are likely now safe and do not warrant a fear response. Because of the distress associated with

© 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

TABLE 1. Demographics, Risk for Depression and PTSD (ITTS), and Trauma Exposure (LEC) at Baseline, 1-, 3-, and 6-Month Timepoints

Baseline			
Variable	**Ketamine, n = 44**	**Placebo, n = 38**	***p***
Age, mean (SD)	33.7 (14.6)	35.9 (13.4)	0.5
Males, n (%)	27 (61%)	26 (68%)	0.5
ISS, mean (SD)	24.6 (7.4)	25.35 (9.4)	0.7
Mechanism of injury, n (%)			0.2
GSW	5 (11%)	8 (21%)	
MVC	18 (41%)	15 (39%)	
MCC	6 (14%)	7 (18%)	
Fall	9 (20%)	1 (2.6%)	
Other	6 (13.6%)	7 (18.4%)	
Baseline risk of depression (ITSS) ≥ 2 n (%)	23 (53%)	18 (47%)	>0.9
Baseline risk of PTSD (ITSS) ≥ 2 n (%)	21 (47.7%)	21 (55%)	0.4
Baseline trauma exposure (LEC)* Mean (SD)	11.3 (9.6)	9.7 (9.6)	0.5
1 month			
Variable	**Ketamine, n = 36**	**Placebo, n = 33**	***p***
Age, mean (SD)	35.1 (14.1)	35.5 (13.3)	>0.9
Males, n (%)	22 (61%)	22 (66.7%)	0.6
ISS, mean (SD)	23.9 (6.9)	26.1 (18.8, 29.3)	0.96
Mechanism of injury			0.09
GSW	4 (11.1%)	7 (21.2%)	
MVC	15 (41.6%)	13 (39%)	
MCC	4 (11.1%)	7 (19.4%)	
Fall	9 (25%)	1 (3%)	
Other	4 (11.1%)	5 (15%)	
Baseline risk of depression (ITSS) ≥ 2, n (%)	19 (52.7%)	17 (51.5%)	0.8
Baseline risk of PTSD (ITSS) ≥ 2, n (%)	16 (44.4%)	19 (57.6%)	0.4
1 month Trauma exposure (LEC)* Mean (SD)	3.36 (6.03)	5.58 (9.51)	0.3
3 months			
Variable	**Ketamine, n = 27**	**Placebo, n = 28**	***p***
Age, man (SD)	35.1 (15)	37.4 (14.9)	0.6
Males, n (%)	16 (59%)	18 (64%)	0.7
ISS, mean (SD)	23.9 (7.2)	24.6 (7.62)	0.7
Mechanism of Injury			0.3
GSW	2 (7.4%)	5 (18%)	
MVC	11 (41%)	10 (36%)	
MCC	5 (11.9%)	7 (19.4%)	
Fall	6 (22%)	1 (3.6%)	
Other	3 (11.1%)	5 (18%)	
Baseline risk of depression (ITSS) ≥ 2 n (%)	14 (51.8%)	14 (50%)	>0.9
Baseline Risk of PTSD (ITSS) ≥ 2 n (%)	12 (44.4%)	15 (53.6%)	0.9
3 month trauma exposure (LEC),* mean (SD)	5.59(10.2)	3.14(7.03)	0.3

Continued next page

TABLE 1. *(Continued)*

6 Months			
Variable	**Ketamine, n = 26**	**Placebo, n = 24**	***p***
Age, mean (SD)	33 (13.4)	36.9 (14.9)	0.3
Males, n (%)	18 (69%)	15 (63%)	0.6
ISS, mean (SD)	24.6 (7.5)	26.1 (10.7)	0.6
Mechanism of injury			0.08
GSW	3 (12%)	5 (21%)	
MVC	8 (31%)	8 (33%)	
MCC	5 (11.9%)	6 (25.0%)	
Fall	7 (16.7%)	1 (2.8%)	
Other	2 (7.7%)	4 (16.7%)	
Baseline risk of depression (ITSS) ≥ 2 n (%)	13 (50%)	12 (50%)	0.8
Baseline risk of PTSD (ITSS) ≥ 2 n (%)	40 (95.2%)	34 (94.4%)	0.2
6 month trauma exposure (LEC)* Mean (SD)	5.85 (10.51)	2.58 (5.01)	0.2

*Weighted total score (LEC).[38]

repeatedly activating the fear response, individuals with PTSD tend to avoid cues and context that remind them of the trauma, which further prevents learning that those contexts are safe (e.g., extinction learning). For PTSD symptoms to abate, the association of triggers and fear needs to be extinguished, which is known as fear extinction. Based on this model, and the known effects of ketamine on NMDA receptors in regions key for fear conditioning and extinction, some researchers have investigated the use of ketamine as an intervention for PTSD.[21,22] Ketamine appears to impact the hippocampus (among other brain regions), which is vital for memory formation.[41] Given our results that specifically reexperiencing symptoms (i.e., nightmares, flashbacks) are significantly reduced in those with ketamine intervention, it is

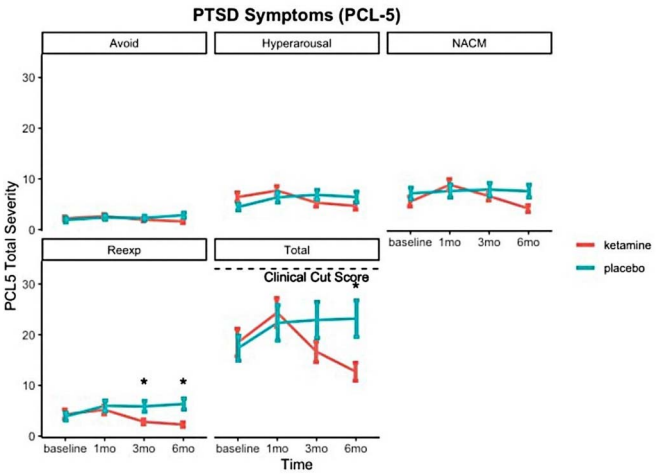

Figure 1. PTSD Symptoms (PCL-5) (error bar depicting standard error).

© 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

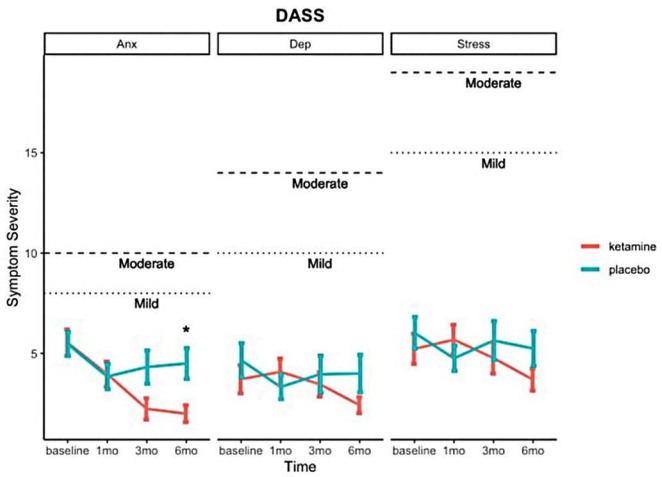

Figure 2. Anxiety, Depression, Stress (Depression Anxiety Stress Scales 21).

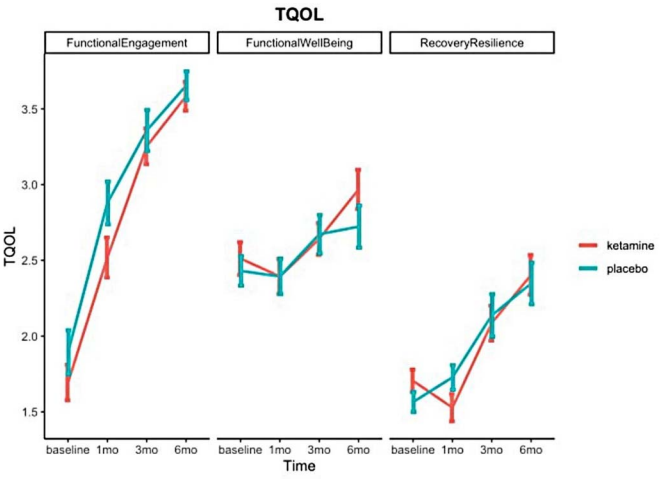

Figure 4. Quality of life (TQOL).

possible that the mechanism of action related to PTSD for ketamine maybe found partly in this brain region.

It is important to note that a review of the small number of studies[26] in which ketamine has been administered peritrauma indicated mixed findings, with some studies showing that ketamine reduced PTSD symptoms at follow-up, whereas others found that those administered ketamine during the peritrauma period had worse or similar levels of PTSD severity. It should be acknowledged that this literature is small, and studies vary on the nature of the comparison group (e.g., placebo, opioids, other), the rigor of the research methods (RCT vs. observational trial), timing of ketamine administration, and mechanism and severity of injury. Nonetheless, future research should include rigorous evaluation of ketamine on PTSD and anxiety, which a specific focus on understanding the underlying mechanisms of action to further preventative intervention.

While the results of the present study are quite promising and suggest that acute ketamine administration has an impact on long-term mental health of injured patients, there are limitations important to note. First, the sample size is relatively small and

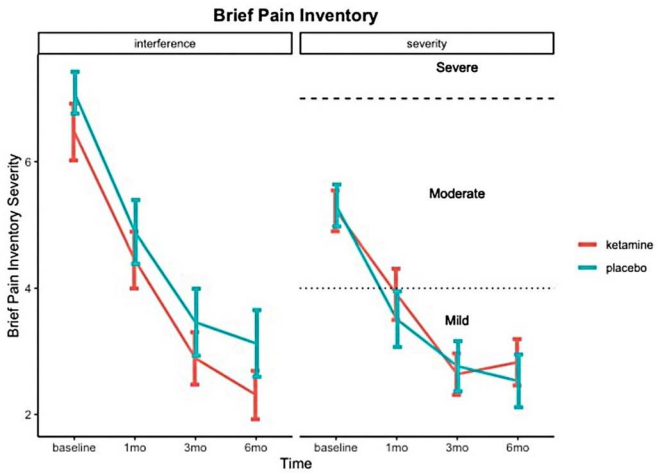

Figure 3. Pain (Brief Pain Inventory).

there was attrition across time, yet the demographic similarities in the samples did not change, suggesting that the differences between the two groups were minimized. Second, the study was focused on those with the most severe injuries, as the first aim of the study was to evaluate the impact of ketamine on pain and use of opioid medication in-hospital. A new study is necessary to specifically target the impact that ketamine has on those at risk for poor mental health after injury, to clarify its role in the development of non-remitting PTSD or anxiety symptoms, and for which patients and under which circumstances it may be beneficial. Third, pre-trauma history of mental health diagnoses was not collected. This could have provided additional understanding of how prior mental health could affect quality of life outcomes after ketamine utilization. Fourth, information on mental health interventions was not collected. This information could have potentially provided information on other interventions mitigating mental health outcomes. Finally, further details on cultural consideration and social determinants of health were not collected. This information could provide additional insight into how these variables would affect quality of life outcomes both with and without ketamine utilization.

Even with limitations, the findings of the present study provide promising research that ketamine may serve to function as a preventative treatment for PTSD and anxiety following injury. Ketamine use in the peritrauma period, possibly paired with additional interventions such as non-pharmacological intervention which have shown benefit in other samples with PTSD,[41] could have dual benefit on pain and mental health long-term, helping to address poor quality of life prevalent in traumatically injured patients.

Conflicts of interest

All JTACS Disclosure forms have been supplied and are provided as supplemental digital content (http://links.lww.com/TA/E953).

Author Contributions
Literature search: CMT
Study design: CMT
Data collection: CMT, MMW
Data analysis: CT
Data interpretation: CMT, CT, TDC, TC, WJP
Writing: CMT, CT, TDC, TC, MMW
Critical revision: CMT, CT, TDC, TC, MMW, WJP

© 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.

ACKNOWLEDGMENTS

Thank you Isabel Johnson and Ariel Berry for the successful recruitment and retention of the subjects involved in this study.

REFERENCES

1. Trevino CM, Essig B, deRoon-Cassini T, Brasel K. Chronic pain at 4 months in hospitalized trauma patients: incidence and life interference. *J Trauma Nurs*. 2012;19(3):154–159.
2. Trevino C, Harl F, Deroon-Cassini T, Brasel K, Litwack K. Predictors of chronic pain in traumatically injured hospitalized adult patients. *J Trauma Nurs*. 2014;21(2):50–56.
3. Trevino CM, deRoon-Cassini T, Brasel K. Does opiate use in traumatically injured individuals worsen pain and psychological outcomes? *J Pain*. 2013;14(4):424–430.
4. Jennings PA, Cameron P, Bernard S. Ketamine as an analgesic in the prehospital setting: a systematic review. *Acta Anaesthesiol Scand*. 2011;55(6): 638–643.
5. Miller JP, Schauer SG, Ganem VJ, Bebarta VS. Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial. *Am J Emerg Med*. 2015;33(3):402–408.
6. Walters MK, Farhat J, Bischoff J, Foss M, Evans C. Ketamine as an analgesic adjuvant in adult trauma intensive care unit patients with rib fracture. *Ann Pharmacother*. 2018;52(9):849–854.
7. Klugh JM, Puzio TJ, Wandling MW, Guy-Frank CJ, Green C, Sergot PB, et al. Ketamine for acute pain after trauma: a pragmatic, randomized clinical trial. *J Trauma Acute Care Surg*. 2024;97(4):514–519.
8. Carver TW, Kugler NW, Juul J, Peppard WJ, Drescher KM, Somberg L, et al. Ketamine infusion for pain control in adult patients with multiple rib fractures: results of a randomized control trial. *J Trauma Acute Care Surg*. 2019;86(2):181–188.
9. Kugler NW, Carver TW, Juul J, Peppard WJ, Boyle K, Drescher KM, et al. Ketamine infusion for pain control in elderly patients with multiple rib fractures: results of a randomized controlled trial. *J Trauma Acute Care Surg*. 2019;87(5):1181–1188.
10. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. *Cochrane Database Syst Rev.* 2013;2013(7):CD008307.
11. Jennings PA, Cameron P, Bernard S, Walker T, Jolley D, Fitzgerald M, et al. Long-term pain prevalence and health-related quality of life outcomes for patients enrolled in a ketamine versus morphine for prehospital traumatic pain randomised controlled trial. *Emerg Med J*. 2014;31(10):840–843.
12. Peyton PJ, Wu C, Jacobson T, Hogg M, Zia F, Leslie K. The effect of a perioperative ketamine infusion on the incidence of chronic postsurgical pain-a pilot study. *Anaesth Intensive Care*. 2017;45(4):459–465.
13. Haagsma JA, Polinder S, Olff M, Toet H, Bonsel GJ, van Beeck EF. Posttraumatic stress symptoms and health-related quality of life: a two year follow up study of injury treated at the emergency department. *BMC Psychiatry*. 2012;12:1.
14. Tsapakis EM, Travis MJ. Glutamate and psychiatric disorders. *Advances in Psychiatric Treatment*. 2002;8(3):189–197.
15. Burgos-Robles A, Vidal-Gonzalez I, Santini E, Quirk GJ. Consolidation of fear extinction requires NMDA receptor-dependent bursting in the ventromedial prefrontal cortex. *Neuron*. 2007;53(6):871–880.
16. Davis M. NMDA receptors and fear extinction: implications for cognitive behavioral therapy. *Dialogues Clin Neurosci*. 2011;13(4):463–474.
17. Chen J, Fang Z, Zhang X, Zheng Y, Chen Z. How fear memory is updated: from reconsolidation to extinction? *Neurosci Bull*. 2025;41(6):1054–1084.
18. Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB, et al. Ketamine and other NMDA antagonists: early clinical trials and possible mechanisms in depression. *Am J Psychiatry*. 2015;172(10):950–966.
19. Davis M, Myers KM, Chhatwal J, Ressler KJ. Pharmacological treatments that facilitate extinction of fear: relevance to psychotherapy. *NeuroRx*. 2006;3(1):82–96.
20. Heresco-Levy U, Kremer I, Javitt DC, Goichman R, Reshef A, Blanaru M, et al. Pilot-controlled trial of D-cycloserine for the treatment of posttraumatic stress disorder. *Int J Neuropsychopharmacol*. 2002;5(4):301–307.
21. Feder A, Parides MK, Murrough JW, Am Perez, Morgan JE, Saxena S, et al. Efficacy of intravenous ketamine for treatment of chronic posttraumatic stress disorder: a randomized clinical trial. *JAMA. Psychiatry*. 2014;71:681–688.
22. Feder A, Costi S, Rutter SB, Collins AB, Govindarajulu U, Jha MK, et al. A randomized controlled trial of repeated ketamine administration for chronic posttraumatic stress disorder. *Am J Psychiatry*. 2021;178(2):193–202.
23. McGhee LL, Maani CV, Garza TH, Gaylord KM, Black IH. The correlation between ketamine and posttraumatic stress disorder in burned service members. *J Trauma*. 2008;64(2 Suppl):S195–S198.
24. Du R, Han R, Niu K, Xu J, Zhao Z, Lu G, et al. The multivariate effect of ketamine on PTSD: systematic review and Meta-analysis. *Front Psych*. 2022;13:813103.
25. Tully JL, Dahlén AD, Haggarty CJ, Schiöth HB, Brooks S. Ketamine treatment for refractory anxiety: a systematic review. *Br J Clin Pharmacol*. 2022;88(10):4412–4426.
26. Brodeur J, Mancine R, Ley A, Magen J. Does Peritraumatic ketamine reduce symptoms of post-traumatic stress disorder? *Spartan Med Res J*. 2020;5(2): 17647.
27. Serafini G, Howland RH, Rovedi F, Girardi P, Amore M. The role of ketamine in treatment-resistant depression: a systematic review. *Curr Neuropharmacol*. 2014;12(5):444–461.
28. Voute M, Lambert C, Pereira B, Pickering G. Assessment of initial depressive state and pain relief with ketamine in patients with chronic refractory pain. *JAMA Netw Open*. 2023;6(5):e2314406.
29. Carver TW, Peppard WJ, Gellings JA, Thapa R, Trevino C, Mantz-Wichman M, Peschman JR, Szabo A, Yang Y, Schroeder ME, Milia DJ, Elegbede AF, de Moya MA, de Roon-Cassini TA. Ketamine infusion for pain control in severely injured patients: results of a randomized controlled trial. *J Trauma Acute Care Surg*. 2025;98(6):858–866.
30. Hunt JC, Chesney SA, Brasel K, deRoon-Cassini TA. Six-month follow-up of the injured trauma survivor screen: clinical implications and future directions. *J Trauma Acute Care Surg*. 2018;85(2):263–270.
31. Lovibond SH, Lovibond PF. *Manual for the Depression Anxiety Stress Scales*. 2nd. ed. Sydney: Psychology Foundation; 1995.
32. Blevins CA, Weathers FW, Davis MT, Witte TK, Domino JL. The posttraumatic stress disorder checklist for DSM-5 (PCL-5): development and initial psychometric evaluation. *J Trauma Stress*. 2015;28(6):489–498.
33. Wanner JP, deRoon-Cassini T, Kodadek L, Brasel K. Development of a trauma-specific quality-of-life measurement. *J Trauma Acute Care Surg*. 2015;79(2):275–281.
34. Bush K, Kivlahan DR, McDonell MB, Fihn SD, Bradley KA. for the ambulatory care quality improvement project (ACQUIP). The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. *Arch Intern Med*. 1998;158(16):1789–1795.
35. Cleeland CS. Brief pain inventory short form (BPI-SF) [database record]. *APA PsycTests*. 1991. doi:10.1037/t04175-000.
36. Connor KM, Davidson JRT. Connor–Davidson Resilience Scale [Database record]. *APA PsycTests*. 2003. doi:10.1037/t06346-000.
37. Gray MJ, Litz BT, Hsu JL, Lombardo TW. Psychometric properties of the life events checklist. *Assessment*. 2004;11(4):330–341.
38. Weis CN, Webb EK, Stevens SK, Larson CL, deRoon-Cassini TA. Scoring the life events checklist: comparison of three scoring methods. *Psychol Trauma*. 2022;14(4):714–720.
39. Girgenti MJ, Ghosal S, LoPresto D, Taylor JR, Duman RS. Ketamine accelerates fear extinction via mTORC1 signaling. *Neurobiol Dis*. 2017;100:1–8.
40. Orsini CA, Maren S. Neural and cellular mechanisms of fear and extinction memory formation. *Neurosci Biobehav Rev*. 2012;36(7):1773–1802.
41. Duek O, Korem N, Li Y, et al. Long term structural and functional neural changes following a single infusion of ketamine in PTSD. *Neuropsychopharmacology*. 2023;48(11):1648–1658.

© 2025 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2025 Wolters Kluwer Health, Inc. Unauthorized reproduction of this article is prohibited.