Pain Medicine 2013; 14: 1088–1100
Wiley Periodicals, Inc.

ACUTE PAIN & PERIOPERATIVE PAIN SECTION

Original Research Article

Effects of Low-Dose IV Ketamine on Peripheral and Central Pain from Major Limb Injuries Sustained in Combat

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Conflict of Interest/Disclosure: There are no perceived conflicts of interests by any authors related to the conduct of this research.

Funding: This work was supported by institutional funding and the Defense and Veterans Center for Integrative Pain Management.

Abstract

Objective. Examine response patterns to low-dose intravenous (IV) ketamine continuous infusions on multiple pain outcomes, and demonstrate effectiveness, safety, and tolerability of ketamine administration on general wards.

Design. Retrospective case series of consecutive patients given low-dose IV ketamine continuous infusions.

Setting. Walter Reed Army Medical Center, Washington, DC.

Patients. Nineteen eligible inpatients with neuropathic pain from major limb injuries sustained in combat with inadequate pain control from multimodal analgesia.

Interventions. A 3-day IV infusion of ketamine at doses ≤120 μg/kg/h.

Outcome Measures. Daily present (PPI), average (API), and worst (WPI) pain intensity (0–10), global pain relief (GPR) (1 "no relief" to 5 "complete relief"), daily assessments of adverse events, and daily opioid requirements measured during therapy.

Results. A significant reduction in PPI ($P < 0.001$) and improvement in GPR ($P = 0.031$) was noted over time. Higher baseline WPI (≥7; N = 14) was associated with a significant decrease in WPI ($P = 0.0388$), but lower baseline WPI (N = 5) was not. Significant mean percent decreases in PPI with higher baseline PPI (N = 8; $P = 0.0078$) and WPI with no phantom limb pain (PLP) (N = 10; $P = 0.0436$) were observed. Mean percent increase in overall GPR was better for those reporting GPR scores ≤3 (N = 13) in the first 24 hours of therapy ($P = 0.0153$). While not significant, mean opioid requirement (IV morphine equivalents) decreased from 129.9 mgs ± 137.3 on day 1 to 112.14 ± 86.3 24 hours after therapy.

Conclusions. Low-dose ketamine infusions for complex combat injury pain were safe and effective, and demonstrated response patterns over time and by baseline pain score stratification and presence or absence of PLP.

Key Words. Acute Pain; Ketamine; Chronic Pain

Introduction

Ketamine, classified as a dissociative anesthetic, has been used for more than 40 years for procedural sedation and surgical anesthesia. Growing interest in this agent, as an adjunct analgesic for both acute and chronic pain, centers on its unique pharmacological properties [1–4]. Specifically, S(+)-ketamine exerts N-methyl-D-aspartate (NMDA) antagonist effects from noncompetitive binding to the phencyclidine (PCP) site of the NMDA receptor [1,2]. This receptor binding counteracts the excitatory effects of glutamate brought about by nociceptive and neuropathic pain transmission, and interactions with other sites such as opioid receptors, muscarinic receptors, voltage-gated Ca++ channels, and monoamine receptors [5]. Consequently, ketamine is believed to minimize early windup associated with acute pain, suppress central sensitization, reduce the likelihood for NMDA receptor-mediated neuroplasticity, and perhaps prevent opioid hyperalgesia [6–9]. Its widespread use is tempered by the psychomimetic effects associated with NMDA receptor antagonists, but these effects are typically seen with higher anesthetic doses and infrequently with analgesic doses or low doses of ketamine [10,11].

Low-dose ketamine has been routinely administered as part of multimodal analgesia for acute and chronic pain for injured service members in the Afghanistan and Iraq wars sustaining major polytrauma including multiple limb trauma and amputations. At Walter Reed Army Medical Center (WRAMC—now closed), Washington, DC, and the newly established Walter Reed National Military Medical Center (WRNMMC), Bethesda, MD, low-dose ketamine infusion was often added to multimodal analgesic regimens to maximize analgesia in particularly challenging pain patients. Combat-injured service members who require multiple wound care procedures, residual limb revisions, and limb salvage operations for mangled limbs or those with persistent pain from major limb trauma who are refractory to multimodal analgesic treatments may receive low-dose ketamine as another therapeutic option. Few studies have systematically evaluated the short-term outcomes associated with low-dose ketamine infusions to treat neuropathic pain from major limb injuries sustained in combat. The primary aim of this investigation was to examine patterns in short-term patient-reported pain outcomes to continuous low-dose intravenous (IV) ketamine infusions added to individualized standard multimodal analgesia regimens in a cohort of combat wounded with major limb injuries experiencing neuropathic pain. A secondary aim was to demonstrate the effectiveness, safety, and tolerability of continuous low-dose IV ketamine (doses of 120 mcg/kg/h or less) over 3 consecutive days on general care wards.

Methods

A retrospective review of hospital and Acute Pain Service (APS) records was conducted on a cohort of 19 hospitalized combat wounded with major limb trauma experiencing acute and chronic pain with a component of neuropathic pain. All patients were treated in the context of usual care with outcomes collected on response to therapy. The study was approval by the WRAMC, Department of Clinical Investigation, Human Use Committee, and met the criteria for waiver of informed consent; however, only limited data collection procedures were allowed as part of this study. As such, patient electronic medical records were only followed for the duration and day after the treatment. A confounding variable in the study was that nine (47.4%) had a surgical procedure either before or after receiving the ketamine infusion. All research procedures were in accordance and compliance with the Health Insurance Portability and Accountability Act regulations and WRAMC's policies and guidelines for the protection of human subjects.

Sample and Setting

Patients who were part of this case series were hospitalized patients at the former WRAMC who were currently

being followed by the APS. Because this was a descriptive study examining trends in pain outcomes, a power analysis was not conducted a priori to determine the sample size. Data from 19 patients were available to investigators for analyses.

Study patients were consecutively selected after receiving continuous IV low-dose ketamine infusion when conventional therapy with multimodal analgesia including opioids, nonopioids, adjuvant analgesics, and regional anesthesia techniques were not effectively controlling episodes of acute pain and chronic persistent pain as evaluated by the APS attending physician. Patients who received low-dose IV ketamine infusions were identified by the APS as appropriate candidates based on eligibility criteria that included: 1) major limb trauma to one or more extremities sustained in combat in the previous Iraq and current Afghanistan wars; 2) presence of moderate to severe pain that was consistently refractory to standard pain management protocols. This was defined by regular documented pain intensity levels of >4 on an 11-point (0–10) numeric rating scale (NRS); 3) no evidence of cognitive or short-term memory impairment from traumatic brain injury (TBI) as documented in the medical record; 4) ability to interpret and report pain outcomes as determined by the APS; and 5) diagnosis of neuropathic pain confirmed by the APS physician by the presence of dysesthesia and/or allodynia. Eligible patients defined by the earlier criteria also included those who had surgical procedures prior to ketamine therapy or were anticipated to have surgery following ketamine therapy.

For the first 4 hours of therapy, the treatment took place in areas with available monitoring equipment and one-to-one nursing staffing (e.g., critical care units or postanesthesia care unit). Patients were then transferred to general care wards for the remaining 3-day duration of low-dose IV ketamine infusion.

Study Outcomes

Levels of pain intensity were collected daily prior to and during the ketamine infusion therapy. An 11-point NRS with 0 indicating “no pain” and 10 indicating “pain as bad as you can imagine” was used to measure pain right now (present pain intensity—PPI), average (usual) pain intensity (API) over the last 24 hours, worst pain intensity (WPI) over the last 24 hours, and least pain intensity (LPI) over the last 24 hours. These dimensions of pain intensity using the NRS and anchors are similar to the Brief Pain Inventory measures for pain intensity, which have been validated in studies of acute and chronic pain, and hospitalized patients [12,13].

Global pain relief (GPR) was reported using a 5-point categorical pain relief scale; 1 = no relief, 2 = slight relief, 3 = moderate relief, 4 = good relief, 5 = complete relief; this scale has also been validated in pain-related research [14]. Overall internal consistency reliability (Cronbach’s alpha) across four time points with our patient cohort was 0.71, which is above the acceptable threshold of 0.70 for limited item sets [15].

For each 24-hour period of ketamine infusion therapy, the amount of scheduled and as needed opioid analgesics consumed was recorded. Daily requirements were converted to IV morphine equivalents for each 24-hour period during therapy. All patients were assessed daily for eight possible types of adverse events including sedation, nausea and/or vomiting, cardiovascular effects (e.g., hypotension, tachycardia, etc.), hallucinations, night mares, vivid dreams, nystagmus, and allergic reactions. Additionally, investigators and clinical staff observed patients for any unusual episodes or adverse effects. Daily assessment ratings were obtained using a sedation scale with the following rating categories: alert, drowsy, dosing intermittently, sleeping but awakens only when aroused, and sleeping with difficulty arousing. Agreement for sedation level ratings was confirmed between at least two of the APS anesthesiologists or research nurses.

Study Procedures

All patients were evaluated for a component of neuropathic pain and the presence of phantom pains (defined by pain and not simply sensations) by the APS. At the start of the ketamine infusion (day 0), PPI and WPI over the past 24 hours were documented. Ketamine doses were initiated at 120 mcg/kg/h, except for the first patient who started at a lower dose, 60 mcg/kg/min. This patient was treated cautiously because of concerns regarding his borderline hemodynamic status. The starting dose for another patient (no. 13) was 100 mcg/kg/h for the same concerns. The infusion was initiated by the APS research nurse, and patients were closely monitored using standard American Society of Anesthesiologists monitoring criteria with one-to-one nursing care for the first 4 hours of therapy as an internal safeguard against any immediate adverse events. Patients were then transferred to a general care ward where nurses were familiar with the ketamine protocol and monitoring procedures, which included vital signs at least every 2–4 hours, pulse oximetry, sedation levels, and frequent observations (every 1–2 hours) for any adverse outcomes. At each 24-hour interval (during morning hours), the APS research nurse remained at the bedside for 1 hour and collected patient-reported outcomes for PPI, API, WPI, and LPI over the past 24 hours, and GPR. Opioid requirements for the 24-hour period were totaled, including opioids administered on a regular scheduled and as needed. Patients were observed for any adverse events, and any documentation of these in the patient’s medical record was recorded.

The APS visited all patients at least twice a day, and APS anesthesiologists and research nurses were available for any issues 24 hours a day. Dose adjustments were made for three patients. The first patient remained on 60 mcg/kg/h for the duration of therapy, although he had a measurable response with day 2 and 3 PPI, API, and WPI 4 or

less. Patient 2 started at 120 mcg/kg/h, but was decreased to 60 mcg/kg/h for the 2nd and 3rd infusion due to nausea and vomiting. Patient 13 remained on 100 mcg/kg/h for the entire treatment period. This patient reported hallucinations on day 1, which was a one-time episode described as not distressing to him, and subsequently, he had no other reportable adverse events during therapy.

Statistical Analyses

Descriptive statistics (e.g., frequencies means, standard deviations [SD], medians, and ranges) were used to quantify demographic and clinical characteristics for study participants, and treatment outcomes measured over the 3-day time period. Linear mixed models were used to assess significant overall linear trends during the course of treatment for pain intensity levels and GPR. Mixed-effects modeling is appropriate for analyzing continuous repeated measures outcomes with non-normally distributed datasets. For this study, it allowed the analyses of levels of pain variables to detect differences in response trends over time based on pre- and early treatment pain intensity and global relief scores as well as with the presence or absence of phantom pain. This statistical method is also ideal for testing differences in samples and subsets of samples with variability in measures or non-normally distributed data sets that might otherwise violate assumptions required for specific statistical tests. Both random intercept and slope parameters were included in these models. Likelihood ratio tests were used to evaluate significant linear trends over time. An unstructured covariance matrix was assumed for all three models: present pain, worst pain, and GPR. Least square mean (LSM) estimates of outcomes, generated from mixed-effect models and closely approximating raw means, are reported along with standard errors (SEs), confidence intervals, and level of statistical significance. Linear models were constructed using SAS version 9.1 (SAS Institute Inc., Cary, NC, USA). Nonparametric statistics, e.g., Mann–Whitney *U*, were used to compare mean ranks for percent change in outcome measures from baseline and early treatment to the end of therapy between subsets of patients. The Wilcoxon signed-rank test was applied to detect differences in percent change in pain outcomes and within-subject changes over time for daily opioid requirements. Nonparametric tests were performed with SPSS version 19 (SPSS Inc., Chicago, IL, USA) and SAS version 9.1.

Results

Demographic and injury-related characteristics for the sample are provided in Table 1. The mean age for this all male cohort was 24.95 years ± 4.5 (range 18–37; median 25 years), and time from initial injury was 141.0 days ± 223.4 (range 19–852; median 39.5 days). Eleven (57.9%) had an amputation with 10 patients having experienced a traumatic or surgical amputation of one limb, and one patient having two limbs involved. Nine (47.4%) of patients reported experiencing phantom limb pain (PLP).

Table 1 Sample characteristics and clinical information

Variables	Mean and Standard Deviation (SD) Median
Age (mean and SD)	24.95 ± 4.5 (range 18–37 years)
(median)	25 years
Days from initial injury (mean and SD)	141.0 ± 223.4 (range 19–852 days)
(median)	39.5 days
	N (Frequency)
Sex (male)	19 (100%)
Type of limb(s) injuries*	
Mangled limb	7 (36.8%)
Traumatic/Surgical amputation	11 (57.9%)
One limb amputated	10 (52.6%)
Two limbs amputated	1 (5.3%)
Crush injury	2 (10.5%)
Fracture	11 (57.9%)
Mechanism of injury	
Improvised explosive device (IED)	12 (63.2%)
Rocket propelled grenade (RPG)	2 (10.5%)
Multivehicle accident (MVA)	2 (10.5%)
Gunshot	2 (10.5%)
Suicide bomber	1 (5.3%)
Other	1 (5.3%)
Pain location(s)	
Extremity	13 (68.4%)
Stump	11 (57.9%)
Phantom (central pain)	9 (47.4%)
Number of peripheral nerve blocks (PNB) at the time of therapy	
One PNB	3 (15.8%)
Two PNBs	5 (26.3%)

* Represents injury type to more than one limb.

The mechanism of injury for the majority of patients was an improvised explosive device (12, 63.2%). The range for the mean number of adjuvant analgesic doses in the prior 24 hours assessed on each day (1–4, 24 hours after completing the ketamine treatment regimen) was approximately 5.0 ± 1.9 to 5.3 ± 2.7 (range 2–15). These included more commonly multimodal analgesia regimens with combinations of anticonvulsants (e.g., gabapentin or pregabalin), tricyclic antidepressants, serotonin–norepinephrine reuptake inhibitors, acetaminophen, and nonsteroidal anti-inflammatory drugs. Eight patients at the time of therapy had been receiving continuous peripheral nerve blocks. Despite these aggressive analgesic approaches, these patients continued to complain on poorly controlled pain and were considered appropriate candidates for low-dose IV ketamine infusions.

Table 2 Descriptive statistics (raw means and standard deviations) for pain outcomes

Variables	All Patients N = 19	Stratification of Outcomes			
Present pain intensity (PPI)		Baseline <7 N = 11	Baseline ≥7 N = 8	No Phantom Limb Pain N = 10	Phantom Limb Pain N = 9
Baseline day 0	5.92 ± 1.8	4.73 ± 1.3	7.56 ± 1.1	5.95 ± 1.6	5.89 ± 2.1
Day 1	6.37 ± 2.9	5.64 ± 2.7	7.38 ± 2.9	5.70 ± 2.8	7.11 ± 2.8
Day 2	4.16 ± 2.3	4.00 ± 2.4	4.38 ± 2.3	3.80 ± 2.5	4.56 ± 2.2
Day 3	3.74 ± 1.8	3.91 ± 1.8	3.50 ± 2.0	3.00 ± 1.7	4.56 ± 1.7
Worst pain intensity (WPI)		Baseline <7 N = 5	Baseline ≥7 N = 14		
Baseline day 0	7.58 ± 1.8	5.20 ± 0.8	8.43 ± 1.2	7.60 ± 1.8	7.56 ± 1.9
Day 1	7.00 ± 2.8	5.20 ± 3.1	7.64 ± 2.5	6.40 ± 2.9	7.67 ± 2.7
Day 2	6.47 ± 2.2	5.20 ± 2.4	6.93 ± 2.0	5.70 ± 2.2	7.33 ± 1.9
Day 3	6.37 ± 2.3	5.40 ± 2.6	6.71 ± 2.2	5.30 ± 2.1	7.56 ± 2.0
API					
Day 1	4.12 ± 1.9	nd	nd	3.9 ± 2.3	4.33 ± 1.5
Day 2	4.00 ± 1.6	nd	nd	4.0 ± 1.8	4.00 ± 1.4
Day 3	3.95 ± 1.7	nd	nd	3.2 ± 1.8	3.78 ± 1.4
LPI					
Day 1	2.47 ± 2.1	nd	nd	3.10 ± 2.3	1.78 ± 1.8
Day 2	2.74 ± 2.0	nd	nd	3.00 ± 2.3	2.44 ± 1.7
Day 3	2.32 ± 1.5	nd	nd	3.20 ± 1.6	2.44 ± 1.5
GPR (1 No Relief to 5 Complete Relief)		GPR ≤3 on day 1 N = 13	GPR >3 on day 1 N = 6		
Day 1	2.95 ± 1.1	2.38 ± 0.8	4.17 ± 0.4	3.00 ± 1.1	2.89 ± 1.2
Day 2	3.37 ± 1.1	3.23 ± 0.9	3.61 ± 1.4	3.40 ± 0.8	3.33 ± 1.3
Day 3	3.53 ± 1.1	3.23 ± 1.1	4.17 ± 0.8	3.80 ± 1.0	3.22 ± 1.1
Day 4	3.63 ± 0.8	3.54 ± 0.9	3.83 ± 0.8	3.60 ± 1.0	3.67 ± 0.7

Baseline Day 0 = prior to initiating therapy; Day 1 = 24 hours after initiating therapy and before the 2nd infusion; Day 2 = 48 hours after initiating therapy and before the 3nd infusion; Day 3 = 72 hours after initiating therapy and the end of therapy; Day 4 = 24 hours after discontinuing the infusion.
API = average pain intensity; LPI = least pain intensity; nd = no baseline pain data collected.

All descriptive statistics (raw means and SD) for PPI, API, WPI, LPI, and GPR across the time points are reported in Table 2 for the entire sample (N = 19), and stratified by baseline levels for PPI and WPI over the past 24 hours and first 24 hour GPR scores, and the presence or absence of PLP for all variables. Baseline API in the prior 24 hours to initiating therapy was not collected due to some patients having procedures the day before enrollment with general anesthesia and/or sedating agents making it difficult to estimate an average pain level for the prior 24 hours. LSMs and SEs generated from mixed-effects modeling used to examine the patterns of response to low-dose IV ketamine therapy for PPI, WPI, and GPR are reported in association with the mixed-effects modeling analyses. These means that approximate the arithmetic (raw) means and SEs around the LSMs are described later for each pain outcome, except API, and examples of interpretations presented in Tables 3–5. Due to the variations in API, it was not possible to apply mixed-effects modeling to the data. Mean percent changes in all pain outcomes across the duration of therapy based on raw data were calculated and tested for differences (Table 6).

PPI

Parameter estimates for mixed-effects modeling for PPI for the entire sample (N = 19) were obtained, and are estimates of change by day (Table 3), and stratification by baseline PPI, <7 (N = 11) and ≥7 (N = 8) (Table 4), and the

Table 3 Mixed model parameters*—tests of fixed effects by day

	Parameter Estimate	SE	95% CI	*P* value
Model for PPI				
Intercept	6.06	0.41	5.20 to 6.92	<0.0001
Day	–0.87	0.20	–1.29 to –0.46	<0.001
Model for WPI				
Intercept	7.51	0.41	6.45 to 8.37	<0.0001
Day	–0.30	0.18	–0.69 to 0.08	0.113
Model for GPR				
Intercept	2.77	0.27	2.20 to 3.34	<0.0001
Day	0.21	0.09	0.02 to 0.40	0.031

* Interpretation of table content using PPI: Overall predicted PPI is 6.06 at baseline, and decreases by 0.87 by day, which is statistically significant.
Intercept = the overall mean estimate at baseline in the presence of adjusting covariate time points (days); Day = mean estimate for the slope of change across days for the parameter; SE = standard error; CI = confidence interval; PPI = present pain intensity; WPI = worst pain intensity; GPR = global pain relief.

presence (N = 9) or absence (N = 10) of phantom pain (Table 5). These estimates are presented for intercepts and "day," with intercept estimates representing an overall mean estimate of PPI at baseline, and "day" representing the change in outcome with each incremental day (Table 3). The model for PPI for all 19 patients showed a significant decrease in present pain over the course of therapy ($P < 0.001$). LSM estimates and SEs from baseline to the end of therapy reflected an overall reduction in PPI, despite a slight increase in day 1: LSMs from day 0 to day 3 were 5.95 ± 0.42, 5.89 ± 0.68, 4.16 ± 0.53, and 3.74 ± 0.42, respectively. When stratified by PPI baseline pain (<7 vs ≥ to 7), a significant decline in PPI over the course of therapy ($P < 0.0001$), and the differences in the incremental changes in PPI over time between baseline pain groups was significant ($P = 0.0078$) indicating the groups were dissimilar in how they responded and higher baseline pain may have led to a greater reduction in PPI outcomes (Table 4). LSMs and SEs from day 0 to day 3 for baseline pain <7 vs ≥ to 7 were 4.47 ± 0.33 vs 7.60 ± 0.38, 5.63 ± 0.91 vs 6.25 ± 1.07, 4.0 ± 0.72 vs 4.38 ± 0.84, and 3.91 ± 0.56 vs 3.50 ± 0.66, respectively. The patient cohort was also stratified according to the presence (N = 9) or absence (N = 10) of PLP. Table 5

Table 4 Mixed model parameters*—tests of fixed effects by day and baseline measure stratification

	Parameter Estimate	SE	95% CI	*P* value
Model for PPI				
Intercept	7.64	0.38	6.83 to 8.45	<0.0001
Day	–1.42	0.25	–1.96 to –0.89	<0.0001
BPPI <7 (N = 11)	–2.91	0.50	–3.97 to –1.85	<0.0001
BPPI ≥7 (N = 8)	ref			
Day by BPPI <7	1.01	0.33	0.30 to 1.7	<0.0078
Day by BPPI ≥7	ref			
Model for WPI				
Intercept	8.41	0.29	7.80 to 9.02	<0.0001
Day	–0.46	0.21	–0.90 to –0.03	0.0388
BWPI <7 (N = 5)	–3.22	0.57	–4.41 to –2.02	<0.0001
BWPI ≥7 (N = 14)	ref			
Day by BWPI <7	0.57	0.40	–0.28 to 1.42	0.1756
Day by BWPI ≥7				
Model for GPR				
Intercept	4.07	0.35	3.33 to 4.81	<0.0001
Day	–0.10	0.14	–0.40 to 0.20	0.4852
D1GPR ≤3 (N = 13)	–1.93	0.42	–2.82 to –1.03	<0.001
D1GPR >3 (N = 6)	ref			
Day by D1GPR ≤3	0.46	0.17	0.10 to 0.82	0.0153
Day by D1GPR >3	ref			

* Interpretation of table content for WPI by baseline worst pain intensity (BWPI): Overall predicted WPI in the BWPI ≥7 is 8.41, and decreases by 0.46 by day, which is statistically significant. Overall, predicted WPI in the BWPI <7 group is 5.19 (8.41 minus 3.22) and increases by 0.11 (–0.46 plus 0.57) per day, which is not statistically significant.
Intercept = the overall mean estimate at baseline in the presence of adjusting covariate time points (days); SE = standard error; CI = confidence interval; PPI = present pain intensity; BPPI = baseline present pain intensity; WPI = worst pain intensity; BWPI = baseline worst pain intensity; GPR = global pain relief; D1GPR = day 1 global pain relief score (24 hours after the first infusion) of treatment; ref = reference group.

Table 5 Mixed model parameters*—tests of fixed effects by day and no phantom limb pain (no PLP) (N = 10) and phantom limb pain (PLP) (N = 9)

	Parameter Estimate	SE	95% CI	*P* Value
Model for PPI				
Intercept	6.00	0.61	4.71 to 7.29	<0.0001
Day	–0.58	0.28	–1.17 to –0.004	0.0515
No PLP	0.10	0.84	–1.68 to 1.88	0.9065
PLP	ref			
Day by no PLP	–0.54	0.38	–1.35 to 0.27	0.178
Day by PLP	ref			
Model for WPI				
Intercept	7.50	0.61	5.21 to 8.71	<0.0001
Day	0.07	0.24	–0.30 to 0.75	0.7808
No PLP	0.02	0.85	–2.33 to 2.53	0.9806
PLP	ref			
Day by no PLP	–0.73	0.33	–1.54 to –0.08	0.0436
Day by PLP	ref			
Model for GPR				
Intercept	2.91	0.40	2.07 to 3.76	<0.0001
Day	0.23	0.13	–0.05 to 0.51	0.1042
No PLP	–0.29	0.55	–1.46 to 0.88	0.6028
PLP	ref			
Day by no PLP	–0.04	0.18	–0.43 to 0.35	0.8261
Day by PLP	ref			

* Interpretation of table content for GPR by no PLP and PLP: Overall predicted GPR in the PLP group is 2.91, and increases by 0.23 by day, which is not statistically significant. Overall, predicted GPR for the no PLP group is 2.62 (2.91 minus 0.29), and increases by 0.19 (0.23 minus 0.04) per day, which is not statistically significant.
Intercept = the overall mean estimate at baseline in the presence of adjusting covariate time points (days); SE = standard error; CI = confidence interval; PPI = present pain intensity; WPI = worst pain intensity; GPR = global pain relief.

demonstrates that there were no significant differences in how groups with and without phantom pain responded on the PPI outcome ($P = 0.965$) or by group over time ($P = 0.178$).

WPI

Similar mixed-effects modeling procedures were performed for WPI outcomes with parameter estimates of change by day (Table 3), baseline WPI stratification (Table 4), and the presence or absence of phantom (Table 5). Modeling for WPI for the entire group by day did not show statistically significant differences ($P = 0.113$) (Table 3). LSM estimates from baseline (day 0) to the end of therapy (day 3) were 7.58 ± 0.41, 7.0 ± 0.64, 6.47 ± 0.50, and 6.37 ± 0.53, respectively. The model for WPI based on stratification by baseline WPI (<7, N = 5 and ≥7, N = 14) did indicate a greater reduction in WPI overall for the higher baseline WPI group ($P < 0.001$) (Table 4). Over time, the groups did not responded differently to the treatment ($P = 0.1756$). LSMs at baseline to the end of therapy (day 3) for the lower baseline WPI group were 5.20 ± 0.49 to 5.4 ± 1.03, respectively, and for higher baseline WPI, the LSM dropped from 8.43 ± 0.29 to 6.71 ± 0.62. There was no overall group effect for WPI by patients reporting no PLP or PLP ($P = 0.9806$) (Table 5). Analyzing responses to treatment by day did, however, demonstrate the patients with no PLP had a significantly greater reduction on WPI scores over time ($P = 0.0436$) with LSMs deceasing from 7.40 ± 0.89 at baseline to 5.30 ± 0.65 at day 3, compared with the PLP group which increased from 6.92 ± 0.91 to 7.56 ± 0.69.

GPR

Table 2 provides the raw data for GPR and the numbers for group stratification based on day 1 scores as the first measurement of perception of relief was taken 24 hours after the infusion was started. The results of mixed-effects models with parameter estimates for intercept and day for GPR are provided in Table 3, and group stratification based on day 1 GPR in Table 4 and no PLP and PLP in Table 5. Overall, perceptions of GPR improved from day 1 to 24 hours after therapy, day 4 ($P = 0.031$) (Table 3). GPR LSM estimates between those with lower raw GPR ratings ≤3 (N = 13) on the scale of 1 "no relief" to 5 "complete relief" after the first 24 hours of therapy were significantly different from those with higher ratings >3 (N = 6) ($P < 0.001$), and the difference across time (day) by group

Table 6 Mean percent changes from baseline to end of therapy calculated from raw data (Table 2)

Present pain intensity (PPI) (NRS 0–10)	N	Mean Percent Change ± Standard Deviation	Direction	*Sig. *P* Value
Day 0 PPI <7	11	15.04 ± 40.10	↓	0.0078
Day 0 PPI 7 or >	8	53.71 ± 28.6	↓	
No PLP	10	44.54 ± 37.5	↓	0.1780
PLP	9	16.64 ± 39.4	↓	
Worst pain intensity (WPI) (NRS 0–10)				
Day 0 WPI <7	5	1.67 ± 43.4	↓	0.365
Day 0 WPI 7 or >	14	19.88 ± 25.5	↓	
No PLP	10	28.96 ± 24.6	↓	0.0436
PLP	9	–0.33 ± 31.0	↑	
Average pain intensity (API) (NRS 0–10)				
No PLP	10	5.93 ± 40.1	↓	0.178
PLP	9	–9.37 ± 35.3	↑	
Global pain relief (GPR) (1 no relief to 5 complete relief)				
Day 1 GPR ≤3	13	–29.87 ± 28.7	↑	0.0153
Day 1 GPR >3	6	7.50 ± 21.4	↓	
No PLP	10	–14.5 ± 34.3	↑	0.8261
PLP	9	–22.04 ± 29.6	↑	

* Statistical significance (*P* values) tests the differences in overall change over time including all time points.
NRS = numeric rating scale; PLP = phantom limb pain.
Comparisons using Wilcoxon signed-rank tests.

was also significant ($P = 0.0153$) (Table 4). LSMs derived from mixed-effects modeling increased in those with lower day 1 scores from 2.38 ± 0.19 on day 1 to 3.54 ± 0.23 on day 4, which was 24 hours after therapy was discontinued. LSMs decreased from 4.17 ± 0.28 to 3.83 ± 0.34 for patients who obtained a more favorable response after the first 24 hours of therapy. Table 5 reports the GPR parameter estimate. While there was a greater reduction in WPI for those with no PLP, there was no significant group effect for those experiencing PLP for perceptions of GPR ($P = 0.60$), and when analyzed across days of therapy, this was also not significant ($P = 0.83$).

Mean Percent Changes in Outcomes

Table 6 reports mean percent changes (±SD) calculated from baseline to the end of therapy with raw data from PPI and WPI based on pretreatment stratification of mild to moderate pain, <7, and severe pain, ≥7 and group stratification for day 1 pain relief scores to 24 hours after therapy. Mean percent change values for PPI, WPI, API, and GPR are also reported for those experiencing phantom pain. The direction of the average percent change is shown in Table 6 and represented in graphs (Figure 1). For PPI scores, the mean percent change reduction from baseline to the end of therapy was significantly greater for those experiencing higher baseline pain ≥7 ($P = 0.0078$), and no difference for the presence or absence of PLP ($P = 0.1780$). The reverse was true for WPI. There was no difference in mean percent change based on baseline WPI scores ($P = 0.365$), but patients without PLP experienced a higher mean percent decrease in WPI ($P = 0.0436$). Those without PLP also experienced a decreased change in API compared with those with PLP who reported an increase, but this was not statistically significant ($P = 0.178$). The mean percent change in GPR from day 1 to day 4 increased for those with lower (≤3) GPR after the first 24 hours of therapy and decreased for those reporting higher (>3) initially ($P = 0.0153$). Groups with and without PLP did not differ in their mean percent increases in GPR from day 1 to day 4 ($P = 0.8261$).

Daily Opioid Requirements

Daily 24-hour opioid requirements in IV morphine equivalents were calculated for each day of ketamine therapy, which included all opioids administered on a regular schedule and as needed. In the first 24 hours of therapy, the mean IV morphine equivalent was 129.9 mgs ± 137.3, and on subsequent days and 24 hours after

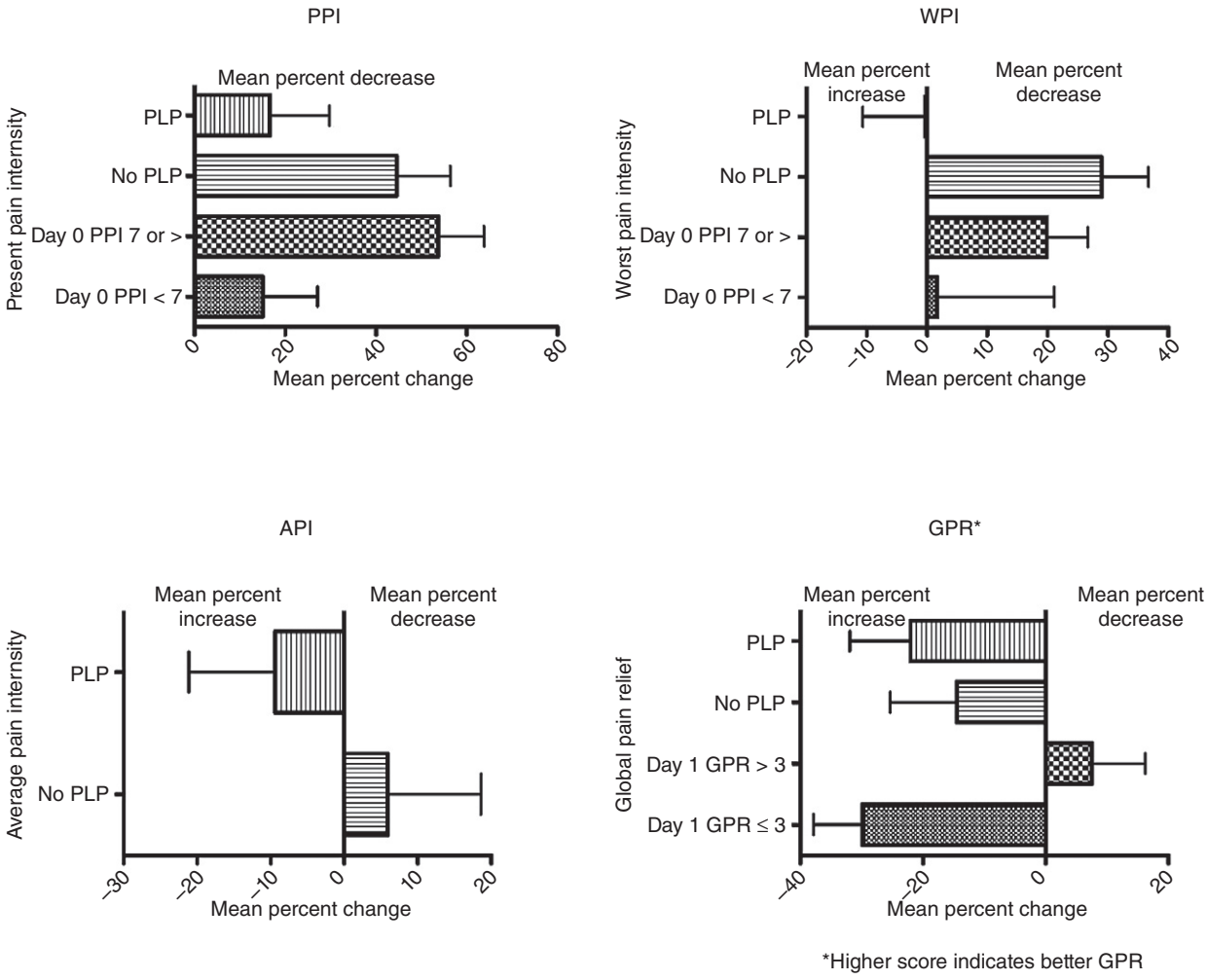

Figure 1 Mean percent changes in pain outcomes. Mean percent change values, directions of change, and tests for statistical significance are reported in Table 6.

therapy was discontinued, opioid requirements were 132.9 ± 146.1, 117.7 ± 131.7, and 112.14 ± 86.3, respectively. Due to considerable variability in opioid use during the 3 days of therapy and 24 hours after therapy was discontinued (day 4), it was not possible to examine within-subject differences over time using mixed-effects modeling. Between time point variations for the sample were examined using Wilcoxon signed-ranks tests, but no statistical differences were noted between day 1 and day 3 ($P = 0.363$), and day 1 and day 4 ($P = 0.586$). Comparisons between patients with no PLP (N = 9) and PLP (N = 10) also showed no statistical differences (Mann–Whitney *U*-tests) for opioid requirements on day 3 ($P = 0.278$) and day 4 ($P = 0.133$).

Adverse Events

Overall, the therapy was extremely well tolerated by the majority of patients with adverse events minimal in occurrence and severity. Daily assessments of sedation levels were done by the research nurses, and determinations for levels of sedation were made by observing patients for at least 30 minutes. Eleven (57.9%) of patients were alert on day 1, four (21.1%) appeared drowsy, two (10.5%) were dosing intermittently, one (5.3%) was sleeping and only awakened when aroused, and one patient who was sleeping had been reported to be fine with the therapy and was not awakened. By day 2, nine (47.4%) patients were completely alert, and four (21.1%) remained drowsy, and four (21.1%) were dosing intermittently. Two patients only awakened when aroused (10.5%). At the end of therapy, the majority of patients were either alert (57.9%) or slightly drowsy (10.5%). Five patients (26.3%) were dosing intermittently, and just one (5.3%) was only awakened when aroused. No dose adjustments were made based on level of sedation, as none of the patients experiencing sedation were difficult to arouse.

Hallucinations occurred in just one patient on day 1 (5.3%) described as being back in the Iraq war zone; however,

the patient did not seem distressed by this event. Notably, this type of perceptual experience is not uncommon in wounded service members, and can be attributed to posttraumatic stress disorder and mild TBI in combat injured service members [16,17]. One patient who was slightly sedated during therapy did report having vivid dreams on day 2. Two patients (10.5%) had a slight decrease in blood pressure on day 2; however, these patients remained stable and no adjustments in therapy were required. Only one patient (5.3%) reported nausea during the therapy, and this was effectively treated with antiemetics.

Discussion

In this case series, we describe patterns in the pain outcomes with low-dose IV ketamine infusions in a cohort of combat wounded service members with major limb trauma also treated with standard pain regimens. Over the course of therapy, there was a significant reduction in PPI, and a better response was observed in those with higher baseline WPI and lower GPR scores after the first day of therapy. GPR scores for patients reporting "good" to "complete" GPR following the initial 24-hour dose remained unchanged. We were not able to detect differential responses in patients with and without PLP; however, over time, patients without PLP showed improvements in WPI.

Randomized controlled trials using ketamine for pain have demonstrated analgesic efficacy by improvements in pain and other patient outcomes with postoperative pain [18–21], mixed and neuropathic chronic pain syndromes such as complex regional pain syndrome [22], PLP [23], peripherally mediated neuropathic pain [24–27], cancer pain [28], and chronic posttraumatic pain [29]. An extensive review of ketamine as an adjunct to perioperative analgesic regimens by IV bolus and/or postoperative continuous infusion (≤48 hours) documents favorable effects from ketamine with an acceptable safety profile [18]. Two Cochrane Collaborative reviews of pooled data from 37 and 27 randomized controlled trials (RCTs) for perioperative pain provide strong evidence for ketamine's early effects on reducing pain, and its opioid-sparing effects when added to opioid regimens [19,30]. An extensive evaluation of clinical trials with IV ketamine for the treatment of chronic pain using more long-term therapy (days to weeks) identifies a number of studies showing extended pain relief over months, but often at the cost of dose-dependent psychotropic adverse events such as "drug high," hallucinations, panic attacks, depersonalization, and less commonly, psychosis [3]. Any pain-relieving effects from infusions of short duration (<4 hours) generally dissipated soon after infusions were discontinued.

Despite considerable evidence to support the use of ketamine in the treatment of neuropathic pain, less is known about its effectiveness for peripherally and centrally mediated neuropathic pain from major limb trauma and amputation. Limited studies of patients with limb amputations make it difficult to draw definitive conclusions regarding the effectiveness of ketamine for residual limb and phantom pain. An evidence-based review of ketamine for the treatment of PLP and postherpetic neuralgia showed substantial benefit with reduced hyperpathia and pain relief [31]. Low-dose ketamine may act as an "anti-hyperalgesic," "anti-allodynic," or "tolerance-protective" agent, and therefore, it may have an important role in treating difficult pain syndromes unresponsive to other analgesic modalities [32]. Three patients from a small cohort of eight with cancer-related pain refractory to opioid analgesics, one of whom had PLP, had notable decreases in hyperalgesia and allodynia with adjunct doses of ketamine [33]. Responsiveness of residual limb pain and PLP to ketamine was also assessed in a double-blind, placebo-controlled trial with ketamine bolus at 0.1 mg/kg/5 min followed by an infusion of 7 mcgs/kg/min in 11 patients. Both pain in the stump and PLP were significantly reduced with ketamine vs placebo. Low-dose ketamine increased mechanical pressure-pain thresholds from repetitive stimulation of the stump; however, ketamine did not alter thermal sensitivity and temporal summation of heat-evoked pain in the residual limb [34]. Similarly, ketamine reduces punctuate mechanical hyperalgesia and temporal summation of mechanical stimuli, believed to be responsible for "windup" pain [10].

Contrary to these findings, an RCT with ketamine and placebo with a larger cohort (N = 45) who underwent above- or below-knee amputation and received preemptive ketamine followed by 72 hours of ketamine infusion (0.5 mg/kg) showed no difference in surface area of residual limb allodynia or morphine consumption. As an unexpected finding, stump pain was exacerbated in the ketamine group at 3 days postoperatively [35]. The incidence of both residual limb pain and PLP at the 6-month follow-up was statistically equivalent to controls. Differences in findings might be explained by small sample sizes, variations in ketamine dosing and regimens, timing of administration from amputation, and duration of studies. Of importance, our cohort had been subjected to multiple surgical procedures and stump revisions. In a double-blind crossover RCT, ketamine dosed at 0.4 mg/kg (only 10 patients) demonstrated superior effects on pain reduction compared with both placebo and 200 international unit (IU) of calcitonin [23]. The median time from amputation for this small sample was 10.9 years, which was dramatically different from our soldier cohort more recently injured and still requiring multiple procedures on their stump area(s).

In the present study of 19 male patients with significant limb trauma, we demonstrated an improvement in PPI scores over the 3-day infusion period of ketamine at or below doses of 120 mcg/kg/h. This generalized trend for improved PPI was accompanied by a reduction in overall opioid loads, though this change was not statistically significant. Nevertheless, the decreasing trend in opioid requirement might have achieved statistical significance with a larger sample and longer duration of therapy. Our findings also suggest that low-dose ketamine infusions

used in complicated trauma patients is safe even when concurrently administered with aggressive opioid and adjunct analgesics. A recent review of multiple studies of ketamine for complex regional pain syndrome review also document its safety profile as an analgesic [36].

This study also demonstrated that patients receiving low-dose IV ketamine can be safely managed on general wards with active involvement and oversight from an APS. APS physicians and nurses provided education to general ward nurses caring for this cohort of patients. This included information on ketamine's mechanisms of action, considerations with ketamine administration, potential adverse events, and monitoring parameters. APS coverage was 24/7 and included at least two visits per day at the bedside. More frequent visits occurred in response to concerns or issues that arose during the course of therapy. Nurses communicated frequently with members of the APS on the status of their patients, and no significant issues arose that would have precluded patients from being managed on the general care wards.

Interestingly, low-dose ketamine infusion in this cohort did not have a significant overall time effect on WPI, which could have been attributed to pain provoking episodes of care such as frequent wound procedures and dressing changes that could not be avoided. When patients were stratified for baseline pain scores (<7 or ≥7) and the presence or absence of phantom pain, ketamine did lead to a significant decrease in WPI among those with greater baseline scores and no PLP. Unlike previous studies that have demonstrated reduced phantom pain using ketamine in the perioperative period or in outpatients with residual limbs that were healed, this study was undertaken during the acute phase of trauma recovery and a complicated recovery. While ketamine in varying doses provides short-term pain relief, its differential effects on PLP are inconclusive mostly because of small and diverse samples, time-dependent factors with dosing and duration of administration, and the inability to discern the features of phantom pain [37,38]. As such, larger, controlled trials are needed to specifically evaluate the impact of ketamine on central pain syndromes.

From a clinical perspective, perhaps the most important finding in this cohort was the improvement in perceptions of GPR with the addition of ketamine to patients already exposed to significant doses of opioids and complex adjunct pain regimens. The former WRAMC APS viewed ketamine infusions as an alternative to standard pain therapies alone, that for whatever reason, are not effective for the multiple mechanisms of pain associated with extensive trauma, repeated surgical interventions, and complications of injury.

This case series has significant limitations that must be factored into any conclusions drawn from the data. There was absolutely no attempt to achieve consistency in **routine care** pain medication regimens. Pain plans of care were individualized resulting in wide variability in the type and dose of pain medications when ketamine was added. Complex multimodal analgesic regimens are a reality for combat-sustained pain management. The inability to construct mixed-effects models for API data might have been influenced by the small sample size and variations in pain levels throughout the days of therapy caused by wound procedures, activity, or even inactivity. We acknowledge that the sample size was small, but the goal of this preliminary study was to examine short-term patterns during therapy and to generate point estimates around pain outcomes to calculate sufficient statistical power to conduct a randomized, placebo-controlled trial. Performing a post hoc power analysis, a sample of 19 subjects achieves 80% power to detect a significant mixed model parameter estimate of absolute magnitude equal to 0.50 assuming an SD of 0.80 (or SE = 0.18) using a significance level of 0.05 and a two-sided one-sample *t*-test. Given the heterogeneity of combat injuries and variability in response to analgesic therapies, preliminary data are important, if not essential, to proceed with further investigations of ketamine. Last, long-term follow-up was not possible as some of the patients continued to require surgical management of residual and existing limbs.

Despite these limitations, this case series demonstrated that the addition of ketamine generally improved pain and perceptions of relief in patients who were otherwise not reaching acceptable benefits from standard analgesic therapies. This retrospective review illustrates that 120 ug/kg/h was well tolerated; however, more case reports and retrospective or prospective investigations are needed to examine the effects of dose manipulations (e.g., higher doses) on pain responses and adverse events (e.g., hypotension).

Conclusion

Low-dose ketamine infusion was effective in reducing PPI and improving perceptions of GPR in complex combat trauma patients not achieving desired outcomes with standard aggressive multimodal pain management therapies. The effect of ketamine in this population was most pronounced when baseline pain scores were high and PLP was not an issue. This finding must be cautiously interpreted as the pattern for responses to ketamine in patients with central pain must be further evaluated in systematic controlled trials.

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