

Prehospital and En Route Analgesic Use in the Combat Setting: A Prospectively Designed, Multicenter, Observational Study

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ABSTRACT Background: Combat injuries result in acute, severe pain. Early use of analgesia after injury is known to be beneficial. Studies on prehospital analgesia in combat are limited and no prospectively designed study has reported the use of analgesics in the prehospital and en route care setting. Our objective was to describe the current use of prehospital analgesia in the combat setting. Methods: This prospectively designed, multicenter, observational, prehospital combat study was undertaken at medical treatment facilities (MTF) in Afghanistan between October 2012 and September 2013. It formed part of a larger study aimed at describing the use of lifesaving interventions in combat. On arrival at the MTF, trained on-site investigators enrolled eligible patients and completed standardized data capture forms, which included the name, dose, and route of administration of all prehospital analgesics, and the type of provider who administered the drug. Physiological data were retrospectively ascribed as soon as practicable. The study was prospectively approved by the Brooke Army Medical Center institutional review board. Results: Data were collected on 228 patients, with 305 analgesia administrations recorded. The predominant mechanism of injury was blast (50%), followed by penetrating (41%), and blunt (9%). The most common analgesic used was ketamine, followed by morphine. A combination of analgesics was given to 29% of patients; the most common combination was ketamine and morphine. Intravenous delivery was the most commonly used route (55%). Patients transported by the UK Medical Emergency Response Team (MERT) or U.S. Air Medical Evacuation (Dust-off) team were more likely to receive ketamine than those evacuated by U.S. Pararescue Jumpers (Pedro). Patients transported by Medical Emergency Response Team or Pedro were more likely to receive more than 1 drug. Patients who received only ketamine had a higher pulse rate ($p < 0.005$) and lower systolic blood pressure ($p = 0.01$) than other groups, and patients that received hydro-morphine had a lower respiratory rate ($p = 0.04$). Conclusions: In our prospectively designed, multicenter, observational, prehospital combat study, ketamine was the most commonly used analgesic drug. The most frequently observed combination of drugs was ketamine and morphine. The intravenous route was used for 55% of drug administrations.

INTRODUCTION

High-energy devices in the wars in Iraq (2003–2012) and Afghanistan (2001–2014) have resulted in thousands of severely wounded military personnel.¹ The numerous injuries sustained from blast has resulted in a significant number of soldiers with disabling conditions related to pain, including neuropathic pain, degenerative arthritis, and lumbago.² Malchow and Black³ reported that over 80% of U.S. combat casualties were transported from Baghdad to Germany with uncontrolled pain.

Multiple analgesics are available and used in the combat setting. The combat medic has access to both opioid and

nonopioid analgesics.³ Morphine and fentanyl are effective opioid analgesics and are commonly used prehospital, in both combat and civilian settings.^{4,5} However, opioids can cause hypotension and respiratory depression that may worsen the effects of hemorrhage shock.⁶ Morphine was issued to combat medics in the Second World War, and continues to be issued today.^{6,7} Other analgesics include oral transmucosal (TM) fentanyl^{8,9} or parenteral ketamine. YM fentanyl has been shown to be a safe, effective, and easy method of administering analgesics in a combat environment.^{8–10} Ketamine is a nonopioid anesthetic that provides profound analgesia at sub-anesthetic doses,¹¹ and has been reported in prehospital settings. It is opioid sparing, and can be administered intravenously, intramuscularly, or intranasally.¹² Ketamine, in analgesic doses, does not cause hypotension or respiratory depression. In combination with morphine, it may produce superior analgesia as compared with morphine alone in the prehospital environment⁵ and may also reduce the total opioid dose required.

Early effective pain control for acute traumatic injury is important for successful outcomes.^{1,10,13–15} Despite the demonstrated importance of prehospital pain management, few studies have reported the use of analgesics and the type of analgesics in combat.^{4,6,16–18} To date, there have been no published prospectively designed studies of the incidence of administration or types of analgesics used in a prehospital setting in combat. Our objective was to report the different

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doi: 10.7205/MILMED-D-14-00383

Report Documentation Page				Form Approved OMB No. 0704-0188	
Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.					
1. REPORT DATE 01 MAR 2015		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE Prehospital and En Route Analgesic Use in the Combat Setting: A Prospectively Designed, Multicenter, Observational Study				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Petz L. N., Tyner S., Barnard E., Ervin A., Mora A., Clifford J., Fowler M., Bebarta V. S.,				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, Tx 78234				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT SAR	18. NUMBER OF PAGES 5	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

analgesics administered in prehospital care, including route of administration, dose, and vital signs after use through a prospectively designed, multicenter, observational combat theater study.

METHODS

This prospectively designed, multicenter, observational, prehospital combat study was undertaken at medical treatment facilities (MTF) in Afghanistan between October 2012 and September 2013. It formed part of a larger study that aimed to describe the use of lifesaving interventions in the prehospital and en route combat setting.¹⁹ All U.S. military, coalition military, and local national civilian patients who were transported directly from point of wounding to one of the enrolling MTFs were eligible for enrollment. Captured personnel were excluded from enrollment in accordance with institutional review board guidelines.

On arrival at the MTF, specifically trained on-site investigators from the Joint Combat Casualty Research Team (JC2RT) enrolled patients and used a standardized data capture form to record demographics, mechanism of injury, and analgesia data. Analgesia data included the names, doses, and routes of administration of all prehospital and en route analgesics used, and the type of provider who administered them. Additional retrospective data capture was undertaken, in theatre, by the JC2RT to record vital signs, clinical events, and any missing data on drug doses. Predefined lifesaving interventions were recorded but not included in this analysis.¹⁹ The study was prospectively approved by the Brooke Army Medical Center institutional review board.

Statistics

For this descriptive analysis, categorical data were reported as percentages although normally distributed continuous data were reported with means and standard deviations and skewed data reported using median and interquartile ranges (IQR). Chi-Square test was conducted when comparing categorical data using a Fisher exact test when appropriate. Continuous variables were evaluated using *t* test/analysis of variance for normally distributed data or a Wilcoxon/Kruskal–Wallis for skewed data. All statistical tests were two-sided using an $\alpha < 0.05$ for significance.

RESULTS

Data were collected on 237 patients in the study period. Nine patients were excluded from this analysis as they received an infrequently used analgesia (acetaminophen or ibuprofen $n = 6$, ketorolac $n = 2$, oxycodone $n = 1$). Of the remaining 228 patients, 100% were male, with a median age of 24 years (IQR_{25–75} 22–30). The predominant mechanism of injury was blast (50%), followed by penetrating (41%), blunt (9%); burn injuries were recorded as a secondary injury to blast in eight patients.

We recorded 305 analgesia episodes. An individual episode was ascribed when a patient received a dose of analgesia (i.e., initial drug administration, a subsequent different drug, or the same drug via an alternative route). Ketamine was most frequently administered, followed by fentanyl, morphine, and hydromorphone (Table I). Intravenous (IV) administration was the most frequently used route for all drugs; 55% of episodes (Table I). The median doses for IV, intraosseous (IO), and intramuscular (IM) ketamine and morphine were similar and were analyzed together (Table I). The IV and TM fentanyl dosing (75 and 800 μ g, respectively) were not similar and were reported separately.

More than 1 analgesic was administered in 29% of patients. The most frequently coadministered drugs were ketamine and morphine, followed by ketamine and fentanyl (Table II). More patients received ketamine alone than patients who received morphine alone (Fig. 1). Individual doses were not timed and thus we could not determine whether the drug was administered for analgesia at point of injury or during transport by the medical evacuation teams. Patients transported by Medical Emergency Response Team (MERT) or Dust-off were more likely to receive ketamine than those evacuated by Pedro. MERT patients were also more likely to have been administered TM fentanyl than those on Pedro or Dust-off (Table III). Patients transported by MERT or Pedro were more likely to have been administered two or more drugs than those evacuated by Dust-off (Table IV).

To better understand the physiological effects of drugs in this study, only patients who received a single medication, with the exception of ketamine and morphine combination, were included in the analysis of vital signs on arrival at a combat hospital. The combination of ketamine and morphine was included as it was the most commonly observed

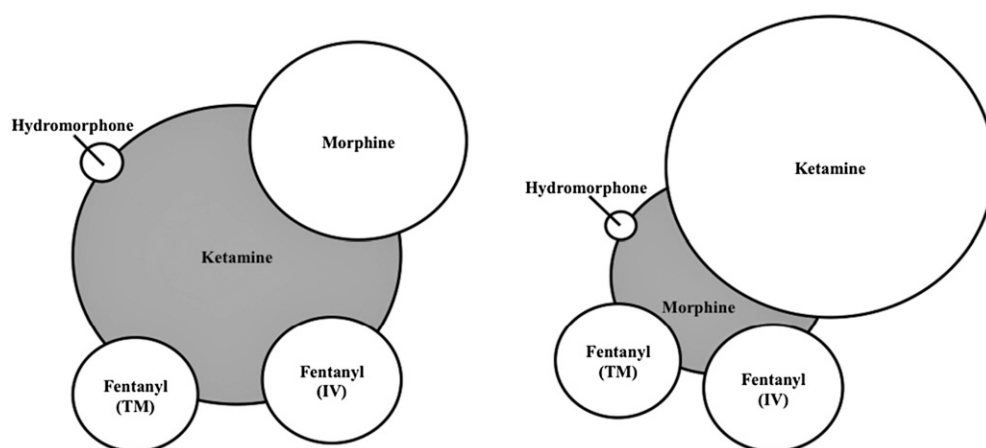
TABLE I. Drugs Administrated by Route and Total Doses

Drug	Percent of Study Sample	IV	IM	TM	IO	Unk	Total Dose
	% (n/study sample)	n	n	n	n	n	Median (IQR)
Ketamine	52 (118/228)	62	21	—	20	15	50 mg (25–50)
Morphine	34 (78/228)	42	24	—	6	6	10 mg (8–10)
Fentanyl (IV)	22 (50/228)	50	—	—	—	—	75 mcg (50–100)
Fentanyl (TM)	20 (45/228)	—	—	45	—	—	800 mcg (800–800)
Hydromorphone	6 (14/228)	13	—	—	—	1	1 mg (0.9–1.3)
Percent of Episodes by Route		54.5	15	15	8.5	7	

Unk, Unknown.

TABLE II. The Frequency of Individual and Combination Analgesia Administration (Limited to $n \geq 5$)

Frequencies % (n)	Ketamine	Morphine	Fentanyl (IV)	Fentanyl (TM)	Hydromorphone
20 (62)	•				
13 (39)		•			
10 (31)				•	
10 (29)			•		
8 (25)	•	•			
6 (18)	•		•		
4 (11)	•			•	
3 (9)					•
3 (8)		•	•		
2 (7)		•		•	
2 (5)	•				•

**FIGURE 1.** Graphical representation of the coadministration relationships for ketamine (left) and morphine (right). The area of each circle represents the number of analgesia episodes for each drug. The area of overlap between circles represents the number of coadministration of those 2 analgesics.**TABLE III.** Analgesics Administered by Platform

Drug/Platform	n	MERT	Pedro	Dust-Off	Others*
		% (Proportion)	% (Proportion)	% (Proportion)	% (Proportion)
Ketamine	118	24 (28)	11 (13/118)	22 (26/118)	43 (51/118)
Morphine	78	24 (19/78)	17 (13/78)	12 (9/78)	47 (37/78)
Fentanyl (IV)	50	16 (8/50)	2 (1/50)	34 (17/50)	48 (24/50)
Fentanyl (TM)	45	31 (14/45)	16 (7/45)	13 (6/45)	40 (18/45)
Hydromorphone	14	0 (0/14)	0 (0/14)	36 (5/14)	64 (9/14)

Unk, Unknown. *Other—inclusive of battle buddy, medic, or unknown.

TABLE IV. Number of Analgesics Administered to Patients by Evacuation Platform

	MERT (%)	Pedro (%)	Dust-Off (%)	Other (%)	Overall (%)
1 Analgesic	53 (24)	64 (16)	80 (40)	75 (81)	71 (161/228)
2 Analgesics	42 (19)	36 (9)	20 (10)	22 (24)	27 (62/228)
>2 Analgesics	4 (2)	0 (0)	0 (0)	3 (3)	2 (5/228)
Percent of Subjects Per Platform	20 (45/228)	11 (25/228)	22 (50/228)	47 (108/228)	—

combination, and morphine is very commonly carried by combat medics, whereas ketamine is favored by both MERT and Pedro. It would therefore be advantageous to better understand the potential physiological effects of this commonly used

combination. We found that ketamine was associated with a significantly higher heart rate ($p < 0.005$), lower blood pressure ($p = 0.01$), and lower Glasgow Coma Scale (GCS) score ($p < 0.0001$) when compared to other analgesics. TM fentanyl

TABLE V. Patients' Vital Signs on Arrival at a Combat Hospital With Respect to the Drugs They Received Prehospital

	Ketamine <i>n</i> = 59	Morphine <i>n</i> = 41	Ketamine-Morphine <i>n</i> = 25	Fentanyl (IV) <i>n</i> = 24	Fentanyl (TM) <i>n</i> = 26	Hydromorphone <i>n</i> = 9
VITALS	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Heart Rate (beats/min)	110 (90–134)	95 (77–120)	95 (80–130)	102 (79–120)	89 (68–120)	105 (89–128)
SBP (mm Hg)	113 (90–140)	118 (96–150)	121 (90–150)	129 (105–139)	122 (90–139)	145 (128–153)
RR (breaths/min)	20 (18–25)	18 (16–23)	22 (16–27)	20 (18–28)	18 (14–21)	16 (11–20)
SaO ₂	99 (95–100)	98 (96–100)	100 (98–100)	97 (95–100)	98 (95–100)	100 (97–100)
GCS	15 (6–15)	15 (15–15)	15 (14–15)	15 (15–15)	15 (15–15)	15 (14–15)
3T (<i>n</i>)	7	1	0	1	1	0

IQR, interquartile range; SBP, systolic blood pressure; RR, respiratory rate; SaO₂, oxygen saturation; GCS, Glasgow Coma Scale; 3T (*n*), GCS 3/15 and intubated.

was associated with a lower heart rate ($p = 0.02$). Hydromorphone was associated with a higher systolic blood pressure ($p = 0.01$) and a lower respiratory rate ($p = 0.04$) (Table V).

DISCUSSION

There are few published studies on either the practices or effectiveness of prehospital analgesia,^{20,21} and more specifically no studies in combat settings. The primary aim of our study was to describe the use of analgesics in this combat setting, and we believe that this is the first prospectively designed study examining this.

Ketamine was the most frequently used drug (20% of patients), and the most common combination of drugs was ketamine and morphine. The most common route was IV (55%) with comparable frequencies of IM, TM, and IO administration (15%, 15%, and 8.5%, respectively).

The high use of morphine in this study maybe due to the drug's availability and familiarity²² (carried by all UK combat personnel²³ and U.S. medics on operations) rather than a decision to use the most suitable drug. TM fentanyl has previously been shown to be an effective (and noninvasive) analgesia in the prehospital combat setting,^{8,9} and was administered to 15% of patients (Table I). However, in our study almost a third of prehospital combat patients received more than one drug, most commonly ketamine and morphine, or ketamine and fentanyl. Although this could represent the availability of analgesic drugs to different practitioners or availability at different locations, it may be that practitioners were using ketamine to reduce the total opioid requirement or to produce a greater degree of pain relief than morphine alone.^{5,24} However, because of the small sample size, we were unable to draw any correlations or conclusions comparing those patients that received both ketamine and an opioid to those that received a single medication. The high use of fentanyl may be secondary to the availability of a practical noninvasive delivery device (TM), rather than its faster onset of action in comparison to morphine, and or the evidence of its effectiveness in the prehospital combat environment.^{8,23}

Of the drugs included in this study, ketamine has a unique combination of cardiovascular effects—tachycardia, hypertension, and increased cardiac output.^{25,26} It would therefore be expected that patients given ketamine would present with an increased heart rate. The significantly lower blood pres-

sure, however, is more difficult to explain but may be because the patients receiving it were hemodynamically unstable and the provider chose a drug that would not lower blood pressure or may increase it slightly.⁶ The reduced GCS, is again, an expected feature of ketamine; however, this cannot be differentiated from injury-associated reduced consciousness. It is likely that a number of MERT patients received higher doses of ketamine as an anesthetic, resulting in a GCS of 3. However, because of the limited data collected on timing of drug administration and specific indication, we could not exclude them from the analysis.

The significantly lower heart rate associated with TM fentanyl may be due to this cohort being physiologically more stable or may reflect more complete analgesia. The relatively low respiratory rate associated with hydromorphone may be a side effect of this potent opioid; however, the high blood pressure combined with a low respiratory rate is probably a function of these patients having lower injury acuity—reinforced by the fact that none of them were evacuated by MERT or Pedro—assets that are routinely tasked to evacuate the more seriously wounded.

Our study has limitations. Prehospital documentation is well recognized to be of a lower standard than hospital patient records²⁷—and this is accentuated by the difficulties of working in a combat setting⁴; however, performing a prospectively designed, observational study, improves documentation over a truly retrospective record review. We were unable to confirm the time, indication, and the level of practitioner who administered the analgesia (e.g., ketamine for analgesia or sedation to intubate); however, based on the lower ketamine doses used, we concluded that most doses were administered for analgesia. Our sample size was small and thus a large sample may have produced different results. However, this is the first study describing different analgesic use in the prehospital combat setting.

Injury severity scores (ISS) are retrospectively ascribed to combat patients and this information is stored within the U.S. Department of Defense Trauma Registry. Because of a large proportion of patients being local national civilians and coalition military, we have been unable to obtain a significant amount of ISS data without adversely affecting the sample size. ISS data may have provided information about injury severity, which could have better described the

use of analgesics and MTF vital signs. Our study was performed in a combat setting, and the training and experience of the providers, the patients and their injuries, and the availability of different analgesics may limit the applicability to the civilian setting, particularly to elderly civilian patients. We were also unable to definitively identify the individual that administered a specific drug; for example, a medic may have been instructed to administer ketamine to a subject by a physician, but this data was not recorded.

For prehospital analgesia in combat, there is a need for an ideal drug. This drug, or combination of drugs, should be safe to be administered by all provider levels, provide immediate analgesia, have minimal suppressive effects on blood pressure and respiratory effort, have limited sedative effects, and have few adverse effects.²⁸ Historically IM morphine has been the primary prehospital combat analgesic.²² However, in light of its ineffectiveness,²⁹ the availability and use of IO infusion, the availability of TM fentanyl,⁹ and evidence of the safety and effectiveness of prehospital ketamine,³⁰ this paradigm may be challenged.

Further prehospital research should aim to compare the analgesic effectiveness in an interventional trial of the most frequently used drugs in this study, via different routes (including intranasal), and record their side effect profiles, hemodynamic effects, effect on pain reduction, and ease of use by the provider.

CONCLUSION

In our prospectively designed, multicenter, observational, prehospital combat study, ketamine was the most commonly used analgesic drug. The most frequently observed combination of drugs was ketamine and morphine. The IV route was used for 55% of drug administrations.

ACKNOWLEDGMENTS

This study was funded by Air Force Medical Support Agency (EM-I-12-005). We thank the current and former members of the on-site Joint Combat Casualty Research Team that helped to collect critical data to make this study possible and John Jones of USAISR for statistical analysis assistance.

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