American Journal of Emergency Medicine 37 (2019) 1455–1459

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

Original Contribution

Prehospital ketamine administration to pediatric trauma patients with head injuries in combat theaters

Guyon J. Hill, MD [a,b,*], Michael D. April, MD, DPhil [c], Joseph K. Maddry, MD [c,d], Steven G. Schauer, DO, MS [c,d,e]

[a] Madigan Army Medical Center, Joint Base Lewis-McChord, WA, United States of America
[b] Dell Children's Medical Center, Austin, TX, United States of America
[c] Brooke Army Medical Center, JBSA-Fort Sam Houston, TX, United States of America
[d] 59th Medical Wing, JBSA-Lackland, TX, United States of America
[e] US Army Institute of Surgical Research, JBSA-Fort Sam Houston, TX, United States of America

ARTICLE INFO

Article history:
Received 15 June 2018
Received in revised form 10 October 2018
Accepted 20 October 2018

Keywords:
Pediatric
Prehospital
Ketamine
Head
Trauma
TBI

ABSTRACT

Background: Head injuries frequently occur in combat. Tactical Combat Casualty Care (TCCC) guidelines recommend pre-hospital use of ketamine for analgesia. Yet the use of this medication in patients with head injuries remains controversial, particularly among pediatric patients. We compare survival to hospital discharge rates among pediatric head injury subjects who received prehospital ketamine versus those who did not.
Methods: We queried the Department of Defense Trauma Registry (DODTR) for all pediatric (<18 years of age) subjects from January 2007 to January 2016. We performed a sub-analysis of subjects with an abbreviated injury severity score for the head of 3 (serious) or higher and at least one documented Glasgow Coma Score (GCS) ≤13.
Results: Of the 3439 pediatric patients within our dataset, 555 subjects met inclusion criteria for head injury – 36 (6.5%) received prehospital ketamine versus 519 (93.5%) who did not. There was no significant difference noted between groups regarding median age (10 versus 8, $p = 0.259$), percent male gender (72.2% versus 76.3%, $p = 0.579$), mechanism of injury ($p = 0.143$), median composite injury scores (22 versus 20, $p = 0.082$), median ventilator-free days (28 versus 27, $p = 0.068$), median ICU-free days (27.5 versus 27, $p = 0.767$), median hospital days (3.5 versus 4, $p = 0.876$) or survival to discharge (66.7% versus 70.7%, $p = 0.607$).
Conclusions: Within this data set, we were unable to detect any differences in mortality among pediatric head trauma subjects administered ketamine compared to subjects not receiving this medication in the prehospital setting.

Published by Elsevier Inc.

1. Introduction

1.1. Background

Head injuries occurred frequently during the recent conflicts in Iraq and Afghanistan in both adults and children, primarily from improvised explosive devices. By 2007 as many as 320,000 returning U.S. service members experienced a probable traumatic brain injury (TBI) [1]. Data on head injury rates for the local population, to include pediatric patients, are unavailable but are likely to be similarly high.

Ketamine is a drug commonly used for induction during intubation, procedural sedation, and analgesia. Tactical Combat Casualty Care (TCCC) guidelines recommend prehospital administration of ketamine for casualties that have moderate to severe pain. Providers can further combine ketamine with other agents for synergistic effects [2-4]. Ketamine provides hemodynamic and respiratory stability unlike opioids, making it an ideal agent for prehospital pain control among trauma patients [5-7]. Providers can administer ketamine via intravenous, intramuscular, intraosseous, or intranasal routes thereby offering multiple options during prehospital trauma care.

Despite its widespread use, controversy still exists regarding the safety of ketamine in the setting of head trauma due to potential effects on intracranial pressure (ICP) [8,9]. Previous studies suggest that ketamine use in patients with head injuries may not have deleterious effects and may even be neuroprotective [9-13]. Recently, the American College of Emergency Physicians removed head trauma from their clinical practice guidelines as a relative contraindication to the use of ketamine [14]. Despite this change, there is little evidence available to determine whether ketamine administration is safe in pediatric patients that have sustained head injuries [10,15].

* Corresponding author at: Department of Emergency Medicine, Madigan Army Medical Center, 9040 Jackson Ave., Tacoma, WA 98431, United States of America.
E-mail address: guyon.j.hill.mil@mail.mil (G.J. Hill).

https://doi.org/10.1016/j.ajem.2018.10.046
0735-6757/Published by Elsevier Inc.

1.2. Goal of this investigation

We seek to determine if an association exists between prehospital administration of ketamine to pediatric trauma subjects with head injuries and increased mortality.

2. Methods

2.1. Data acquisition

We identified subjects as part of a study evaluating prehospital and emergency department (ED) life-saving interventions for pediatric trauma patients [16,17]. The US Army Institute of Surgical Research regulatory office reviewed protocol H-16-014 and determined it was exempt from Institutional Review Board oversight. We obtained only de-identified data.

2.2. Subjects and setting

We queried the Department of Defense Trauma Registry (DODTR) for all pediatric encounters from January 2007 and January 2016. We included subjects with missing data if there was a documented age or estimated age within the records. The research database contained all available information for both prehospital and fixed-facility based care. This was a retrospective review of prospectively collected data within the registry.

2.3. Department of Defense Trauma Registry (DODTR) description

The DODTR, formerly known as the Joint Theater Trauma Registry (JTTR), is the data repository for DoD trauma-related injuries [18,19]. The Joint Trauma System (JTS) manages this system. The DODTR includes documentation regarding demographics, injury-producing incidents, diagnoses, treatments, and outcomes of injuries sustained by US/non-US military and US/non-US civilian personnel in wartime and peacetime from the point of injury to final disposition. The most recently updated data dictionary for the DODTR is readily available [20]. Subject enrollment in the DODTR occurs if he or she undergoes admission to a Role 3 (fixed-facility) or forward surgical team (FST) with an injury diagnosis using the International Classification of Disease 9th Edition (ICD-9) between 800 and 959.9, near-drowning/drowning with associated injury (ICD-9994.1) or inhalational injury (ICD-9987.9), and trauma occurring within 72 h from presentation. The DODTR considers the prehospital environment to comprise any location prior to reaching a FST or a combat support hospital (CSH, role 3) to include the Role 1 (point of injury, casualty collection point, battalion aid station) and Role 2 (temporary limited-capability forward-positioned hospital inside the combat zone without surgical support).

2.4. Identification of subjects

We searched for all subjects with an abbreviated injury score by body region (AISBR) of 3 or greater for the head region (AISBR1) and at least one ED Glasgow Coma Score (GCS) of 13 or less. When more than one GCS was available we used the lowest value documented. We then searched for all prehospital subjects for at least one documented ketamine administration. The JTS uses AIS 2005 with Update 2008 Coding Standard 2. The majority of JTS coders are Certified AIS Coding Specialists (CAISS). All coders receive an orientation and regularly occurring quality assurance measures are implemented.

2.5. Data analysis

We performed all statistical analysis using Microsoft Excel (version 16 Redmond, Washington) and JMP Statistical Discovery from SAS (version 13, Cary, NC). We compared study variables using a student *t*-test for continuous variables, Wilcoxon Rank Sum test for ordinal variables, and chi-squared test for nominal variables. For regression analyses with a binary outcome we performed a binary logistic regression. We reported the following: categorical variables as numbers and percentages, ordinal variables reported as medians with interquartile ranges, and continuous variables as means with standard deviations. We performed multiple subgroup analyses as described and stratified age-based analyses based on Centers for Disease Control (CDC) age groupings: <1, 1–4, 5–9, 10–14, 15–17 [16,17,21]. We defined a severe head injury as a GCS of 8 or less [22].

3. Results

From January 2007 through January 2016 there were 42,790 encounters in the DODTR. Of those, 3439 (8.0%) were pediatric by either documented or estimated age. Of the 3439, we identified 555 subjects that had an AISBR1 (head) score of ≥3 and at least one GCS ≤ 13.

3.1. Overall cohort analysis

Of the 555 subjects available for comparison, there were 36 (6.5%) that received prehospital ketamine versus 519 (93.5%) that did not. There were no significant differences noted between the baseline patient demographics of the groups with regards to age, gender, mechanism of injury, or remaining AIS scores. We also found no significant differences when looking at outcome data in terms of ICU-free and ventilator-free days, hospital days or survival to hospital discharge status. We did note a significantly lower median GCS score upon arrival to the emergency department in the ketamine group (median 3, IQR 3–3 versus median 3, IQR 3–8, $p = 0.016$). A higher proportion of subjects in the ketamine group sustained injuries in Afghanistan as compared to subjects that did not receive ketamine (OEF 100.0% versus 75.1%, $p = 0.003$). There was also a trend towards median higher composite injury severity scores in the ketamine group (ISS, median 22, IQR 16.32.25 versus 20, 14–26, $p = 0.082$, Table 1). We did not find any significant differences in the rates of tympanic membrane rupture, facial fractures, intracranial hemorrhage or diffuse axonal injury between the two groups. However, we did note a trend towards higher rates of skull penetrating injuries in the ketamine group (50.0% versus 35.5%, $p = 0.079$, Table 2).

3.2. Age subgroup analysis

When stratified by age categories, we did not find any significant differences in ventilator days, ICU days, hospital days or survival to hospital discharge for any of the age groups. There were no subjects in the <1-year age group that received ketamine. There was a trend towards a shorter hospital course in the ketamine group (median days 1, IQR 0–5 versus 5, IQR 2–8, $p = 0.073$) for subjects in the 15–17 years age group (Table 3).

3.3. Intubated prehospital subgroup analysis

Among subjects who underwent prehospital intubation, we did not find any significant difference with regards to baseline characteristics of the cohort to include age, gender, lowest recorded GCS, or mechanism of injury. We also did not find any significant difference when looking at the clinical course in terms of ventilator-free days, ICU-free days, hospital days or survival to hospital discharge among patients receiving prehospital ketamine as compared to patients not receiving prehospital ketamine (Table 4).

3.4. Severe head injury subgroup analysis

In subjects with a lowest recorded GCS of 3–8, we also did not find any significant differences with the regards to the basic characteristics

Table 1
Comparisons of head injured subjects based on administration of prehospital ketamine versus no ketamine.

		Ketamine (n = 36)	No ketamine (n = 519)	p-Value
Demographics	Age (median, IQR)	10 (6.25–13)	8 (5–12)	0.259
	Male	72.2% (26)	76.3% (396)	0.579
	Lowest total GCS	3 (3–3)	3 (3–8)	0.016
Country where injury occurred	Iraq	0% (0)	24.9% (129)	0.003
	Afghanistan	100% (36)	75.1% (390)	
Mechanism of injury	Explosive	55.6% (20)	44.1% (229)	0.143
	GSW	27.8% (10)	20.2% (105)	
	MVC	8.3% (3)	17.9% (93)	
	Other	8.3% (3)	17.7% (92)	
Injury severity scores	Composite ISS	22 (16–32.25)	20 (14–26)	0.082
	AISBR2	0 (0–2)	0 (0–2)	0.280
	AISBR3	0 (0–2)	0 (0–0)	0.224
	AISBR4	0 (0–0)	0 (0–0)	0.553
	AISBR5	0 (0–1.5)	0 (0–2)	0.985
	AISBR6	0 (0–1)	1 (0–1)	0.257
Outcome data	30-day ventilator-free days	28 (26–29)	27 (25–29)	0.068
	30-day ICU-free days	27.5 (20.5–29)	27 (25–29)	0.767
	Hospital days	3.5 (1–14.25)	4 (1–8)	0.876
	Discharge alive	66.7% (24)	70.7% (367)	0.607

GCS = Glasgow Coma Scale; GSW = gunshot wound; MVC = motor vehicle collision; ISS = injury severity score; AISBR = abbreviated injury score by body region; AISBR2 = face; AISBR3 = thorax; AISBR4 = abdomen; AISBR5 = extremity; AISBR6 = external (including superficial wounds from all the body regions, burns); ICU = intensive care unit; IQR = interquartile range.

of the cohorts when looking at median age, gender, or mechanism of injury. Furthermore, we did not find a significant difference when examining the clinical course with respect to ventilator-free days, ICU-free days, hospital days or survival to hospital discharge among patients receiving prehospital ketamine as compared to patients not receiving prehospital ketamine (Table 5).

4. Discussion

Our study found no evidence of harm following the prehospital administration of ketamine to pediatric patients who sustained head trauma in Iraq or Afghanistan and underwent admission to US or coalition medical facilities. We were also unable to detect a difference in outcome when performing subgroup analyses based on age, patients intubated in the prehospital setting, or those with severe head injuries. While we found significantly lower GCS scores in the group receiving ketamine, we did not detect a mortality difference.

These findings suggest that it may be possible to extrapolate TCCC recommendations for ketamine usage to the pediatric population with head injuries. This could give prehospital providers an additional indication for a medication which they already carry and with which they are familiar. Current TCCC guidelines apply only to the adult combatant population and make no pediatric-specific recommendations [23]. They caution against the use of ketamine only in the case of severe TBI in which the casualty cannot communicate pain due to a concern that it may worsen this condition.

The literature increasingly suggests that the use of ketamine in adult patients that have suffered head injuries is not harmful and may potentially be beneficial [9-13]. There are no reports of patients with normal flow of cerebrospinal fluid having resultant harm from the administration of ketamine and some authors posit that the only contraindication to its use is obstructive hydrocephalus [24]. However, the evidence specifically examining the pediatric population remains limited. Our study adds to this small but growing literature, demonstrating the safety of ketamine in pediatric patients who have sustained head injuries [10,15].

Of note, we found no pediatric patients in the registry that sustained head injuries in Iraq and subsequently received ketamine and a low rate of usage overall in this population. There are several possible explanations for this finding. Most likely, its related to limitations on access and use within that theater with generally low use all around by the majority of forces [25]. Conversely, documentation omissions may be contributory [26].

There are several limitations to the study. We are only able to query the registry for information entered into it and cannot determine how many records are incomplete or how many data items are missing. Previous studies demonstrate poor prehospital documentation [26,27]. While we found significantly lower GCS scores in the ketamine group, pre-administration scores were not available per the registry these score measurements occurred after the patients received ketamine as these were scores upon arrival in the emergency department. Therefore, we are unable to say if the lower GCS scores were due to medication effect or the characteristics of the cohort. Our investigation is also

Table 2
Comparisons of select injuries.

	Ketamine	No ketamine	p-Value
TM rupture	8.3% (3)	3.7% (19)	0.165
Facial fracture	80.6% (29)	79.2% (411)	0.845
Skull penetration	50.0% (18)	35.5% (184)	0.079
Intracranial hemorrhage	69.4% (25)	70.3% (365)	0.911
Diffuse axonal injury	2.8% (1)	1.2% (6)	0.399

TM = tympanic membrane.

Table 3
Comparison of outcome data by age grouping.

		Ketamine	No ketamine	p-Value
1–4 years (n = 102)	30-day ventilator-free days	26 (23–28)	28 (25–29)	0.103
	30-day ICU-free days	26 (20–28)	27 (24–29)	0.404
	Hospital days	6 (1–24)	3 (1–8)	0.379
	Discharge alive	71.4% (5)	64.2% (61)	0.700
5–9 years (n = 207)	30-day ventilator-free days	27 (23–29.25)	28 (27–29)	0.330
	30-day ICU-free days	26 (17.75–29)	27 (25–28)	0.619
	Hospital days	5.5 (1–18.25)	4 (2–9)	0.751
	Discharge alive	60.0% (6)	77.7% (153)	0.197
10–14 years (n = 185)	30-day ventilator-free days	28 (24.5–28.5)	28 (26–29)	0.312
	30-day ICU-free days	28 (16.75–29)	27 (25–29)	0.821
	Hospital days	2.5 (1–14.25)	4 (1–8)	0.969
	Discharge alive	78.6% (11)	66.1% (113)	0.339
15–17 years (n = 52)	30-day ventilator-free days	29 (25.5–29.5)	28 (26–29)	0.837
	30-day ICU-free days	29 (26–30)	28 (23–29)	0.187
	Hospital days	1 (0–5)	5 (2–8)	0.073
	Discharge alive	40.0% (2)	72.3% (34)	0.136

No subjects in the <1 year group received ketamine and were excluded from this table.

Table 4
Comparison of outcome data in subjects intubated prehospital.

		Ketamine (n = 21)	No ketamine (n = 98)	p-Value
Demographics	Age	10 (7.5–14)	9.5 (5–12)	0.334
	Male	76.2% (16)	72.5% (71)	0.726
	Lowest total GCS	3 (3–3)	3 (3–3)	0.310
Mechanism of injury	Explosive	47.6% (10)	42.9% (42)	0.760
	GSW	28.6% (6)	24.5% (24)	
	MVC	9.5% (2)	19.4% (19)	
	Other	14.3% (3)	13.3% (13)	
Outcome data	30-day ventilator-free days	27 (24.5–29)	28 (26–29)	0.398
	30-day ICU-free days	27 (17.5–29)	28 (25–29)	0.353
	Hospital days	3 (1–13.5)	3 (1–7)	0.975
	Discharge alive	57.1% (12)	63.3% (62)	0.600

observational in nature therefore we can only demonstrate correlation and not causation between prehospital ketamine administration and survival to discharge. Also, encounter inclusion within the DODTR requires subject arrival to an FST or fixed-facility alive or with on-going interventions so we are unable to characterize subjects that died on the battlefield. An additional limitation is that we do not have sufficient data to determine the impact of intervention upon transport times or the tactical situation. Furthermore, we do not have data on functional outcomes or data on the neurological status upon discharge. There were only 39 records in the registry for pediatric patients that sustained head injuries and received prehospital ketamine therefore these had to be compared with a much larger number of patients that did not receive ketamine. While usually not feasible in the prehospital combat setting, a controlled study would yield more robust data. While we used mortality as the overall study outcome, we are unable to assess differences in functional status at discharge. Similarly, we are unable to assess for physiologic effects such as intracranial pressure. A final limitation is that we included data even if it was incomplete in the registry [27].

Further study of pediatric patients with head injuries will help confirm this versatile medication's safety profile in this population. Research should include both hospital-based and prehospital studies. Such studies could give deployed military medical providers or those working in austere settings an additional pharmaceutical option when caring for injured children.

Table 5
Comparison of outcome data in severe head injury (GCS 3-8).

		Ketamine (n = 34)	No ketamine (n = 313)	p-Value
Demographics	Age	9.5 (5.75–12.25)	8 (5–12)	0.467
	Male	73.% (25)	75.4% (313)	0.806
Mechanism of injury	Explosive	52.9% (18)	44.1% (183)	0.235
	GSW	29.4% (10)	21.2% (88)	
	MVC	8.8% (3)	17.8% (74)	
	Other	8.8% (3)	16.9% (70)	
Outcome data	30-day ventilator-free days	27 (24.5–29)	28 (26–29)	0.157
	30-day ICU-free days	27 (19.5–29)	27 (25–29)	0.580
	Hospital days	3.5 (1–15.25)	4 (1–8)	0.968
	Discharge alive	64.7% (22)	65.8% (273)	0.899

5. Conclusions

Within this data set, we were unable to detect any differences in mortality among pediatric head trauma subjects administered ketamine compared to subjects not receiving this medication in the prehospital setting. While further research is necessary, this study adds to the growing body of evidence suggesting that ketamine use in the setting of a head injury is likely safe in both children and adults. These findings may ultimately have important implications for the practice patterns of military and civilian providers alike.

Conflicts

We have no conflicts to report.

Funding

We received no funding for this study.

Acknowledgements

We would like to thank the Joint Trauma System Data Analysis Branch for their efforts with data acquisition.

Disclaimer

Opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Air Force, the Department of the Army, or the Department of Defense.

References

[1] Tanielian T, et al. Invisible wounds of war: psychological and cognitive injuries, their consequences, and services to assist recovery. Santa Monica, CA: RAND Corporation; 2008https://www.rand.org/pubs/monographs/MG720.html [23 December 2017].
[2] Butler FK, et al. A triple-option analgesia plan for tactical combat casualty care: TCCC guidelines change 13-04. J Spec Oper Med 2014 Spring;14(1):13–25.
[3] Schauer SG, et al. Multicenter, prospective study of prehospital administration of analgesia in the U.S. combat theater of operations. Prehosp Emerg Care 2017 Nov–Dec; 21(6):744–9.
[4] Schauer SG, et al. Battlefield analgesia: TCCC guidelines are not being followed. J Spec Oper Med 2015 Spring;15(1):85–9.
[5] Green SM, et al. Inadvertant ketamine overdose in children: clinical considerations and outcome. Ann Emerg Med 1999 Oct;34(4 Pt 1):492–7.
[6] Green SM, et al. Intramuscular ketamine for pediatric sedation in the emergency department: safety profile in 1,022 cases. Ann Emerg Med 1998 Jun;31(6):688–97.
[7] Jabre P, et al. Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised trial. Lancet 2009 Jul 25;374(9686):293–300.
[8] Albanese J, et al. Ketamine decreases intracranial pressure and electroencephalographic activity in traumatic brain injury patients during propofol sedation. Anesthesiology 1997 Dec;12(87):1328–34.
[9] Pfenninger E, et al. The effect of ketamine on intracranial pressure during haemorrhagic shock under the conditions of both spontaneous breathing and controlled ventilation. Acta Neurochir 1985 Sep;78(3–4):113–8.
[10] Zeiler FA, et al. The ketamine effect on ICP in traumatic brain injury. Neurocrit Care 2014 Aug;21(1):163–73.
[11] Cohen L, et al. The effect of ketamine on intracranial and cerebral perfusion pressure and health outcomes: a systematic review. Ann Emerg Med 2015 Jan;65(1):43–51.
[12] Wang X, et al. Ketamine does not increase intracranial pressure compared with opioids: meta-analysis of randomized controlled trials. J Anesth 2014 Dec;28(6):821–7.
[13] Chang LC, et al. The emerging use of ketamine for anesthesia and sedation in traumatic brain injuries. CNS Neurosci Ther 2013 Jun;19(6):390–5.
[14] Green SM, et al. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med 2011;57(5):449–61.
[15] Bar-Joseph G, et al. Effectiveness of ketamine in decreasing intracranial pressure in children with intracranial hypertension. J Neurosurg Pediatr 2009 Jul;4(1):40–6.
[16] Schauer SG, et al. Prehospital interventions performed on pediatric trauma patients in Iraq and Afghanistan. Prehosp Emerg Care 2018 Mar;1:1–6.
[17] Schauer SG, et al. Emergency department resuscitation of pediatric trauma patients in Iraq and Afghanistan. Am J Emerg Med 2018 Jan 4. https://doi.org/10.1016/j.ajem.2018.01.014 [pii: S0735-6757(18)30014-7].
[18] Glenn MA, et al. Implementation of a combat casualty trauma registry. J Trauma Nurs 2008;15(4):181–4.
[19] O'Connell KM, et al. Evaluating the Joint Theater Trauma Registry as a data source to benchmark casualty care. Mil Med 2012;177(5):546–52.

[20] Joint Trauma System. Joint Trauma System: The Department of Defense Center of Excellence for Trauma. jts.amedd.army.mil/index.cfm/data/registries; 9 Oct. 2018.
[21] Johansen K, et al. Cannot ventilate-cannot intubate an infant: surgical tracheotomy or transtracheal cannula? Paediatr Anaesth 2010;20(11):987–93.
[22] Ingebrigtsen T, Romner B, Kock-Jensen C. Scandinavian guidelines for initial management of minimal, mild, and moderate head injuries. The Scandinavian Neurotrauma Committee. J Trauma 2000;48(4):760–6.
[23] TCCC guidelines for medical personnel. U.S. Army Institute for Surgical Research; 31 Jan. 2017 http://www.usaisr.amedd.army.mil/pdfs/TCCCGuidelinesforMedicalPersonnel170131Final.pdf. [23 December 2017].
[24] Green SM, et al. Ketamine and intracranial pressure: no contraindication except hydrocephalus. Ann Emerg Med 2015;65(1):52–4.
[25] Schauer SG, et al. Trends in prehospital analgesia administration by U.S. forces from 2007 through 2016. Prehosp Emerg Care 2018 Aug 17:1–6. https://doi.org/10.1080/10903127.2018.1489022.
[26] Schauer SG, et al. A descriptive analysis of data from the Department of Defense Joint Trauma System Prehospital Trauma Registry. US Army Med Dep J 2017 Oct–Dec (3–17):92–7.
[27] Robinson JB, et al. Battlefield documentation of tactical combat casualty care in Afghanistan. US Army Med Dep J 2016(2–16):87–94.