The Safety and Effectiveness of Ketamine for Battlefield Pain Management: What have we learned in CENTCOM over 20 years

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Disclaimers

- The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of the Defense Health Agency, Department of Defense, nor the U.S. Government.
- The authors have no relevant financial interests or relationships to disclose.

Battlefield Analgesics: Opioids

- Injectable Morphine (IM/IV)
  - Easy-to-use autoinjector
  - Potentially life-threatening side effects (respiratory and circulatory depression)
- Oral Transmucosal Fentanyl Citrate (OTFC) Lozenge
  - Easy to use, fast acting
  - Same risks
  - Pulled from FDA and no longer manufactured
- Sublingual Sufentanil tablets
  - Easy to use, ultra-fast acting
  - Same opioid risks
  - Pending market shortages and withdrawals

Battlefield Analgesics: Ketamine

- FDA-approved in 1970 for general anesthesia, but never for analgesia
- Multiple civilian studies have shown efficacy in off-label use for analgesia in acute post-traumatic pain setting
- Increasingly used among US and foreign military forces
  - Most studies are limited in scope and sample size or primarily descriptive in nature
- Preferred agent for sever pain in the 2014 TCCC guidelines
  - Given by IV or IM injection without an autoinjector
  - Lack of FDA approval blocks development of an easy-to-use injector

Study Objectives

- Hypothesis
  - ketamine is equally safe and effective compared to morphine and fentanyl when used for analgesia in tactical combat casualty care
- Aim 1: Safety
  - Adverse events
  - Overall survival
- Aim 2: Effectiveness
  - Pain score
  - Resource utilization

Methods: Study Population

- Sourced from the Department of Defense Trauma Registry
- US active-duty service members serving in CENTCOM
- Ages 18+ years of age
- Received prehospital ketamine, morphine, *or* fentanyl
- 2004 – 2024

Methods: Study Variables

- Demographic variables
  - Age
  - Sex
  - Race
  - Military operation
  - Rank
  - Service branch
- Variable of interest
  - Type of pain medication
- Injury related variables
  - Injury Severity Score (ISS)
  - Head Abbreviated Injury Scale (hAIS)
  - Thorax Abbreviated Injury Scale (tAIS)
  - Mechanism of injury
  - Number of analgesic doses
  - Shock status
    - ✓ Transfusion
    - ✓ Shock index
  - Administration of a benzodiazepine

Methods: Outcome Variables

Safety (Aim 1)

Adverse outcomes

- ✓ Airway
- ✓ Cardiovascular
- ✓ Other

Patient survival at discharge

Effectiveness (Aim 2)

Change in vital statistics

- ✓ Systolic blood pressure
- ✓ Diastolic blood pressure
- ✓ Respiratory rate
- ✓ Heart rate
- ✓ Oxygen saturation
- ✓ Glasgow coma scale
- ✓ Pain scale

Resource use

- ✓ Bed days
- ✓ ICU days
- ✓ Ventilator days

Methods: Preparation

- Multiple Imputation
  - Missing predictor variables estimated using logistic regression multiple imputation
    (Mice R package, version 3.18.0)
- Propensity
  - Propensity score weighting (age, sex, race, military operation, rank, branch, ISS, hAIS, tAIS, MOI) estimated with logistic regression
    (MatchIt R package, version 4.7.2)

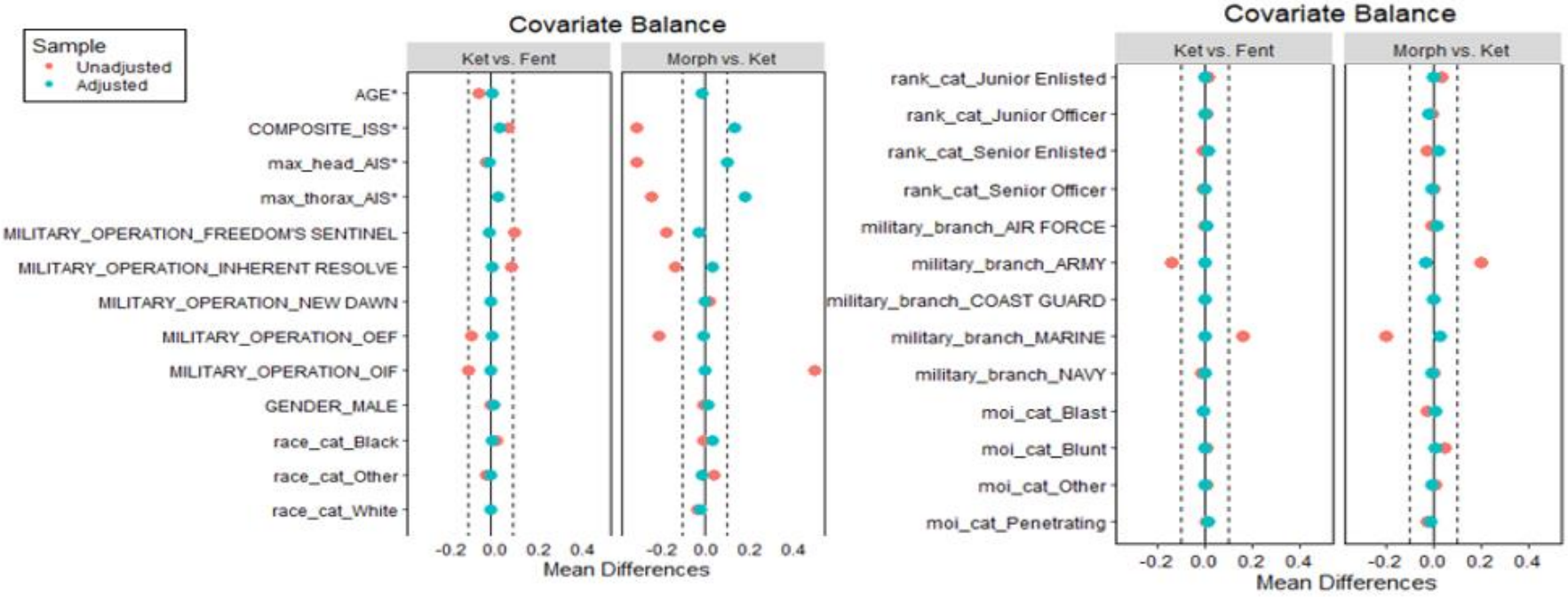
Methods: Univariable Analysis

- Demographic and injury variables correlated to analgesic type
- Compared distributions using chi square and the mood median test
  (Stats, base R package, version 4.4.3 and Survey R package, version 4.4-8)
- Compared balance before and after propensity score weighting
  (Cobalt R package, version 4.6.1)

Methods: Multivariable Analysis

- Aim 1: **Safety** – mortality and adverse outcomes
  - conditional logistic regression (Epi R package, version 2.60)
- Aim 2: **Effectiveness** – change in vital signs
  - linear regression (lme4 R package, version 1.1-37)
- Aim 2: **Effectiveness** – resource utilization
  - negative binomial regression (glmmTMB R package, version 1.1.12)

Results: Post Weighting Balance



Results: Demographic Characteristics

	Ketamine (n=307)	Morphine (n=2,590)	Fentanyl (n=1,167)	Pre match P value	Post match P value
Age					
Median (IQR)	24 (22-29)	24 (21-28)	24 (22-29)	0.116	0.811
Gender					
Male	299 (97.4%)	2,511 (96.9%)	1,140 (97.7%)	0.438	0.282
Race					
White	254 (82.7%)	2,059 (79.5%)	965 (82.7%)	0.019	0.557
Black	33 (10.7%)	238 (9.2%)	89 (7.6%)		
Other	20 (6.5%)	293 (11.3%)	113 (9.7%)		
Rank					
Junior Enlisted	80 (26.1%)	756 (29.2%)	291 (24.9%)	0.130	0.886
Junior Officer	17 (5.5%)	118 (4.6%)	62 (5.3%)		
Senior Enlisted	208 (67.8%)	1,691 (65.3%)	798 (68.4%)		
Senior Officer	2 (0.7%)	25 (1.0%)	16 (1.4%)		
Branch					
Army	185 (60.3%)	2,087 (80.6%)	870 (74.6%)	<0.001	0.954
Air Force	7 (2.3%)	37 (1.4%)	27 (2.3%)		
Marine	109 (35.5%)	45 (15.6%)	233 (20.0%)		
Navy	6 (2.0%)	59 (2.3%)	37 (3.2%)		
Coast Guard	0 (0.0%)	2 (0.1%)	0 (0.0%)		
Military Operation					
OEF	206 (67.1%)	1,198 (46.3%)	884 (75.7%)	<0.001	0.826
OIF/New Dawn	0 (0.0%)	1,334 (51.5%)	125 (10.7%)		
Inherent Resolve	46 (15.0%)	41 (1.6%)	70 (6.0%)		
Freedom's Sentinel	55 (17.9%)	17 (0.7%)	88 (7.5%)		
Injury Year					
2004-2009	21 (6.8%)	1,530 (59.1%)	221 (18.9%)	<0.001	0.112
2010-2014	186 (60.6%)	1,005 (38.8%)	789 (67.6%)		
2015-2019	73 (23.8%)	40 (1.5%)	125 (10.7%)		
2020-2024	27 (8.8%)	15 (0.6%)	32 (2.7%)		

Results: Injury Characteristics

	Ketamine (n=307)	Morphine (n=2,590)	Fentanyl (n=1,167)	Pre match P value	Post match P value
Composite ISS					
Median (IQR)	9 (4-18)	6 (4-11)	9 (4-17)	<0.001	0.115
Max head AIS					
Median (IQR)	1 (0-2)	0 (0-1)	0 (0-2)	<0.001	0.464
Max thorax AIS					
Median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	<0.001	0.409
Number of pain doses					
Median (IQR)	1 (1,1)	1 (1, 1)	1 (1, 1)	<0.001	0.214
Mech of injury					
Blast	174 (56.7%)	1,407 (54.3%)	673 (57.7%)	0.002	0.999
Blunt	54 (17.6%)	573 (22.1%)	203 (17.4%)		
Penetrating	73 (23.8%)	538 (20.8%)	273 (23.4%)		
Other	6 (2.0%)	72 (2.8%)	18 (1.5%)		
Benzo administered					
Yes	59 (19.2%)	156 (6.0%)	165 (14.1%)	<0.001	0.023
Transfusion					
Yes	125 (40.7%)	584 (22.5%)	352 (30.2%)	<0.001	0.005
Shock index					
Median (IQR)	0.8 (0.6-1.0)	0.7 (0.6-0.8)	0.7 (0.6-0.9)	<0.001	0.001

Results: Aim 1 – Safety

	Ketamine (n=307)	Morphine (n=2,590)	Fentanyl (n=1,167)	Pre match P value	Post match P value
Airway outcomes	8 (2.6%)	22 (0.8%)	20 (1.7%)	0.006	0.043
CV outcomes	6 (2.0%)	36 (1.4%)	19 (1.6%)	0.680	0.384
Other outcomes	7 (2.3%)	30 (1.2%)	32 (2.7%)	0.002	0.531
Mortality	13 (4.2%)	29 (1.1%)	25 (2.1%)	<0.001	0.034

	Morphine OR (95% CI)	Fentanyl OR (95% CI)
Adverse Airway Events	0.15 (0.04, 0.53) *	1.27 (0.49, 3.30)
Adverse CV Events	0.58 (0.19, 1.83)	1.48 (0.53, 4.18)
Adverse Other Events	0.62 (0.20, 1.95)	1.18 (0.47, 2.98)
Mortality	1.16 (0.40, 3.36)	3.97 (1.35, 11.65) *

* Statistically significant (p<0.05)

Model adjusted for demographic variables, injury variables, transfusion, pain doses, and benzodiazepine.

Sensitivity Analysis	Morphine OR (95% CI)	Fentanyl OR (95% CI)
Adverse Airway Events	0.05 (0.00, 0.76) *	1.15 (0.42, 3.16)
Adverse CV Events	0.17 (0.02, 1.86)	1.08 (0.30, 3.82)
Adverse Other Events	1.29 (0.18, 9.40)	2.55 (0.67, 9.72)

* Statistically significant (p<0.05)

Only includes data from **2012+**

(sample size was too small to calculate OR for mortality)

Results: Aim 2 – Effectiveness (change in vital signs)

model 1 change in...	Morphine β (95% CI)	Fentanyl β (95% CI)
Systolic BP	-5.50 (-7.69, -3.31) *	-2.73 (-4.92, -0.55) *
Diastolic BP	-2.78 (-4.63, -0.93) *	-0.78 (-2.65, 1.10)
Resp Rate	-0.17 (-0.70, 0.37)	0.34 (-0.19, 0.87)
Heart Rate	-0.73 (-2.57, 1.11)	0.03 (-1.81, 1.87)
Oxygen Sat	-0.04 (-0.44, 0.36)	-0.24 (-0.64, 0.16)
GCS	-0.02 (-0.27, 0.23)	0.09 (-0.16, 0.33)
Pain Score	0.29 (-0.04, 0.62)	0.24 (-0.08, 0.57)

* Statistically significant (p<0.05)

Model adjusted for demographic variables, injury variables, transfusion, pain doses, and benzodiazepine.

model 2 change in...	Morphine β (95% CI)	Fentanyl β (95% CI)
Systolic BP	-5.44 (-8.22, -2.67) *	-3.46 (-6.24, -0.68) *
Diastolic BP	-4.10 (-6.13, -2.07) *	-1.56 (-3.64, 0.53)
Resp Rate	0.61 (-0.15, 1.37)	0.48 (-0.27, 1.23)
Heart Rate	-0.93 (-3.29, 1.43)	-0.45 (-2.85, 1.95)
Oxygen Sat	0.20 (-0.39, 0.79)	-0.41 (-1.01, 0.18)
GCS	-0.07 (-0.34, 0.20)	0.21 (-0.06, 0.47)
Pain Score	0.73 (0.19, 1.27) *	1.18 (0.65, 1.71) *

* Statistically significant (p<0.05)

Model adjusted for demographic variables, injury variables, transfusion, pain doses, and benzodiazepine.

This model only includes individuals with **confirmed timing** of prehospital and ER vitals

Results: Aim 2 – Effectiveness (resource utilization)

model 1	Morphine β (95% CI)	Fentanyl β (95% CI)
Hospital Days		
role 2	-0.33 (-0.54, -0.11) *	0.14 (-0.08, 0.36)
role 3	0.03 (-0.06, 0.12)	0.03 (-0.07, 0.13)
ICU Days		
role 2	-0.46 (-1.04, 0.12)	0.28 (-0.30, 0.86)
role 3	-0.10 (-0.27, 0.07)	0.07 (-0.11, 0.25)
Ventilator Days		
role 2	-1.28 (-1.73, -0.83) *	-0.04 (-0.43, 0.36)
role 3	-0.04 (-0.25, 0.17)	0.28 (0.06, 0.50) *

* Statistically significant (p<0.05)

Model adjusted for demographic variables, injury variables, **transfusion**, pain doses, and benzodiazepine.

model 2	Morphine β (95% CI)	Fentanyl β (95% CI)
Hospital Days		
role 2	-0.54 (-0.84, -0.25) *	-0.04 (-0.34, 0.26)
role 3	-0.03 (-0.15, 0.09)	0.00 (-0.12, 0.12)
ICU Days		
role 2	-0.29 (-1.12, 0.54)	0.36 (-0.48, 1.19)
role 3	-0.21 (-0.47, 0.05)	0.36 (-0.48, 1.19)
Ventilator Days		
role 2	-1.61 (-2.33, -0.89) *	-0.24 (-0.87, 0.39)
role 3	-0.11 (-0.46, 0.25)	0.34 (-0.03, 0.70)

* Statistically significant (p<0.05)

Model adjusted for demographic variables, injury variables, **shock index**, pain doses, and benzodiazepine.

Discussion: Study Limitations

- Medication administration and outcome assessment timing cannot be consistently or reliably assessed
- Pre-hospital data from austere battlefield environment is often incomplete or missing
- Long term outcomes were not evaluated
- Although propensity score weighting was used, there may still be some confounding from unmeasured variables

Discussion

- Those given ketamine had
  - higher odds of an adverse airway event (vs morphine)
  - lower odds of death (vs fentanyl)
  - minimal differences in most vital signs, but improved systolic blood pressure
  - longer Role 2 hospital stays and ventilator use (vs morphine)
  - shorter time on ventilator (vs fentanyl)

- More adverse airway events and longer resource use may be explained by ketamine being preferentially administered to more severely injured patients

- **Overall, Ketamine is a safe and effective analgesic for prehospital battlefield pain management and is at least comparable to morphine and fentanyl**

Acknowledgments

- I would like to thank my co-investigators
  - Dr. Jonathan Stallings
  - COL (Ret) Brian Sonka
  - COL Jennifer Gurney
  - Dr. Frank Butler
  - CAPT (Ret) Travis Deaton
  - MSG (Ret) Harold Montgomery
  - CDR Jan-Michael Van Gent
  - CDR Russell Wier
- And my colleagues
  - Dr. Caryn Stern
  - Marissa Rodriguez
  - Janet LaFauci
  - Keith Fischer
  - Brock Graham
  - Christopher Wells

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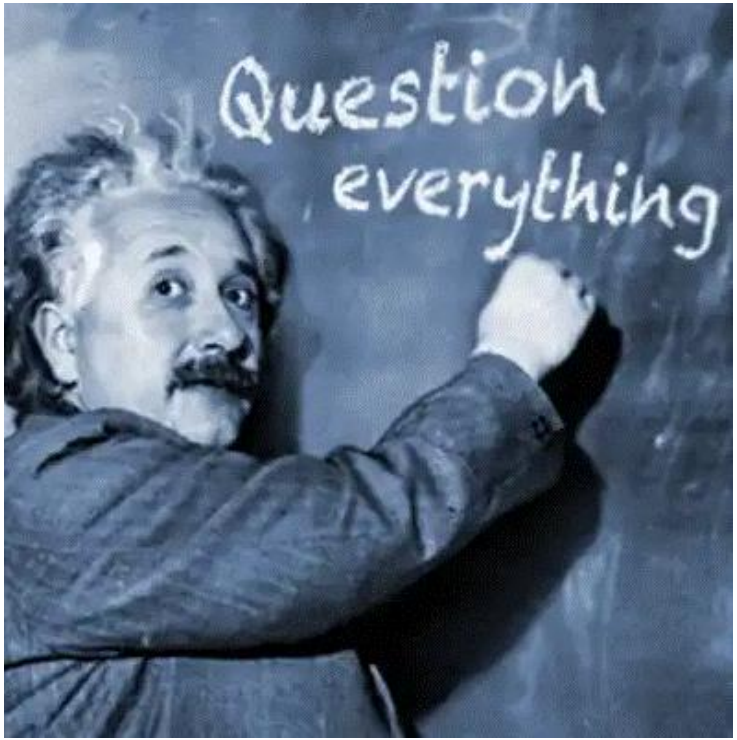
Questions



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Complication List

	DoDTR Complication pick list	ICD-9 code	ICD-10 code
Adverse Airway Events			
Aspiration	aspiration	934.x, 770.16	Y84.4
Intubation	Unplanned intubation	96.04, 96.05	0BH17EZ
Desaturation		799.02	R09.02
Respiratory arrest	Acute respiratory failure	518.51, 518.81	J96.00, J96.01
Narcan	(from medication list)		
Adverse Cardiovascular Events			
Arrhythmia	Major arrhythmia	427.0	I49.8
Hypertension		401.9, 405.9	I10, I15.9
Hypotension		458.x	I95.85, I95.9
Other Adverse Events			
Delirium	delirium	292.81, 293.0	F05
Adverse reaction	Adverse drug reaction	292, 292.1, 292.11, 292.12, 292.2, 292.8, 292.81, 292.89, 292.9, 693.0, 708, 995.0, 995.2, 995.22, 995.27, 995.29, E935.2, E935.7, E935.8, E938.2, E938.3, E938.4	T39.8X5, T39.8X5A, T40.695a, T41.0X5, T41.0X5A, T41.1X5, T41.1X5A, T41.2X5, T41.2X5A, T41.295, T41.295A
Vomiting		507.0, 787.0, 787.01, 787.03,	R11.10, R11.11
Nausea		787.02	R11.0
Antihistamine	(medication list)		