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INTRANASAL KETAMINE AS AN ADJUNCT TO FENTANYL FOR THE PREHOSPITAL TREATMENT OF ACUTE TRAUMATIC PAIN

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14. ABSTRACT Parenteral opiates, including fentanyl, are the mainstay of prehospital treatment of pain after traumatic injuries, but many experience suboptimal pain control. Ketamine is increasingly used/may offer opiate-sparing effects, but fentanyl w/ketamine is inadequately studied. We hypothesized adding intranasal ketamine (IK) to standard of care (SOC) fentanyl, compared to fentanyl alone, improves early pain control. **Methods:** A single center, placebo controlled, blinded, randomized clinical trial was conducted. Men 18-65 requiring SOC fentanyl to treat pain prehospital were screened/consented. Randomized to receive 50 milligrams (mg) IK or placebo, fentanyl route. The primary outcome was proportion of subjects experiencing two-point reduction in self-described pain on 11-point Verbal Numerical Rating Scale post IK/placebo administration. **Results:** 192, aged 36 [27-51] (median [IQR]) years old, rating pain of 10 [IQR 9-10] were enrolled. There was no difference in proportion experiencing improved pain thirty minutes after treatment (32/89 receiving fentanyl and placebo and 46/103 receiving fentanyl and IK, p=0.22) or at any time through 180 minutes. There was no difference in the proportion requiring additional pain medications at any time or those experiencing side effects/adverse events. **Conclusion:** 50mg IK to SOC fentanyl prehospital did not improve early pain management or reduce additional pain medication need.

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1.0 SUMMARY/DISCLAIMER

The following final technical report provides results regarding a clinical trial that explored the use of 50mg Intranasal Ketamine in addition to Fentanyl Standard of Care. The primary reasons were to determine if Intranasal Ketamine could improve early pain control after an injury and reduce the rates of PTSD and chronic pain 90 days after injury. The University of Cincinnati Institutional Review Board and the United States Air Force Human Research Protection Office approved the clinical trial. Intranasal ketamine administration was approved by the Food and Drug Administration under an Investigational New Drug application (IND: 131,895). The trial has been registered at ClinicalTrials.gov (NCT02866071). The final report will include information covering the methods, results for each research activity.

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2.0 ABSTRACT

Introduction: Parenteral opiates, including fentanyl, are the mainstay of prehospital treatment of pain after traumatic injuries, but many experience suboptimal pain control. Ketamine is increasingly used and may offer opiate-sparing effects, but the combination of fentanyl and ketamine is inadequately studied. Early pain management, with or without ketamine, may decrease the risk of developing PTSD and/or chronic pain. We hypothesized that adding intranasal ketamine to standard of care fentanyl, compared to fentanyl alone, improves early pain control after an injury and reduces the rates of PTSD and chronic pain 90 days after injury.

2.1. Methods

This single center, placebo controlled, blinded, randomized clinical trial was conducted by our region's largest, urban, fire-based EMS agency and only adult Level I Trauma Center. Consecutive men, ages 18-65 years, requiring standard of care fentanyl to treat severe acute traumatic pain prior to hospital arrival were screened for inclusion. Women were excluded because required pregnancy testing was not available. After obtaining informed consent, subjects were randomized to receive 50mg intranasal ketamine or placebo; fentanyl route and dose was determined by the treating paramedic as standard of care. The primary outcome was the proportion of subjects experiencing at least a two-point reduction in self-described pain on the 11-point Verbal Numerical Rating Scale (VNRS) administered thirty minutes after ketamine/placebo administration. Secondary outcomes included adverse events, pain control, and the need for additional pain medications through three hours of care. The study was powered to detect a 20% absolute difference in the proportion of subjects meeting the primary outcome. Analyses used descriptive statistics and Chi-square testing. To assess for PTSD and chronic pain development, enrolled subjects were recruited to complete additional surveys prior to discharge and at 90-days.

2.2. Results

192 men aged 36 [27-51] (median [IQR]) years old, rating pain of 10 [9-10] were enrolled and analyzed. There was no difference in the proportion experiencing improved pain thirty minutes after treatment (32/89 receiving fentanyl and placebo and 46/103 receiving fentanyl and ketamine, $p=0.22$) or at any time point through 180 minutes. There was no difference in the proportion requiring additional pain medications at any time point or those experiencing side effects or adverse events. Prior to discharge after the index injury, 154 subjects agreed to 90-day follow-up, with 96/154 completing all follow-up assessments. At 90-days, there was no difference in the rate of PTSD development (7/39 receiving fentanyl and placebo and 7/49 receiving fentanyl and ketamine, $p=0.165$), pain severity or pain interference with activities, or overall satisfaction with life ($p>0.9$).

2.3. Conclusion

Adding 50mg intranasal ketamine to standard of care fentanyl prior to hospital arrival did not improve early pain management or reduce additional pain medication need. Other strategies for prehospital pain management may be more effective. There were no long-term benefits with the addition of ketamine to standard of care fentanyl.

3.0 BACKGROUND

Pain management after an acute traumatic injury is a fundamental part of trauma care [1] and treatment of acute pain after injury has been identified as a need by the US military [2]. There is little to no comparative evidence to guide decision-making about treatment of severe, acute, pain in the prehospital setting (i.e., preferred agent, dose, route of administration accounting for efficacy, onset, feasibility of use, and adverse effects) [3].

The ideal agent should be administered without requiring intravenous (IV) access, have a short onset of action, and minimally impact hemodynamic or respiratory status. Fentanyl meets many of these characteristics but, as an opiate, may lead to respiratory depression at higher doses [4-6]. Ketamine, a non-opiate N-methyl-D-aspartate (NMDA)-receptor antagonist, is a promising agent that also meets the attributes of an ideal agent for field care of the injured soldier. Ketamine has been used by prehospital providers for more than a decade [7-9] including the resource constrained environments of civilian EMS in Vietnam [9] and Iraq [10]. Ketamine, alone or combined with opiates, is the most common analgesic used on the battlefield by the US military [11]. The use of ketamine with a short acting opiate such as fentanyl may have a synergistic analgesic effect [12] such that higher doses of narcotics can be avoided while maintaining a calm and comfortable patient. When used in Afghanistan by US Special Forces medics at the point of injury or during tactical evacuation, the combination of fentanyl and ketamine was as safe as use of morphine alone [13].

As a secondary consequence, effective acute pain management may have beneficial long-term effects, such as reducing the development of post-traumatic stress disorder (PTSD) and chronic pain syndromes. Even in the civilian environment, development of chronic pain [14] or PTSD [15,16] is common after injury. The early administration of morphine, and to a lesser extent fentanyl, has a decreased association with PTSD development in combat casualties [17,18]. Early ketamine has not been evaluated, but intra-operative ketamine has been associated with decreased PTSD in burned soldiers [19] and single-dose ketamine may be an effective treatment of chronic PTSD [20]. A Cochrane review suggests that intravenous ketamine may decrease the risk of chronic pain [21]. The Tactical Combat Casualty Care (TCCC) analgesia guidelines have recently been updated to prioritize the use of fentanyl and ketamine as first line agents for management of acute pain in the combat setting. The use of ketamine in US combatants has been approved at the level of the Assistant Secretary of Defense/Health Affairs. Ketamine has replaced morphine as the most frequently used analgesic agent in the military setting [11].

The primary objective of the trial is to determine whether the addition of intranasal ketamine to fentanyl is more effective for the treatment of acute traumatic pain than administration of fentanyl alone. Secondary outcomes include reduction in reported pain at the time of ED arrival and at 30 minutes intervals for up to three hours of ED care; the incidence of adverse events; additional opiate requirements prior to ED arrival and within the first three hours of ED care; overall satisfaction with life and development of post-traumatic stress disorder or chronic pain at 90-days after injury as measured by the Satisfaction With Life Scale, PTSD Checklist for DSM-5, and the Brief Pain Inventory, respectively.

4.0 METHODS

4.1. Design

We performed a single center, placebo controlled, blinded, randomized clinical trial conducted 10/3/2017 to 12/31/2021. Enrollment was paused 3/13/2020 to 5/31/2021 due to COVID-19. The trial methods [22] and regulatory approval process [23] have been previously published. The study was approved by the University of Cincinnati Institutional Review Board and the United States Air Force Human Research Protection Office. Intranasal ketamine administration was approved by the Food and Drug Administration under an Investigational New Drug application (IND: 131,895). The trial has been registered at ClinicalTrials.gov (NCT02866071).

4.2. Interventions and Duration

Adult men qualifying for prehospital pain treatment under paramedic standing orders were screened for inclusion. Paramedics obtained signed informed consent to administer study drug and for up to three hours of observation in the ED. After ED arrival, subjects who consented for the primary trial were approached to provide additional informed consent for inclusion in the follow-up trial.

Prehospital consent for primary trial enrollment and study drug administration occurred concurrent with receiving a single dose fentanyl (IV, IM, or IN per current standard practice). Consenting subjects were 1:1 randomized to receive either 50mg IN ketamine or IN saline placebo. Subjects rated pain on a 0-10 scale by the subject prior to treatment and at 30 minutes following treatment, with additional pain assessments at 30-minute intervals for the first three hours of their ED care. Additional pain medications given prior to hospital arrival and within the first three hours of ED care were be recorded. Baseline overall satisfaction with life and symptoms of PTSD and chronic pain were assessed before hospital disposition (in-person) and via phone follow-up at 90-days (+/- 14 days) after injury.

4.3. Data Safety and Monitoring

A trial-appointed study monitor oversaw protocol compliance and data reporting. A data safety and monitoring board used interim safety and outcomes data to make recommendations on trial continuation or suspension.

4.4. Study Setting and Organization

The University of Cincinnati and Cincinnati Fire Department (CFD) partnered for this trial. CFD is a large, urban, fire-based EMS agency that is the sole 911 responder for the City of Cincinnati. All first-responding fire apparatus and ambulances are staffed with at least one paramedic. University of Cincinnati Medical Center (UCMC) is the region's only adult Level I Trauma Center, and CFD represents approximately 85% of ground EMS volume to UCMC's Center for Emergency Care.

4.5. Selection of Subjects

Adults (18-65 years old) experiencing acute pain after trauma were considered for enrollment if paramedics planned to administer parenteral fentanyl as part of standard of care. Females were excluded due to the inability to perform pregnancy testing. Complete inclusion and exclusion criteria are shown in the Box.

4.6. Interventions

All subjects received intravenous or intramuscular fentanyl at the dose and route of the paramedic's discretion based on local protocols. During the trial, the maximum initial dose of fentanyl was changed from 50mcg to 100mcg. After informed consent was obtained and documented, subjects received a single intranasal dose of 50mg ketamine, or matching volume of saline placebo. All other treatments, including additional pain medications, were determined by the prehospital and emergency department clinical teams. Subjects, paramedics, emergency department staff, and study team members were blinded to the study intervention.

The single dose of 50mg was based on existing clinical practice and TCCC recommendations [24]. Based on the bioavailability of ketamine after intranasal administration [25,26], the dose is equivalent to 18-23mg given intravenously and within the typical 0.1-0.3 mg/kg range for treating pain in an adult.

4.7. Randomization

Study kits containing ketamine (or placebo) were prepared by the investigational pharmacy in a 1:1 randomized ratio using permuted small blocks with no stratification or control for imbalance. Each EMS unit was stocked with a single study kit, and kits were replaced after each enrollment.

4.8. Outcomes

The primary outcome was the proportion of subjects experiencing a two-point reduction in pain at 30 minutes after study drug administration. Pain was self-reported by subjects using the eleven-point (0-10) Verbal Numerical Rating Scale (VNRS). 27,28 Secondary outcomes included pain control measured every thirty minutes after hospital arrival for three hours, additional pain medication use through three hours, and side effects at arrival and after three hours. Total opiate use will be converted to "morphine equivalents" for statistical comparisons (Appendix 4 Opiate Conversion) [29]. Side effects were assessed using the Side Effects Rating Scale for Dissociative Anesthetics (SERSDA) [30,31], the Richmond Agitation-Sedation Scale (RASS) [32] and select items from the General Assessment of Side Effects (GASE) tool. Except for the "general discomfort" item on the SERSDA, any side effect rated as "bothersome" or "very bothersome" was considered an adverse event. Sedation at ED arrival and after 3 hours was assessed using the Richmond Agitation-Sedation Scale (RASS).

To evaluate for longer-term outcomes, symptoms of PTSD [33], chronic pain [34], and overall satisfaction with life [35] were assessed prior to the time of hospital disposition and three months after enrollment. A score of 33 or more (out of 80) on the PTSD Checklist for DSM-5 (PCL-5) tool is indicative of possible PTSD and considered positive in analysis; any subject with a "positive" score was referred to a hospital-based stress center for further evaluation and care. The Brief Pain Inventory (BPI) short form was used to assess the severity of pain and its impact on function. Subjects score several domains on a zero (none/does not interfere) to ten (as bad as can be imagined/completely interferes). The Satisfaction with Life Scale (SWLS) assesses the subject's overall satisfaction with their life and classifies into one of seven ranked categories from "extremely satisfied" to "extremely dissatisfied."

4.9. Sample size and Power

A 2-point reduction in pain is considered clinically significant, and thus our primary outcome compared the proportion of subjects achieving a 2-point reduction in pain at 30 minutes post-medication administration between the treatment group and the control group. Sample size considerations were based on this primary analysis, using an intent to treat approach. A 20% difference in the proportion of subjects experiencing important pain relief was felt to be a reasonable threshold to prompt operational changes or changes in care guidelines. We expected the response rate in the two groups to be 40% and 60%, respectively, based on the response rates in a study comparing pain management efficacy between subjects treated with morphine alone and morphine plus ketamine [36]. With this magnitude of effect, a sample size of 97 per group would have 80% power to detect the difference between the two groups when the critical level of significance is set to 5%. To allow for subject drop-out, protocol deviations, and missing outcome data, we planned to enroll up to an additional 15% in each arm, for a maximum total of 224 subjects.

4.10. Data Analysis

Primary and secondary outcomes were analyzed on an intention-to-treat basis. The Chi-Square Test was used to compare the proportion of subjects with a two-point reduction in pain. The difference in proportions with 95% confidence intervals was also computed.

Sensitivity analyses for the primary and secondary outcomes were performed using a per-protocol approach. These analyses include all randomized participants who correctly received the assigned treatment (study drug or placebo) and did not incur any major protocol deviations or violations, with participants classified according to the treatment they received. Exclusions were based on major protocol violations defined prior to unblinding: i) found to violate any inclusion or exclusion criterion ii) administration of study treatments in a manner inconsistent with the protocol.

5.0 RESULTS

5.1. Subject Characteristics

Of 569 men receiving fentanyl as part of prehospital clinical care, 199 were randomized, and 192 included in the primary analysis (103/192 receiving intranasal ketamine and 89/192 receiving placebo, Figure). Two subjects were enrolled twice, with each randomized to each of the interventions. Reasons for non-enrollment are further described in Table 1; subject demographic and clinical characteristics are shown in Table 2.

Dose and route of initial pain treatment was incompletely documented in the prehospital care reports. For subjects receiving placebo, initial prehospital fentanyl was given intravenously (48/70, median dose 100mcg), intramuscularly (10/70, median dose 100mcg), or intranasally (12/70, median dose 50mcg). Subjects receiving ketamine were treated similarly (intravenous 48/88, 100mcg; intramuscular 19/88, 75mcg; intranasal 19/88, 100mcg; intraosseous 2/88, 100mcg).

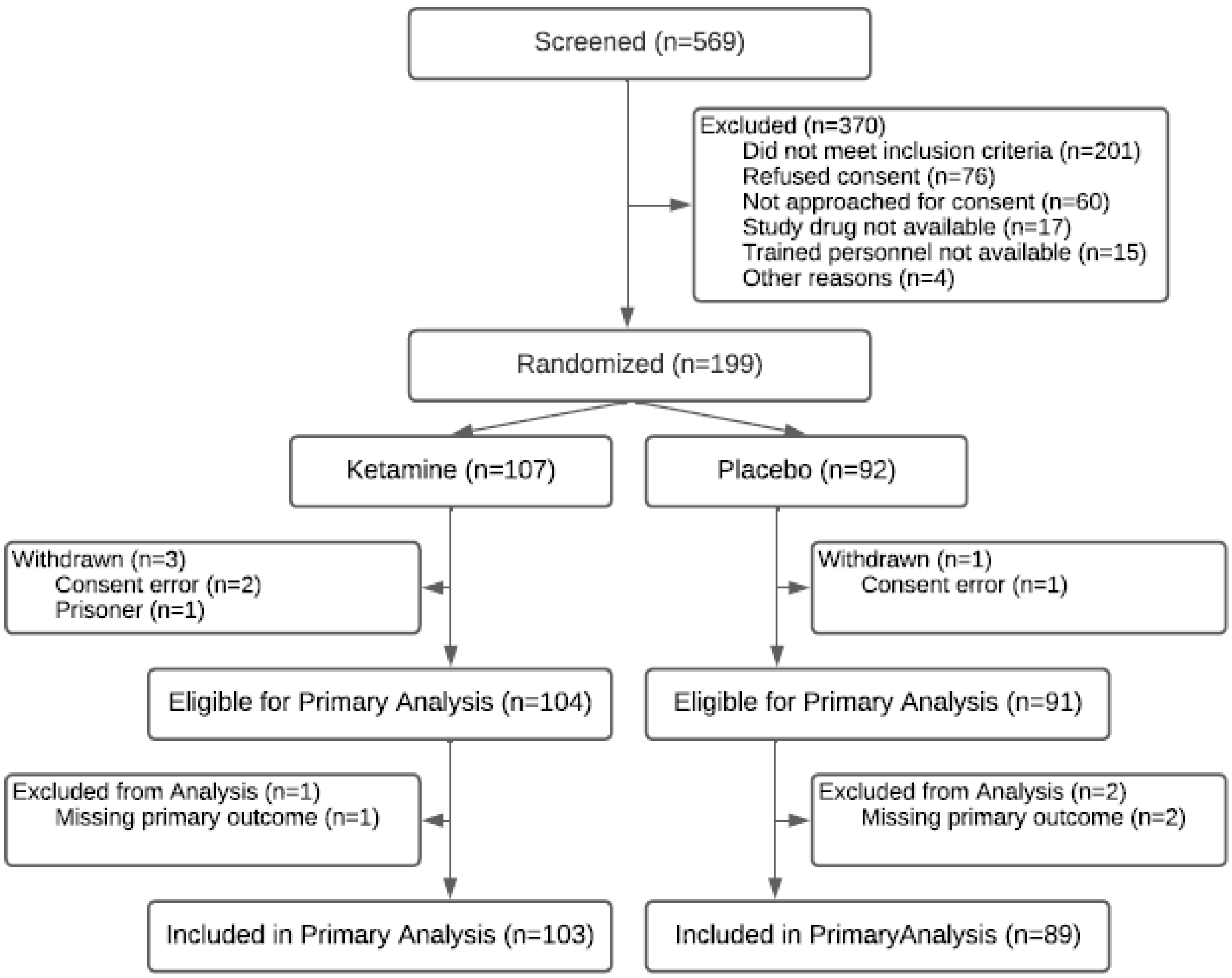

Table 1: Screened participants (unenrolled). Multiple exclusion reasons are possible

	N
Unenrolled Eligible Patients (n=169)	
Approached but refused consent	76
Not approached	60
No box available	17
Paramedic not trained	15
Other	4
Ineligible Patients (n=201)	
Age < 18 or >65	49
Altered level of consciousness, mental status change, or suspected head injury	30
Systolic blood pressure >=180mmHg	29
Pain not due to acute trauma	23
Systolic blood pressure < 100mmHg	20
Paramedic judgment that subject cannot consent due to underlying cognitive impairment.	20
Facial injury or suspicion of nasal bone fracture	18
VNRS < 7	14
Not English-speaking	9
Other	8
Prisoners or those in police custody	5
EMS treatment with ketamine (any), morphine (any), or >50mcg of fentanyl prior to enrollment	3
Paramedic clinical concern of circulatory shock)	3
Subject reported allergy to morphine, fentanyl, or ketamine	1
Inter-facility transfers	1

VNRS: verbal numerical rating scale

Table 2. Participant characteristics by randomization group

	Placebo		Ketamine		Total	
Age	33	(25, 50)	42	(30, 53)	36	(27, 51)
Race						
Black	49	(55)	45	(44)	94	(49)
White	35	(39)	54	(52)	89	(46)
Other	3	(3)	3	(3)	6	(3)
Unknown	2	(2)	1	(1)	3	(2)
Ethnicity						
Not Hispanic or Latino	83	(93)	101	(98)	184	(96)
Unknown	4	(4)	2	(2)	6	(3)
Hispanic or Latino	2	(2)	0	(0)	2	(1)
BMI	26	(23, 29)	27	(23, 31)	26	(23, 30)
Pre-treatment pain assessment	10	(9, 10)	10	(9, 10)	10	(9, 10)
Study Medication to ED Arrival (minutes)	14	(8.5, 19.5)	14	(10.0, 18.0)	14	(10.0, 19.0)
Initial Vital Signs						
Heart rate (bpm)*	93	(82, 101)	93	(78, 103)	93	(81. 101)
Systolic blood pressure (mmHg)*	140	(126, 152)	142	(127, 160)	141	(127, 156)
Diastolic blood pressure (mmHg)*	90	(76, 95)	85	(80, 98)	86	(78, 97)
Mean Arterial Pressure (Baseline)	107	(93, 115)	106	(93, 120)	107	(93, 116)
ISS	4	(4, 9)	4	(2, 9)	4	(2, 9)
ISS 15+	2	(3)	5	(6)	7	(5)
Blunt Injury	65	(73)	76	(74)	141	(73)
Fall	21	(32)	32	(42)	53	(38)
Machinery	3	(5)	6	(8)	9	(6)
Motor vehicle collision	13	(20)	10	(13)	23	(16)
Motorcycle	5	(8)	5	(7)	10	(7)
Other	10	(15)	8	(11)	18	(13)
Pedestrian Struck	2	(3)	8	(11)	10	(7)
Assault	9	(14)	5	(7)	14	(10)
Bicycle	2	(3)	2	(3)	4	(3)
Penetrating Injury	25	(28)	27	(26)	52	(27)
Gunshot Wound	18	(72)	14	(52)	32	(62)
Stabbing (knife)	2	(8)	3	(11)	5	(10)
Impalement	1	(4)	1	(4)	2	(4)
Other	4	(16)	9	(33)	13	(25)
ED Disposition						
Admit ED Observation	4	(6)	5	(6)	9	(6)
Admit medical floor	22	(31)	29	(35)	51	(33)
Admit ICU	2	(3)	3	(4)	5	(3)
Admit operating room	8	(11)	14	(17)	22	(14)

Discharge AMA	1	(1)	0	(0)	1	(1)
Discharge Home	33	(47)	32	(39)	65	(42)

ISS: injury severity score; ICU: intensive care unit; AMA: against medical advice. *Not all categories are equal due to not documented and not reported elements. Continuous variables presented as median (IQR); categorical variables presented as n (%).

5.2. Primary Outcome

Thirty minutes after receiving study medication, 32/89 given placebo and 46/103 given ketamine reported at least 2-points of pain reduction (difference in proportions 0.087 (95%CI -0.051-0.225, p=0.221) (Table 3).

Table 3. Reported pain reduction of two or more points between the VNRS obtained prior to treatment by EMS (baseline) and the VNRS obtained at each timepoint over up to three hours

	Placebo		Ketamine		Total	
	N	%	N	%	N	%
30 minutes post dose	32	(36)	46	(45)	78	(41)
30 minutes after ED arrival	30	(36)	44	(46)	74	(41)
60 minutes after ED arrival	39	(48)	47	(50)	86	(49)
90 minutes after ED arrival	34	(47)	47	(54)	81	(51)
120 minutes after ED arrival	41	(55)	47	(57)	88	(56)
150 minutes after ED arrival	40	(61)	45	(56)	85	(58)
180 minutes after ED arrival	34	(56)	44	(62)	78	(59)

VNRS: verbal numerical rating scale; EMS: emergency medical services. Not all subjects were assessed at all time points after ED arrival: 30 minutes (n=179), 60 minutes (n=175), 90 minutes (n=159), 120 minutes (n=156), 150 minutes (n=146), 180 minutes (n=132).

5.3. Secondary Outcome

Pain over three hours of Emergency Department care, the proportion of those needing additional pain medications, and the total amount of pain medications received were similar (Tables 3 and 4). Adverse events were largely expected (31/89 vs 37/103, difference in proportions 0.011 (95%CI -0.125, 0.146, p=0.875) and side effects were mostly minor and common, with similar occurrences between groups (Tables 5 and 6).

Table 4. Requirements for additional pain medication prior to hospital arrival or in the first three hours of ED care

	Placebo		Ketamine		Total	
Subjects Receiving Additional Prehospital Pain Medication	15	(17)	15	(15)	30	(16)
Total Prehospital* MME	10	(10, 10)	10	(8, 10)	10	(10, 10)

Subjects Receiving Additional ED Pain Medication	67	(75)	65	(63)	132	(69)
Total ED MME**	8	(5, 20)	10	(5, 20)	10	(5, 20)

Continuous variables presented as median (IQR); categorical variables presented as n (%). MME: morphine milligram equivalents
*For participants who received additional doses. Excludes the first recorded dose of fentanyl.
**For participants who received additional doses. Includes all doses given in the ED

Table 5. Adverse events by study group

	Placebo		Ketamine		Total	
	N	%	N	%	N	%
Any adverse event	31	(35)	37	(36)	68	(35)
Any expected adverse event	30	(34)	34	(33)	64	(33)
Any unexpected adverse event	2	(2)	3	(3)	5	(3)
Any serious adverse event	0	(0)	0	(0)	0	(0)
Any predefined serious adverse event	0	(0)	0	(0)	0	(0)

Side effects are considered adverse events. Expected adverse events are attributed to known side effects of ketamine. Predefined serious adverse events included respiratory depression requiring intervention, endotracheal intubation, laryngospasm, elevated blood pressure requiring treatment, agitation/hallucination requiring treatment, or anaphylaxis within six hours of study drug administration.

Table 6. Side effects rated bothersome or very bothersome at ED arrival by study group

	Placebo		Ketamine	
	N	%	N	%
Fatigue	9	(10.8)	7	(7.3)
Dizziness	1	(1.2)	8	(8.3)
Nausea	2	(2.4)	4	(4.2)
Headache	2	(2.4)	5	(5.2)
Feeling of unreality	2	(2.4)	4	(4.2)
Changes in hearing	1	(1.2)	0	(.0)
Changes in vision	0	(.0)	2	(2.1)
Mood change	3	(3.6)	9	(9.5)
Generalized discomfort	28	(33.7)	25	(26.3)
Hallucination	0	(.0)	0	(.0)
Dry mouth	20	(24.1)	19	(20.0)
Abdominal pain	3	(3.7)	0	(.0)
Breathing problems	3	(3.6)	1	(1.1)
Vomiting	1	(1.2)	0	(.0)
Skin rash or itching	0	(.0)	0	(.0)
Agitation	9	(10.8)	5	(5.3)
Irritability, nervousness	8	(9.6)	7	(7.4)
Anxiety	5	(6.0)	7	(7.4)

Items are from the Side Effects Rating Scale for Dissociative Anesthetics

5.4. Follow-up Outcomes

Of the subjects included in the primary analysis, 152/192 consented for the additional assessments for pain and PTSD and the 90-day follow-up. Five subjects were withdrawn during the follow-up interval (3 became a prisoner, 1 died, and one consent was signed by the legally authorized representative instead of the subject), 51 were lost to follow-up, and four refused to complete the 90-day assessments. Of the 96 subjects with complete 90-day outcomes, 54/96 received intranasal ketamine and 42/96 received placebo.

There was no difference in the proportions of subjects developing PTSD (based on PCL-5) or new dissatisfaction with quality of life (based on SWLS) (Table 7, p=ns). There was no difference in PTSD symptoms (PCL-5), pain symptoms (BPI severity and interference), or quality of life (SWLS) among groups (Table 8).

Table 7. PTSD and Satisfaction with Life outcomes by group

		Placebo		Ketamine		Total	
		N	%	N	%	N	%
New PTSD positive PCL-5 at 90 days							
	Yes	7	(19)	7	(16)	14	(17)
	No	30	(81)	38	(84)	68	(83)
	Total	37	(100)	45	(100)	82	(100)
New Dissatisfaction with Life on SWLS at 90 days							
	Yes	11	(30)	6	(14)	17	(21)
	No	26	(70)	37	(86)	63	(79)
	Total	37	(100)	43	(100)	80	(100)

PCL-5: PTSD Checklist for DSM 5; SWLS: Satisfaction With Life Scale.

Table 8. Difference in median PCL-5, BPI, and SWLS scores at 90 days with 95% confidence intervals

	Placebo			Ketamine				95% CI		
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	Diff	Lower	Upper	P Value
PCL-5	15	6	36	18	1	27	3	-4.00	8.00	0.904
BPI Severity	1	0	1	1	0	2	0	-0.50	0.25	0.989
BPI Interference	0	0	0	0	0	0	0	0.00	0.00	0.935
Satisfaction with Life Scale Total Score	21	15	30	26	17	30	-2	-6.00	2.00	0.153

PCL-5: PTSD Checklist for DSM 5; BPI: Brief Pain Inventory; SWLS: Satisfaction With Life Scale. Higher PCL-5 and BPI scores portray more negative outcomes; high SWLS scores represent better outcomes. PCL-5 ≥33 is indicative of possible PTSD

5.5. Sensitivity Analyses

There was no difference in outcomes between primary and sensitivity analyses.

6.0 DISCUSSION

In this prehospital randomized clinical trial, there was no difference in the proportion of patients achieving clinically significant reduction in pain 30 minutes after receiving a combination of intranasal ketamine and fentanyl (46/103) compared to fentanyl alone (32/89). Intranasal ketamine did not impact additional pain medication requirements prior to hospital arrival or during the first three hours of care, and there was no change in pain, PTSD, or quality of life outcomes 90 days after injury.

Our methodologies may have had an impact on the observed outcomes. To our knowledge, this trial is the first time paramedics in the United States obtained informed consent for research. Pain research most often enrolls subjects in the emergency department and excludes those receiving prehospital pain management; our prehospital enrollment captures hyperacute therapy at the point of injury and during initial en route care. However, the requirement for consent may have excluded those with the most potential benefit, as our subjects were not severely injured. Paramedics excluded several subjects based on perceived inability to provide consent, and many others refused consent, possibly due to more severe pain or trauma. While we were unable to obtain any type of alteration or exception from the consent from the FDA during trial planning, our experience (and limitations) contributed to investigators in the LITES network receiving approval for Exception From Informed Consent for the upcoming PAIN trial (intravenous fentanyl vs. intravenous ketamine).

Ketamine was administered via the intranasal route in this trial, whereas other studies comparing a combination of opiates and ketamine to opiates alone used the intravenous route. Intranasal administration has reduced bioavailability, and poor technique may result in drug condensing in the posterior nasopharynx instead of being distributed to the nasal mucosa. At least 31 subjects received intranasal fentanyl as part of initial care, which may have saturated the nasal mucosa prior to ketamine administration, but route of administration was similar between groups/

We powered the study to detect a 20% effect size and using conservative estimates of the efficacy of fentanyl alone. Our 36% response rate with standard of care fentanyl is comparable to other studies evaluating opiates to control prehospital pain. We observed an approximate 10% absolute improvement in pain reduction with intranasal ketamine. However, a trial to confirm the statistical significance of our observed difference would require almost 1000 subjects.

While adding ketamine was not effective in any measured outcome, ketamine did not increase the risk of any adverse events. Importantly, there was no difference in sedation after receiving ketamine and fentanyl, and no episodes of laryngospasm or emergence phenomenon. These findings suggest that a single 50mg intranasal dose of ketamine is safe.

Finally, this trial evaluated the benefit of adding intranasal ketamine to standard of care fentanyl, with the majority of doses given intravenous or intramuscular. Results may differ when intranasal ketamine is added to transmucosal fentanyl. Our findings cannot be directly compared to trials evaluating ketamine vs. fentanyl as a single agent.

CONCLUSION

While safe, a single intranasal 50mg dose of ketamine offers no additive benefit to standard of care fentanyl to early pain control, early need for additional pain medications, or important functional outcomes after 90 days. Other strategies for prehospital pain management may be more effective.

7.0 REFERENCES

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LIST OF SYMBOLS, ABBREVIATIONS and ACRONYMS

%: Percent
-: Minus
+: Plus
<: Less Than
=: Equals
>: Greater Than
BPI: Brief Pain Inventory
CFD: Cincinnati Fire Department
COVID-19: Caronavirus Disease
DSM: Diagnostic and Statistical Manual
ED: Emergency Department
EMS: Emergency Medical Services
GASE: General Assessment of Side Effects
HPW: Human Performance Wing
IK: Intranasal Ketamine
IM: Intramuscular
IN: Intranasal
IND: Investigational New Drug
IQR: InterQuartile Range
IV: Intravenous
Kg: Kilograms
LITES: Linking Investigations in Trauma and Emergency Services
Mcg: Micrograms
Mg: Milligrams
MME: Morphine Milligram Equivalents
mmHg: Millimeters of Mercury
NMDA: non-opiate N-methyl-D-aspartate
PCL-5: Post Traumatic Stress Disorder Checklist
PTSD: Post Traumatic Stress Disorder
RASS: Richmond Agitation-Sedation Scale
SERSDA: Side Effects Rating Scale for Dissociative Anesthetics
SOC: Standard of Care
SWLS: The Satisfaction with Life Scale
TCCC: Tactical Combat Casualty Care
UCMC: University of Cincinnati Medical Center
US: United States
VNRS: Verbal Numerical Rating Scale