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Original Research

Evaluation of Nonintubated Analgesia Practices in Critical Care Transport

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A B S T R A C T

Objective: Current analgesia recommendations in the prehospital setting are not specific to critical care transport. Variation exists in the recommended agent and dosing strategies. Furthermore, there is a paucity of literature evaluating benzodiazepine and opiate coadministration, which may place patients at risk for respiratory decompensation.

Methods: This was a retrospective chart review of nonintubated adult critical care transport patients between July 1, 2020, and July 1, 2022, who received fentanyl or ketamine during transport. The primary outcome was the proportion of patients oversedated. The secondary outcomes were characterization of analgesic medication use during transport, the percentage of patients coadministered benzodiazepines, naloxone administration, and escalation of respiratory intervention.

Results: Three hundred seventy-six patients were administered fentanyl or ketamine during transport. Eleven patients were oversedated. Three hundred twenty-four patients received fentanyl monotherapy, and 52 received combination therapy. Patients who received benzodiazepines had higher odds of oversedation (odds ratio = 5.75; 95% confidence interval, 1.6-20.7). Two hundred thirty-six patients required an escalation in respiratory support, most commonly an increase from room air to nasal cannula. No patients had naloxone administered.

Conclusion: The rate of oversedation of nonintubated adult critical care transport patients receiving fentanyl or ketamine is low. Coadministration of benzodiazepines increases the risk of oversedation.

Current analgesia recommendations in the prehospital setting surround general prehospital transport, trauma populations, or military populations. Recent guidelines recommend intravenous (IV) acetaminophen or IV nonsteroidal anti-inflammatory medications over IV opiates alone for moderate to severe pain. IV ketamine was also described as an alternative to traditional IV opiate therapy; however, guidelines state that there is limited evidence to support the coadministration of IV ketamine and IV opiates.[1] Despite these guideline recommendations, the most common agents used for the treatment of moderate to severe pain consist of fentanyl, morphine, or ketamine.[2,3] These agents are likely preferred because of pharmacokinetic factors, rapid reduction in pain scores, and historic preferential use.[3] The overall evidence levels for analgesic selection and opioid administration are low.[3] We did not find any literature reviewing analgesia practices in the nonintubated critical care transport population. Furthermore, no literature exists reviewing adverse events when opiate analgesics, ketamine, and/or benzodiazepines are coadministered in this population.

Practice variations exist in agent selection and dosing based on a lack of standardization between state emergency medical service protocols, institution protocols, and guideline recommendations. Initial fentanyl dosing is described throughout the prehospital literature as either a weight-based (0.5-2 μg/kg intravenously) or non–weight-based approach (25-100 μg intravenously).[2] Despite popularity in the literature, fentanyl dosing recommendations are not provided in the most recent prehospital analgesia guideline.[1] Ketamine is less frequently described with doses ranging from 10 to 30 mg intravenously for initial boluses.[2] Guideline recommendations reference emergency

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department literature of 0.1 to 0.3 mg/kg IV ketamine to be effective for pain management but do not recommend a defined dose in the prehospital transport setting.[1]

Prior quality improvement projects performed at this institution showed that intubated patients arrived at the emergency department deeply sedated. Studies have shown that among intubated critical care transport patients, moderate and deep levels of sedation, as well as benzodiazepine administration, were associated with an increase in hospital length of stay.[4] Although these reviews were completed in intubated patients, the risk of oversedation with analgesic medications in nonintubated patients could result in untoward adverse events. This could be further exacerbated when opiate medications are coadministered with benzodiazepines. A review article noted the increased mortality risk and respiratory decompensation for patients who received opioid and benzodiazepine coadministration.[5] The purpose of this review was to assess the current use of analgesic medications in the prehospital and critical care transport population, evaluate the rate of coadministration with benzodiazepines, and evaluate the safety of this practice.

Methods

Study Design and Patient Population

The patient population was a retrospective cohort of nonintubated adults (≥18 years old) transported via critical care transport from July 1, 2020, to July 1, 2022, who received IV or intranasal fentanyl or IV ketamine. Transport was performed using a helicopter and ground service based at the medical center and a second helicopter based at an airport approximately 80 miles away. The critical care transport team consisted of a nurse and paramedic crew. Patients were excluded if they were intubated pretransport or if they had a depressed mental status upon initial evaluation. A depressed mental status was defined as a Richmond Agitation Sedation Scale (RASS) score ≤ −3 and/ or a Glasgow Coma Scale (GCS) score ≤ 10. This study was approved by the hospital's institutional review board. A subgroup analysis was performed on fentanyl monotherapy versus combination therapy and traumatically injured patients. Combination therapy was defined as patients who received fentanyl and ketamine or an analgesic medication (fentanyl or ketamine) plus a benzodiazepine. Cohorts were determined by the medications administered during transport.

Data abstraction was performed through manual chart review. Patient contact time was calculated using the time of crew arrival at the patient's bedside as documented in the chart and handoff time to the receiving hospital unit. The primary outcome was the proportion of patients oversedated, which was defined as a RASS score ≤ −3 and/or a GCS score ≤ 10. The secondary outcomes included characterization of analgesic medication use during transport, the percentage of patients coadministered benzodiazepines, the percentage of patients who received naloxone, and escalation of respiratory intervention (defined as new oxygen requirement, escalation of oxygen delivery, or positive pressure ventilation). Study data were collected and managed using REDCap (Vanderbilt University, Nashville, TN).

Statistical Analysis

Statistical analysis was performed using STATA IC/16 (StataCorp, College Station, TX). The groups were compared using summary statistics. Continuous variables were presented as mean values with standard deviation or medians with interquartile ranges as appropriate. Categoric variables were presented as counts with percentages. Analysis was conducted using the Student *t*-test or Wilcoxon rank sum test for continuous variables and the Pearson chi-square test for categoric variables. A *P* value <.05 was considered statistically significant.

Results

Three hundred seventy-six patients met the inclusion criteria. Patient characteristics are displayed in Table 1. Two hundred sixty-two were male (69.7%), the mean contact time was 68.3 ± 23.3 minutes, 351 (93.4%) were transported by rotor wing, and 277 (73.7%) were interfacility transports. Traumatic injury accounted for a total of 174 (46.3%) of the transports. The initial pain score (range, 0-10) was 6.3 ± 2.7, the initial GCS was 14.8 ± 0.6, and the initial RASS was 0 (interquartile range, 0-1).

Eleven patients met the definition of oversedation at the end of transport (2.9%). A description of these patients is included in Supplemental Appendix 1. Of the subgroups, fentanyl monotherapy had a lower rate of oversedation than combination therapy (1.9% vs. 9.6%; odds ratio [OR] = 0.19; 95% confidence interval [CI], 0.05-0.6). Nontraumatically injured patients who received combination therapy were more likely to be oversedated (5.7% vs. 0.6%; OR = 1.4; 95% CI, 0.42-4.69) (Table 2). However, traumatically injured patients received a higher dose of fentanyl, but this did not impact the rate of oversedation.

Three hundred seventy-two patients (98.9%) of the cohort received fentanyl, and 86.2% received fentanyl monotherapy. The mean total quantity of fentanyl received during transport was 1.5 ± 1.1 μg/kg. There was not a statistically significant difference in the total fentanyl quantity between the oversedated and nonoversedated groups. Sixteen (4.3%) patients received ketamine, 3 of whom received ketamine monotherapy. Eleven of the 16 patients received ketamine in combination with fentanyl. The remaining patients received ketamine with benzodiazepines. The median total quantity of ketamine received during transport was 0.4 mg/kg (IQR, 0.3-0.7). Thirty-eight (10.1%) received coadministration of a benzodiazepine with fentanyl or ketamine. A description of the medication practices is provided in Table 3.

Of the 11 oversedated patients, 2 (18.2%) received a medication other than fentanyl first compared with 11 of the 365 (3%) of the nonoversedated group (OR = 0.14; 95% CI, 0.03-0.72). The total quantity of medication did not differ between groups (Table 3). Patients who received a benzodiazepine had higher odds of being oversedated (OR = 5.75; 95% CI, 1.60-20.7). The administration of midazolam was associated with higher rates of oversedation (27.3%) compared with lorazepam (18.2%).

A total of 236 (62.7%) patients had an escalation of oxygen therapy during transport. This was most frequently through a nasal cannula (54.5%). Two patients received noninvasive positive pressure ventilation, and four patients were intubated during transport. There was no administration of naloxone.

Discussion

Oversedation was infrequently observed in our cohort of nonintubated patients during critical care transport. The initial and total fentanyl doses administered were consistent with current practice guidelines and did not significantly differ between the oversedated and nonoversedated groups.[2] Traumatically injured patients received higher doses of fentanyl, but it did not impact the rate of oversedation. Acetaminophen and nonsteroidal anti-inflammatory drugs were not administered to patients in our cohort during transport. The coadministration of analgesics and benzodiazepines was associated with an increased rate of oversedation. In alternative settings, coadministration with opiate analgesics, ketamine, and benzodiazepines is often referred to as procedural sedation.[6] Although the rates of serious adverse events such as intubation during procedural sedation in emergency departments is low, critically ill patients may have rapid changes in respiratory drive and airway patency.[7] While sedation may not be intended at the time, the side effects of coadministration leads to higher rates of oversedation and should be weighed when choosing medication combinations during transport. Although

Table 1
Baseline Characteristics

Characteristic	All (N = 376)	Fentanyl Monotherapy (n = 324)	Combination Therapy (n = 52)	*P* Value
Age (y)	57.2 ± 17.2	57.9 ± 17.7	52.8 ± 17.0	.05
Male	262 (69.7)	225 (69.4)	99 (30.6)	.8
Weight (kg)	89.5 ± 23	89.3 ± 23.3	90.8 ± 23.3	.66
Patient contact time (min)	68.3 ± 23.3	67.6 ± 23	72.6 ± 25.3	.15
Transport mode				
Ground	25 (6.7)	23 (7.1)	2 (3.9)	.55
Rotor wing	351 (93.4)	301 (92.9)	50 (96.2)	
Transport type				
Scene	99 (26.3)	86 (26.5)	13 (25)	.82
Interfacility transfer	277 (73.7)	238 (73.5)	39 (75)	
Reason for transport				
Neurologic	19 (5.1)	18 (5.6)	1 (1.9)	.64
Medical	74 (19.7)	64 (19.8)	10 (19.2)	
Trauma	174 (46.3)	147 (45.4)	27 (51.9)	
Cardiac	109 (29)	95 (29.3)	14 (26.9)	
Receiving unit				
ED	244 (64.9)	210 (64.8)	43 (65.4)	.84
Floor	3 (0.8)	3 (0.9)	0 (0)	
ICU	47 (12.5)	42 (13)	5 (9.6)	
Other	82 (21.8)	69 (21.3)	13 (25)	
Initial GCS	14.8 ± 0.6	14.8 ± 0.6	14.7 ± 0.8	.67
Initial RASS	0 (0-1)	0 (0-0)	1 (0-2)	<.001
Initial pain score	6.3 ± 2.7	6.2 ± 2.6	7.1 ± 2.8	.03
Low pain score	3.6 ± 2.7	3.6 ± 2.6	3.6 ± 3.1	.95
Initial SBP (mm Hg)	132.3 ± 28.1	131.9 ± 28.2	134.6 ± 27.4	.53
Initial DBP (mm Hg)	79 ± 16.1	78.9 ± 16.3	80 ± 15.3	.63
Initial MAP (mm Hg)	96.7 ± 18.9	96.5 ± 19.1	98.2 ± 18	.56
Administered vasopressors	20 (5.3)	15 (4.6)	5 (9.6)	.17
Administered antihypertensives	96 (25.6)	85 (26.3)	11 (21.2)	.43
Initial RR	20.5 ± 9.3	20.4 ± 9.1	21.6 ± 10.7	.39
Initial oxygen requirement				
RA	226 (60.3)	192 (59.4)	34 (65.4)	.62
NC	119 (31.7)	104 (32.2)	15 (28.9)	
HFNC	1 (0.3)	1 (0.3)	0	
NRB	25 (6.7)	23 (7.1)	2 (3.9)	
BiPAP	4 (1.1)	3 (0.9)	1 (1.9)	

Values are mean ± standard deviation or n (%).
BiPAP = bilevel positive airway pressure; DBP = diastolic blood pressure; ED = emergency department; GCS = Glasgow Coma Scale; HFNC = high-flow nasal cannula; ICU = intensive care unit; IQR = interquartile range; MAP = mean arterial pressure; NC = nasal cannula; NRB = nonrebreather; RA = room air; RASS = Richmond Agitation and Sedation Scale; RR = respiratory rate; SBP = systolic blood pressure; SD = standard deviation.

for most patients who received escalation of oxygen therapy, it was in the form of a nasal cannula, the few patients who received noninvasive positive pressure ventilation or endotracheal intubation and mechanical ventilation highlight an opportunity for the administration of naloxone to reverse opiate-induced respiratory depression.

Despite a small percentage of patients with the primary outcome of oversedation, a review of these patients (Supplemental Appendix 1) showed that patients who received benzodiazepines during transport, received narcotics before arrival, had an underlying neurologic injury, and/or underwent deterioration of the shock state were at the highest risk of decompensation. Although conclusions cannot be drawn from this limited review, this can be hypothesis generating when thinking about treating different patient populations and the selection of high-risk medication combinations. For instance, patients who are prescribed buprenorphine versus opiate-naive patients with neurologic injury carry different levels of risk with the same dose of narcotic administered. Although the medication totals were within the recommended limits, the identification of high-risk patients offers the opportunity to change the bolus quantity or frequency of administration to mitigate risks while treating pain. In patients with a high risk of respiratory deterioration (eg, neurologically injured), the degree of pain reduction and administering subsequent doses of sedating medications should be weighed against the risk of respiratory or neurologic decompensation. The association of pain and anxiety in the transport environment is also challenging. Anxiety or agitation may represent a physiological deterioration or shock state versus feelings of worry and nervousness about an uncertain and rapidly changing environment. This highlights the importance of clinical evaluation and monitoring during critical care transport.

This retrospective review was conducted at a single transport agency, which may limit generalizability. Because of the nature of the transport environment, there was an incomplete evaluation of past medical history including assessments of renal and hepatic dysfunction, opiate naivety, or utilization of home medications for substance use disorder. Ideally, these factors should influence analgesic medication selection and dosing. Although this may not be obtainable at the

Table 2
Subgroup Analysis of Primary Outcome Results

Outcome	Fentanyl Monotherapy (n = 324)	Combination Therapy (n = 52)	*P* Value
Oversedated, n (%)	6 (1.9)	5 (9.6)	.01
Trauma patients oversedated, n (%)	4 (1.2)	2 (3.8)	.2
Nontrauma patients oversedated, n (%)	2 (0.6)	3 (5.7)	.02

Table 3
Description of Medication Use During Transport

Medication Information	All (N = 376)	Oversedated (n = 11)	Nonoversedated (n = 365)	*P* Value
Fentanyl	376 (98.9)	11 (100)	361 (98.9)	1.00
First medication	363 (96.5)	9 (81.8)	354 (97)	.05
Time to first dose (min)	10 [5-18.5]	10 [6-37]	10 [5-18]	.59
Time to second dose (min)	17 [10-25]	19 [4-20]	17 [10-25]	.34
Initial dose (μg)	50 [50-75]	50 [25-100]	50 [50-75]	.75
Total quantity (μg)	100 [50-150]	50 [25-150]	100 [50-150]	.34
Total quantity (μg/kg)	1.2 [0.68-1.98]	0.9 [0.4-1.7]	1.2 [0.7-2]	.36
Number of boluses	1 [1-2]	2 [1-3]	2 [1-2]	.53
Ketamine	16 (4.3)	3 (27.3)	13 (3.6)	.009
First medication	3 (0.8)	0	3 (0.8)	1.00
Time to first dose (min)	14 [5-20]	11 [10-17]	14.5 [5-23]	.87
Time to second dose (min)	10 [5.5-15]	18 [6-22]	10 [5-10]	.37
Initial dose (mg)	10 [10-12.5]	15 [9-20]	10 [10-10]	.49
Total quantity (mg)	36.4 [24-65]	70 [18-100]	32.8 [30-50]	.31
Total quantity (mg/kg)	0.4 [0.3-0.7]	0.8 [0.2-1.4]	0.4 [0.3-0.5]	.29
Number of boluses	2 [1-4]	1 [1-2]	3 [2-5]	.15
Lorazepam	28 (7.5)	2 (18.2)	26 (7.1)	.19
First medication	8 (2.1)	2 (18.2)	6 (1.6)	.02
Time to first dose (min)	19 [15-31]	23.5 [16-31]	19 [15-30]	.81
Time to second dose (min)	20 [15-30]	10 [10-10]	20 [15-32]	.44
Initial dose (mg)	0.5 [0.5-1]	1.3 [0.5-2]	0.5 [0.5-1]	.52
Total quantity (mg)	1 [0.5-2]	2 [2-2]	1 [0.5-2]	.2
Total quantity (mg/kg)	0.01 [0.01-0.02]	0.02 [0.02-0.02]	0.01 [0.01-0.02]	.23
Number of boluses	1 (1-2)	3 (3-3)	1 (1-1.5)	.44
Midazolam	10 (2.7)	3 (27.3)	7 (1.9)	.002
First medication	1 (0.3)	0	1 (0.3)	1.00
Time to first dose (min)	12.5 [7-29]	29 [7-50]	11 [6-29]	.43
Time to second dose (min)	11.5 [5-19]	17 [15-19]	6.5 [5-15.5]	.53
Initial dose (mg)	2 [1-2]	2 [2-2]	1 [1-2]	.33
Total quantity (mg)	2 [2-3]	3 [2-3]	1 [1-2]	.47
Total quantity (mg/kg)	0.03 [0.02-0.04]	0.03 [0.02-0.04]	0.03 [0.01-0.04]	.67
Number of boluses	2 [1-2]	1 [1-2.5]	2 [1-2]	.55

Values are n (%) or median [interquartile range].

point of care, it offers an opportunity to perform a targeted history in high-risk individuals when able. The low rate of the primary outcome limits establishing weighted risks and establishing causal relationships.

Considerations for improvement in critical care transport analgesia selection should incorporate obtaining a targeted history of medications before transport coupled with early identification of high-risk patient populations when considering the coadministration of analgesics and benzodiazepines. In our cohort, despite the fentanyl quantities being within the dosing recommendations, the paucity of nonnarcotic analgesia highlights room for improvement. To further improve care, early nonnarcotic administration should be evaluated in conjunction with opiate utilization patterns, coadministration of benzodiazepines, and rates of oversedation. The utilization of nonnarcotic analgesics has mixed data when used in conjunction with opiates for severe pain in the emergency department setting.[8] The evaluation of pain severity and individualization of pain regimen should be considered. A reduction in adverse event outcomes should also be considered when adding nonnarcotic analgesics to prehospital transport formularies despite potential increases in medication expenditure. Future work can inform the creation of best practices by defining the most important aspects of patient history and physiology when making analgesia decisions.

Conclusion

The rate of oversedation of nonintubated adult critical care transport patients receiving fentanyl or ketamine is low. The coadministration of benzodiazepines increases the risk of oversedation. The administration of naloxone to prevent opioid-induced respiratory decompensation and the incorporation of nonnarcotic analgesia is an opportunity for practice improvement.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amj.2023.03.006.

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