Out-of-Hospital Ketamine: Indications for Use, Patient Outcomes, and Associated Mortality

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Study objective: To describe out-of-hospital ketamine use, patient outcomes, and the potential contribution of ketamine to patient death.

Methods: We retrospectively evaluated consecutive occurrences of out-of-hospital ketamine administration from January 1, 2019 to December 31, 2019 reported to the national ESO Data Collaborative (Austin, TX), a consortium of 1,322 emergency medical service agencies distributed throughout the United States. We descriptively assessed indications for ketamine administration, dosing, route, transport disposition, hypoxia, hypercapnia, and mortality. We reviewed cases involving patient death to determine whether ketamine could be excluded as a potential contributing factor.

Results: Indications for out-of-hospital ketamine administrations in our 11,291 patients were trauma/pain (49%; n=5,575), altered mental status/behavioral indications (34%; n=3,795), cardiovascular/pulmonary indications (13%; n=1,454), seizure (2%; n=248), and other (2%; n=219). The highest median dose was for altered mental status/behavioral indications at 3.7 mg/kg (interquartile range, 2.2 to 4.4 mg/kg). Over 99% of patients (n=11,274) were transported to a hospital. Following ketamine administration, hypoxia and hypercapnia were documented in 8.4% (n=897) and 17.2% (n=1,311) of patients, respectively. Eight on-scene and 120 in-hospital deaths were reviewed. Ketamine could not be excluded as a contributing factor in 2 on-scene deaths, representing 0.02% (95% confidence interval 0.00% to 0.07%) of those who received out-of-hospital ketamine. Among those with in-hospital data, ketamine could not be excluded as a contributing factor in 6 deaths (0.3%; 95% confidence interval 0.1% to 0.7%).

Conclusion: In this large sample, out-of-hospital ketamine was administered for a variety of indications. Patient mortality was rare. Ketamine could not be ruled out as a contributing factor in 8 deaths, representing 0.07% of those who received ketamine. [Ann Emerg Med. 2021;78:123-131.]

Please see page 124 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Ketamine has become an increasingly popular out-of-hospital medication because of its potent effects, wide therapeutic window, and favorable risk profile.[1-7] As an analgesic, ketamine may provide equal or better pain relief when compared with other available out-of-hospital medications and is associated with a lower incidence of nausea and vomiting.[3,6,8-10] Ketamine's sedative properties are utilized to facilitate airway management[8,11,12] and for patients with acute agitation or behavioral health emergencies who may require sedation to protect themselves, the public, and the first responders.[1,2,6,13-15] Ketamine has also been used for status epilepticus.[5,15-19]

Complications associated with ketamine include respiratory depression, excessive airway secretions, emergence reactions, hypertension, tachycardia, and laryngospasm.[18,20] Safe use of ketamine requires proper patient selection and close monitoring.

Importance

There has been recent discourse regarding the appropriateness and safety of out-of-hospital ketamine.[21] Given limited data, our large sample may advance understanding regarding the optimal role of ketamine in out-of-hospital practice.[21-25]

Goals of This Investigation

Using a large, national dataset of out-of-hospital patient care records, we sought to describe emergency medical

Editor's Capsule Summary

What is already known on this topic

Ketamine is used often in the out-of-hospital setting.

What question this study addressed

What are the indications for and the outcomes after use of out-of-hospital ketamine?

What this study adds to our knowledge

In this EMS electronic health care record study of 1,322 emergency medical services agencies throughout the United States, 11,291 patients received ketamine primarily for pain or agitation control. Subsequent hypoxia and hypercapnia were not uncommon, and ketamine may have contributed to 2 of 8 on-scene deaths and 6 of 120 in-hospital deaths.

How this is relevant to clinical practice

Out-of-hospital ketamine use has benefit and risks. Closer surveillance would help better define the best use of this agent.

services' (EMS) use of ketamine, including indications, dosing, routes of administration, and patient outcomes. In cases in which a patient died after receiving out-of-hospital ketamine, we sought to determine whether ketamine could reasonably be excluded as a contributing factor to patient death.

MATERIALS AND METHODS

Study Design and Setting

We retrospectively analyzed out-of-hospital patient care records from January 1, 2019 to December 31, 2019 reported to the ESO Data Collaborative (Austin, TX). ESO is a large EMS electronic health record provider,[26] and the ESO Data Collaborative consists of participating EMS agencies who permit research using their deidentified records. The 2019 research dataset used for this investigation contained 8,340,148 EMS encounters from 1,322 US agencies distributed in the South (58%), Midwest (22%), West (16%), and Northeast (5%) census regions. Using US Census categorizations, most encounters occurred in urbanized areas (76%) or urban clusters (18%), with 6% occurring in rural areas. Most records stemmed from emergency (9-1-1) responses (83%; n=6,780,966) and 3,846,501 resulted in patient transport to a hospital. Approximately 17% (n=666,144) of EMS records had software linkage to hospital outcome information, with representation from 25% (n=337) of participating agencies.

The institutional review board at St. David's HealthCare (Austin, TX) determined that this study was exempt.

Selection of Participants

We included consecutive records for all emergency (9-1-1) EMS responses with documented out-of-hospital administration of ketamine, regardless of patient age and for whom ketamine dose and route were recorded. We excluded interfacility transfers, cardiac arrests prior to EMS arrival, and cases with ketamine used only as a continuous infusion.

Measurement

The electronic health record software data (including out-of-hospital dispatch information, patient demographics, clinical presentation and course, interventions, treatments, and outcomes at transfer of care) were entered by EMS personnel during the normal course of clinical care, with items coded using the National Emergency Medical Services Information System (NEMSIS) data standard.[27]

We assessed the indications for ketamine based on the EMS provider primary impression data field, which is a NEMSIS national mandatory data element defined as "EMS personnel's impression of the patient's primary problem or most significant condition which led to the management given to the patient (treatments, medications, or procedures)."[28,29] Indications were collapsed into 5 categories: trauma/pain, altered mental status/behavioral emergencies, cardiovascular/pulmonary indications, seizure, and other. We calculated the cumulative total ketamine dose during the EMS encounter in mg and additionally in mg/kg when patient weight was recorded. Routes specified were intravenous, intramuscular, or intraosseous.

The NEMSIS data standard requires an EMS provider to document each patient's response to each medication administration as improved, unchanged, or worse.[28,29] Patient transport disposition was categorized as transported by EMS, released on scene (both against medical advice and per protocol), or dead on scene. Using documented timestamps, we considered a patient to have a ketamine-associated first episode of hypoxia if there was an EMS-documented oxygen saturation (SpO_2) of less than 88% after ketamine administration without prior such hypoxia. Similarly, we considered a patient to have a ketamine-associated first episode of hypercapnia if there was a documented end-tidal carbon dioxide ($EtCO_2$) of more than 45 mm Hg after ketamine administration but without prior such hypercapnia.

For the subset of patients with linked hospital outcome data, we collapsed emergency department dispositions into 4 categories: admitted, discharged/against medical advice, died in the ED, or transferred to another facility. For admitted patients, in-hospital dispositions were collapsed into 3 categories: discharged/left against medical advice, died in the hospital, or transferred to another facility. We classified mortality as alive at the end of the study period (discharged from the ED, left against medical advice, discharged from the hospital, or hospital disposition of "still a patient") or deceased (died in the ED or died in the hospital), with mortality status unavailable when patients were transferred to another facility or missing hospital disposition information.

The 4 physician coauthors (JBM, PA, ESB, and KAS), all board certified in emergency medicine and EMS, independently reviewed the free-text, out-of-hospital narratives for all patient deaths. We excluded additional cases of cardiac arrest prior to EMS arrival not otherwise identified earlier. We considered ketamine excluded as a contributing factor if, based on the information available, it was clinically more likely than not that the patient's condition prior to the administration of ketamine would have led to death during the episode of care. When all 4 reviewers were not initially in consensus, we performed a second round of independent reviews using the complete out-of-hospital care report. If consensus was not reached then with group discussion, the case was categorized as "unable to exclude ketamine as a contributing factor to patient death."

Primary Data Analysis

We descriptively reported our data and calculated Fleiss' kappa using STATA IC version 15.1 (StataCorp LP; College Station, TX).

RESULTS

During the study period, there were 15,204 administrations of ketamine among 11,291 unique patient encounters from 458 EMS agencies (Figure). For these records, we were missing data for $EtCO_2$ (32.5%; n=3,664), estimated patient weight (15.5%; n=2,358), SpO_2 (5.1%; n=575), and patient response to medication (2.5%; n= 379). Table 1 displays descriptive data for demographics, indications, dosing, route, and disposition. EMS providers documented that patients' responses were improved or unchanged following 99.4% (n=14,734) of ketamine administrations.

Of all transported patients who received out-of-hospital ketamine, 18.0% (n=2,030) of records included linked ED dispositions, of which 1,877 had mortality data available; Table E1 and Figure E1 (both available at http://www.annemergmed.com) broken down by demographics, indication, and dosing. Hospital disposition for admitted patients is shown in Figure E2 (available at http://www.annemergmed.com) for the 94.1% (n=1,005) of patients who had this data available. The overall ED or hospital mortality rate was 6.4% (95% confidence interval [CI] 5.3% to 7.6%), and it was highest among patients in the cardiopulmonary/respiratory (25.0%; 52 of 208) indication group, followed by other (7.7%; 3 of 39), seizure (5.7%; 3 of 53), trauma/pain (4.2%; 37 of 890), and altered mental status/behavioral indications (3.8%; 26 of 688).

Review of Deceased Patient Care Narratives

For the 8 on-scene deaths and 120 in-hospital deaths that underwent review (Figure), our physicians found substantial agreement[30] (kappa, 0.78; 95% CI 0.64 to 0.92) with respect to the potential role of ketamine as a contributing factor in each patient's death.

Among the on-scene deaths, the contribution of ketamine was not excluded in 2 cases, representing 0.02% (95% CI 0.00 to 0.07%) of out-of-hospital exposures. In the first case, EMS was requested by law enforcement for a woman in her 50s who presented with severe agitation and bleeding from 2 lacerations that was controlled with simple dressings. Attempts were made to move the patient to the stretcher, which resulted in combativeness for which the patient received 250 mg of intramuscular ketamine. Patient weight was not recorded, and there were no additional physical examination findings. Subsequent extrication took 9 minutes, after which the patient was found in asystolic cardiac arrest that occurred prior to the recording of any other vital signs. The patient remained in asystole throughout resuscitative efforts. No autopsy results were available; however, bystanders report methamphetamine use.

For the second case, EMS responded to the scene of a motor vehicle crash. The patient was a woman in her 60s. She was alert and responsive on arrival but was entrapped in her vehicle and had obviously suffered significant traumatic injuries. Abdominal distention was noted, as well as an obvious closed forearm fracture. During a 13-minute vehicular extrication, the patient became combative and received 4 mg/kg of ketamine. There was inconsistency within the documentation of route as either intramuscular or intravenous. The patient was extricated 4 minutes after ketamine administration and suffered a witnessed pulseless electrical activity arrest 5 minutes later. The patient remained in pulseless electrical activity throughout resuscitative efforts.

Of the 120 in-hospital deaths, ketamine was not excluded as a contributor to death in 5% (n=6) of cases

(which are described in Table 2), yielding a mortality rate of 0.3% (95% CI 0.1% to 0.7%) among the 1,877 records with known ED or hospital mortality status. The remaining in-hospital deaths are described in Table E2 (available at http://www.annemergmed.com).

LIMITATIONS

Despite the importance of linking EMS and hospital outcomes,[31-33] our study is limited in that only 18% of our sample was so linked. Nevertheless, this linkage rate is still more than twice that reported to the National EMS

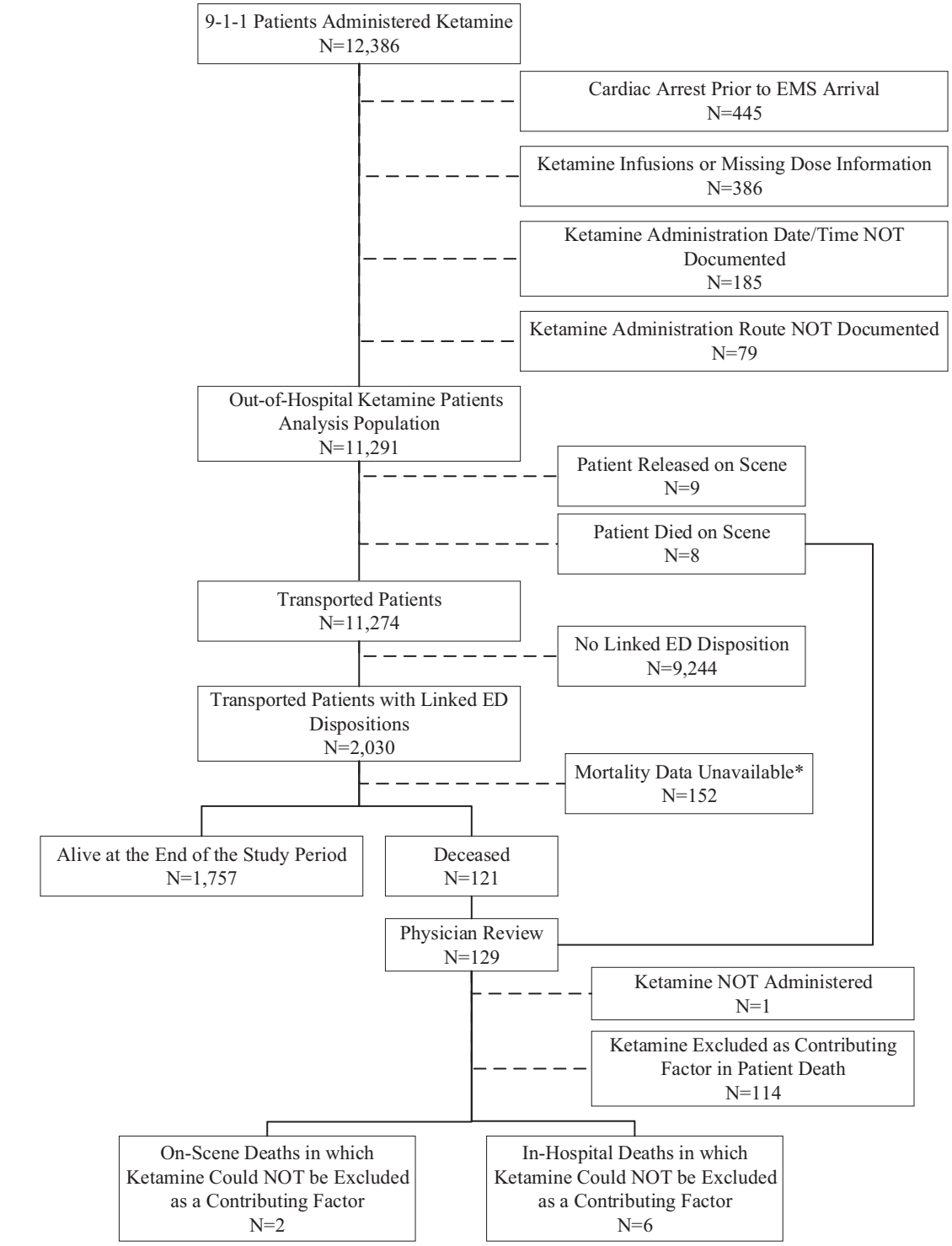

Figure. Inclusion of patients and outcomes.

Table 1. Patient and encounter characteristics for all records with documented out-of-hospital ketamine administration.

		EMS Indication Category				
Variable No. (%)	**Unique Patient Records (N=11,291)**	**Trauma/Pain (n=5,575)**	**Altered Mental Status /Behavioral (n=3,795)**	**Cardiovascular/ Pulmonary (n=1,454)**	**Seizure (n=248)**	**Other (n=219)**
Sex						
Female	4,759 (42.3)	2,615 (47.1)	1,290 (34.1)	693 (47.9)	71 (28.6)	90 (41.3)
Male	6,484 (57.7)	2,936 (52.9)	2,489 (65.9)	754 (52.1)	177 (71.4)	128 (58.7)
Race/Ethnicity						
White, not Hispanic or Latino	7,739 (70.5)	3,967 (73.3)	2,386 (64.6)	1,086 (76.8)	155 (65.1)	145 (68.1)
Black, not Hispanic or Latino	1,785 (16.3)	681 (12.6)	824 (22.3)	200 (14.1)	52 (21.9)	28 (13.2)
Other Race, not Hispanic or Latino	266 (2.4)	126 (2.3)	97 (2.6)	31 (2.2)	5 (2.1)	7 (3.3)
Hispanic or Latino	1,182 (10.8)	640 (11.8)	385 (10.4)	98 (6.9)	26 (10.9)	33 (15.5)
Age (deciles)						
0–9 years	76 (0.7)	55 (1.0)	7 (0.2)	7 (0.5)	6 (2.6)	1 (0.5)
10–19 years	694 (6.4)	419 (7.7)	248 (6.9)	7 (0.5)	12 (5.2)	8 (3.7)
20–29 years	1,836 (16.9)	844 (15.5)	886 (24.8)	45 (3.2)	35 (15.0)	26 (12.0)
30–39 years	1,875 (13.3)	828 (15.2)	901 (25.2)	65 (4.6)	56 (24.0)	25 (11.6)
40–49 years	1,469 (13.5)	737 (13.6)	561 (15.7)	97 (6.9)	46 (19.7)	28 (13.0)
50–59 years	1,461 (13.4)	771 (14.2)	398 (11.1)	210 (14.8)	36 (15.5)	46 (21.3)
60–69 years	1,420 (13.1)	725 (13.3)	268 (7.5)	366 (25.8)	25 (10.7)	36 (16.7)
70–79 years	1,122 (10.3)	549 (10.1)	170 (4.8)	364 (25.7)	9 (3.9)	30 (13.9)
80–89 years	708 (6.5)	376 (6.9)	106 (3.0)	207 (14.6)	8 (3.4)	11 (5.1)
≥90 years	220 (2.0)	136 (2.5)	30 (0.8)	49 (3.5)	0 (0.0)	5 (2.3)
Dose (mg/kg)						
Median (IQR)	1.5 (0.5–3.5)	0.5 (0.2–1.0)	3.7 (2.2–4.4)	2.0 (1.1–3.1)	2.4 (1.8–3.9)	1.7 (0.6–3.1)
Dose ≥10 mg/kg						
No. (%)	32 (0.3)	4 (0.1)	23 (0.6)	5 (0.3)	0 (0.0)	0 (0.0)
Number of Ketamine Administrations						
One	8,308 (73.6)	4,006 (71.9)	2,986 (78.7)	958 (65.9)	186 (75.0)	172 (78.5)
Two	2,322 (20.6)	1,209 (21.7)	666 (17.5)	360 (24.8)	54 (21.8)	33 (15.1)
Three or more	661 (5.8)	360 (6.4)	143 (3.8)	136 (9.3)	8 (3.2)	14 (6.4)
Out-of-hospital SpO_2 (%)						
Records with SpO_2 documented	10,716 (94.9)	5,322(95.5)	3,515(92.6)	1,431(98.4)	242(97.6)	206(94.1)
SpO_2 median (IQR)	97 (94–99)	98 (95–99)	97 (94–99)	95 (86–99)	97 (95–99)	97 (93–99)
SpO_2 <88 before ketamine administration	1,697 (15.8)	378 (7.2)	376 (10.7)	846 (59.1)	46 (19.0)	51 (24.8)
SpO_2 <88 after ketamine administration without previous hypoxia	897 (8.4)	392 (7.4)	358 (10.2)	117 (8.2)	14 (5.8)	16 (7.8)
Out-of-hospital $EtCO_2$ (mm Hg)						
Records with $EtCO_2$ documented	7,627 (67.5)	3,288 (59.0)	2,658 (70.0)	1,326 (91.2)	198 (79.8)	157 (71.7)
$EtCO_2$ median (IQR)	34 (25–41)	32 (24–38)	35 (27–42)	35 (22–47)	35 (27–43)	29 (17–38)
$EtCO_2$ >45 before administration of ketamine	640 (8.4)	89 (2.7)	164 (6.2)	346 (26.1)	31 (15.7)	10 (6.4)
$EtCO_2$ >45 after ketamine administration without previous hypercapnia	1,311 (17.2)	306 (9.3)	612 (23.0)	329 (24.8)	38 (19.2)	26 (16.5)

Table 1. Continued.

Variable No. (%)	Unique Patient Records (N=11,291)	EMS Indication Category				
		Trauma/Pain (n=5,575)	Altered Mental Status /Behavioral (n=3,795)	Cardiovascular/ Pulmonary (n=1,454)	Seizure (n=248)	Other (n=219)
EMS Disposition						
Transported	11,274 (99.8)	5,565 (99.8)	3,793 (99.8)	1,449 (99.6)	248 (100.0)	219 (100.0)
Released on scene	9 (0.1)	7 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)
Dead on scene	8 (0.1)	3 (0.1)	1 (0.1)	4 (0.3)	0 (0.0)	0 (0.0)

IQR, Interquartile range.

Information System.[34] However, it should be noted that the population without reported outcomes was demographically similar to the population with linked outcomes.

Although patient weight was recorded for most records, we assume that most were estimates and therefore may be inaccurate. Furthermore, vital sign cut-off points were selected based on common clinical ranges but could not account for geographic variation for variables such as altitude and SpO_2. SpO_2 was documented for almost all patients; however, approximately one third had no $EtCO_2$ readings reported. Finally, our study focused on hypoxia, hypercapnia, and mortality, but it did not address other known potential consequences of ketamine administration, such as the need for in-hospital airway management, hypersalivation, or emergence reactions.

DISCUSSION

In this study of 11,291 out-of-hospital patients, EMS administered ketamine for a variety of indications. Patient death following out-of-hospital ketamine was a rare occurrence, both in the field and after arrival at the hospital. Most of the observed deaths were clearly attributed to serious underlying medical or traumatic conditions. In a very small number of patient deaths, ketamine was unable to be ruled out as a potential contributing factor; however, the inability to exclude ketamine does not directly imply causation. Collectively, these findings offer an ecologic perspective of current out-of-hospital practices related to ketamine use and patient outcomes.

Out-of-hospital ketamine was most commonly used for patients with traumatic injuries or pain. The median total ketamine dose observed in this indication group (0.5 mg/kg) was well within dosing recommendations for out-of-hospital analgesia (0.1 mg/kg to 0.9 mg/kg).[35] Additionally, to facilitate safe assessment and treatment, patients with agitation stemming from severe traumatic injuries may require higher doses of ketamine to achieve sedation rather than solely analgesic effects. Sedative doses of ketamine may also facilitate treatment of patients with acute behavioral emergencies, including excited delirium syndrome. Our median total ketamine dose (3.7 mg/kg) and the 75th percentile (4.4 mg/kg) fell within the therapeutic window of 3 mg/kg to 5 mg/kg intramuscularly.[35]

Although ketamine is often favored for its ability to preserve upper airway reflexes, there is a risk of transient respiratory depression, particularly if the medication is administered too quickly and at high doses.[35,36] In our study, large doses of ketamine were rare; less than 1% of patients received a total dose of 10 mg/kg or higher. Nevertheless, following any ketamine administration, EMS clinicians should closely monitor a patient's respiratory status and be prepared to intervene. At least 1 episode of hypercapnia was observed in approximately 1 of every 6 patients with $EtCO_2$ recorded after administration. Hypoxia was observed in less than 10%.

In this study, nearly all patients administered out-of-hospital ketamine were transported to hospitals; our admission rate (53%) is comparable to that previously reported (54%)[16] and higher than that for all EMS patients regardless of ketamine use (36%),[37] suggesting more serious underlying conditions. Although some studies have described the mortality associated with ketamine administration in ICU or head trauma patients,[38,39] there have been no comprehensive investigations describing mortality among EMS patients who receive ketamine. A retrospective study of 135 patients who received out-of-hospital ketamine for profound agitation reported a 1.5% mortality rate, but it was unclear whether ketamine was a contributing factor in these deaths.[40] In the present study of ketamine use for various indications, physician review of records for patients who died found that the vast majority of on-scene and in-hospital deaths could be attributed to substantial pathologies present prior to EMS arrival. As this

Table 2. Deidentified out-of-hospital patient care narrative summaries for records where ketamine could not be excluded as potentially contributing to in-hospital death.

Patient	Out-of-hospital Ketamine Dose (mg/kg or mg if Missing Weight)	Out-of-hospital Ketamine Route (Ordered Sequentially if Multiple Routes)	Time Between Last Out-of-hospital Ketamine Administration and Out-of-hospital Initiation of CPR or In-Hospital Death	EMS Indication Category	Narrative Summary
In-Hospital Deaths					
Patient 1	20 mg	IM	2 days, 23 hours, 38 minutes, 0 seconds	Trauma/Pain	Age in the 80s, female with known history of lung cancer and chronic pain on home opioid regimen. Presents after fall with 10/10 hip pain and doppler SBP of 74. Twenty mg of ketamine administered for pain.
Patient 2	0.4 mg/kg	IV	0 days, 15 hours, 49 minutes, 0 seconds	Trauma/Pain	Age in the 50s, major MVC, initially hypoxic (SpO_2 on RA 71%), blood pressure 123/101 mm Hg, pulse 142 beats/min. Provided ketamine for pain control.
Patient 3	0.4 mg/kg	IM, IV	10 days, 23 hours, 21 minutes, 10 seconds	Cardiovascular/ Pulmonary	Age in the 70s, male with COPD and chronic pain and opioid use, presents with exacerbation of chronic pain and slight worsening of baseline hypoxia (baseline 80%, "70s%" on presentation). Two doses of ketamine provided.
Patient 4	0.5 mg/kg	IV	Unable to Calculate*	Altered Mental Status/Behavioral	Age in the 70s, female with "stage 4 cancer" and home narcotic regimen who presents with pain exacerbation and decreased appetite. Twelve mg of ketamine IV provide times 3 during transport.
Patient 5	1.0 mg/kg	IV	17 days, 3 hours, 2 minutes, 0 seconds	Altered Mental Status/Behavioral	Age in the 60s, male on construction site with altered mental status, hyperthermic to touch, and SBP of 200 mm Hg with no known injury. Ketamine 90 mg for RSI.
Patient 6	0.2 mg/kg	IM	Unable to Calculate*	Cardiovascular/ Pulmonary	Age in the 90s, male with 1-hour history of altered mental status and prior history of CVA.

COPD, chronic obstructive pulmonary disease; *CPR*, cardiopulmonary resuscitation; *CVA*, cerebrovascular accident; *IM*, intramuscular; *IV*, intravenous; *MVC*, motor vehicle crash; *RSI*, rapid sequence induction; *SBP*, systolic blood pressure; *SpO2*, oxygen saturation.
*Hospital discharge date/time missing, nonsensical, or not in sequential order.

is true with all retrospective evaluations, it is not possible to directly attribute causation in these complex cases.

In conclusion, ketamine was commonly administered by EMS for a variety of clinical indications. Repeat or large-dose administrations were rare, and the vast majority of patients were transported to the hospital for definitive care. Ketamine could not be ruled out as a contributing factor in 8 deaths, representing 0.07% of those who received the medication. Further research is required to evaluate the safety profile of ketamine in comparison to alternative interventions in a similar patient population.

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