Air Medical Journal 40 (2021) 36–40

Contents lists available at ScienceDirect

Air Medical Journal

journal homepage: http://www.airmedicaljournal.com/

Original Research

Prehospital Ketamine Use for Rapid Sequence Intubation: Are Higher Doses Associated With Adverse Events?

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A B S T R A C T

Objective: Ketamine for rapid sequence intubation (RSI) is typically dosed at 1 to 2 mg/kg intravenously. The need to ensure dissociation during RSI led some to administer ketamine at doses greater than 2 mg/kg. This study assessed associations between ketamine dose and adverse events.

Methods: This multisite, retrospective study included adult subjects undergoing RSI with intravenous ketamine. Subjects were categorized into 2 groups: a standard ketamine dose (≤ 2 mg/kg intravenously) or a high dose (> 2 mg/kg intravenously). Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for adverse events.

Results: Eighty subjects received standard-dose ketamine, and 50 received high-dose ketamine. The high-dose group had a significantly ($P < .05$) higher proportion of trauma patients, were younger, and had higher predose blood pressure compared with the standard-dose group. High-dose ketamine was associated with greater odds of adverse events including hypotension (OR = 7.0; 95% CI, 3.0-16.6), laryngospasm (OR = 10.8; 95% CI, 1.3-93.4), bradycardia (OR = 7.5; 95% CI, 1.5-36.6), repeat medications (OR = 12.9; 95% CI, 1.5-107.9), oxygen desaturation (OR = 6.0; 95% CI, 1.8-19.9), multiple attempts (OR = 3.2; 95% CI, 1.5-6.8%), and failed airway (OR = 3.6; 95% CI, 1.0-12.7).

Conclusion: Ketamine at higher doses was associated with increased odds of adverse events. Studies assessing adverse events of ketamine at lower than standard doses in shock patients are needed.

Rapid sequence induction (RSI) is 1 of the most widely used techniques for securing a definitive airway.[1] Ideal medications for RSI include those that have a rapid onset, a minimal effect on hemodynamics, and few adverse effects.[2] Ketamine possesses many characteristics of an ideal agent. In particular, this medication has rapid onset, typically within 30 seconds when being given intravenously, and the presence of catecholamine release, which may be beneficial in hemodynamically unstable patients.[3,4]

Ketamine works as a competitive antagonist of N-methyl-D-aspartate receptors, blocking the action of glutamate causing a dissociation of the cortex and limbic system to external stimuli while maintaining cardiovascular stability. In addition, it exerts analgesic effects as an agonist of mu- and kappa-opioid receptors.[5] Ketamine produces its dissociative effects in a narrow therapeutic range. Patients receiving a low (subanesthetic) dose experience analgesia and central sensitization, whereas those receiving higher doses experience anesthetic effects.[5]

Ketamine has grown in popularity as 1 of the most frequently used agents for RSI in the emergency setting. It is most commonly

Supported by Mercy Health North St. Vincent Medical Center Graduate Medical Education/Academic Affairs as required by the Accreditation Council for Graduate Medical Education for support of residency program research and scholarly activity.

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1067-991X/$36.00

https://doi.org/10.1016/j.amj.2020.11.007

dosed at 1 to 2 mg/kg intravenously.[6-12] It is thought to produce little effect on the hemodynamic status of the patient.[13] This is beneficial in patients in whom hemodynamic compromise in the peri-intubation period increases mortality.[14,15] Hemodynamically unstable patients do not always receive adequate sedation in the postintubation period.[16] A larger than standard dose of a hemodynamically stable medication such as ketamine could prevent this complication while avoiding postintubation hypotension.[17] If ketamine could safely be given at higher doses to hemodynamically tenuous intubated patients without increasing adverse events, this could lead to improved pain management and sedation in this population. Ketamine's theoretically favorable hemodynamic profile has led to the administration of ketamine at greater than 2 mg/kg intravenously (IV) to ensure dissociation before intubation during RSI.[18,19] Although theoretical, ketamine use at higher intravenous doses potentially could increase adverse events and may not decrease episodes of hypotension.[20-22] To date, this has not been well studied with prehospital administration of ketamine. The goal of this study was to determine if there was an increased risk of adverse events with higher ketamine doses in the prehospital setting.

Methods

Study Design

This study received expedited institutional review board approval with a waiver of protected health information and a waiver of consent. A second site was recruited with similar approvals from their institutional institutional review board and a data sharing agreement with the primary site.

This was a multisite retrospective observational cohort study of adult subjects undergoing RSI by prehospital agencies with intravenous ketamine as the initial induction drug. Chart reviews of subjects from January 1, 2014, to July 31, 2019, who met the parameters were included.

Setting

Each of the 3 sites included used different doses of ketamine administration as part of their RSI protocol. Each site was an unrelated institution with a separate organizational structure with the exception of site A and C sharing a common medical director at the beginning of the study time frame.

Site A

Site A was a regional critical care transport agency that used both standard ketamine dosing and high-dose ketamine for both air and ground transport. The start date of the study was related to the initial approval of ketamine as 1 of several options for RSI. This site used standing orders for the majority of their transport teams. These teams were made up of paramedic and registered nurse (RN) teams with the exception of a single flight base that was made up of a physician/RN team. The base operating with a physician/RN team used on-site medical control for medication dosing orders and did not necessarily follow the standing orders of typical paramedic/RN crews in all cases. The fixed standing orders dose for ketamine was 3 mg/kg IV at this site with no adjustment for shock index.

Site B

Site B was a regional critical care transport agency that used standard ketamine dosing for air and ground mobile intensive care unit transport given by all paramedic/RN crews. The fixed standing orders dose for ketamine was 2 mg/kg IV with no adjustment for the shock index. Ketamine had been used as an option since 2013, in addition to other induction agents available for RSI.

Site C

Site C was a rural county third-service high-level advanced life support agency that met or exceeded the current state standards for RSI[23] and was made up of paramedic crews. This agency used a fixed high-dose ketamine for transport at a dose of 3 mg/kg IV, and there was no adjustment for the shock index. The study start date was related to the initial approval of ketamine as 1 of several options for RSI.

The administered doses for the purpose of this study were subdivided into 2 groups consisting of a standard dose, defined as less than or equal to 2 mg/kg, and a high dose of greater than 2 mg/kg.

Population

The subject population included patients 18 years or older in whom RSI was performed and ketamine was used as the induction agent. The excluded cases included pediatric patients, cases in which ketamine was not the sole RSI medication, cases in which ketamine was given after attempts by other providers, cases in which ketamine was used as a sedative, or when a different sedative agent was used for agitation or pain management before the administration of ketamine for RSI. The mode of transportation was documented between 2 groups as either ground emergency medical services (EMS) or by air for flight. Indications for transport were divided into trauma, surgical, medical, and other, which included 2 cases in which indication was not documented.

Data Collection and Study Protocol

Data were collected from the patient care records (PCRs) by trained abstractors (K.S., H.H., M.R., S.F., and C.B.). A second review of PCRs was performed to ensure no data were missed or entered incorrectly (W.K., S.F., H.H., and C.B.). Data collected included the actual dose of ketamine administered, as well as pre- and postketamine dose vital signs of systolic blood pressure (SBP), diastolic blood pressure, heart rate (HR), patient estimated weight, and oxygen saturation (Sa_{O_2}). Vital sign measurements were to be measured before ketamine dose and not more than 30 minutes after administration based on the expected half-life of ketamine. There were a few subjects with a value of 0 for 1 or more of the vital signs (SBP, diastolic blood pressure, or Sa_{O_2}). The vital signs in these cases, often before ketamine dosing, were assumed to be normal. The exception were cases with absent pulses in the radial artery but present carotid or femoral pulses (which was noted in the narratives). In these cases, it was assumed that the SBP was less than 90 preketamine because pulseless patients did not receive RSI and were not included in the study.

Adverse events were generated from the side effects of ketamine listed in Lexicomp Online (Lexicomp, Hudson, OH). The subject charts were reviewed for adverse events that occurred during transport within 30 minutes after ketamine administration. These adverse events included hypotension (SBP < 90 mmHg or absence of radial pulses but palpable central pulses), hypertension (SBP > 180 mm Hg), tachycardia (> 150 beats/min), bradycardia (< 60 beats/min), cardiac arrest (absent central pulses), vomiting before ketamine administration and after ketamine administration, agitation requiring rescue medication (agitation described in the narrative and additional doses of ketamine or other analgesia/sedation medication), oxygen desaturation (based on Sa_{O_2} measurement < 90%), laryngospasm, multiple intubation attempts (defined as any additional attempt after a first pass), and unsuccessful endotracheal intubation (placement of supraglottic airway, cricothyrotomy, or bag valve ventilation). Vomiting after ketamine was attributed to the drug only if there was no documented vomiting before drug administration. These adverse events could be noted in the vital signs section of the PCR as well as the narrative sections during data extraction. Paralytic medication dosing was not recorded. Data collection was limited to

the 30-minute time interval immediately after ketamine administration based on the half-life of ketamine and typical EMS transport times in the region.

Data Analysis

Demographic data and vital signs are presented as n (%), mean (standard deviation), or median (interquartile range, 25th-75th percentile). The number (%) of subjects with adverse events is calculated for the total study population as well as by dosing group (standard dose ≤ 2 mg/kg and high dose > 2 mg/kg). The increased odds of experiencing individual adverse events for high-dose ketamine was compared with standard dosing and is presented as an odds ratio (OR) with 95% Wald confidence limits.

Because of the higher incidence of trauma patients in the high-dose ketamine group, a subgroup analysis using just trauma patients was explored. Data were analyzed with SAS v9.4 (SAS Institute Inc, Cary NC).

Results

We identified 130 adult patients who underwent RSI with intravenous ketamine in the prehospital, helicopter, or mobile intensive care unit setting from January 1, 2014, to July 31, 2019. Table 1 shows the demographic characteristics of these patients. Overall, 80 patients (61.5%) were given standard dosing of ketamine (median dose = 2.0 mg/kg; interquartile range, 1.1-2.0 mg/kg). Fifty (38.5%) received the high-dose ketamine (median dose = 3.0 mg/kg; interquartile range, 2.9-3.1 mg/kg). The high-dose and standard-dose groups were similar with regard to the mode of transportation, sex, and weight. Overall, 90 (69.8%) patients were transported via helicopter, and patients were predominantly male (74 (56.9%)) with a mean age of 55.2 ± 19.9 years. In 1 case, sex was not properly documented. Sixty-seven (52.3%) cases were medical in nature, whereas 59 (46%) cases were trauma patients. There were 69 patients from site B (53.1% of overall patients), all of whom received the standard dose of ketamine. There were 49 patients from site A (37.7% of the total patients), 10 of whom received the standard dose of ketamine, and 39 received the high dose of ketamine. Finally, there were 12 patients from site C (9.2%), only 1 of whom received the standard dose of ketamine; 11 received the high dose of ketamine. The high- and standard-dose groups were similar regarding the mode of transportation via air (68% and 70.9%, respectively) and ground (29.1% and 32%, respectively). An indication of trauma was statistically higher in the high-dose ketamine group (64% vs. 34.6%, $P = .002$) as well as younger age (50.5 vs. 58.1 years old, $P = .03$).

Table 2 displays the percentage of subjects within a dosing group who experienced each adverse event, along with the OR for having the adverse event. There were no significant differences in the incidence of hypertension, tachycardia, cardiac arrest, or emesis between the groups. There was a statistically significant higher incidence of hypotension in the higher-dose ketamine group, as well as laryngospasm, bradycardia, agitation requiring repeat medications, oxygen desaturation, multiple attempts, and failed airways.

There was a higher incidence of hypotension noted in the high-dose group (OR = 7.0; 95% confidence interval [CI], 3.0-16.6). The preketamine blood pressures varied, with an average SBP of 109 ± 32.1 in the standard-dose group versus 124 ± 34.7 in the high-dose group. However, the standard-dose ketamine group had an increase in blood pressure postketamine, resulting in an average SBP of 119 ± 37.4 versus a drop in blood pressure to 112 ± 42.6 in the high-dose group. There was also a higher incidence of bradycardia in the high-dose group with 16% incidence versus 2.5% of cases in the standard-dose group (OR = 7.5; 95% CI, 1.5-36.6). There was a statistically significant incidence of agitation requiring

Table 1
Demographic Characteristics and Vital Signs

	All	Standard Dose (≤ 2 mg/kg)	High Dose (> 2 mg/kg)	*P* Value Comparing Standard vs. High
No. of subjects	130	80 (61.5)	50 (38.5)	
Site				
A	49 (37.7)	10 (12.5)	39 (78.0)	
B	12 (9.2)	1 (1.3)	11 (22.0)	
C	69 (53.1)	69 (86.3)	0 (0)	
Mode				.73
Ground	39 (30.2)	23 (29.1)	16 (32.0)	
Air (1 missing)	90 (69.8)	56 (70.9)	34 (68.0)	
Sex				.40
Male	74 (56.9)	43 (53.8)	31 (62.0)	
Female	55 (42.3)	36 (45.0)	19 (38.0)	
Other	1 (0.8)	1 (1.3)	0 (0)	
Indication				.002
Trauma	59 (46.0)	27 (34.6)	32 (64.0)	
Surgical	0 (0)	0 (0)	0 (0)	
Medical	67 (52.3)	49 (62.8)	18 (36.0)	
Other (2 missing)	2 (1.6)	2 (2.6)	0 (0)	
Age (y)	55.2 (19.9)	58.1 (19.2)	50.5 (20.2)	.03
Weight (kg)	82.0 (70.0-100.0)	81.0 (65.0-100.0)	82.0 (70.0-100.0)	.40
Actual dose ketamine (mg)	197.0 (114.0-250.0)	138.0 (95.0-192.0)	287.5 (204.0-300.0)	
Actual dose ketamine (per kg body weight)	2.0 (1.9-3.0)	2.0 (1.1-2.0)	3.0 (2.9-3.1)	
SBP preketamine	114.5 (33.7)	109.0 (32.1)	124.2 (34.7)	.01
DBP preketamine	70.4 (21.7)	66.2 (20.0)	77.6 (22.7)	.01
HR preketamine	101.2 (31.1)	98.5 (30.1)	106.0 (32.5)	.25
Sao_2 preketamine	95.0 (90.0-99.0)	95.0 (91.0-100.0)	95.5 (90.0-99.0)	.61
SBP postketamine	116.0 (39.4)	118.6 (37.4)	112.0 (42.6)	.24
DBP postketamine	71.1 (25.5)	72.2 (21.7)	69.5 (30.8)	.27
HR postketamine	99.0 (27.5)	98.0 (26.6)	100.7 (29.1)	.69
Sao_2 postketamine	98.0 (94.0-100)	99.0 (95.0-100.0)	97.0 (93.0-100)	.04

DBP = diastolic blood pressure; HR = heart rate; Sao_2 = oxygen saturation; SBP = systolic blood pressure.
Data are presented as frequency count (percentage), mean (standard deviation), or median (interquartile range). The chi-square or Mann-Whitney-Wilcoxon *P* value reported to compare the standard- versus high-dose groups.

Table 2
Adverse Events

	All	Standard Dose (≤ 2 mg/kg)	High Dose (> 2 mg/kg)	Odds Ratio for Having the Adverse Event (High vs. Standard)
No. of patients	130	80	50	
Hypotension	26.9	12.5	50.0	7.0 (3.0-16.6)
Hypertension	6.2	5.0	8.0	1.7 (0.4-6.9)
Tachycardia	2.3	1.3	4.0	3.3 (0.3-37.3)
Bradycardia	7.7	2.5	16.0	7.5 (1.5-36.6)
Arrest	10.8	8.8	14.0	1.7 (0.6-5.2)
Vomit prior to ketamine	4.6	5.0	4.0	0.8 (0.1-4.5)
Vomit after ketamine	3.9	1.3	8.0	6.9 (0.7-63.3)
Agitation requiring rescue meds	6.2	1.3	14.0	12.9 (1.5-107.9)
Oxygen desaturation	12.3	5.0	24.0	6.0 (1.8-19.9)
Laryngospasms	5.4	1.3	12.0	10.8 (1.3-93.4)
Multiple attempts	33.9	23.8	50.0	3.2 (1.5-6.8)
Not successfully intubated	9.2	5.0	16.0	3.6 (1.0-12.7)

Data are presented as the percentage of subjects with the adverse event. The odds ratio is the increase in the odds of having the adverse event with the high dose compared with the standard dose (95% Wald confidence limits).

rescue medications in 14% for the high-dose group versus 1.3% in the standard-dose group (OR = 12.9; 95% CI, 1.5-107.9). There was a higher incidence of oxygen desaturation in the high-dose ketamine group compared with the standard-dose group (24% vs. 5%; OR = 6.0; 95% CI, 1.8-19.9). There was also a higher incidence of laryngospasm of 12% in the high-dose ketamine group versus 1.3% in the standard-dose group (OR = 10.8; 95% CI, 1.3-93.4). There were more cases of multiple intubation attempts, with 50% required in the high-dose ketamine group versus 23.8% in the standard-dose group (OR = 3.2; 95% CI, 1.5-6.8). There were also more unsuccessful intubation attempts with 16% in the high-dose ketamine group versus 5.0% in the standard-dose group (OR = 3.6; 95% CI, 1.0-12.7).

In a subgroup of only trauma patients (27 standard dose, 32 high dose), the high-dose group demonstrated higher OR for developing hypotension (OR = 26.0; 95% CI, 3.1-215.3) and oxygen desaturation (OR = 10.2; 95% CI, 1.2-86.5). All subjects in the standard-dose group were successfully intubated compared with 81% in the high-dose group (Fisher exact test, $P = .03$).

Discussion

There is a paucity of literature evaluating the safety of ketamine doses beyond 2 mg/kg IV, especially for RSI in the prehospital setting. The results of our study do not support using higher doses of ketamine beyond the standard 1 to 2 mg/kg intravenous induction dose because such dosing was associated with an increased incidence in several adverse events. Most striking was the increased incidence in hypotension and hypoxia in patients who received high-dose ketamine despite the fact that the patients in the high-dose groups started at a higher mean systolic blood pressure than the standard-dose group. Both groups had a decline in mean SBP, but the high-dose group suffered hypoxia and hypotension at a much higher rate. Hypotension and hypoxia were even more striking in trauma patients, which is concerning given that head injury patients suffer twice the mortality when either hypoxia or hypotension occurs.[14,24] Prior studies suggest that ketamine may not prevent hypotension,[24] and, in catecholamine-depleted patients, may actually result in hypotension.[25,26] If ketamine has a ceiling effect, one would expect to see similar rates of adverse events in both standard and high-dose ketamine groups even with shock physiology present at induction. In patients with a high shock index, hypotension was more common.[26] This study lacked a shock-adjusted dose of ketamine (0.5-1 mg/kg) for patients with a high shock index that has been suggested to prevent hypotension.[25,27,28] The increase in hypotensive events with a higher dose makes this suggestion plausible and a key for further investigation.

Additional adverse outcomes were also significant including bradycardia, potentially because of the effects of hypoxia. This drop in heart rate may have been an additional cue for the higher-dose group crewmembers to abort an attempt at passing an endotracheal tube. This could also explain the higher incidence of additional airway attempts and rescue airways in the high-dose group. Although relatively rare at standard doses,[29] high doses of ketamine may have actually increased the rates of laryngospasm as shown by the increased odds compared with the standard dose in this study. This very high incidence of laryngospasm may have been due to several factors. These may include a lack of paralytics for RSI, inadequate time before the intubation attempt after paralytic use, and crews could have confused muscle spasms with true laryngospasm. These increased odds of laryngospasm, along with hypoxia, bradycardia, and hypotension, may have led providers to abort attempts at intubation and resulted in the differences noted in the intubation success rates.

Those who received higher doses of ketamine also required rescue medications at higher rates. This seems counterintuitive because one would expect a higher dose of ketamine to provide a longer period of dissociation. This was an unexpected finding and may be multifactorial in etiology. It is possible that patients in the ketamine group were more likely to receive no paralytic or a short-acting paralytic (succinylcholine) because long-acting paralytics like rocuronium are associated with a delay in administering postintubation sedation.[30] However, the type of paralytic was not ascertained in this study. It also could have been due to infiltrated or failed venous access or even mischaracterization of seizures or myoclonus as agitation. Additionally, the type of additional sedation coadministered may have played a role in the adverse events, with benzodiazepines being more protective and less likely to cause adverse events.[21]

A subgroup analysis was performed between those trauma patients who received high-dose versus standard-dose ketamine. It was found that trauma patients had a similar risk of adverse events of hypotension and oxygen desaturation compared with the entire study population. There is also a need for further examination of ketamine use at shock doses of 0.5 to 1 mg/kg in the catecholamine-depleted patient with a high shock index.

Limitations

This was a retrospective and relatively small sample size study of only 130 patients intubated with the RSI procedure and meeting the strict criteria for inclusion. Although many more intubations occurred during this time, the exclusion criteria used to ensure limited other drugs would be in the system before the ketamine and most crews RSI preference for other induction medication had a substantial effect on the sample size. This small sample size may have led to small changes in blood pressure appearing more significant. Because this

was a retrospective review, we cannot attribute causation of high-dose ketamine for causing the adverse events.

Some limitations with the variables themselves included the following: the patient's body weights were taken from the EMS charts, and, therefore, weights may have been estimated weights, ideal body weights, or hospital bed–based exact weights from an interfacility transfer. This may have caused some differences not accounted for in the statistical analysis.

The timing of variables collection may have affected the significance of the results. Some adverse events may not have been obtained in the data collection tool because of the timing of the event. Specifically, shorter transports may not have captured some adverse events if the prehospital agency arrived at the hospital before the 30-minute time frame. This time frame was chosen based on the expected half-life of ketamine to ensure that events occurring when ketamine had already washed out of the system would not be attributed to the drug. This time interval was also chosen because the institutions participating in the study typically provided patient care for at least 30 minutes after drug administration. It is possible that a short transport time may have caused some missed adverse events. Blood pressures were typically obtained with a pneumatic device, and their accuracy may have been affected by helicopter or transport vibration.

Another limitation of our study was that we did not include the specific paralytic agent used in the data collection tool. The paralytic may have impacted the success of intubation,[31,32] the incidence of laryngospasm, and the need for rescue medication.

It is also possible that, with the differences in crew configuration and EMS protocols, there may have been other factors in patient preparation for intubation. With different training methods, provider characteristics, and lack of Injury Severity Score classification of trauma patients, there may be other unexplored differences in the groups such as the shock index. Because no EMS systems are exactly alike, this study used agencies with similar missions, transport times, and high-performing providers who used varying doses of ketamine for induction.

Lastly, in the few cases in which a vital sign was not listed before the administration of ketamine, other physical findings were used to assess for hypotension, which may have impacted our results. These missing data made shock index calculations unavailable based on the data entered in the PCR. It would have been interesting to see if the differences in the shock index could have been used to adjust medication dosing. However, there were no dose adjustments based on the shock index for crews at the time of the study. This would be an excellent area of further study.

Conclusion

This study found an association between higher doses of ketamine and increasing adverse effects. Despite the limitations of this study, the pronounced differences in the adverse events suggest that ketamine should only be used within its recommended dose range of less than or equal to 2.0 mg/kg for RSI. Future prospective studies should validate these findings in order to ensure the optimal use of ketamine for prehospital RSI.

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