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Brief Report

Hemodynamic consequences of ketamine vs etomidate for endotracheal intubation in the air medical setting☆

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ABSTRACT

Objective: Recent drug shortages have required the occasional replacement of etomidate for endotracheal intubation (ETI) by helicopter emergency medical services (HEMS), with ketamine. The purpose of this study was to assess whether there was an association between ketamine vs etomidate use as the main ETI drug, with hemodynamic or clinical (airway) end points.

Methods: This retrospective study used data entered into medical records at the time of HEMS transport. Subjects, 50 ketamine and 50 etomidate, were accrued from 3 US HEMS programs. The study period was from August 2011 through May 2012. Data collection included demographics, diagnostic category, ETI drugs use, ETI success, and complications. Hemodynamic parameters were assessed for up to 2 sets of vital signs before airway management and up to 5 sets of post-ETI vital signs. Significance was defined at the $P < .05$ level.

Results: Patients on ketamine and etomidate were similar ($P > .05$) with respect to age, sex, scene/interfacility mission type, trauma vs nontrauma, neuromuscular blocking agent use, and rates of coadministration of fentanyl or midazolam. All patients had successful airway placement. Peri-ETI hypoxemia was seen in 10% of etomidate and 16% of ketamine cases ($P = .55$). The pre-ETI and post-ETI were similar between the ketamine and etomidate groups with respect to systolic blood pressure and heart rate at every vital signs assessment after ETI.

Conclusion: Initial assessment of ETI success and complication rates, as well as peri-ETI hemodynamic changes, suggests no concerning complications associated with large-scale replacement of etomidate with ketamine as the major airway management drug for HEMS.

1. Introduction

Prehospital endotracheal intubation (ETI) is one of the more important interventions provided by helicopter emergency medical services (HEMS) and critical care transport (CCT) services. Although outcome data and opinion are mixed with regard to prehospital ground EMS ETI, existing evidence suggests that HEMS-performed ETI is highly successful and improves outcomes in selected patients [1–4].

The commendable ETI performance of HEMS crews is related, in part, to training and skills maintenance, but there is an additional contributor: access to an airway pharmacopoeia that is more extensive than that which is often available to ground EMS [1,2].

With the demonstration of safe achievement of high ETI success rates using neuromuscular blockade (NMB), more attention has become focused on peri-ETI physiology as an airway management end point [5]. In clinical practice, ETI success rates in patients receiving NMB are not likely to be profoundly affected by choice of coadministered sedative/anesthetic drugs.

Peri-ETI physiology questions have understandably focused on oxygenation and ventilation [5,6]. However, hemodynamic issues have also garnered attention. Concern over hypotension has been a predominant force driving the adoption of the blood pressure (BP)–sparing agent etomidate as a preferred agent for HEMS crew airway management [7]. Despite some lingering debate over etomidate's

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safety in some patient subsets, the imidazole hypnotic has been a top choice for air medical providers [1,8,9]. Although its potential use in situations in which NMB is contraindicated contributes to etomidate's widespread use, the main advantage of the drug is its maintenance of peri-ETI BP in critically ill and injured patients [7,10–14].

In 2011, many areas' etomidate supplies began to run short. Principles that spurred the selection of etomidate as a preferred medication assisted intubation agent rendered difficult the search for a replacement. Although the shortages of etomidate developed too quickly for organized consideration of alternatives, many HEMS services arrived at the same conclusion as to a replacement drug: ketamine.

Dissociative anesthesia with ketamine was first described in the literature roughly a half century ago [15,16]. The drug continues to be used in a widespread fashion worldwide, including as an ETI agent for patients with trauma in the emergency department (ED) [17]. There are some data supporting ketamine's use for facilitation of prehospital ETI, but even the most recent reports of ketamine use for trauma ETI lack detailed evidence on hemodynamics effects of ketamine use [17,18].

Given the concerns over ketamine's use that persist despite limited reports of the drug's safety, the Critical Care Transport Collaborate Outcomes Research Effort study group embarked upon an analysis of hemodynamic changes associated with ketamine replacement of etomidate for prehospital airway management. The study's primary goals were to assess hemodynamics before and after ketamine use for airway management and to compare peri–ketamine hemodynamic changes with those seen with etomidate in a similar population. Secondary study goals included assessment of ETI success and complication rates.

2. Methods

2.1. Design

This study was a retrospective assessment of data collected and entered at the time of HEMS transport, as per the usual custom of air medical crews at participating programs. The study was noninterventional, in that no protocol changes were dictated, but the design approached a "natural experiment." External forces (nationwide drug shortages) forced the study HEMS programs to seek an alternative primary intubation drug for use on those occasions in which etomidate was unavailable. Drug shortages were intermittent and inconsistent over the study period. Thus, the study was a retrospective analysis of the impact of participating programs' intermittent replacement of etomidate with ketamine, and the ketamine vs etomidate selection for ETI occurred in a fashion that (very) coarsely approximated a randomized trial.

2.2. Setting

Study subjects were accrued from 3 HEMS services. Most patients (74%) came from 47 Air Evac bases across 17 states in the US southwest, midwest, and east coast regions. Other cases came from Flight for Life Colorado (n = 18) and LifeFlight of Maine (n = 8). All 3 programs use registered nurse/emergency medical transport paramedic crew configurations that operate under direct and indirect medical oversight; medical care protocols for all 3 services allow for use of ketamine (1-2 mg/kg) or etomidate (0.3 mg/kg) to facilitate airway management.

2.3. Subjects and time frame

Subjects were those patients who received, as their major ETI drug, either ketamine or etomidate. Subjects were divided into 1 of 2 major groups, depending on the major ETI drug used: *ketamine* patients received that drug (and not etomidate) and *etomidate* patients were intubated using etomidate (and not ketamine). There were no exclusion criteria based on demographics, diagnosis, or other drugs or interventions used in a given case.

Accrual began in August 2011 and continued through the May 2012. Consecutive cases of ketamine-facilitated ETI were assessed, with the first 50 cases from the participating HEMS programs constituting the ketamine group. The etomidate group was developed by accruing, again starting in August 2011, a consecutive series of etomidate-facilitated ETIs with a program-specific n that equaled that program's etomidate n (ie, if a program contributed 9 ketamine cases, its first 9 etomidate cases from the study period were used).

2.4. Data and end points

The "index time" for hemodynamic end point assessment was set as the time of administration of the primary ETI drug (ie, etomidate or ketamine). For the purposes of this study, the time of primary ETI drug administration constituted the "ETI time." The time intervals for the pre-ETI and post-ETI vital signs assessments were calculated from this index time. Up to 2 pre-ETI vital signs sets were recorded (the 2 vital signs sets just before ETI), and up to 5 post-ETI vital signs sets were recorded. The protocols for the HEMS study services called for vital signs assessments every 5 minutes, but the actual time intervals for vital signs assessment often vary because of clinical exigencies; thus, the actual times of assessment were recorded for this study.

The vital signs upon which the study focused were systolic BP (SBP) and heart rate (HR) because these are the vital signs that would be expected to be affected most by ketamine's sympathomimetic activity. Oxygen saturation (S_pO_2) was also tracked, with hypoxemia defined at the level of less than 90%.

Hypotension was defined as SBP less than 90 mm Hg or mean arterial pressure (MAP) less than 60 mm Hg. Pre-ETI hypotension was said to be present in cases in which there was any recording or report (including before HEMS arrival) of low SBP or MAP. Post-ETI hypotension was defined by the consecutive vital signs readings (up to 5) after administration of the etomidate or ketamine.

New hypotension or hypoxemia was defined if a case met the definition for these vital signs abnormalities after ETI, for which the corresponding pre-ETI vital signs were normal. Heart rate reference range was defined as 60 to 100 beats/min. Given the lower boundary of the study cases' age (12 years), vital signs normal values were not adjusted for age.

In terms of defining hypertension, the study specifically defined 2 points a priori. Systolic BP elevations to above 140 mm Hg were selected as constituting potentially significant levels of BP elevation. A second set of arbitrarily defined a priori hypertension end points was established as SBP elevations (from normotensive pre-ETI measurements) exceeding 25%, to levels above 180 mm Hg.

2.5. Analysis

Descriptive statistics include reporting of mean ± SD or median with interquartile range (IQR). Proportions were reported with binomial exact 95% confidence intervals (CIs).

For continuous data, normality was assessed with the skewness-kurtosis test. When skewness-kurtosis testing indicated nonnormal distribution, medians (with IQR) were used as the measure of central tendency, and comparisons between ketamine and etomidate groups were conducted using nonparametric methods (Kruskal-Wallis testing). When data were normally distributed, the measure of central tendency used was the mean (±SD), and intergroup analysis was conducted with a parametric approach (*t* test).

For categorical data, univariate comparisons of ketamine vs etomidate patients were conducted with Fisher exact test.

All analyses used $P < .05$ to define statistical significance. Calculations were performed with STATA 12MP (StataCorp, College Station, TX).

3. Results

General patient information is shown in Table 1. The table also depicts information about medications used as part of the airway management regimen for the 50 etomidate cases and the 50 ketamine cases. The table demonstrates baseline similarity between the etomidate and ketamine groups. There were no "crossover" cases in which patients received both etomidate and ketamine.

3.1. Adjunctive medications administered periintubation

The medications followed in this study focused on those medications that were administered as part of the index airway management attempt (ie, the airway management attempt for which etomidate or ketamine was used as the primary facilitating drug).

All patients in the study received pre-ETI short-acting NMB as part of their rapid sequence intubation. In nearly all 100 cases (95%), succinylcholine was administered. Rocuronium was administered in the remaining 5 cases, 2 for ketamine patients and 3 for etomidate patients. There was no association between study group and NMB agent ($P = 1.00$).

After paralytics, the most commonly administered adjunctive medication was fentanyl. No other opioid was used in study patients. Fentanyl was given in similar proportions of etomidate and ketamine cases (80% and 76%, respectively; $P = .81$); mean doses for each group are provided in Table 1.

Additional pre-ETI sedation was administered in 47% of cases (52% etomidate and 42% ketamine, $P = .42$). Benzodiazepines were administered most commonly, in 46% of overall cases. Midazolam was given most frequently (37 cases), in a mean dose of 0.05 ± 0.03 mg/kg. The other 9 cases of benzodiazepine administration were uses of lorazepam, administered in a mean dose of 0.03 ± 0.01 mg/kg. The only other analgesic or sedative administered in study cases during ETI was propofol, which was administered at a 1-mg/kg dose in 1 (ketamine) patient before ETI. Table 1 shows the analysis of proportions of ketamine and etomidate cases receiving additional sedation (benzodiazepine or propofol) as part of airway management.

Table 1
Patient characteristics and airway drugs for etomidate (n = 50) and ketamine (n = 50) cases

	Etomidate group (n = 50)	Ketamine group (n = 50)	*P*
Patient characteristics			
Age (y), median (IQR)	41 (25-60)	44 (29-73)	.14
% Male	50.7	49.3	1.00
% Trauma	51.5	48.5	.83
% Scene mission	50.0	50.0	1.00
Transport (min), median (IQR)	58.5 (50-78)	62.5 (53-80)	.57
Preairway management physiology			
Preintubation SBP (mm Hg), mean ± SD	134 ± 33	139 ± 36	.53
% Preintubation hypotension	9.1	7.3	1.00
% Preintubation hypertension	40.9	57.5	.19
Preintubation HR (beats/min), mean ± SD	99 ± 20	101 ± 25	.57
Preintubation bradycardia (%)	4.6	4.6	1.00
Preintubation tachycardia (%)	54.6	50.0	.83
Airway management drugs			
Etomidate (mg/kg), mean ± SD	0.3 ± 0.05	–	–
Ketamine (mg/kg), mean ± SD	–	1.2 ± .52	–
Fentanyl (μg/kg), mean ± SD	2.3 ± 0.72	2.4 ± 0.94	.33
% Administered other sedation	52.0	42.0	.42
% Postintubation paralytics use	50.0	50.0	1.00

Table 2
ETI results for etomidate (n = 50) and ketamine (n = 50) cases

	Etomidate group (n = 50)	Ketamine group (n = 50)	*P*
ETI adjuncts and views			
Cormack-Lehane grade[a] (%)			.52
1	48.6	52.9	
2	22.9	23.5	
3	17.1	5.9	
4	11.4	17.7	
% Bougie use	26.0	18.0	.47
Airway management complications			
% (95% CI), multiple ETI attempts	26.0% (15%-40%)	26.0% (15%-40%)	1.00
% (95% CI) requiring rescue airway	10.0% (3%-22%)	6.0% (1%-17%)	.72
% (95% CI) S_pO_2 <90%	10% (3%-22%)	16% (7%-29%)	.55

[a] Assessed in 69 cases.

A dose of 1 mg of atropine was administered 9 times (4 in etomidate patients, 5 in ketamine patients). There was no association between atropine administration and group ($P = 1.00$).

The only post-ETI drug that was assessed was NMB, which was given in 60% of cases. Vecuronium was used in 41 cases and rocuronium in the remaining 19. Table 1 shows analysis of proportions of ketamine and etomidate cases receiving additional post-ETI paralysis.

3.2. Laryngoscopic adjuncts and view

One of the 3 study programs (Air Evac) routinely documents Cormack-Lehane grade (1-4) on intubations. For this program's 74 cases, Cormack-Lehane data were entered in 69 patients. Cormack-Lehane grades on laryngoscopy were similar in etomidate as compared with ketamine cases (see Table 2).

3.3. Complications

Complications are depicted in Table 2. There were no cases of laryngospasm. No surgical airways were performed. One (ketamine) patient died of what were judged nondrug causes (a 30-in. limb had penetrated the thorax) approximately 20 minutes after intubation.

The airway performance complications followed were requirement for multiple ETI attempts and success at ultimate placement of an endotracheal tube (as compared with a rescue airway). Similarities between etomidate and ketamine groups for these end points are depicted in Table 2.

A primary airway management variable of physiologic consequence is peri-ETI S_pO_2 nadir (lowest S_pO_2 occurring during airway management) [5]. For the 16 cases in which there was new peri-ETI hypoxemia (S_pO_2 nadir <90% during airway management, when pre-ETI S_pO_2 had been above 90%), S_pO_2 data were available for 9 cases. In 6 of these 9 cases, the S_pO_2 dropped to the 80s; in 2 cases, the S_pO_2 dropped to the 70s; and in 1 case, the S_pO_2 dropped to the 60s. For the 9 new hypoxemia cases in which the S_pO_2 was known, testing (with limited statistical power) failed to identify a difference between ketamine and etomidate group median S_pO_2 readings ($P = .81$). Table 2 demonstrates similarity between *etomidate* and *ketamine* cases with respect to the proportion developing peri–airway management hypoxemia.

3.4. Heart rate and BP data before airway management

At least 1 pre-ETI HR was recorded for 88 cases (2 pre-ETI HRs were recorded in 48 cases). At least 1 pre-ETI BP was recorded in 85 cases (all of which were included in the 88 cases with at least 1 HR data point); 2 pre-ETI BPs were recorded in 44 cases. Thus there were

12 cases missing pre-ETI HR data and 15 cases missing pre-ETI BP data. In none of these cases was there arrest before ETI, and none were hypotensive or bradycardic in the first available (immediate post-ETI) time frame.

3.5. Time frames for vital signs assessment

As mentioned previously, for the purposes of this study, ETI time was defined as the time of administration of the intubating dose of either etomidate or ketamine. Vital signs assessed before the ETI time were pre-ETI vital signs; up to 2 sets of these were recorded. Vital signs assessed after the ETI time were post-ETI vital signs; up to 5 sets of these were recorded. Fig. 1 depicts the timeline for data recording, the total n of available data for each assessment time, and the median intervals for all 100 cases, between the various assessment times (eg, interval between the first and second sets of after-ETI vital signs). Protocols for the participating study programs generally call for vital signs every 5 minutes, but the circumstances of critical patient care often translate into varying time intervals, as shown in the Fig. 1.

Table 3 illustrates the breakdown of intervital sign times for etomidate and ketamine cases. There were no statistically significant differences by Kruskal-Wallis testing when comparing the (nonnormally distributed) vital signs intervals between the etomidate and ketamine groups.

3.6. Bradycardia

There were 4 cases (2 etomidate, 2 ketamine) in which there was preairway management bradycardia with HRs as low as the 40s. Bradycardia persisted after airway management in only 1 (etomidate) case (there was also persistent hypotension).

Transient new bradycardia occurred in 1 adult (ketamine) patient whose HR dropped to 28 beats//min after succinylcholine and before airway management. The bradycardia, associated with no hypotension and present on only 1 post-ETI vital sign set, was attributed by the flight crew to succinylcholine administration. It occurred in the absence of any hypoxemia and was immediately corrected with a second dose of 1 mg atropine (an initial dose had been given as part of the ETI medication administration).

In additional 9 cases (4 etomidate and 5 ketamine), there was new bradycardia after ETI. One of these patients had a trauma cardiac arrest roughly 20 minutes after ketamine administration. In the other 8 patients, bradycardia was present in at least 1 set of post-ETI vital signs.

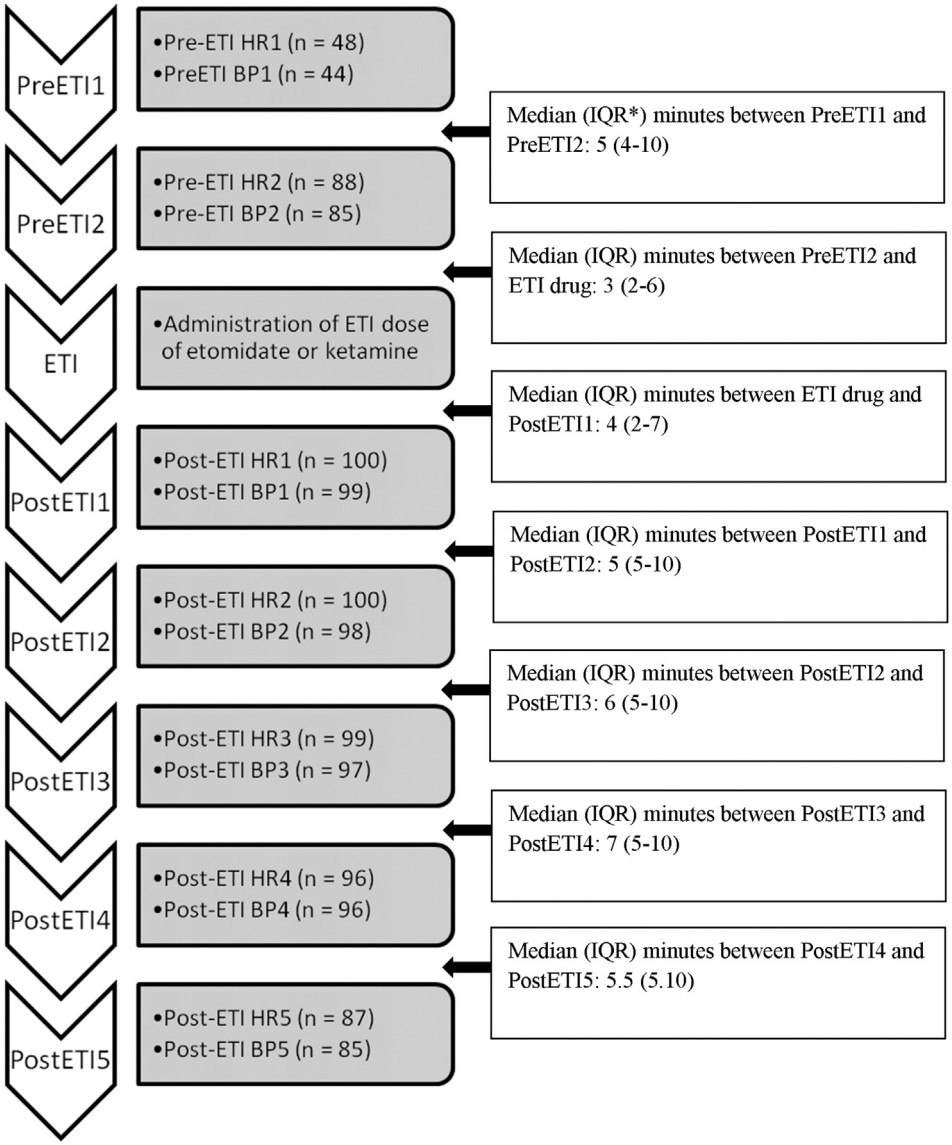

Fig. 1. Time line for data recording.

Table 3
Hemodynamic changes associated with etomidate and ketamine administration

	Etomidate group	Ketamine group	*P*
Median (IQR) (min), interval between:			
1st and 2nd sets of predrug (ie, preetomidate or preketamine) VS	5 (4.5-9)	5 (4-10)	.89
2nd set of predrug VS and drug administration	3 (2-7)	3 (1-6)	.65
Drug administration and 1st set of postdrug VS	3.5 (2-6)	5 (3-9)	.07
1st and 2nd sets of postdrug VS	5 (5-10)	8 (5-10)	.06
2nd and 3rd sets of postdrug VS	8 (5-10)	5.5 (5-9)	.16
3rd and 4th sets of postdrug VS	8.5 (5-10)	6.5 (5-10)	.57
4th and 5th sets of postdrug VS	6 (5-10)	5 (5-10)	.34
HR results, median (IQR)			
1st predrug HR	93 (82-109)	100 (88-112)	.48
2nd predrug HR	99 (87-111)	99 (84-120)	.72
1st postdrug HR	98 (86-108)	101 (83-112)	.40
2nd postdrug HR	96 (80-110)	96 (84-115)	.61
3rd postdrug HR	93 (80-109)	92 (78-108)	.96
4th postdrug HR	91 (78-105)	92 (77-105)	.94
5th postdrug HR	86 (77-100)	92 (76-108)	.42
New postdrug abnormalities (not present predrug)			
% (CI) any new postdrug bradycardia	8 (2-19)	12 (5-24)	.74
% (CI) any new postdrug bradycardia associated with new hypotension	4 (0.5-14)	4 (0.5-14)	1.00
% (CI) any new postdrug tachycardia	11 (4-24)	18 (8-33)	.38
% (CI) any new postdrug tachycardia associated with new hypotension	4 (0.5-14)	0 (0-7.1)	.50
% (CI) any new postdrug hypotension	10 (3-22)	24 (13-38)	.11
% (CI) any new postdrug hypertension	28 (16-42)	30 (18-45)	1.00
SBP results, median (IQR)			
1st predrug SBP	127 (112-156)	128 (106-157)	.71
2nd predrug SBP	129 (112-161)	140 (118-156)	.48
1st postdrug SBP	132 (112-151)	137 (109-148)	.84
2nd postdrug SBP	130 (109-155)	135 (107-153)	.76
3rd postdrug SBP	130 (111-140)	131 (102-148)	.94
4th postdrug SBP	121 (108-141)	129 (100-146)	.88
5th postdrug SBP	115 (105-141)	123 (111-142)	.67

VS, vital signs; CI, 95% CI, except where point estimate is 0%, in which case 1-sided 97.5% CI is reported.

In 3 of the 8 new bradycardia cases (2 etomidate and 1 ketamine), none of which were hypotensive before ETI, there was post-ETI hypotension. An etomidate patient with gunshot wounds to the head, back, and chest had persistent post-ETI hypotension (SBP, 70-80 mm Hg) that was associated with bradycardia (HR, 40s-50s). A second etomidate patient with trauma (fall) also had persistent hypotension (SBP in the 80s) with ongoing HR in the 50s. The third new bradycardia case with hypotension was a ketamine patient with HR in the 40s to 50s and 4 normotensive SBPs (113-134 mm Hg) with a single hypotensive SBP of 87 mm Hg. Table 3 provides information demonstrating similar incidence rates of bradycardia post-ETI, in ketamine vs etomidate cases.

Atropine was administered in 9 patients (5 ketamine and 4 etomidate, $P = 1.0$). Two had had pre-ETI bradycardia, which did not recur after atropine administration. Hemodynamically inconsequential bradycardia was recorded on 1 set of vital signs in 2 of the other cases; there was no bradycardia in the remaining 5 cases.

3.7. Tachycardia

Tachycardia before ETI was present in 46 cases. The likelihood of pre-ETI tachycardia was similar in etomidate and ketamine cases (54.6% and 50.0%, respectively; $P = .83$). Predrug HR data are depicted in Table 3.

Post-ETI tachycardia as defined by HR more than 100 beats/min at any time after ETI was present in 58 cases. In 13 cases, the post-ETI tachycardia was new (ie, occurring in the absence of any recorded pre-ETI tachycardia).

In 2 cases, both in the ketamine group, there was new tachycardia in patients who also had new hypotension. In 1 of these cases, the pre–ketamine HR was 95 beats/min. The first post–ketamine HR in this case was 108 beats/min; subsequent HRs were in the reference range. After the HR had already normalized, there were 2 hypotensive SBPs (59 and 67 mm Hg) that normalized by the end of the transport of this pneumosepsis patient. The second patient with new tachycardia who also had new hypotension had taken an alprazolam overdose and had persistent post–ketamine tachycardia (101-120 beats/min) for the first 4 HR assessments before the HR normalized on the fifth post–ketamine assessment. This patient's initial 2 post–ketamine SBPs were normal, with the next 2 SBPs being 80 and 82 mm Hg before the fifth and final SBPs normalized to 104.

Comparative analysis identified similarity in proportions of etomidate and ketamine patients with any tachycardia and any new tachycardia (ie, tachycardia postdrug, in patients with no predrug tachycardia). These results are shown in Table 3.

3.8. Blood pressure

Baseline SBP recordings, which were similar for etomidate and ketamine cases, are summarized in Table 3. The differences in BP that were observed for the 2 groups were neither clinically nor statistically significant at any time point during the 5 postdrug BP assessments.

In addition to comparison of median SBP at up to 2 predrug and up to 5 postdrug time points, the study analysis also included categorical assessments. The first such categorical assessment was the depiction of BP tracking for the patients who had any hypotension in the time frame before “time zero” (T0), which was the administration time of ETI drug (ketamine or etomidate). Fig. 2 depicts the BP tracking for these patients.

Another method of tracking postmedication BP changes was the definition of a “potentially significant” change as an increase in postmedication SBP (for any of the up to 5 post-ETI recordings) of greater than 25% from the SBP just before medication administration. Systolic changes met this criterion in 18 cases (8 etomidate, 10 ketamine, $P = .80$). In 6 (4 etomidate, 2 ketamine) of these cases, the large SBP increment occurred in patients who were hypotensive before ETI; SBP changes in these cases are included in Fig. 2. In the remaining 12 cases (6 each from etomidate and ketamine groups), an SBP increase of greater than 25% occurred in patients who, before ETI, were either normotensive ($n = 8$) or hypertensive ($n = 4$). In 8 cases (5 etomidate and 3 ketamine), the post-ETI SBP peak met the criteria for “new hypertension” (ie, post-ETI SBP exceeding 140 mm Hg, in a case in which pre-ETI SBP was <140 mm Hg).

For the 12 cases in which the peak post-ETI SBP was greater than 25% higher than the pre-ETI SBP, the magnitude of SBP elevation of greater than 25% was seen in only 1 post-ETI vital sign set in 6 cases (3 each from etomidate and ketamine groups). For the other 6 cases in which the peak post-ETI SBP reached more than 25% higher than the pre-ETI SBP, readings of greater than than 25% higher than pre-ETI SBP were seen in 2 or more sets of post-ETI vital signs. Fig. 3 shows the change from pre-ETI SBP to peak post-ETI SBP (recorded on any of the 5 post-ETI vital signs assessments) in the dozen cases in which the peak post-ETI SBP was greater than 25% higher than pre-ETI SBP.

Of the dozen cases with SBP peak exceeding pre-ETI SBP by more than 25%, half (3 in each of the etomidate and ketamine groups) met the a priori criterion for “very high BP” of SBP greater than 180 mm Hg. These 6 cases are labeled in Fig. 3.

4. Discussion

Prehospital ETI is a major part of HEMS care. Available evidence suggests that HEMS-performed ETI is highly successful and improves outcomes in some types of patients [1–4]. Helicopter emergency

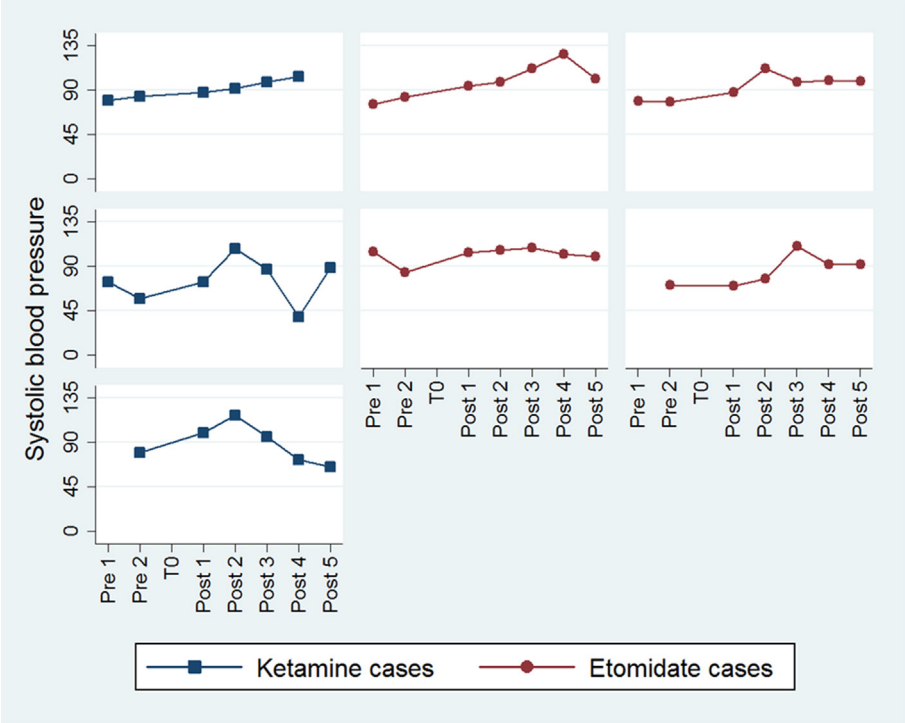

Fig. 2. Blood Pressure tracking for patients with hypotension between TO and ETI drug administration.

medical services crews' ETI and its putative effects on outcome are related to both training and access to advanced pharmacology [1,2]. Although the importance of ETI success rates is clear, other end points have been acknowledged as critical [5,6]. One such additional end point is peri-ETI hemodynamics.

Other than concerns about succinylcholine-associated bradycardia —which has not emerged as a major clinical problem in field ETI—the main questions about peri-ETI hemodynamics have revolved around drug-related hypotension. Some agents (eg, midazolam) that were initially used with high frequency in the prehospital setting were shown to have an association with peri-ETI hypotension [19]. Data suggesting that etomidate avoided these hypotension concerns contributed to the adoption of the imidazole for HEMS airway management [1,7–14].

Although some HEMS programs have been using ketamine as a primary ETI drug for years, there are sparse data describing its safety and efficacy. The primary motivation for this study was the forced search for an alternative to etomidate, necessitated by nationwide shortages of that drug. Poor availability of many ETI drugs (eg, benzodiazepines and opioids) prompted some HEMS to search for an alternative agent to facilitate ETI.

Although the shortages of etomidate and other drugs developed too quickly for organized consideration of alternatives, many HEMS and CCT services arrived at the same conclusion as to a replacement

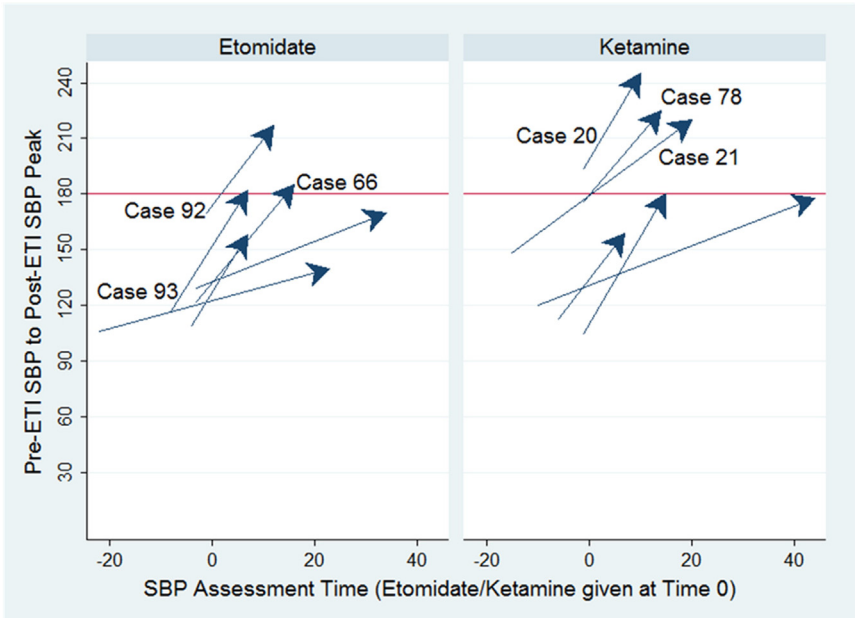

Fig. 3. Change in SBP from pre-ETI to peak post-ETI for 12 patients who had a greater than 25% change.

drug: ketamine. Dissociative anesthesia with ketamine was first described in the literature roughly a half century ago [15,16]. Ketamine continues to be used in a widespread fashion worldwide, but for varying indications. In the United States, ketamine is used mostly for procedural sedation and analgesia, where its BP support is noted as an advantage [20]. In Europe, literature since the early 1980s has cited ketamine's hemodynamic advantages in support of its use in prehospital and acute care administration to facilitate ETI in patients with shock/trauma [21,22]. In fact, German experts have called for preferential use of ketamine over etomidate for trauma airway management, owing to etomidate's potential effects on the adrenal axis [23]. Although recent data [17] suggest that there may be a change toward more frequent use of ketamine for trauma ETI in the ED setting in the United States, multicenter airway management studies have suggested that ketamine is not commonly used for airway management [1].

There are few data directly addressing the question as to why ketamine use is uncommon in the United States, but some possible reasons emerge upon consideration. This discussion is not the place for a detailed review of ketamine's pharmacology and uses, but a brief overview of ketamine's risks—perceived and real—can help inform decisions regarding its adoption for airway management.

Although ketamine is commonly used for pediatric procedural sedation and analgesia, many do not use the drug in adults because of risk of emergence reactions [24]. Other potential problems associated with ketamine include laryngospasm (rare), hypersalivation, and vomiting [25]. It is true that emergence reactions appear to be more frequent in older pediatric patients and adults and that intraprocedural hypersalivation and postprocedural vomiting sometimes occur, risks of these complications can be mitigated by prophylactic measures (eg, benzodiazepines, antisialogogues, and ondansetron) [25]. In fact, the available adult sedation data regarding ketamine—including cases in which the drug is administered in environments even more austere than the prehospital/HEMS setting—suggest both safety and efficacy of dissociative anesthesia in nonpediatric patients [26,27]. Emerging literature describing ketamine's use for trauma ETI in the ED is also suggesting the safety and even preferability of the agent, based on both physiology and simplicity (ie, single anesthetic plus NMB) [17].

With the previously mentioned adverse effects of ketamine being rare, subject to prevention, or of marginal relevance to intubation in a critically ill or injured patient, the issues with ketamine and ETI are, in practice, reduced to cardiovascular stimulation. Ketamine has sympathomimetic effects that are clinically noticeable. In fact, the hemodynamic stimulation associated with ketamine administration is sufficient that the drug is sometimes used in combination with other sedatives (eg, propofol) to counteract the hypotensive effects of the latter agents [20]. The hemodynamic "boost" from ketamine is, in fact, specifically mentioned by some experts, as rendering the drug ideal for use in the prehospital and acute care shock/trauma setting [18,23].

There is literature specifically describing ketamine use by HEMS crews. Most of the evidence addresses ketamine's administration by a variety of routes, for analgesic purposes in adults and children [28–33]. Although most studies have emanated from Europe, there are US reviews supporting ketamine use for analgesia administered by HEMS crews [34].

A few studies discuss ketamine specifically for use in ETI. In 1997, Gofrit et al [35] provided a descriptive review of ketamine's moderate success (66% ETI rate) in facilitating ETI in HEMS patients who failed at least 1 prior (non–medication assisted intubation) ETI attempt. Sibley et al [18] assessed 71 patients (70 adults), receiving an average ketamine dose of 1 mg/kg, for intubation by English HEMS crews. Most ETIs were performed by paramedics, with NMB administered in three-fourths of cases. Mean arterial pressure and HR changes with 95% CIs after ketamine administration were 2.3 (−8.0 to 3.3) and 0.5 (−4.9 to 4.0). Complications seen after, but not necessarily attributed to, ketamine included failed ETI (7%), hypotension (7%), hypertension (6%), bradycardia (1%), tachycardia (3%), and death (7%). Most recently, Ballow et al [17] addressed the ETI success rates and hypotension incidence found with administration of ketamine for trauma ETI in the ED setting.

The primary reason often cited for reticence over ketamine use in the United States and elsewhere is the effect of the drug's sympathomimesis on intracranial pressure (ICP) [36]. The ketamine-ICP issue and whether/how it can be ameliorated with pretreatment (eg, with benzodiazepines) have been discussed and debated for many decades [37,38]. The physiology of ketamine and ICP is far too broad for detailed discussion, but detailed reviews of sedation in patients with traumatic brain injury, the group for whom ICP concerns are most acute, are available in the critical care literature. A representative review concluded that ketamine is no worse than alternative sedatives, in its effects on ICP, cerebral perfusion pressure, or patient-centered outcomes [39]. In fact, the one sedation approach in patients with severe traumatic brain injury that was found to have potentially deleterious effects on the outcomes assessed was the use of high bolus doses of opioids [39].

Consistent with the review articles from critical care literature are findings that ketamine may, in fact, have salutary effects on cerebral perfusion in patients with trauma (including those with head injury) [36]. Thus, it is not surprising to find emergency medicine experts labeling as "myth" the belief that ketamine should not be used for induction in the setting of head injury [40]. The most recent report of ketamine's use for trauma ETI includes discussion supporting the safety of ketamine for head-injured patients [17].

A retrospective, nonrandomized trial will not provide definitive answers to questions about ketamine's appropriateness for HEMS use. However, the conditions associated with acute and unpredicted shortages of the main HEMS ETI drug (etomidate) created an opportunity for an informative "natural experiment."

Although ICP issues are the main concern with ketamine, this parameter is rarely (if ever) measured during HEMS or CCT crews' ETI. This inability to monitor ICP during ketamine administration by HEMS crews for ETI is regrettable, but it should be acknowledged that global measurements such as ICP are in themselves surrogate end points—they may or may not reflect perfusion to a particular part of injured or at-risk brain [41]. In fact, the most recent literature seems to question the very practice of performance of ICP monitoring in patients with acute head injury [42]. Thus, use of non-ICP physiologic surrogates appears justifiable.

As surrogate physiologic indicators, hemodynamic measures are the most promising variables that are actually assessed with regularity in the peri-ETI period. Systolic BP, HR, and MAP have been measured in previous studies addressing ketamine's peri-ETI hemodynamic effects [18]. These variables have also been assessed in other studies addressing peri-ETI pharmacology [19].

What is different about this study is the comparison between post-ETI vital signs seen with ketamine vs post-ETI vital signs seen with the most commonly used HEMS ETI alternative (etomidate). On every assessment of vital signs post-ETI, there was no statistically or clinically significant difference between patients receiving ketamine and patients receiving etomidate. In addition, categorical analysis of potentially important end points (eg, proportion with new hypertension or tachycardia) failed to identify any hemodynamic parameter changes with ketamine as compared with etomidate.

That post-ETI SBP and HR were similar in ketamine and etomidate patients could be related to coadministered medications that were not assessed in detail in this study (which only assessed peri-ETI drugs). Adjustment for these variables was rendered impractical by relatively small numbers and substantial potential for complexity in accounting for myriad possible combinations of patient acuity, hemodynamics, and medication combinations over flights of varying lengths. The assessment of specific coadministered drug combinations is less

important than emphasizing the point that—in real clinical practice in which HEMS crews know to coadminister sedatives—ketamine's sympathomimetic effects do not appear to result in profound physiologic derangement.

Similarity in hemodynamics could also be related to residual confounding caused by differences in patient population, but this is relatively unlikely given the natural experiment nature of the study (ie, ketamine was used for patients in whom etomidate would usually be used, owing to intermittent unavailability of the latter). The suggestion of similarity between etomidate and ketamine cases is supported by the lack of findings of significant intergroup differences with respect to patient characteristics, preairway management vital signs, adjunctive drugs used with ETI, post-ETI paralytics use, or intervals between vital signs assessments.

The study is characterized by other limitations that restrict interpretation of the findings. First, with respect to airway management success and complications, because NMB use was virtually universal, the coadministered drugs would not be expected to impact ETI success. Therefore, this study's results with respect to airway management or complications should not be extrapolated to situations in which NMB is not used.

In terms of the study sample, there was suboptimal precision surrounding some of the end points. A larger study could potentially identify as statistically significant, some of the changes observed in this data set that were found not significant.

The study focused on peri-ETI physiology, but there are few data that guide clinical interpretation of the impact of hemodynamic changes occurring during airway management. Obviously, hypotension is undesirable (eg, as a mediator of secondary brain injury), but the consequences of BP or HR elevation—the changes expected with ketamine—are unclear. It is acknowledged that this study's hemodynamic cutoffs (eg, defining hypertension) are arbitrary. End points were selected to provide indicators of potentially important physiologic changes with the understanding that these cutoffs do not have ideal sensitivity or specificity for defining clinically significant changes.

The focus of this study is therefore emphasized to be on the hemodynamic changes associated with use of ketamine for airway management. Placement of those hemodynamic changes into clinical context will be case specific and is not addressed in this study. It is hoped that the results from this data set will help inform clinicians faced with decisions about which ETI drugs to use in their own patients.

5. Conclusions

The choice of prehospital ETI medication depends on a variety of factors. One of the more important is the need for hemodynamic stability. There have been few studies providing detailed information on hemodynamic changes (in either direction) associated with use of ketamine for prehospital ETI. This study's data provide evidence, with limitations as previously outlined, that replacement of etomidate with ketamine as currently used (eg, with NMB and coadministered sedatives) for prehospital ETI is not associated with adverse effects on either ETI success or peri-ETI physiology.

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