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After completion of this exercise the participant will be better able to identify the roles of ketamine and etomidate in emergent airway management.

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# CME Retrospective Analysis of Etomidate Versus Ketamine for First-pass Intubation Success in an Academic Emergency Department

Asad E. Patanwala, PharmD, Courtney B. McKinney, PharmD, Brian L. Erstad, PharmD, and John C. Sakles, MD

## Abstract

***Objectives:*** The objective of this study was to compare first-pass intubation success between patients who received etomidate versus ketamine for rapid sequence intubation (RSI) in the emergency department (ED).

***Methods:*** This was a retrospective analysis of prospectively collected data recorded in a quality improvement database between July 1, 2007, and December 31, 2012. The study was conducted in an academic ED in the United States. All patients who received etomidate or ketamine as part of RSI were included. The primary outcome measure was first-pass success. A multivariate analysis was conducted to determine if sedative type was associated with first-pass success, after adjusting for potential confounders and baseline differences.

***Results:*** The final cohort consisted of 2,098 RSI procedures using either etomidate ($n$ = 1,983) or ketamine ($n$ = 115). First-pass success occurred in 77.0% of patients in the etomidate group and 79.1% of patients in the ketamine group (difference = –2.1%; 95% CI = –5.5% to 9.8%). In the multivariate analysis, after adjusting for potential confounders, sedative type was not associated with first-pass success (odds ratio = 0.89; 95% CI = 0.5 to 1.5; p = 0.632).

***Conclusions:*** Etomidate and ketamine are associated with equivalent first-pass success when used in RSI. Ketamine may be an appropriate alternative to etomidate for RSI in the ED.

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Rapid sequence intubation (RSI) is the mainstay of airway management in critically ill emergency department (ED) patients. With the possible exception of patients who are unconscious and unresponsive, all patients needing RSI require the use of a sedative agent prior to neuromuscular blockade. The intent of the sedative is to render the patient unconscious and unaware, while the paralytic facilitates passage of the tracheal tube via muscular relaxation. Most studies evaluating intubation conditions or success rates have traditionally focused on comparisons of neuromuscular blockers.[1,2] However, the sedative used may also influence intubating conditions and success rates by potentiating the effect of the neuromuscular blocker; reducing the time to maximal neuromuscular blockade; and affecting diaphragmatic, laryngeal, and pharyngeal reactivity to the intubation stimulus.[3–5]

In previous systematic reviews and registry studies, the effect of the paralytic on intubation conditions was modified based on the sedative used.[2,5] This suggests that sedative selection could also influence intubation success, which is a more clinically relevant outcome compared to intubation conditions.[6] A previous study by Jabre et al.,[7] in which the primary focus was organ failure, reported intubation conditions and difficulty between etomidate and ketamine, but first-pass intubation success has not been evaluated as an outcome. The complications related to intubation (such as hypoxemia,

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aspiration, bradycardia, and cardiac arrest) increase as the number of intubation attempts increase.[6,8] Therefore, it is important that intubation success is achieved on the first-pass, and studies are needed to ascertain if ketamine use is associated with a reduction in intubation success compared to etomidate before it can be routinely recommended.

The primary goal of this study was to compare first-pass RSI success in ED patients who received etomidate versus ketamine. We hypothesized that there is no difference in first-pass success between the two agents.

## METHODS

### Study Design

This was retrospective analysis of prospectively collected data recorded in a quality improvement database between July 1, 2007, and December 31, 2012. The intent of the database is to evaluate resident performance, medications, and devices used for intubation in the ED. This study was granted exemption by the institutional review board.

### Study Setting and Population

The study was performed in a 61-bed academic tertiary care ED with a census of approximately 75,000 patient-visits annually. Emergency physicians (EPs) primarily perform all intubations. During each intubation, physicians have access to a standardized intubation medication box containing the sedative etomidate, and the neuromuscular blockers succinylcholine, rocuronium, and vecuronium. Ketamine is available as an alternative agent via controlled access cabinets located in the ED. Sedative and neuromuscular blocker selection is primarily dependent on physician preference. All patients who underwent RSI in the ED were included. Patients were excluded if RSI was performed using a sedative other than etomidate or ketamine or if vecuronium was used for neuromuscular blockade instead of succinylcholine or rocuronium.

### Study Protocol

The EP performing the intubation recorded data prospectively using a standardized data collection form, which was completed following the intubation. Pharmacy, billing, and admission records were used to identify any intubations performed without corresponding data forms, in which case the operators were contacted for form completion. Data collected included patient age, sex, trauma status (trauma or nontrauma), failure of prehospital intubation (failed or not attempted), presence of any difficult airway characteristics (blood or vomit in the airway, short neck, cervical collar, small mandible, obesity, airway edema, facial trauma, or large tongue), laryngoscopy device used, reason for device selection (standard, anticipate difficult airway, or educational reasons), reason for intubation (airway protection, respiratory failure, cardiac arrest, patient control, hypoxia), level of physician training (classified by postgraduate year [PGY] of residency training), medications used, and number of intubation attempts. The data were then entered into the electronic database program HanDBase 4.0 for the iPad (DDH Software, Wellington, FL) with subsequent transfer to Excel for Windows 2010 (Microsoft, Redmond, WA).

The primary outcome measure was first-pass success. The definitions of intubation attempt and intubation success were similar to those used in previous investigations.[9] An intubation attempt was defined as the insertion and subsequent removal of the laryngoscopic device from the patient's mouth, regardless of whether an attempt was made to pass a tracheal tube. Intubation success was defined as correct placement of the tracheal tube into the trachea, which was confirmed by end-tidal $CO_2$ capnometry, pulse oximetry, chest auscultation, observation of chest excursion, absence of epigastric sounds, and misting of the endotracheal tube.[9]

### Data Analysis

Patients were categorized into two groups based on the sedative used for intubation: etomidate or ketamine. Demographic and intubation data were compared between the two groups. An unpaired Student's t-test was used to compare continuous, normally distributed variables. Normality was determined by visually inspecting the data. Fisher's exact test was used to compare categorical variables. A multivariate logistic regression analysis was performed to determine the effect of sedative agent on first-pass success, after adjusting for confounders. Potential confounders that were included in the model were age, sex, paralytic used, trauma status, reason for intubation, device used, failure of prehospital intubation, reason for device selection, difficult airway parameters, and physician training. These were selected based on previous studies evaluating intubation success in this setting, and all variables were forced into the model.[1,9] Age was categorized in the model as younger than 18, 18 to 65, and older than 65 years, since it did not meet the assumption of linearity in the log-odds. Difficult airway characteristics were entered into the model as ordinal variables. The model was checked for interactions and model fit was assessed by the Hosmer-Lemeshow goodness-of-fit test. No interactions were identified, allowing for all potential variables to be added in the same model. All statistical analyses were performed using Stata version 12 (StataCorp, College Station, TX) with significance for all analyses defined a priori as $p < 0.05$.

## RESULTS

During the study period there were 2,258 RSIs performed in the ED. Of these, 113 were performed with sedatives other than etomidate or ketamine, 42 were performed with paralytics only, and five were performed with paralytics other than succinylcholine or rocuronium. Therefore, the final cohort consisted of 2,098 intubations using either etomidate ($n$ = 1,983) or ketamine ($n$ = 115). Overall, most intubations were performed by EPs ($n$ = 2,019), followed by medical students or paramedics ($n$ = 59) and physicians from other specialties ($n$ = 20). The mean (±SD) patient age was 45.6 (±22.5) years, 63.5% of the patients were male, and the proportion of trauma patients was 44.0%. Comparison of baseline patient demographics and intubation

Table 1
Demographics and Intubation Characteristics of Etomidate Versus Ketamine Groups

| Characteristic | Etomidate ($n$ = 1,983) $n$ (%; 95% CI) | Ketamine ($n$ = 115) $n$ (%; 95% CI) |
|---|---|---|
| Age group (yr)* | | |
| <18 | 171 (8.6; 7.4–9.9) | 23 (20.0; 13.1–28.5) |
| 18 to 65 | 1,415 (71.4; 69.3–73.3) | 71 (61.7; 52.2–70.6) |
| >65 | 397 (20.0; 18.3–21.9) | 21 (18.3; 11.7–26.5) |
| Sex* | | |
| Female | 711 (35.9; 33.7–38.0) | 55 (47.8; 38.4–57.3) |
| Male | 1,272 (64.2; 62.0–66.3) | 60 (52.2; 42.7–61.6) |
| Trauma* | | |
| Medical | 1,081 (54.5; 52.3–56.7) | 94 (81.7; 73.5–88.3) |
| Trauma | 902 (45.5; 43.3–47.7) | 21 (18.3; to 11.7–26.5) |
| Prehospital intubation | | |
| Not attempted | 1,870 (94.3; 93.2–95.3) | 113 (98.3; 93.9–99.8) |
| Failed | 113 (5.7; 4.7–6.8) | 2 (1.7; 0.2–6.1) |
| Paralytic used | | |
| Rocuronium | 1,006 (50.7; 48.5–53.0) | 57 (49.6; 40.1–59.0) |
| Succinylcholine | 977 (49.3; 47.0–51.5) | 58 (50.4; 41.0–59.9) |
| Reason for intubation* | | |
| Airway protection | 1,407 (71.6; 68.9–72.9) | 56 (48.7; 39.3–58.2) |
| Respiratory failure | 315 (16.0; 14.3–17.6) | 49 (42.6; 33.4–52.2) |
| Cardiac arrest | 43 (2.2; 1.6–2.9) | 1 (0.9; 0.0–4.7) |
| Patient control | 171 (8.7; 7.4–9.9) | 3 (2.6; 0.5–7.4) |
| Hypoxia | 29 (1.5; 1.0–2.1) | 6 (5.2; 1.9–11.0) |
| Device used* | | |
| Direct laryngoscopy | 951 (48.0; 45.7–50.2) | 41 (35.7; 26.9–45.1) |
| GlideScope | 556 (28.0; 26.1–30.1) | 28 (24.4; 16.8–33.2) |
| C-MAC | 415 (20.9; 19.2–22.8) | 35 (30.4; 22.2–39.7) |
| Other | 61 (3.1; 2.4–3.9) | 11 (9.6; 4.9–16.5) |
| Reason for device selection* | | |
| Standard | 1,230 (62.0; 59.8–64.2) | 57 (49.6; 40.1–59.0) |
| Difficult | 485 (24.5; 22.6–26.4) | 31 (27.0; 19.1–36.0) |
| Education | 268 (13.5; 12.0–15.1) | 27 (23.5; 16.1–32.3) |
| Operator level of training | | |
| Nonphysician (medical students and paramedics) | 57 (2.9; 2.2–3.7) | 2 (1.7; 0.2–6.1) |
| PGY1 | 411 (20.7; 19.0–22.6) | 27 (23.5; 16.1–32.3) |
| PGY2 | 754 (38.0; 35.9–40.2) | 42 (36.5; 27.7–46.0) |
| PGY3 | 722 (36.4; 34.3–38.6) | 42 (36.5; 27.7–46.0) |
| Attending | 39 (2.0; 1.0–2.1) | 2 (1.7; 0.2–0.6) |
| Difficult airway characteristics* | | |
| None | 722 (36.4; 34.3–38.6) | 45 (39.1; 30.2–48.7) |
| 1 | 586 (29.6; 27.6–31.6) | 41 (35.7; 26.9–45.1) |
| 2 | 289 (14.6; 13.1–16.2) | 18 (15.7; 9.6–23.6) |
| 3 or more | 386 (19.5; 17.7–21.3) | 11 (9.6; 4.9–16.5) |

PGY = postgraduate year.
*Significant difference between groups.

parameters between the etomidate and ketamine groups is provided in Table 1.

First-pass success occurred in 77.0% of patients in the etomidate group and 79.1% of patients in the ketamine group (difference = –2.1; 95% CI = –5.5 to 9.8). In the multivariate analysis, after the potential confounders and baseline differences were adjusted for, ketamine use was not associated with a reduction in first-pass success (odds ratio = 0.89; 95% CI = 0.5 to 1.5; p = 0.632) compared to etomidate. The data fit the model well (Hosmer-Lemeshow goodness-of-fit, p = 0.944).

## DISCUSSION

First-pass intubation success is highly desirable because complications increase as the number of attempts increases.[6,8] Previous studies have primarily focused on the effects of neuromuscular blockers, since they are directly responsible for muscular relaxation for passage of the tracheal tube.[1] However, the sedative used can affect this outcome by a variety of potential mechanisms. For instance, the response to the intubation stimulus, such as diaphragmatic movement and coughing, can be influenced by the sedative used.[3] Also, the onset time of neuromuscular blockade can be modified by the sedative.[4] This is particularly important in the context of our study because ketamine has a longer onset of effect compared to etomidate. Therefore, if intubation is attempted prior to maximal neuromuscular blockade, intubation success could be affected.

Sivilotti et al.[5] evaluated the effect of a wide range of sedatives on intubation success in a multicenter observational study. They found that collectively, thiopental, methohexital, and propofol were associated with improved first-pass success, compared to other sedatives such as etomidate, ketamine, and benzodiazepines. They

hypothesized that the former group of sedatives produce a deeper plane of anesthesia, thereby facilitating intubation before complete neuromuscular blockade is achieved with paralytics alone. However, these former agents are seldom used for emergency intubation because of the potential for adverse effects such as hypotension. Our study builds on the results of Sivilotti et al. by focusing on etomidate and ketamine, two of the most commonly used sedatives for this indication due to their favorable hemodynamic profile. In addition, we included important confounders such as the intubation device used, which has recently been shown to be highly predictive of intubation success.[10] Thus, our results are pertinent in an era in which video laryngoscopy is common.

In a recent randomized controlled trial by Jabre at al.,[7] 655 patients who required emergency intubation were given either etomidate or ketamine for induction. There was no difference between groups with regard to the development of organ failure, which was the primary outcome. Although intubation success was not an outcome in this study, the difficulty of intubation was measured and was found to be comparable between the two groups. However, since this was not the focus of the study, important confounders were not measured. Our study is unique because we measured first-pass success, which was our primary outcome. We were unable to measure adverse effects, which is an important consideration in terms of sedative selection. However, the much larger study by Jabre et al.[7] did not show differences in adverse effects, and these agents are considered to have similar safety profiles. Thus, given the fact that multiple intubation attempts are associated with an increase in adverse effects, we felt that first-pass success was the most important outcome to study.

## LIMITATIONS

The study has a few limitations related to its design. The results should be extrapolated with caution to nonacademic EDs. There is a possibility for measurement bias because physicians performing each intubation completed the data forms themselves. Ideally, an independent observer would collect this information. However, our main outcome variable was intubation attempts, and it is very unlikely that this variable would be erroneously documented. Some data collection forms were not completed immediately after the intubations and required the senior investigator (JCS) to contact individual physicians as part of a quality improvement process. Although this was done as quickly as possible, the delay in recording information in these cases could have led to recall bias. Nonetheless, the senior investigator verified information provided against medical records to ensure accuracy of documentation. It is possible that there was selection bias with regard to ketamine and etomidate. There were many more patients in the etomidate group, but we included all patients to minimize the potential for selection bias. Ideally, a randomized controlled trial would overcome this bias. However, we adjusted for differences between groups and performed the necessary model diagnostics. In addition, there could be individual variation between operators, but we could not stratify the results by operator because there were more than 150 operators in the database. Also, operator success could improve with number of previous intubations. Nonetheless, we included level of training as a surrogate for operator skill. We did not have dosing information of the paralytics, which could influence intubation conditions. There were several baseline differences between groups. However, we adjusted for this in our multivariate model. Finally, it is possible that there are additional confounders that were not included in our model. However, we have included the most likely variables, based on previous studies that could affect our outcome.

## CONCLUSIONS

Etomidate and ketamine were associated with equivalent first-pass success in this retrospective review. A prospective randomized trial of first-pass success is needed to confirm these findings.

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