Epilepsy & Behavior Reports 25 (2024) 100645

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Comparison of induction agents for rapid sequence intubation in refractory status epilepticus: A single-center retrospective analysis

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ARTICLE INFO

Keywords:
Refractory status epilepticus
Intubation
Electroencephalography
Etomidate
Propofol
Ketamine

ABSTRACT

Endotracheal intubation, frequently required during management of refractory status epilepticus (RSE), can be facilitated by anesthetic medications; however, their effectiveness for RSE control is unknown. We performed a single-center retrospective review of patients admitted to a neurocritical care unit (NCCU) who underwent in-hospital intubation during RSE management. Patients intubated with propofol, ketamine, or benzodiazepines, termed anti-seizure induction (ASI), were compared to patients who received etomidate induction (EI). The primary endpoint was clinical or electrographic seizures within 12 h post-intubation. We estimated the association of ASI on post-intubation seizure using logistic regression. A sub-group of patients undergoing electroencephalography during intubation was identified to evaluate the immediate effect of ASI on RSE. We screened 697 patients admitted to the NCCU for RSE and identified 148 intubated in-hospital (n = 90 ASI, n = 58 EI). There was no difference in post-intubation seizure (26 % (n = 23) ASI, 29 % (n = 17) EI) in the cohort, however, there was increased RSE resolution with ASI in 24 patients with electrographic RSE during intubation (ASI: 61 % (n = 11/18) vs EI: 0 % (n = 0/6), p =.016). While anti-seizure induction did not appear to affect post-intubation seizure occurrence overall, a sub-group of patients undergoing electroencephalography during intubation had a higher incidence of seizure cessation, suggesting potential benefit in an enriched population.

1. Introduction

Airway management is an important early consideration in the treatment of status epilepticus (SE). Intubation is recommended to stabilize patients with evidence of impaired gas exchange, airway compromise, concern for elevated intracranial pressure or refractory status epilepticus (RSE), defined as ongoing seizure activity despite first and second line treatment with benzodiazepines (BZD) and an IV bolus of an anti-seizure medication (ASM), respectively, thus prompting administration of a continuous intravenous anesthetic drug (CIVAD). [1].

Approximately one in three patients with SE requires intubation, and the incidence of intubation during SE appears to be increasing over the past 25 years.[2] While there is high quality evidence supporting first and second line SE treatment, strong evidence guiding RSE treatment is lacking.[1,3–7] Similarly, guidance on optimal anesthetic induction medication selection during rapid sequence intubation (RSI) for RSE is lacking.[8] While BZD, propofol, and ketamine have anti-seizure and seizure abortive properties, the effect of etomidate on seizures is less certain. Small case series and animal studies suggest that etomidate can control seizures,[9–13] while other studies purport its use results in longer seizure duration during electroconvulsive therapy.[14] Given the conflicting data, albeit of low quality, we felt it was clinically important to investigate the association of etomidate on seizures cessation since etomidate is the most commonly used RSI induction agent and intubation is a fundamental step in RSE treatment algorithms.[15,16].

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https://doi.org/10.1016/j.ebr.2024.100645
Received 29 November 2023; Received in revised form 2 January 2024; Accepted 3 January 2024
Available online 8 January 2024

We performed a retrospective analysis of patients intubated for suspected or confirmed RSE to assess the impact of RSI with etomidate induction (EI) as compared to anti-seizure induction (ASI) on post-intubation seizure occurrence. We hypothesized that patients undergoing ASI intubation would have fewer clinical and electrographic seizures in the 12 h post-intubation when compared to patients undergoing EI intubation. We also hypothesized that ASI would be associated with faster recovery of command following, decreased duration of CIVAD use, and decreased duration of mechanical ventilation (MV). Additionally, patients induced with ASI agents while on electroencephalography (EEG) would have higher rates of seizure cessation at the time of induction.

2. Methods

2.1. Study design

Using our prospectively collected database of patients with potentially life-threatening neurological illness (*NCT04189471*), we performed a single center retrospective cohort study of patients with suspected RSE. Collection of data was approved by the local institutional review board. Informed consent was waived given minimal risk of the study.

2.2. Patient population

Patients admitted to the neurocritical care unit at University of Maryland Medical Center and University of Maryland Midtown Medical Center from 1/1/2016–1/31/2023 for management of RSE, including both convulsive and non-convulsive SE, and intubated in the hospital as part of RSE management were included. Intubation occurred in the emergency department, ward, or intensive care unit settings. Patients were excluded if: intubation occurred prior to hospital arrival, intubation was performed after a single seizure not meeting criteria for SE or RSE, RSE was suspected to be secondary to hypoxic ischemic brain injury, intubation occurred for an alternate indication, e.g. agitation, cardiac arrest, or coordination of medical tests or procedures. Patients undergoing EEG not in definite electrographic status epilepticus (ESE) at the time of intubation were excluded. We excluded patients intubated with no induction agent. Patients were not excluded if intubation occurred prior to receiving appropriate dosing of BZD and ASM; however, deviations from SE management guidelines were noted. Patients were divided into two groups: those intubated with anti-seizure agents (BZD, propofol, ketamine), referred to as ASI, and those intubated with etomidate, referred to as EI. Management of SE was guided by an institutional protocol that did not make any recommendations regarding induction agent selection in SE. Treatment decisions were at the discretion of the clinical teams.

2.3. Data collection

Retrospective electronic health record review was employed to obtain details regarding patient demographics, clinical course, continuous EEG (cEEG) reports, medication administration records, including dosing, and nursing notes to characterize patients and treatments administered before, during and after intubation, including use of CIVADs. Abstracted data were also used to assign a Status Epilepticus Severity Score (STESS) and APACHE-II scores (excluding the Glasgow coma scale) for each patient.[17,18] Regarding the process for clinical cEEG report generation, EEG recordings were reviewed by attending epileptologists at our center. Studies were reviewed twice daily, with additional interval reviews in the event of seizures or SE. Reports for cEEG were generated for each 24-hour epoch and updates were provided to the clinical teams.

2.4. Outcomes

The primary outcome was detection of clinical or electrographic seizures (ESz) in the 12 h following intubation. This duration was selected to ensure adequate time for cEEG connection and monitoring, as well as based on a prior study examining etomidate vs. sodium thiopental.[19] We included any routine EEG, limited montage EEG, or cEEG obtained during this 12-hour period for review. Secondary outcomes included time to treatment failure, duration of CIVAD infusion, time to recovery of command following based on a Glasgow coma scale motor score of six, intensive care unit (ICU) length of stay, duration of mechanical ventilation, and *peri*-intubation complications. Peri-intubation complications were defined as new-onset hypotension (systolic blood pressure less than 100 mmHg requiring treatment with intravenous fluids or vasopressors within 120-minutes of intubation), as well as cardiac arrest. Patients whose systolic blood pressure was less than 100 mmHg or required vasopressor drugs prior to intubation were not considered to have post-intubation hypotension.

2.5. Sub-group analysis

We conducted an exploratory analysis of patients with evidence of electrographic SE (ESE) undergoing monitoring with cEEG at the time of intubation. We included patients for whom a time of RSE resolution could be determined based on review of clinical EEG reports. We identified treatment response as ESE resolution immediately following induction administration and treatment failure as those with ongoing ESE following administration of an induction agent. Patients were routinely started on a CIVAD following intubation both to treat RSE and to prevent consciousness during paralysis. We utilized the same definition for ASI and EI strategies as for the whole cohort.

2.6. Statistical analysis

We used descriptive statistics to characterize the ASI and EI groups. Wilcoxon rank-sum tests and Chi-square or Fisher Exact tests were used to identify differences between groups. We built a multiple logistic regression model to examine the association between post-intubation seizure detection and ASI use. ASI use was forced into the model. Age, sex, STESS, seizures at time of intubation, pre-RSI BZD dose by weight (in lorazepam equivalents), neuromuscular blockade agent (NMBA) (none, succinylcholine, rocuronium, vecuronium), renal function by GFR category (>60, 45–60, 30–44, 15–29, <15), an interaction term of NMBA*GFR category, APACHE-II without GCS, time to initiate EEG monitoring, and pre-RSI SE treatment (coded as: none [reference group], only BZD, only ASM, both BZD and ASM) were included as covariates in the model, utilizing a stepwise removal method. Differences in time to seizure occurrence were calculated using Cox Regression, using intubation agent (ASI vs. EI) and time to EEG monitoring as covariates. For the survival analysis, we included all seizures which within 48 h of intubation to capture seizure recurrence during weaning of CIVADs. Patients who did not have seizures following intubation were censored at 48 h post intubation. We used multivariable linear regression models to examine the association between ASI and duration of MV, duration of CIVAD use, and time to recovery of command following. Pre-intubation GCS was added to each linear regression model, while hypoxia at time of intubation and body mass index were added to the model for hours of mechanical ventilation. Renal function and NMBA were included in models for time to command following and duration of mechanical ventilation, but not ICU duration or duration of CIVAD use. A stepwise elimination process was used to remove variables from the models without significant association, with $p = .10$ as the threshold for removal. For our exploratory analysis of patients in cEEG-proven ESE at the time of intubation, we performed a Fisher exact test, given the small sample size. We used SPSS for statistical analyses (SPSS for Windows, released 2021. Version 28.0. Chicago, SPSS Inc).

2.7. Data availability

Anonymized study data will be available to qualified investigators from the corresponding author upon reasonable request.

3. Results

We screened 697 patients admitted to the neurocritical care unit for management of seizures, and 148 patients with RSE were included in the cohort. Four patients had two admissions and one patient had three admissions for RSE, respectively. (Fig. 1) Ninety patients were intubated using ASI (57 propofol, 15 ketamine, 14 BZD, 4 ketamine + propofol) and 58 were intubated with EI. The median dose of ASI agent was 1.19 mg/kg (inter-quartile range [IQR]: 0.85–1.80) propofol, 1.44 mg/kg (IQR:1.00–1.88) ketamine, 6 mg (IQR: 4–10) lorazepam, and 10 mg (IQR: 4–20) midazolam. The median dose of etomidate was 0.29 mg/kg (IQR: 0.25–0.33). In the EI group, 3 (5.2 %), 51 (87.9 %), and 4 (6.9 %) patients received succinylcholine, rocuronium, and vecuronium, respectively, vs. 7 (7.6 %), 76 (84.8 %), and 1 (1.1 %) in the ASI group. Notably, six (6.5 %) patients in the ASI group did not receive NMBA. Group characteristics and induction agents and dosing are detailed in Tables 1 and 2, respectively.

One-hundred-forty-five patients (98 %) were connected to cEEG with a median time to monitoring from intubation of 4.2 h (IQR: 2.2–7.4 h). When excluding the 24 patients on EEG monitoring at the time of intubation, the median time to cEEG connection was 5.1 h (IQR: 3.1–8.1 h). Four patients underwent monitoring with both limited montage cEEG and full montage cEEG during the 12 h post-intubation. Three patients were not monitored on EEG due to recovery of consciousness prior to EEG availability. Patients intubated with ASI more often received high doses of CIVAD during the 12-hour period following intubation (ASI 47.7 %, EI: 19.0 %) ($X^2 = 22.35$, $p < .0001$). (Table 2).

3.1. Outcomes

Seizures were detected in 27 % (n = 40) of patients within 12 h of intubation. We did not find a significant difference in clinical or electrographic seizure occurrence in the 12 h following induction between patients who underwent ASI (n = 23, 25 %) and those who underwent EI (n = 17, 29 %)) (Tables 2 and 3), unadjusted odds ratio for post-intubation seizure was 0.83 (95 % CI: 0.40–1.73, $X^2 = 0.252$, df = 1, p =.616). When including potential covariates in logistic regression models, we did not find a difference in rates of post-intubation seizures between ASI and EI groups (OR: 1.446 (95 % confidence interval [95 % CI] 0.64–3.26) p =.375). (Supplemental Table S1) When examining the time to treatment failure between EI and ASI, no statistically significant difference was observed when controlling for time from intubation to EEG monitoring. (Fig. 2) Twenty patients (34.5 %) intubated with EI and 29 patients (32.2 %) intubated with ASI had a seizure within 48 h of intubation (OR: 0.782 (95 % CI: 0.436–1.401), p = .408).

Variables included in multiple linear regression models are reported in Supplemental Table S1. Based on these models, we did not observe an effect on duration of mechanical ventilation, time to recovery of command following, or duration of CIVAD amongst those intubated with or without ASI.

3.2. Sub-group analysis

We identified 24 (16.2 %) patients undergoing intubation while in ESE based on concurrent cEEG. Six patients (25 %) were intubated with EI while 18 (75 %) were intubated with ASI (propofol = 12, ketamine = 3, propofol + ketamine = 3). Demographic information for this sub-

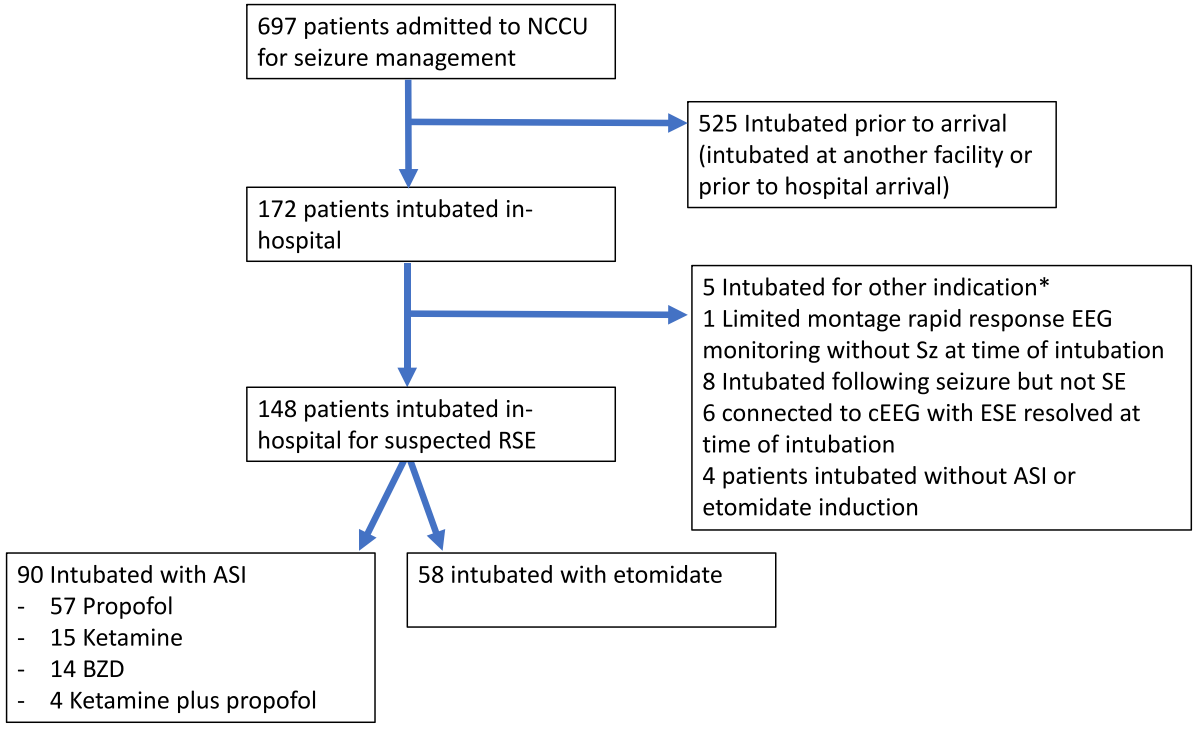

Fig. 1. Flowchart of patient screening. Subjects were identified from a registry of patients admitted to the neurocritical care unit at University of Maryland Medical Center between 1/1/2016 and 1/31/2023. Patients intubated in-hospital for management of status epilepticus were included. We excluded patients intubated prior to arrival, intubated for another indication, patients proven not to be in ongoing ESE on monitoring, patients who presented with a seizure or seizures that did not meet diagnostic criteria for SE. Patients were then grouped by induction agent used during rapid sequence intubation. * – 1 patient intubated for cardiac arrest, 1 patient intubated for agitation, 1 patient intubated for facial trauma, 2 patients intubated for coordination of care/tests. Abbreviations: ASI: anti-seizure induction, BZD: benzodiazepine, cEEG: continuous electroencephalography, EEG: electroencephalogram, ESE: electrographic status epilepticus, NCCU: neurocritical care unit, RSE: refractory status epilepticus, SE: status epilepticus, Sz: seizure.

Table 1
Patient Characteristics.

ASI (n = 90)	EI (n = 58)	Total (n = 148)	
Age in years	58.0 (39.8–69.0)	62.5 (50.8–74.0)	60.5 (42.3–71.8)
Female sex (n,%)	38 (42.2 %)	32 (55.2 %)	70 (47.3 %)
STESS	2 (2–4)	3 (2–4)	2.5 (2–4)
APACHE-II (without GCS)	13 (10–16)	14.5 (12–16)	14 (10–16)
Estimated GFR (n,%)			
>60	64 (61.1 %)	32 (55.2 %)	95 (64.2 %)
45-59	7 (7.8 %)	13 (22.4 %)	20 (13.5 %)
30-44	11 (12.2 %)	7 (12.1 %)	18 (12.2 %)
15-29	4 (4.4 %)	4 (6.9 %)	8 (5.4 %)
<15	4 (4.4 %)	2 (3.4 %)	6 (4.1 %)
History of Seizures (n,%)	55 (62.0 %)	30 (51.7 %)	85 (58.0 %)
GCS prior to intubation*	8 (4.3–11.8)	7 (5–9)	8 (5–11)
Estimated seizure duration in hours*	1 (0.25–48)	0.3 (0.17–21)	0.67 (0.25–36)
Seizure semiology (n,%)			
GTC	54 (60.0 %)	34 (58.6 %)	88 (59.5 %)
ESz	7 (7.8 %)	5 (8.6 %)	12 (8.1 %)
Other	1 (1.1 %)	1 (1.7 %)	2 (1.4 %)
Focal	28 (31.1 %)	18 (31.0 %)	46 (31.1 %)
SE detail (n,%)			
GCSE	20 (22.2 %)	15 (25.9 %)	35 (23.6 %)
Seizures without return to baseline	37 (41.1 %)	25 (43.1 %)	62 (41.9 %)
Focal SE	21 (23.3 %)	15 (25.9 %)	36 (24.3 %)
ESE	12 (13.3 %)	3 (5.2 %)	15 (10.1 %)
SE etiology (n,%)			
Cryptogenic	21 (23.3 %)	7 (12.1 %)	28 (18.9 %)
Cerebrovascular	18 (20.0 %)	19 (32.8 %)	37 (25.0 %)
Trauma	8 (8.9 %)	3 (5.2 %)	11 (7.4 %)
Infection	8 (8.9 %)	1 (1.7 %)	9 (6.1 %)
Toxic	6 (6.7 %)	8 (13.8 %)	14 (9.5 %)
Tumor	3 (3.3 %)	3 (5.2 %)	7 (4.1 %)
ASM withdrawal, dose reduction	24 (26.7 %)	15 (25.9 %)	40 (26.4 %)
Genetic	1 (1.1 %)	0 (0 %)	1 (0.7 %)
Metabolic	1 (1.1 %)	2 (3.4 %)	3 (2.0 %)
GCSE cessation prior to RSI (n,%)	25 (27.8 %)	18 (31.0 %)	43 (29.1 %)
Hypoxia at intubation (n,%)	25 (27.8 %)	16 (27.6 %)	41 (27.7 %)
Pre-intubation BZD dose**	4 (2–8)	4 (2.5–7.5)	4 (2.5–7.9)
Pre-intubation BZD dose by weight**	0.05 (0.02–0.11)	0.06 (0.04–0.09)	0.05 (0.03–0.98)
Neuromuscular Blockade Agent n, %)			
None	6 (6.7 %)	0 (0 %)	6 (4.1 %)
Succinylcholine	7 (7.8 %)	3 (5.2 %)	10 (6.8 %)
Rocuronium	76 (84.4 %)	51 (87.9 %)	127 (85.8 %)
Vecuronium	1 (1.1 %)	4 (6.9 %)	5 (3.4 %)
Pre-intubation management* (n,%)			
No BZD or ASM	4 (4.4 %)	4 (6.9 %)	8 (5.4 %)
BZD only	38 (42.2 %)	34 (58.6 %)	72 (48.6 %)
ASM only	2 (2.2 %)	0 (0 %)	2 (1.4 %)
BZD and ASM	46 (51.1 %)	20 (34.5 %)	66 (44.6 %)

Table 1. Baseline characteristics for 150 patients who underwent in-hospital intubation for management of suspected refractory status epilepticus. Data are reported as median, (interquartile range) unless otherwise specified. No parameters met statistical significance. Patients who received propofol, ketamine, or benzodiazepines were defined as anti-seizure induction (ASI) and were compared to patients who received etomidate induction (EI). * - indicates incomplete data: for GCS prior to intubation 57 missing (30 ASI, 27 EI), for estimated seizure duration 83 missing (45 ASI, 38 EI), for pre-intubation management ** - excluded patients not treated with BZD, or with dosages not recorded, patients included: ASI n = 80, EI n = 51. Abbreviations: APACHE-II: acute physiology and chronic health evaluation II score, ASI: anti-seizure induction, ASM: anti-seizure medication, BZD: benzodiazepine, EI: etomidate induction, ESE: electrographic status epilepticus, ESz: electrographic seizure, GFR: glomerular filtration rate, GCS: Glasgow coma scale, GCSE: generalized convulsive status epilepticus, GTC: generalized tonic-clonic seizure, RSI: rapid sequence intubation, SE: status epilepticus, STESS: status epilepticus severity score.

Table 2
Post-intubation management and outcomes.

	ASI (n = 90)	EI (n = 58)	Total (n = 148)
Post-intubation CIVAD	86 (95.6 %)	57 (98.3 %)	143 (96.%)
Maximum dose †			
Low	*11 (12.8 %)*	*26 (44.8 %)*	*37 (25.9 %)*
Intermediate	*34 (39.5 %)*	*20 (34.5 %)*	*54 (37.8 %)*
High	*41 (47.7 %)*	*11 (19.0 %)*	*52 (36.4 %)*
cEEG	89 (98.9 %)	56 (96.6 %)	145 (98.0 %)
Limited montage EEG*	2 (2.2 %)	2 (3.4 %)	4 (2.7 %)
Hours to cEEG monitoring	4.1 (1.6–7.3)	4.9 (2.6–8.1)	4.2 (2.2–7.4)
Post-intubation seizure	23 (25.6 %)	17 (29.3 %)	40 (27.0 %)
SRSE	8 (8.9 %)	4 (6.9 %)	12 (8.1 %)
Hours of MV	56.0 (26.3–134.6)	52.6 (27.2–194.1)	54.8 (26.6–142.6)
Hours of CIVAD	23.3 (10.6–46.2)	17.9 (7.7–39.5)	20.2 (9.2–42.5)
Hours to command follow‡	37.7 (12.3–67.9)	37.8 (12.8–92.6)	37.8 (12.5–72.1)
Trach	12 (13.5 %)	6 (10.3 %)	18 (12.3 %)
Death	7 (7.8 %)	6 (10.3 %)	13 (8.8 %)
Post-intubation hypotension	23 (25.6 %)	15 (25.9 %)	38 (25.7 %)
Peri-intubation cardiac arrest	1 (1.1 %)	0 (0 %)	1 (0.7 %)
Emergent surgical airway	1 (1.1 %)	0 (0 %)	1 (0.7 %)

Table 2. Details of post-intubation management and clinical outcomes are reported by induction agent. Statistically significant findings are highlighted in bold and italicized font. Post-intubation CIVAD use was defined as any CIVAD infusion during the 12-hour period following intubation. Maximum doses were categorized as follows: propofol: low: <33 mcg/kg/min, intermediate: ≥33 mcg/kg/min to <66, high: ≥66 mcg/kg/min; midazolam: <0.05 mg/kg/hr, intermediate: ≥0.05 mg/kg/hr to <0.1 mg/kg/hr, high: ≥0.1 mg/kg/hr. Ketamine was always administered with high-dose midazolam. Command following was defined as first documented GCS motor score of 6 following intubation. * – limited montage EEG included scalp recording devices without video monitoring capability with fewer than 20 electrodes. One patient in the ASI group was recorded on both limited montage EEG and cvEEG during the study period. †: $X^2 = 22.35$, $p < .0001$, df = 2, ‡: 4 patients in the EI group and 8 patients in the ASI group did not regain command following based on GCS motor score during admission. Abbreviations: ASI: anti-seizure induction, CIVAD: continuous intravenous anesthetic drug, cEEG: continuous video electroencephalogram, EEG: electroencephalogram, EI: etomidate induction, MV: mechanical ventilation (defined as time spent connected to ventilator circuit from intubation until extubation or removal from ventilator following tracheostomy), SRSE: super-refractory status epilepticus.

group is described in Supplemental Table S1. Sixty-one percent (n = 11) of patients intubated with ASI had cessation of ESE at the time of intubation vs. 0 % of patients intubated with EI (Fisher exact test p = 0.016). The median duration to resolve ESE for EI patients was 31.7 min (IQR: 26.3–44.1 min) vs. 0 min (IQR: 0–49 min) with ASI (Wilcoxon, 8.00, df = 1, p =.005). Five of the 24 patients developed SRSE (ASI: n = 3/18, EI: 2/6), of which 2/3 of the SRSE cases in ASI intubation occurred in those who did not initially resolve with intubation. Seventeen percent of patients intubated with ASI (n = 3) and etomidate (n = 1), respectively, went on to meet criteria for super-refractory SE (SRSE) (Fisher Exact Test, p = .999). Details regarding duration of CIVAD use, mechanical

Table 3
Post-intubation seizure detection, stratified by induction agent.

	No seizure (n = 108)	Seizure (n = 40)	Total (n = 148)
Ketamine† (n,%)	13 (86.7 %)	2 (13.3 %)	15 (100 %)
Dose (mg/kg)	1.44 (1.0–1.95)	1.42 (1.0–1.42)	1.44 (1.0–1.88)
Ketamine + Propofol† (n, %)	3 (75 %)	1 (25 %)	4 (100 %)
Ketamine Dose (mg/kg)	1.03 (0.61–1.03)	0.98 (0.98–0.98)	1.0 (0.70–1.06)
Propofol Dose (mg/kg)	0.71 (0.61–0.71)	0.25 (0.25–0.25)	0.66 (0.34–2.25)
Propofol†	39 (68.4 %)	18 (31.6 %)	57 (100 %)
Dose (mg/kg)	1.31 (0.89–1.91)	0.95 (0.85–1.42)*	1.19 (0.85–1.80)*
Benzodiazepine (≥SE dose)† (n,%)	9 (90 %)	1 (10 %)	10 (100 %)
Dose (mg)	6 (5–10)	10 (10–10)	6 (5–10)
Benzodiazepine (<SE dose)† (n,%)	3 (75 %)	1 (25 %)	4 (100 %)
Dose (mg)	2 (1–3)	1 (1–1)	2 (1.5–2.5)
Etomidate (n,%)	41 (70.7 %)	17 (29.3 %)*	58 (100 %)*
Dose (mg/kg)	0.29 (0.26–0.34)	0.26 (0.12–0.3)	0.29 (0.25–0.33)

Table 3. Treatment response by induction drug used. Values presented are medians with interquartile ranges in parentheses, unless otherwise specified. † indicates treatment considered to be RSI with anti-seizure induction (ASI), * indicates one patient with RSI dose information not available. Benzodiazepine doses are reported in equivalents to lorazepam, where 1 mg lorazepam is equal to 2 mg midazolam. Minimum dose of 4 mg lorazepam or 10 mg midazolam required to be considered SE dosing. Etomidate, ketamine and propofol are reported in weight-based doses (mg/kg). Abbreviations: kg – kilogram, mg – milligram, SE – status epilepticus.

ventilation, time to recovery of motor-GCS six, and length of stay are included in Table 4. We did not perform statistical analyses on these outcomes given the exploratory nature of this post-hoc analysis.

3.3. Safety

Post-intubation hypotension occurred in 25.0 % (n = 37) of patients, (n = 22, 25.0 % ASI, n = 15, 25.9 % EI), with an odds ratio of 0.927 (95 % CI: 0.43–1.98, X^2 = 0.014, df = 1, p =.846). The incidence of hypotension was comparable between propofol (n = 16 (28.1 %)), ketamine (n = 3 (20 %)), BZD (n = 2 (14.3 %)), and ketamine + propofol (n = 1 (25 %)). There was one *peri*-intubation cardiac arrest in the ASI group (induction with ketamine) and none in the EI group. In-hospital mortality occurred in 8.8 % (n = 13) of patients (7.8 % (n = 7) ASI, 10.3 % (n = 6) EI, OR: 0.73 (95 % CI: 0.233–2.30, (X^2 = 0. 290, df = 1, p =.590)). (Table 2).

4. Discussion

While high-quality randomized controlled trials guide first and second-line management of SE, few studies support the selection of induction agents for RSI, an important component of RSE management. [3–5,19,20] We present a cohort of patients from a single center who underwent in-hospital intubation as part of the management of RSE. We found no difference in detection of clinical or ESz in the 12 h following intubation with ASI vs EI when controlling for known confounding factors.

Our findings, although exploratory in nature due to a relatively low sample size, are relevant because in recent work examining 124 studies from 22 airway registries worldwide, etomidate is one of the most frequently used induction agents, particularly by emergency medicine physicians who perform over 50 % of intubations for SE in the United States. [2,21] Though the use of etomidate specifically in the intubation of patients with SE is not known, routine use is plausible. Indeed, in our study, etomidate was the most used drug for induction. Etomidate is associated with several potentially deleterious effects, including adrenal suppression, myoclonus, and electroencephalographic excitation after intubation. Myoclonus is usually transient and often masked in patients with seizures due to the concomitant administration of NMBAs.

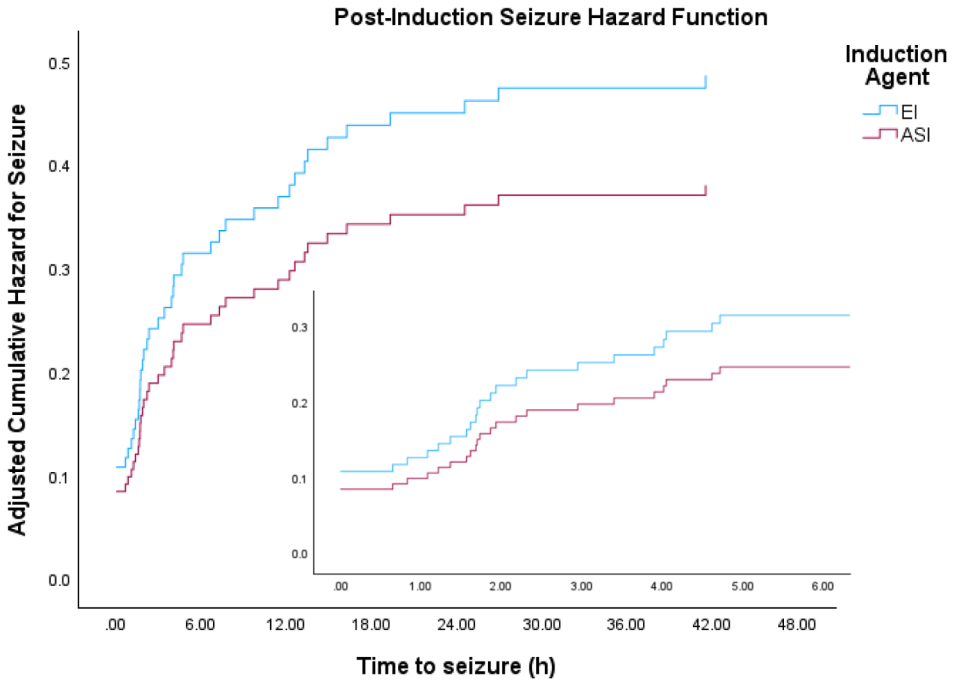

Fig. 2. Hazard function chart depicting time until seizure detection based on intubation with an ASI, including all patients in the cohort, using Cox regression with time to EEG monitoring as a covariate. Time of monitoring was the first 48 h after intubation. Forty-nine patients had seizure recurrence (20 patients intubated with EI, 29 patients intubated with ASI), while 96 did not and were censored at 48 h post-intubation. Three patients who were not monitored with EEG were excluded. Hazard was adjusted for time to EEG monitoring, with mean time to EEG depicted. There was no significant difference in risk for seizure detection (OR: 0.782 (95 % CI: 0.436–1.401), p =.408). Abbreviations: ASI: anti-seizure induction. An inset on the bottom right shows the first 6 h following intubation.

Table 4
Confirmed ESE at time of Intubation.

	ASI (N = 18)	EI (N = 6)	Total (N = 24)
Demographics			
Age	42.0 (26.8–66)	67.0 (51.3–77.3)	55.5 (27–71.3)
Female Sex (n,%)	10 (55.6 %)	2 (33.3 %)	12 (50.0 %)
STESS	2 (0.8–3.3)	2.5 (0.8–3.3)	2 (1–3)
APACHE-II	9 (7–15)	13.5 (8–20.5)	9.5 (7–17)
Hours since SE onset	48 (13.5–72)	36 (18–84)	48 (14–72)
ASMs prior to RSI	3 (2–4)	3.5 (2.3–4)	3 (2–4)
Outcomes			
RSE terminated (n, %) †	*11 (61.1 %)*	*0 (0 %)*	*11 (45.8 %)*
RSE continued (n,%) †	*7 (38.9 %)*	*6 (100 %)*	*13 (54.2 %)*
Time to RSE resolution (min)‡	*0 (0–49)*	*31.7 (26.3–44.1)*	*17.40 (0–41.35)*
SRSE (n,%)	3 (16.7 %)	2 (33.3 %)	5 (20.8 %)
Hours CIVAD duration	36.6 (26.6–68.7)	35.9 (16.3–55.5)	36.6 (26.5–63.9)
Hours MV	117.4 (69.5–171.9)	197.4 (99.5–387.7)	126.5 (72.8–271.2)
Hours to command following*	56.4 (30.1–93.1)	61.4 (55.8–237.3)	56.6 (45.8–93.1)
ICU LOS (days)	7.5 (5.0–12.5)	9.5 (5.8–11.5)	8.5 (5.3–11.8)
Hospital LOS (days)	13.5 (8.5–29.8)	17.5 (13.5–22.5)	15.5 (10.0–27.0)
In-hospital mortality	2 (11.1 %)	2 (33.3 %)	4 (16.7 %)

Table 4. Characteristics and outcomes for 26 patients with ESE undergoing cEEG monitoring at the time of intubation. Results are reported by median (interquartile range) unless otherwise specified and statistically significant results are shown in bold and italics. †:Fisher exact test, p =.016. ‡: Wilcoxon = 8, p =.005 *= A total of seven patients did not regain command following during hospitalization, including five patients in the ASI group and two in the etomidate group. Abbreviations: APACHE-II: acute physiology and chronic health evaluation II score, ASI: anti-seizure induction, ASM – anti-seizure medication, CIVAD – continuous intravenous anesthetic drug, EI: etomidate induction, ESE – electrographic status epilepticus, ICU – intensive care unit, LOS – length of stay, MV – mechanical ventilation (defined as time spent connected to ventilator circuit from intubation until extubation or removal from ventilator following tracheostomy), RSE – refractory status epilepticus, RSI – rapid sequence intubation, SRSE- super-refractory status epilepticus, STESS – status epilepticus severity score.

Etomidate may decrease cerebral oxygen demand and blood flow but preserves cerebral perfusion pressure.[22–25] Regarding seizure cessation after use, our results are consistent with a previous study comparing etomidate and sodium thiopental for RSI induction in patients with SE; however, important differences exist between studies. In the study by Perier et al., intubation occurred in the pre-hospital setting, usually after clinical seizure cessation and before receipt of second line ASMs.[19] Thus, unlike our study, few patients in the study met criteria for RSE. In addition, fewer patients in the study by Perier at al. underwent cEEG monitoring. Lastly, sodium thiopental is no longer used clinically in the United States, thus the results of this trial are not generalizable to practice in the United States.[19].

Beyond the theoretical benefit of ASI, there are several reasons why no difference in clinical or ESz occurrence following induction was observed. First, anesthetic boluses have a relatively short half-life, with an estimated half-life of 3–12 min for etomidate, 5–10 min for propofol, 5–15 min for ketamine, while midazolam is 1–4 h.[26] Thus, transient treatment effect may abate; however, we did not find a significant difference in time to seizure detection following induction based on survival analysis. Further, almost all patients intubated were subsequently started on a CIVAD. Various doses of induction agents and subsequent sedative infusions were started, both of which may affect post-intubation seizure risk, introducing a confounding bias. We did observe a statistically significant difference in CIVAD dosing following intubation between ASI and EI groups with more ASI patients receiving higher doses of CIVAD.

Importantly, our findings suggest that in an enriched population of patients with cEEG-proven ESE, RSI with ASI is strongly associated with post-induction seizure cessation. A similar effect on ESE was not seen in patients who received EI. Given the exploratory nature of this analysis, as well as the small sample size, we were unable to examine whether seizure cessation at the time of intubation was associated with additional potentially meaningful clinical outcomes such as duration of mechanical ventilation, length of stay, and mortality. It is plausible that administering a loading dose of an anesthetic with anti-seizure attributes during intubation followed by initiation of a CIVAD resulted in earlier steady-state concentration, thus facilitating ESE resolution.

In addition, it is possible that certain drug mechanisms may facilitate seizure cessation following first-line treatment targeting GABA receptors. The small sample size limited our ability to compare individual medications used, though within the ASI group, ketamine (16 % post-intubation seizure detection) and benzodiazepines (14.3 % post-intubation seizure detection) appeared to perform better than propofol (31.6 % post-intubation seizure detection). Further studies with a controlled design would allow for comparisons of regimens.

We found that post-intubation hypotension was a common phenomenon following induction regardless of agent used. While EI is often considered hemodynamically neutral, we observed comparable incidence of post-intubation hypotension in both ASI and EI groups.[27,28] Our findings are similar to those of recently released RSI practice guidelines that concluded there is no difference between etomidate and other induction agents with respect to *peri*-intubation hypotension.[29] This may be of particular interest given a recent *meta*-analysis, including randomized controlled trials, of critically ill patients intubated with etomidate who suffered increased mortality when compared to those intubated with other agents.[30].

There are several important limitations that must be considered when interpreting our findings. Given the retrospective nature of our cohort, there may be unidentified confounders between the ASI and EI groups that affected post-intubation seizure detection. Further, clinical factors related to RSE, hemodynamic stability, or other unidentified factors may have influenced clinician choice of induction strategy. There was variation in the dosing drugs used for RSI, as well as post-intubation CIVADs, which may have contributed to likelihood of seizure control. Further, most patients received NMBA with a longer half-life, such as rocuronium or vecuronium which could have limited detection of clinical seizures. There was, however, no imbalance with respect to NMBA used between EI and ASI groups. Since we aimed to capture all patients undergoing intubation for management of RSE, there was significant heterogeneity in the group with respect to seizure semiology, clinical course, and drug choice during RSI. Furthermore, patients intubated for RSE prior to transfer to our institution were excluded as data regarding agents used during intubation were not available. Given the modest sample size these factors may have limited our ability to compare responses to different ASI drugs, e.g., propofol vs. ketamine vs BZD. Underdosing of BZD, a widely recognized phenomenon across multiple studies including our cohort, is associated with poor control of SE and worse outcomes.[31–35] Our dataset lacked reliable data on duration of RSE prior to intubation. As RSE continues, changes at the neuronal synapse occur and likelihood of successful treatment diminishes.[36] It would be important for any future studies assessing intubation induction agents in RSE to include this potentially important covariate. In addition, one of the biggest limitations of our study was the variable timing of EEG monitoring peri- and post-intubation. We found that it took a median of 4.2 h for initiation of EEG monitoring which may have decreased our sensitivity to detect ESz and ESE following intubation thus masking any differences in time to seizure occurrence, though the time to initiate EEG monitoring and incidence of ESE we detected was

comparable to the literature.[37] This variability in timing of EEG monitoring limited our ability to assess incidence of periodic patterns on EEG, a potentially important factor in patients with primary brain injury.[38] Importantly, we were limited to utilization of clinical EEG reports, rather than raw EEG data, to assess our outcome of interest. As such, we were not able to include patients with possible electroclinical SE by 2021 ACNS criteria. Further, patients included in the ESE group were treated between 2016 and 2022, a time in which definitions of NCSE and ESE significantly evolved, introducing potential heterogeneity into this cohort.[39–41] Though beyond the scope of this analysis, future studies of patients with ESE undergoing intubation could utilize blinded raw EEG data to ensure diagnostic consistency and, further, could consider analysis of seizure burden before and after intubation. Future studies, particularly randomized protocols leveraging point of care EEG, would be paramount to understanding the sensitivity of EEG for detecting ESz and ESE following RSI. Alternatively, prospective data from future clinical trials of SE, such as planned follow-up to the Established Status Epilepticus Treatment Trial, could be leveraged to evaluate the effect of induction agent of post-intubation seizures. Such studies would also benefit from consideration of desirable outcomes in SE, specifically weighing the importance of prevention of post-intubation seizures with potential toxicities related to induction.[42].

Based on our findings, an induction agent strategy with or without ASI is associated with a similar prevalence of post-intubation seizures and a similar prevalence of post-intubation hypotension. We did not find evidence to suggest that etomidate is an epileptogenic drug, including in the sub- group of patients with cEEG-confirmed RSE. Our findings do suggest that intubation with an ASI for patients with ESE may confer a benefit over EI, however, these findings should be interpreted with caution given the small sample size.

5. Conclusion

In patients presenting to the hospital with SE who require endotracheal intubation, choice of induction anesthetic agent for intubation is not associated with clinical or ESz incidence, duration of MV, or time to recover consciousness. However, in a subset of patients with EEG-proven ESE at the time of intubation, induction using an anti-seizure induction agent during intubation may be beneficial in SE termination. Further prospective studies employing rapid-response EEG monitoring are needed.

Ethics Statement.

Collection of data was approved by the local institutional review board. Informed consent was waived given minimal risk of the study.

Conflicts of Interest.

Author GYP receives support through the Statistical support via University of Maryland, Baltimore, Institute for Clinical & Translational Research (ICTR) and the National Center for Advancing Translational Sciences (NCATS) Clinical Translational Science Award (CTSA) grant number 1UL1TR003098 and has received honoraria from the Korean Neurocritical Care Society for a platform presentation, travel support to attend the Marinus RAISE North America Investigator Meeting and participates on the Marinus Advisory Board on Leveraging Technology to Support RAISE Trial Enrollment. All other authors declare that they have no conflicts of interest. Author JM reports participation in the Epilepsy Foundation Maryland Chapter Advisory Board. Author SMG has received payment for speaking engagements with Northwest Anesthesia Seminars. Author PC receives funding from the Henry M. Jackson Foundation (Subaward #5920).

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Matthew R. Woodward: Writing – review & editing, Writing – original draft, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Adam Kardon:** Writing – review & editing, Data curation. **Jody Manners:** Writing – review & editing, Data curation. **Samantha Schleicher:** Writing – review & editing, Conceptualization. **Melissa B. Pergakis:** Writing – review & editing, Methodology. **Prajwal Ciryam:** Writing – review & editing, Methodology. **Jamie Podell:** Writing – review & editing, Methodology. **William Denney Zimmerman:** . **Samuel M. Galvagno:** Writing – review & editing, Methodology. **Bilal Butt:** Writing – review & editing, Methodology. **Jennifer Pritchard:** Writing – review & editing, Methodology. **Gunjan Y. Parikh:** Writing – review & editing, Resources, Methodology, Investigation, Data curation. **Emily J. Gilmore:** Writing – review & editing, Methodology, Investigation. **Neeraj Badjatia:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Nicholas A. Morris:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Support

We acknowledge the support Dr. Woodward receives from the University of Maryland Baltimore, Institute for Clinical & Translational Research (ICTR)/Clinical and Translational Science Award (CTSA). Grant number: 5TL1TR003100-04.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ebr.2024.100645.

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