# Succinylcholine Is Associated with Increased Mortality When Used for Rapid Sequence Intubation of Severely Brain Injured Patients in the Emergency Department

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**Objective** To compare succinylcholine and rocuronium regarding mortality in patients with traumatic brain injury (TBI) who are intubated in the emergency department (ED).

**Methods** This was a retrospective cohort study conducted in an academic ED in the United States. Adult patients with TBI who underwent rapid sequence intubation (RSI) in the ED with rocuronium or succinylcholine between October 2010 and October 2014 were included. The main outcome of interest was in-hospital mortality. Subjects were stratified based on severity of injury using head abbreviated injury scores. The high-severity group had a severe or critical head injury (score 4 or higher); the low-severity group had a less than severe head injury (score lower than 4).

**Main Results** The final study cohort included 233 patients who were underwent RSI with succinylcholine (149 patients) or rocuronium (84 patients). In patients who received rocuronium, mortality was 22% (12/54) and 23% (7/30) in the low-severity and high-severity categories, respectively (difference 1%, 95% confidence interval [CI] −18% to 20%). In patients who received succinylcholine, mortality was 14% (14/103) and 44% (20/46) in the low-severity and high-severity categories, respectively (difference 30%, 95% CI 14–46). In the multivariate analysis after adjusting for important confounders, there was no significant association between succinylcholine and mortality in the low-severity category (odds ratio [OR] 0.75, 95% CI 0.29–1.92). However, in patients in the high-severity category, succinylcholine was associated with increased mortality compared with rocuronium (OR 4.10, 95% CI 1.18–14.12).

**Conclusions** In severely brain-injured patients undergoing RSI in the ED, succinylcholine was associated with increased mortality compared with rocuronium.

**Key Words** brain injuries, succinylcholine, intubation, neuromuscular blocking agents.

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Traumatic brain injury (TBI) is an important cause of death and disability in the United States. A third of patients do not survive beyond a week after injury.[1] Airway management is a vital component of care of many of these patients, with tracheal intubation considered the gold standard to control the airway. After the initial damage to brain tissue, hypoxemia is associated with secondary brain injury, which can increase the risk of morbidity and mortality. Thus emergency department (ED) intubation to

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secure a definitive airway is standard practice for patients with TBI who require airway protection. Airway protection is typically required in patients with altered mental status, depressed level of consciousness, or respiratory compromise. Rapid sequence intubation (RSI) is the preferred method to achieve tracheal intubation. This technique utilizes a neuromuscular blocking agent (NMBA) to achieve complete motor paralysis, thereby making the procedure safer and easier to accomplish.

The most common NMBAs used are succinylcholine and rocuronium.[2] Succinylcholine use may be associated with a transient increase in intracranial pressure (ICP) according to official labeling by the Food and Drug Administration.[3] An increase in ICP may worsen cerebral hypoxemia by decreasing cerebral perfusion pressure, and critical increases in ICP may also lead to brain herniation, coma, and death. The mechanism for this increase in ICP is incompletely understood but may be mediated via an increase in afferent spinal neural traffic originating from muscle spindle fibers, followed by an increase in cerebral blood flow. Thus rocuronium is sometimes used as an alternative in patients with TBI. However, rocuronium has a long duration of effect that leads to sustained paralysis for more than an hour postintubation, preventing the possibility of repeat neurologic assessments during this time period.[4] Patients receiving rocuronium have also been shown to receive less sedation and analgesia in the immediate postintubation phase because their pharmacologically induced paralysis may make it appear as if they are calm and sedated.[4, 5] This has implications for patient comfort but may be ameliorated by the presence of pharmacists during resuscitation.[6] Hence there is ongoing variation in practice and debate regarding the optimal NMBA to use for RSI in patients with TBI.

Previous reports evaluating the effect of succinylcholine on intracranial pressure have shown inconsistent results.[7–9] These were generally small studies and typically included fewer than 20 neurosurgical patients. It is unclear if the rise in ICP associated with succinylcholine results in any long-term adverse effects. More specifically, no comparative studies between succinylcholine and rocuronium have been conducted to evaluate their effects on important outcomes such as mortality. Thus there is an important gap in the literature that requires investigation to guide clinicians on the preferred NMBA for RSI in patients with TBI.

The primary objective of this study was to compare succinylcholine and rocuronium with regard to in-hospital mortality in patients with TBI who underwent RSI in the ED. We hypothesized that there would be no difference in mortality between patients intubated with succinylcholine compared with rocuronium.

## Methods

### Study Design and Setting

This retrospective cohort study was conducted in an urban academic ED in the United States. The ED has a seven-bed trauma resuscitation unit. The institution is designated as a level 1 trauma center by the American College of Surgeons. Emergency physicians have access to an RSI kit containing succinylcholine and rocuronium. Selection of either agent is based on provider preference; no institutional protocol is in place. The institutional review board that maintains oversight of the hospital approved the study prior to data acquisition.

### Patient Selection

A combination of hospital databases and electronic medical records were used for data acquisition of patients admitted with TBI during a 4-year period between October 2010 and October 2014. All adult patients (18 years and older) with TBI who were intubated with succinylcholine or rocuronium in the ED were included. Patients were identified based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnoses codes. An automated and validated process was used for selection of patients with TBI, as previously described in the literature.[10, 11]

### Study Variables and Measurements

The following variables were considered relevant to the study: age, sex, race, ethnicity, in-hospital mortality, intensive care unit (ICU) length of stay, NMBA used, induction agent used, intubation attempts, ICD-9-CM diagnosis codes, Charlson Comorbidity Index (index of comorbid conditions calculated as a sum of prespecified conditions),[12] Injury Severity Score (range from 0–75; higher value indicating greater overall severity of injury), and Abbreviated Injury Severity for the head region (head AIS) (range from 0–6; higher value indicating greater injury).[13]

Head AIS was dichotomized as either high severity (severe or critical head AIS [score 4 or higher]) or low severity (less-than-severe head AIS [score lower than 4]). All patients had a head AIS score of at least 1 (minor severity); none had a score of 6 (unsurvivable injury). Head AIS of 4 or higher is associated with much higher mortality compared with head AIS lower than 4; thus this point was chosen for dichotomization of this variable.[14] Injury severity scores were derived from ICD-9-CM codes; these are the basis for the Healthcare Cost and Utilization Project databases created by the Agency for Healthcare Research and Quality, which have been validated as an accurate predictor of survival.[11, 15] Most variables in this study, including our primary outcome of in-hospital mortality, were electronically retrieved from electronic medical records and financial data. Thus measurement bias due to manual data extraction was reduced. Only three variables were obtained manually from medical records because they were not retrievable electronically. These included Glasgow Coma Scale (GCS) (lowest score prior to intubation in the ED), occurrence of hypotension (systolic blood pressure lower than 90 mm Hg), and occurrence of hypoxemia (oxygen saturation less than 90%). For the latter two measurements, all recordings in the prehospital setting and ED were evaluated.

### Outcomes and Data Analysis

The primary outcome of interest was in-hospital mortality. This study was powered for a 20% (30% vs 50%) absolute difference in mortality, which is considered a large effect size. Using an $\alpha$ of 0.05 and power of 80%, we estimated that 93 subjects would be needed in each group. The Fisher exact test was used to compare mortality and other categorical variables between patients who received succinylcholine and rocuronium. Normally distributed continuous variables were compared between the two groups using an unpaired Student *t* test. Nonnormally distributed continuous variables were compared using the Wilcoxon rank sum test. There were no missing values in the data set; thus imputation was not required. A secondary outcome of interest was ICU length of stay. However, this variable is inherently biased by in-hospital mortality. Thus ICU length of stay is reported for both survivors and nonsurvivors.

A logistic regression analysis was conducted for the primary outcome variable of in-hospital mortality. The primary predictor of interest was the NMBA used (succinylcholine or rocuronium). Based on our sample size and patients' probability of death, we anticipated the need to limit the number of potential confounders added to this model. Although several variables can predict mortality, few influence paralytic selection to meet the definition of confounding based on causal pathways. Age, GCS score, and head AIS were considered to be potential confounders. For instance, succinylcholine is considered the standard for most intubations, but providers may avoid use in the elderly due to the possibility for precautions (e.g., renal insufficiency, electrolyte abnormalities, or neuromuscular disease). Also, clinicians may avoid use of succinylcholine when increased ICP is a concern, which is more likely to occur with greater head injury severity (low GCS and high head AIS).

The intent was not to develop a parsimonious or a predictive model, but rather to adjust for potential confounding. The model was checked for interactions. A significant interaction was identified between the NMBA and head AIS. Thus the model was stratified by high-severity head AIS and low-severity head AIS. Continuous variables in the final models were checked for the assumption of linearity in the log odds. Based on this assessment, GCS was divided into four ordinal categories as scores 3–5, 6–8, 9–11, and 12–15. The goodness of fit of the final models were checked with the Hosmer-Lemeshow goodness-of-fit test. The area under the receiver operating characteristic curves was evaluated for discriminatory ability of the final models. The occurrence of hypotension was significantly different between groups; thus we decided to add this variable to the final model to see if it changed the results as part of a sensitivity analysis. Another sensitivity analysis was conducted with all potentially pertinent clinical covariates (age, GCS, hypotension, hypoxia, and total injury severity score, and Charlson Comorbidity Index) to determine if it changed the results. Given the potential for overfitting the model, this latter model was only included as part of a sensitivity analysis. All analyses were conducted using Stata v.13 (College Station, TX), and a two-tailed $\alpha$ of 0.05 was considered statistically significant.

## Results

There were 3258 patients with TBI during the study time period, of which 260 were identified

as adults who were intubated in the ED. Of these, 25 did not receive an NMBA, and 2 received vecuronium for intubation. Thus the final study cohort included 233 adult TBI patients who underwent RSI using succinylcholine or rocuronium. Of these, 149 received succinylcholine and 84 received rocuronium. The median age was 42 years (interquartile range [IQR] 29–56); most patients were male (188 [81%]) and white (40 [60%]). Overall, 33% of patients (76) had a high-severity head injury. Table 1 reports the baseline comparisons in each group. The groups were similar, with the exception of age and occurrence of hypotension. The succinylcholine group was younger and more likely to be hypotensive.

Death occurred in 23% of patients in each group. In patients who received rocuronium, mortality was 22% and 23% in the low-severity head injury and high-severity head injury groups, respectively (difference 1%, 95% confidence interval [CI] −18 to 20). In patients who received succinylcholine, mortality was 14% and 44% in the low-severity and high-severity head injury groups, respectively (difference 30%, 95% CI 14–46). In patients with less-than-severe head AIS, there was no significant association between succinylcholine and mortality after adjusting for pertinent confounders (odds ratio [OR] 0.75, 95% CI 0.29–1.92, p=0.548). However, in patients with severe or critical head AIS, succinylcholine was associated with increased mortality (OR 4.10, 95% CI 1.18–14.12, p=0.026). The Hosmer-Lemeshow goodness-of-fit tests suggested that the data fit the models well, and the area under the receiver operating characteristics curves indicated acceptable discrimination for both models (Table 2). Hypotension was included in the model for patients with high-severity head AIS as part of a sensitivity analysis. A significant association remained between succinylcholine and mortality after inclusion of this additional variable (OR 3.90, 95% CI 1.10–13.76, p=0.034). In the fully adjusted model including all clinical covariates, succinylcholine was still associated with increased mortality in the high-severity head AIS group (OR 4.3, 95% CI 1.2–16.0, p=0.029).

The GCS was predictive of mortality in the final models (Table 2), but no significant interaction was noted between GCS and NMBA. Thus GCS did not determine which patients would benefit from avoidance of succinylcholine. Nonetheless, there was an important association between GCS and head AIS. In patients with high-severity head AIS, the distribution of GCS categories were 3–5 (31 patients [40.8%]), 6–8 (20 [26.3%]), 9–12 (11 [14.5%]), and 13–15 (14 [18.4%]). In patients with low-severity head AIS, the distribution of GCS categories were 3–5 (38 [24.2%], 6–8 (38 [24.2%]), 9–12 (34 [21.7%]), and 13–15 (47 [29.9%]).

The median ICU length of stay overall was 3.5 days (IQR 1–10 days) in the rocuronium

**Table 1. Baseline Comparisons Between Groups**

| Variable | Succinylcholine (n=149) | Rocuronium (n=84) | Difference (95% CI) |
|---|---|---|---|
| Demographics | | | |
| Age, yrs, median (IQR) | 38 (27–51) | 53 (35–62) | 15 (8–21) |
| Sex, male, n (%) | 124 (83) | 64 (76) | 7 (−4 to 18) |
| Race, white, n (%) | 85 (57) | 55 (66) | −8 (−22 to 5) |
| Ethnicity, n (%) | | | |
| Hispanic origin | 43 (29) | 17 (20) | 9 (−3 to 20) |
| Non-Hispanic origin | 14 (9) | 7 (8) | 1 (−6 to 9) |
| Not reported | 92 (62) | 60 (72) | −10 (−22 to 3) |
| Clinical data | | | |
| Glasgow Coma Score, median (IQR) | 8 (4–13) | 8 (5–11) | 0 (−1 to 1) |
| Hypoxemia, n (%) | 23 (16) | 9 (11) | 5 (−4 to 14) |
| Hypotension, n (%) | 52 (35) | 18 (21) | 14 (2 to 25) |
| Injury Severity Score, median (IQR) | 17 (12–24) | 16 (10–25) | −1 (−3 to 1) |
| Head Abbreviated Injury Scale, median (IQR) | 3 (3–4) | 3 (3–4) | 0 (0 to 0) |
| Charlson Comorbidity Index, n (%) | | | |
| 0 | 110 (74) | 55 (65) | 8 (−4 to 21) |
| 1 | 23 (15) | 20 (24) | −8 (−19 to 2) |
| 2 | 16 (11) | 9 (11) | 0 (−8 to 8) |
| Intubation data | | | |
| Induction agent etomidate, n (%) | 140 (94) | 82 (97) | −4 (−9 to 1) |
| First attempt intubation success, n (%) | 121 (81) | 68 (81) | 0 (−10 to 10) |

CI = confidence interval; IQR = interquartile range;

**Table 2. Logistic Regression Models for Effect of Neuromuscular Blocking Agents on Mortality**

| Variable | Odds ratio | 95% CI | p value |
|---|---|---|---|
| Severe or critical head injury patients[a] | | | |
| Paralytic | | | |
| Rocuronium | [Reference] | | |
| Succinylcholine | 4.08 | 1.18–14.13 | 0.026 |
| Glasgow Coma Score[b] | 0.36 | 0.20–0.68 | 0.001 |
| Age[c] | 1.04 | 1.00[d]–1.08 | 0.045 |
| Less-than-severe head injury patients[e] | | | |
| Paralytic | | | |
| Rocuronium | [Reference] | | |
| Succinylcholine | 0.75 | 0.29–1.92 | 0.548 |
| Glasgow Coma Scale[b] | 0.48 | 0.31–0.74 | 0.001 |
| Age[c] | 1.03 | 1.00[f]–1.06 | 0.026 |

CI = confidence interval.
[a]Hosmer-Lemeshow goodness of fit (p=0.577), area under the receiver operating characteristic curve = 0.78.
[b]Ordinal variable categorized as 3–5, 6–8, 9–11, and 12–15. Odds ratio decreased for each category-level increase in Glasgow Coma Score.
[c]One-year increments.
[d]Rounded from 1.0009.
[e]Hosmer-Lemeshow goodness of fit (p=0.655); area under the receiver operating characteristic curve = 0.75.
[f]Rounded from 1.004.

group and 3 days (IQR 1–6 days) in the succinylcholine group. In nonsurvivors, the median ICU length of stay was 2 days (IQR 1–6 days) and 2 days (IQR 0–4 days) in the rocuronium and succinylcholine groups, respectively. In survivors, the median ICU length of stay was 4 days (IQR 2–10 days) and 3 days (IQR 1–8 days) in the rocuronium and succinylcholine groups, respectively.

## Discussion

This is the first study to show an association between succinylcholine use and increased mortality in patients with severe TBI. Mechanistically, this may be related to a significant increase in ICP, leading to greater intracranial injury. Although official labeling by the Food and Drug Administration does list this adverse effect as a caution based on preclinical data,[3] few controlled trials have measured succinylcholine-mediated ICP changes in humans.[16] These have been small-sample studies (10–20 subjects) in patients who required craniotomy or were already hospitalized with a presence of an ICP monitor.[16] This monitoring enabled measurement of ICP changes during intubation. It is difficult to extrapolate the findings of these studies to patients with TBI who are intubated in the ED. Further, it is unlikely that large-scale trials investigating the effect of NMBAs on ICP would be feasible in the ED setting given the time course of intubation. Placement of an ICP monitor typically occurs after the airway is secured, precluding the likelihood of such an investigation. Thus the relationship between succinylcholine use and ICP increase continues to be debated by emergency providers because of insufficient evidence linking this elevated pressure to clinically meaningful outcomes. The findings from this investigation are a first step to help fill this important gap in the literature.

Historically, succinylcholine was the NMBA of choice for RSI. This is because it provides consistently excellent intubating conditions, which is a surrogate for intubation success in the operating room setting.[17] This superiority of succinylcholine is not true when higher doses of rocuronium have been used. A study in the ED showed that intubation success was similar between succinylcholine and rocuronium when a dose of ~1.2 mg/kg was used.[2] This finding is supported by a Cochrane review comparing succinylcholine and rocuronium.[17] Thus the choice of NMBA in the ED setting should not be based on the likelihood of intubation success because both agents are equally effective. Instead, selection of the appropriate agent should be based on adverse-effect profile and pharmacokinetics of the NMBAs available. For instance, succinylcholine should be used with caution in patients susceptible to hyperkalemia, such as those with renal impairment, major burns, crush injuries, or neuromuscular disease. The duration of effect of rocuronium (dose higher than 1 mg/kg) is greater than 45 minutes. Although no dosage adjustment is necessary, there is the potential for increased duration of effect with hepatic impairment. However, succinylcholine's duration of effect is only 6 minutes because it is rapidly hydrolyzed by plasma pseudocholinesterases.[2] This has implications for postintubation care, such as provision of sedation and analgesia.[4, 5] In one study, patients who were intubated with rocuronium had a greater delay in receiving sedatives after intubation because of the appearance of sedation.[5] Similarly, in another investigation, patients who received rocuronium were more likely to receive lower doses of sedatives and analgesics. This patient comfort may be affected when a long-acting neuromuscular blocking agent is used. Assigning additional staff such as pharmacists in the ED or developing

protocols that address this issue may ameliorate this phenomenon.[6]

In patients with TBI, the possibility of a transient increase in ICP due to succinylcholine does not make it an ideal agent.[3] However, succinylcholine's short duration of effect enables postintubation clinical assessment of neurologic function. This assessment aids decision making pertaining to the need for neurosurgical intervention. Conversely, rocuronium has no known effect on ICP, but it has a longer duration of effect, as previously mentioned.[18] This sustained neuromuscular blockade postintubation interferes with neurologic assessment. It is unknown if this delay in clinical assessment affects decision making such as the need for neurosurgery. In our study, the possibility of such delays did not translate into excess mortality.

A significant statistical interaction was noted between head AIS and NMBA in our model. Thus the effect of succinylcholine on mortality was significant only in patients with severe or critical head injuries. This is an expected finding because these are the subset of patients who would most likely be harmed from increases in ICP, assuming this increased pressure was the mechanistic explanation for the mortality. Head AIS is a subjective assessment that may be based on final diagnosis incorporating computed tomography scan or autopsy findings. Unfortunately, this information is not available at the time of injury, precluding real-time stratification of patients who would benefit from avoidance of succinylcholine. Instead, clinicians rely on clinical assessments such as GCS to determine head injury severity. Although GCS did correlate with head AIS, it was unable to predict which patients would benefit from avoidance of succinylcholine. For instance, more than 20% of patients with high GCS (12–15 suggesting mild injury) were ultimately found to have severe or critical head injury. This makes it difficult for clinicians to use GCS assessment to determine which patients should receive rocuronium. One alternative is to avoid succinylcholine for intubation in all patients with TBI, regardless of GCS. In these circumstances, even if patients were finally determined to have a less-than-severe head injury, it would not lead to harm. There do not appear to be any disadvantages to using rocuronium in all patients with TBI undergoing intubation; patients with less-than-severe head AIS would not be harmed from a delay in neurologic assessment because they are less likely to require neurosurgical intervention. Our results indicate that overall mortality was similar in both groups (23% each). Thus although only severely brain-injured patients would benefit, the use of rocuronium can be considered in all patients with TBI.

This study has a few important limitations. We cannot exclude the possibility of selection bias, although we believe there is clinical equipoise with regard to NMBA selection in current practice as evidenced by the increased number of patients receiving succinylcholine compared with rocuronium in this study. If selection bias did occur, then providers most likely would have utilized rocuronium for more severely injured patients, which would have decreased the chances of finding significant differences in outcomes between groups. We found increased mortality in the succinylcholine group, again suggesting selection bias did not occur. A combination of databases was used to acquire our final study cohort that required merging based on medical record number and date of admission. It is possible that some records were missing because of possible errors in these fields, resulting in fewer patients. There were statistically significant differences between groups with regard to age and occurrence of hypotension. The patients in the rocuronium group were older but yet had lower mortality. This supports the safety of rocuronium in patients with high-severity head injury, irrespective of age. Patients in the succinylcholine group were more likely to have hypotension suggesting higher severity of illness. However, this was not verified by other measures of severity such as injury severity scores. Nonetheless, we acknowledge that this is an important imbalance between the groups.Hypotension has been shown to be an important predictor of mortality after TBI. Even a single episode of hypotension in these patients may double the risk of mortality.[19] We adjusted for both of these variables in our multivariate and sensitivity analyses. Doses of the neuromuscular blockers were not available for analysis in this study, and therefore we were unable to make dosing comparisons or determine if this effect on mortality is dose dependent. Finally, the study was powered to compare the overall groups. However, based on a statistical interaction, we had to stratify the data, which led to a loss of power. Nonetheless, we still found significant differences precluding the possibility of a type II error. We were also able to adjust for important confounders, and the results did not change with our sensitivity analysis.

In conclusion, succinylcholine use for RSI in patients with severe TBI was associated with increased mortality. It may not be possible to discriminate reliably which patients are likely to benefit from avoidance of succinylcholine at the time of intubation in the ED. A prospective clinical trial is needed to confirm these findings.

## Conflicts of Interest

None of the authors have any conflicts of interest to disclose.

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