




# Drug Order in Rapid Sequence Intubation

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## ABSTRACT

**Background:** The optimal order of drug administration (sedative first vs. neuromuscular blocking agent first) in rapid sequence intubation (RSI) is debated.

**Objective:** We sought to determine if RSI drug order was associated with the time elapsed from administration of the first RSI drug to the end of a successful first intubation attempt.

**Methods:** We conducted a planned secondary analysis of a randomized trial of adult ED patients undergoing emergency orotracheal intubation that demonstrated higher first-attempt success with bougie use compared to a tracheal tube + stylet. Drug choice, dose, and the order of sedative and neuromuscular blocking agent were not stipulated. We analyzed trial patients who received both a sedative and a neuromuscular blocking agent within 30 seconds of each other who were intubated successfully on the first attempt. The primary outcome was the time elapsed from complete administration of the first RSI drug to the end of the first intubation attempt, a surrogate outcome for apnea time. We performed a multivariable analysis using a mixed-effects generalized linear model.

**Results:** Of 757 original trial patients, 562 patients (74%) met criteria for analysis; 153 received the sedative agent first, and 409 received the neuromuscular blocking agent first. Administration of the neuromuscular blocking agent before the sedative agent was associated with a reduction in time from RSI administration to the end of intubation attempt of 6 seconds (95% confidence interval = 0 to 11 sec).

**Conclusion:** Administration of either the neuromuscular blocking or the sedative agent first are both acceptable. Administering the neuromuscular blocking agent first may result in modestly faster time to intubation. For now, it is reasonable for physicians to continue performing RSI in the way they are most comfortable with. If future research determines that the order of medication administration is not associated with awareness of neuromuscular blockade, administration of the neuromuscular blocking agent first may be a logical default administration method to attempt to minimize apnea time during intubation.

Rapid sequence intubation (RSI) traditionally involves the sequential administration of a sedative and neuromuscular blocking agent.<sup>1</sup> The sedative agent renders the patient unconscious; the neuromuscular blocking agent produces muscle relaxation, which improves laryngeal view, reduces intubation-associated complications, and improves the likelihood of intubation success.<sup>2-4</sup> RSI is the most common method of emergency intubation, used in approximately 85% of ED intubations<sup>5</sup> and 75% of intensive care unit

intubations.<sup>6,7</sup> Although both drugs are administered in quick succession, to our knowledge the order of drug administration is not based on empiric data.<sup>8</sup>

Safe apnea time, the interval between apnea and hypoxemia, is difficult to anticipate for an individual patient. Safe apnea time can be as short as several seconds and as long as several minutes, depending on patient characteristics (e.g., age, body mass index, underlying illness, metabolic rate, acid/base status, shunt physiology, among others) and the method of

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preoxygenation. Because safe apnea time cannot be known prospectively, minimizing total apnea time, the interval from apnea to initial ventilation after intubation, is a goal of RSI when performing intubation in critically ill patients. Drug order in RSI could potentially affect apnea time.

While administration of the sedative agent first is common and increases the likelihood of adequate sedation prior to neuromuscular blockade, sedatives can cause hypoventilation and apnea.<sup>9–14</sup> If hypoventilation or apnea precede the onset of neuromuscular blockade, the patient incurs both an increased risk of hypoxemia and a potential delay between apnea onset and optimal intubating conditions (i.e., full muscle relaxation). In contrast, administration of the neuromuscular blocking agent first may better align the onset of apnea caused by the sedative agent with the onset of optimal intubating conditions, thereby minimizing unnecessary apnea time. While some advocate against this approach for fear of patient awareness while under neuromuscular blockade, it has been studied in the operating room setting.<sup>15–18</sup>

We sought to determine if RSI drug order was associated with the time elapsed from administration of the first RSI drug to the end of a successful first intubation attempt. This interval was chosen as a pragmatic surrogate for apnea time.

## METHODS

### Study Design and Setting

We conducted a planned secondary analysis of a randomized trial demonstrating superiority of the bougie over a tracheal tube + stylet in first attempt intubation success among ED patients with at least one difficult airway characteristic. The trial and protocol were previously published.<sup>19</sup> The trial ED cares for 109,000 patients annually; all endotracheal intubations are performed by either emergency medicine residents (usually PGY-3 or higher) or attending emergency physicians. The timing of laryngoscope insertion after RSI medication administration is not protocolized and it is not routine to track the elapsed time after drug administration before laryngoscope blade insertion. Instead, it is more common for the intubator to insert the blade when the patient appears to achieve complete muscle relaxation. The study was approved by the local institutional review board.

### Selection of Participants

From September 2016 through August 2017 we enrolled consecutive patients undergoing endotracheal intubation with a Macintosh laryngoscope blade, excluding prisoners, pregnant women, and those with known distortion of upper airway or glottic structures.

For this secondary analysis, as we were interested in RSI drug order, we analyzed only those patients who received both a sedative (including ketamine or etomidate) and a neuromuscular blocking agent (with succinylcholine or rocuronium). We excluded those with missing data for the timing of drug administration. We excluded other pharmacologic agents used for RSI (e.g., propofol, midazolam, atracurium) because they are used infrequently in our ED and nationally.<sup>5</sup>

Both sedative and neuromuscular blocking agents should be administered near simultaneously in RSI;<sup>1</sup> a delay of greater than 30 seconds between drug administrations seems unreasonable for RSI, so we chose to exclude those cases. We excluded those not intubated successfully on the first attempt because patient, intubator, and device characteristics are more likely than drug order to influence first attempt success. Conversely, drug order is more likely to influence the time elapsed from drug administration to successful intubation than it is to influence intubation success. Additionally, attempt duration likely varies between failed and successful intubation attempts, potentially confounding the association of interest in this study.

### Interventions

In the main trial, we randomized patients to bougie or tracheal tube + stylet for the first attempt at orotracheal intubation. Drug choice, dose, and the order of sedative and neuromuscular blocking agent were at the discretion of the intubating physician. In both groups (bougie or tracheal tube + stylet), the laryngoscope blade was kept in the mouth until the endotracheal tube was successfully placed into the trachea.

### Methods of Measurement

Trained research associates prospectively collected detailed process and outcome data beginning at randomization and ending 1 minute following the end of the first intubation attempt. Key process data captured by manual timing with a stopwatch included time of drug administration (defined as when the drug syringe was completely empty) and when the intubation attempt began and ended. Intubation attempts began

when the laryngoscope was placed in the mouth and ended when the laryngoscope was removed from the mouth, regardless of whether bougie or tube passage was attempted. After the procedure, the intubating physician completed a structured data collection form to gather additional information about the patient and intubation attempts, including whether any difficult airway characteristics were present, including body fluid (s) obscuring the laryngeal view, airway obstruction or edema, obesity, short neck, small mandible, large tongue, facial trauma, or cervical spine immobilization.

### Outcome Measures

We defined the primary outcome, intubation time, as the time elapsed from administration of the first RSI drug to removal of the laryngoscope blade (end of the attempt). This represents a pragmatic surrogate for apnea time, as there was no way to reliably record the onset of hypopnea, bradypnea, or actual apnea during emergency intubation. Secondary outcomes included first-attempt duration, hypoxemia, and first-attempt success (this final outcome analyzed patients who met other inclusion criteria, regardless of whether the first attempt was successful,  $N = 610$ ).

### Primary Data Analysis

Patients were classified based on which drug they received first (neuromuscular blocking agent or sedative). We present baseline characteristics and intubation process measures stratified by RSI drug order. We describe the outcomes stratified by drug order and neuromuscular blocking agent used, with medians and interquartile ranges (IQR) or proportions and 95% confidence intervals (CIs), as appropriate. Differences in proportion or median differences are reported.

Because this secondary analysis was observational we performed a multivariable analysis to control for potential confounding. We constructed a mixed-effects generalized linear model for the outcome of elapsed time from the end of complete administration of the first RSI drug until the end of the first intubation attempt (intubation time). The independent variable of interest was RSI drug order. We selected other independent variables a priori that could potentially affect the intubation time, including specific neuromuscular blocking agent (succinylcholine or rocuronium), first device passed (bougie or tracheal tube + stylet), whether the video laryngoscope screen was ever viewed during the attempt, presence of any difficult airway characteristics, and Cormack-Lehane grade. A variable

identifying each unique intubating physician was included as a random-effect term.

The specific neuromuscular blocking agent was included because, at recommended doses, succinylcholine has a slightly faster onset than rocuronium.<sup>20,21</sup> Screen viewing was included because intubations requiring screen usage may last longer.<sup>22</sup> We did not include the laryngoscope type as a covariate because in the trial more than 95% of patients were intubated using a C-MAC Macintosh blade. To assess goodness of fit we plotted the deviance residuals against the estimated linear predictor.

We did not perform any sample size calculations for this analysis as the size of this trial because no estimates of intubation time stratified by RSI medication order exist; additionally, the sample size was determined by the parent trial. As the standard deviation for intubation time was 23 seconds, we estimated that the parent trial size of 757 would provide 80% power to detect an absolute difference of 6 seconds between the two groups, a difference that could have clinical relevance in certain patient populations. We used Stata (Version 15, StataCorp) for all data analyses.

### Sensitivity Analyses

We performed two sensitivity analyses to account for patients excluded in the main analysis. The first relaxed our requirement that the first intubation attempt be successful. The second sensitivity analysis additionally relaxed our requirement RSI drugs needed to be administered within 30 seconds of each other. In both sensitivity analyses we used the same mixed-effects generalized linear model with the same covariates as the primary analysis.

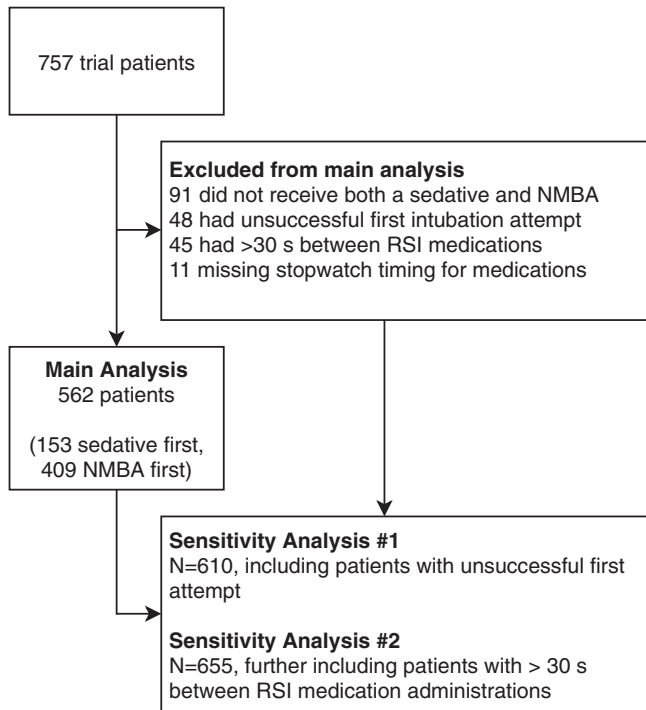
## RESULTS

### Characteristics of Study Subjects

Of 757 patients enrolled in the BEAM trial, 562 were eligible for inclusion in the main analysis, 153 (27%) with the sedative agent administered first and 409 (73%) with the neuromuscular blocking agent administered first (Figure 1). Baseline characteristics and intubation process measures are presented in Tables 1 and 2, respectively.

### Outcomes

In the unadjusted analysis of the primary outcome, the median (IQR) intubation time for the neuromuscular blocking agent group first was 80 (66–99)



**Figure 1.** Enrollment and analysis flow, showing which patients were included in the main analysis and sensitivity analyses. NMBA = neuromuscular blocking agent; RSI = rapid sequence intubation.

seconds and the median (IQR) intubation time for the sedative group first was 84 (66–99) seconds (median difference = 5 seconds [95% CI = 0–10 seconds]). Subject-level data for the time to intubation are presented in Figure 2. Unadjusted analysis of secondary outcomes (attempt duration, rates of hypoxemia, and first-attempt success) were not significantly different (Table 3). Outcomes by specific neuromuscular blocking agents were not different from the unstratified analysis (Data Supplement S1, Table S1, available as supporting information in the online version of this paper, which is available at <http://onlinelibrary.wiley.com/doi/10.1111/acem.13723/full>).

Results of the multivariable analysis are displayed in Table 4. Administration of the neuromuscular blocking agent before the sedative agent was associated with a reduction in time from RSI administration to the end of intubation attempt of 6 seconds (95% CI = 0 to 11 seconds). Not viewing the video screen and more operator experience were associated with shorter intubation times; worsening laryngoscopic view (Cormack-Lehane grade) was associated with longer intubation times (Table 4).

### Sensitivity Analyses

Results of the sensitivity analyses, which performed identical analyses on an expanded group of patients

**Table 1**  
Baseline Characteristics

Characteristic	Sedative First (n = 153)	Neuromuscular Blocking Agent First (n = 409)
Age (years)	46 (30–60)	43 (30–58)
Male sex	103 (67)	291 (71)
Body mass index (kg/m <sup>2</sup> )	26 (23–31)	26 (23–31)
Oxygen saturation (%)*	99 (94–100)	99 (96–100)
<90%	23/147 (16)	34/394 (9)
<80%	6/147 (4)	11/394 (3)
Indication for intubation		
Medical	127 (83)	340 (83)
Altered mental status	78 (51)	199 (49)
Cardiac arrest	1 (1)	15 (4)
Septic shock	13 (9)	27 (7)
Seizure	5 (3)	33 (8)
Asthma, COPD, heart failure, pneumonia	13 (8)	16 (4)
Other	17 (11)	50 (12)
Trauma	26 (20)	69 (18)
Traumatic brain injury	8 (6)	38 (11)
Other	18 (14)	21 (6)
Difficult airway characteristic present†	74 (48)	195 (48)

Data are reported as median (IQR) or n (%).

COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

\*No oxygen saturation available for six in the sedative group and 15 in the neuromuscular blocking first group.

†Including blood or vomit in the airway, obesity, cervical immobilization, large tongue, short neck, facial trauma, small mandible, airway obstruction, or edema.

(including those with first attempt failure and additionally those with elapsed times between RSI agents of  $\geq 30$  seconds) are displayed in Data Supplement S1, Table S2. The direction of the coefficients was unchanged from the main analysis.

## DISCUSSION

Limiting apnea time during orotracheal intubation in critically ill patients is of fundamental importance. Some have postulated that administration of the neuromuscular blocking agent before the sedative agent in RSI may shorten the apnea time.<sup>8</sup> In this secondary analysis of a single-center, randomized trial of ED patients undergoing emergency intubation, the neuromuscular blocking agent was administered before the sedative in 73% of cases using RSI. In this study, administration of the neuromuscular blocking agent first was associated with a 6-second reduction in the elapsed time from RSI administration to the end of intubation, a surrogate for apnea time (95% CI = 0 to

**Table 2**  
Intubation Process Measures

Measure	Sedative First (n = 153)	Neuromuscular Blocking Agent First (n = 409)
Preintubation sedative		
Etomidate	151 (99)	406 (99)
Ketamine	2 (1)	3 (1)
Preintubation neuromuscular blockade		
Succinylcholine	95 (62)	248 (61)
Rocuronium	58 (38)	161 (39)
Elapsed time between administration of first and second RSI drug (seconds)	10 (5–13)	10 (7–14)
Elapsed time between administration of first drug and insertion of laryngoscope blade (seconds)	45 (36–53)	43 (35–53)
Elapsed time between administration of second RSI drug and insertion of laryngoscope (seconds)	35 (28–43)	32 (24–41)
Intubating position		
Sniffing position	99 (65)	252 (62)
Neutral cervical spine	35 (23)	120 (29)
Cervical spine extension without sniffing	19 (12)	35 (9)
Oxygen saturation at the beginning of the intubation attempt (%)	100 (98–100)	100 (98–100)
Apneic oxygenation used	97 (63)	247 (60)
Operator		
Emergency medicine senior resident or fellow (PGY-3 or higher)	118 (77)	356 (87)
Emergency medicine junior resident (PGY-2 or lower)	33 (22)	43 (11)
Emergency medicine faculty	2 (1)	10 (2)
C-MAC Macintosh blade used*	148 (97)	396 (97)
Video screen use†		
Screen never used	85 (56)	247 (60)
Screen viewed for the entire attempt	35 (23)	70 (17)
Screen viewed during passage of the tube or bougie into the glottis	33 (22)	92 (23)
Best Cormack-Lehane laryngeal view		
Grade 1 (best view)	116 (76)	301 (74)
Grade 2	27 (18)	66 (16)
Grade 3	7 (5)	22 (6)
Grade 4 (worst view)	2 (1)	2 (< 1)
First device entered into the mouth after the laryngoscope		
Bougie	85 (56)	216 (53)
Endotracheal tube + stylet	68 (44)	193 (47)

Data are reported as n (%) or median (IQR).

IQR = interquartile range; PGY = postgraduate year; RSI = rapid sequence intubation.

\*The remaining patients were intubated using a hyperangulated blade (five in sedative group, seven in neuromuscular blocking agent group) or with a direct Macintosh laryngoscope (six in neuromuscular blocking agent group).

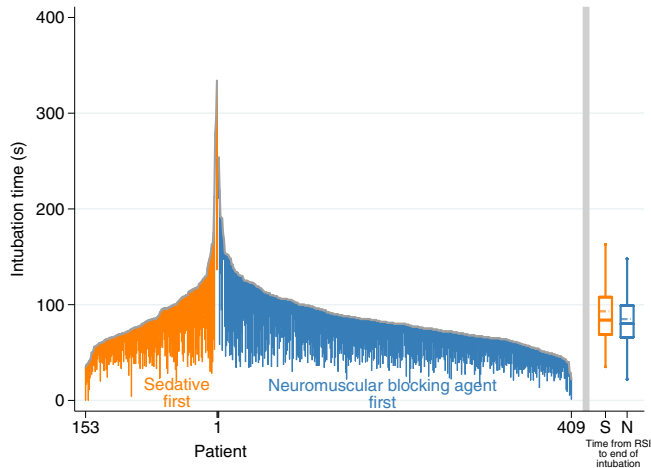
†Patients intubated with nonvideo Macintosh laryngoscope were coded as “screen never used.”

11 seconds). The trend toward shorter intubation times when neuromuscular blocking agents are administered first, if true, is not likely to be clinically significant except in the most critically ill patients requiring endotracheal intubation (i.e., those with the least physiologic reserve, e.g., severe metabolic acidosis, asthma, acute respiratory distress syndrome, among others). However, apart from the theoretical, albeit unlikely, concern of awareness of neuromuscular blockade, it is difficult to think of a compelling reason to administer the sedative agent before the neuromuscular blocking agent.

Administration of a nondepolarizing neuromuscular blocking agent before sedation has been described in the operating room setting. In this practice, termed “the timing principle,” the neuromuscular blocking agent is administered and the patient is monitored for weakness or paralysis; when weakness is detected the sedative agent is administered.<sup>15–18,23,24</sup> This technique is performed so that the peak effect of the sedative agent occurs near the onset of paralysis to avoid sedative-induced hypoventilation or apnea before the neuromuscular blocking agent takes full effect. This “timing principle” practice delays sedative administration after neuromuscular blocking agent administration longer than any delay inherent in RSI.

Administration of the neuromuscular blocking agent first ostensibly allows earlier insertion of the laryngoscope blade from the time of RSI medication administration. In this study, however, the elapsed time from administration of the first RSI medication and insertion of the laryngoscope blade was similar in both groups (2-second difference, Table 2). However, the total intubation time, the time from first RSI medication to the end of the intubation attempt, was 6 seconds shorter when the neuromuscular blocking agent was administered first. This suggests that the difference between the two approaches depends not only on earlier laryngoscope insertion, but additionally on earlier complete muscle relaxation, allowing more facile laryngoscopy and tube delivery.

An objection sometimes proffered against administration of the neuromuscular blocking agent first is the possibility of losing intravenous access between RSI agents or delayed administration of the sedative. This current study cannot answer this query. In emergency intubation, successful first-attempt intubation may be a higher priority than patient experience, especially because if venous access is lost a benzodiazepine can be administered to cause amnesia to the event.<sup>25</sup> In



**Figure 2.** Subject-level data for the time elapsed between the complete administration of the first RSI medication and the start and end of the intubation attempt, by group, sorted in order of elapsed time until the attempt ended. Each participant is displayed as a single vertical line connecting the starting and ending times of the attempt. The attempt began when the laryngoscope was inserted into the mouth and ended when the laryngoscope was removed. Box-and-whisker plots for the elapsed time from the complete administration of the first RSI medication to the end of intubation are displayed on the right side of the graph for the two study groups. N = neuromuscular blocking agent first group; S = sedative first group.

**Table 3**  
Unadjusted Study Outcomes

Outcome	Neuromuscular Blocking Agent First		Difference (95% CI)
	Sedative First (n = 153)	Agent First (n = 409)	
Intubation time (seconds)*	84 (69–108)	80 (66–99)	5 (0 to 10)
Attempt duration (seconds)†	38 (27–55)	35 (25–47)	3 (–1 to 6)
Hypoxemia‡	12/151 (8)	51/404 (13)	–5% (–10% to 1%)
First-attempt success§	153/161 (95; 90–98)	409/449 (91; 88–94)	4% (0% to 8%)

Data are reported as median (IQR), n (%), or n (%; 95% CI). Positive values in the difference column indicate longer duration or higher proportion for the sedative first group.

IQR = interquartile range.

\*Defined as elapsed time from complete administration of the first RSI drug to removal of the laryngoscope blade.

†Defined as the time elapsed between insertion and removal of the laryngoscope blade.

‡Defined as an oxyhemoglobin saturation < 90% (or, if the attempt began with a saturation < 90%, an absolute decrease in saturation of >10%) during or within 1 minute after completion of the intubation attempt. Data not available for seven patients.

§This includes patients regardless of first intubation attempt success (n = 610).

these situations, if a sedative were the only agent administered, intubation is likely to be more difficult and prone to complications, including first-attempt failure and vomiting and aspiration.<sup>2–4,7</sup> It would be difficult for any study to definitively answer this specific question.

**Table 4**  
Mixed-effects Generalized Linear Model Results for Time From RSI Administration to End of Intubation Attempt

Predictor	Coefficient (s)	95% CI (s)
Neuromuscular blocking agent administered first*	–6	–11 to 0
Rocuronium†	4	–2 to 9
First device: tracheal tube + stylet‡	–6	–10 to 0
Video screen not used§	–10	–16 to –4
Difficult airway characteristic present	3	–2 to 8
Cormack-Lehane grade		
2	10	3 to 17
3	18	6 to 30
4	10	–20 to 40

This table displays results from the mixed-effects generalized linear model for the outcome of time from complete administration of the first RSI agent until removal of the laryngoscope blade. The coefficient column displays the amount of time (in seconds) associated with each variable, compared to its reference counterpart. Negative coefficients indicate shorter intubation times.

There were 19 missing values for Cormack-Lehane grade; a model constructed without Cormack-Lehane grade, including all 562 cases, had similar output.

RSI = rapid sequence intubation.

Reference values: \*Sedative agent administered first; †Succinylcholine; ‡Bougie inserted first; §Any use of the video screen; ||Cormack-Lehane grade 1.

Based on the limited available literature, including the current observational study, it is acceptable to administer the sedative and neuromuscular blocking agent in either order. Administration of the neuromuscular blocking agent first, if beneficial at all, is most likely to influence outcomes for patients at the extremes of critical illness where mitigating unnecessary apnea time is of the utmost importance. More important factors are probably the devices used and operator experience. However, because the theoretical downside of administering the neuromuscular blocking agent first is small (i.e., awareness of neuromuscular blockade that is not likely to be remembered if a sedative is administered in a timely fashion), it might be sensible for the default method to be administration of the neuromuscular blocking agent first, potentially shortening apnea time. Future research should determine if the order of medication administration is associated with awareness of neuromuscular blockade or patient memories of intubation. If no association exists, a strong case can be made for administration of the neuromuscular blocking agent before the sedative.

## LIMITATIONS

In this analysis we used the outcome of the elapsed time from RSI administration to end of the intubation

attempt; this served as a surrogate for apnea time, a more patient-important outcome. Depending on the actual effect of sedatives on ventilatory effort, an analysis of apnea time could differ from the present analysis. Although we analyzed 562 patients, only 153 had the sedative agent administered first. This relatively small sample size caused imprecision in the model; a larger, more balanced trial would be required to confirm the modest difference of 6 seconds between groups. In this study we did not record patient memories of intubation and cannot know if administering the neuromuscular blocking agent first has adverse effects such as awareness of paralysis, though this is unlikely given the rapidity of sedation administration. Finally, drug order could theoretically be associated with first-attempt success if the intubating physician attempts intubation before complete muscle relaxation. While this study was not designed to answer this question, future studies should record this outcome.

## CONCLUSION

In conclusion, administration of either the neuromuscular blocking or the sedative agent first are both acceptable. Administering the neuromuscular blocking agent first may result in modestly faster time to intubation. For now, it is reasonable for physicians to continue performing RSI in the way they are most comfortable with. If future research determines that the order of medication administration is not associated with awareness of neuromuscular blockade, administration of the neuromuscular blocking agent first may be a logical default administration method to attempt to minimize apnea time during intubation.

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### Supporting Information

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The following supporting information is available in the online version of this paper available at <http://onlinelibrary.wiley.com/doi/10.1111/acem.13723/full>

**Data Supplement S1.** Supplemental material.