Impact of Paralytic Agent Choice on Time to Post-Intubation Sedation in the Emergency Department

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Article

Impact of Paralytic Agent Choice on Time to Post-Intubation Sedation in the Emergency Department

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Abstract

Background/Objectives: Rapid sequence intubation (RSI) involves nearly simultaneous administration of a rapid-acting induction agent and a neuromuscular blocking agent (NMBA) to facilitate ideal intubation conditions. The NMBAs most commonly used for RSI are succinylcholine and rocuronium, which cause paralysis for 5-15 minutes and 45-70 minutes, respectively. Awareness with paralysis can occur in patients given longer-acting NMBAs with delayed initiation of post-intubation sedation or insufficient sedation depth. Previous literature has associated the use of rocuronium with a significantly longer time to sedation and analgesia. However, a recent study found no difference. The purpose of this study was to assess the association between paralytic agent choice and time to initiation of analgesia and/or sedation after RSI in the emergency department (ED) of a large tertiary care hospital. **Methods**: This study was an institutional review board-approved, single center, retrospective cohort evaluation of adult patients (≥ 18 years of age) who received succinylcholine or rocuronium following administration of an induction agent in the ED for RSI during the study time period. The primary outcome was time to initiation of post-intubation analgesia and/or sedation. Continuous data was analyzed using Mann Whitney U or student's T-test, and categorical data was analyzed using Chi Square test or Fisher's Exact test. **Results**: A total of 400 patients were included in this study. The median time to sedation with succinylcholine was 9 minutes compared to 14 minutes with rocuronium (p<0.01). No significant differences were identified in baseline characteristics or secondary outcomes related to induction agent choice or ED length of stay. **Conclusions**: The results of this study further support that the use of rocuronium for RSI is associated with a significantly longer time to sedation and/or analgesia, making emergency medicine provider awareness essential towards minimizing the risks associated with inadequate post-intubation sedation.

Keywords: awareness with paralysis; critical care; deep sedation; emergency medicine; neuromuscular blocking agents; rapid sequence intubation; pharmacists

1. Introduction

Rapid sequence intubation (RSI) is the preferred method for quickly securing an airway in a critically ill patient [1]. Indications for RSI include risk for aspiration, impending airway loss, or impaired gas exchange requiring mechanical ventilation. RSI involves nearly simultaneous administration of a rapid-acting induction agent followed by a neuromuscular blocking agent (NMBA) to facilitate ideal intubation conditions [2]. The NMBAs most commonly used for RSI are

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succinylcholine and rocuronium. Succinylcholine is a depolarizing NMBA which binds to and activates acetylcholine (ACh) receptors on the motor endplate [3]. It has an onset of action of 30-60 seconds and duration of action of 5-15 minutes. Rocuronium is a non-depolarizing NMBA which competitively blocks ACh receptors on the motor endplate [4]. It has an onset of action of 1-2 minutes, but a significantly longer duration of action of 45-70 minutes.

Awareness with paralysis can occur in patients given longer-acting NMBAs with delayed initiation of post-intubation sedation and/or insufficient sedation depth. In the ED-AWARENESS study, Pappal, et al. (2021) were the first to prospectively study the concept of awareness with paralysis in the emergency department (ED) setting and found a prevalence of possible or definite awareness in 2.9% (10/345 patients) of patients with documented NMBA exposure [5]. Previous literature has associated the use of rocuronium with a significantly longer time to sedation and analgesia as paralyzed patients may not demonstrate movement or signs of distress for a prolonged period of time. Watt, et al. (2013) found a mean time between intubation and post-intubation sedation of 27 minutes in the rocuronium group versus 15 minutes in the succinylcholine group (p<0.001) in their retrospective cohort study which included 200 ED patients [6]. Similarly, Johnson, et al. (2015) found a mean time to sedation or analgesia of 34 minutes in the rocuronium group versus 16 minutes in the succinylcholine group (p=0.002) among their cohort of 106 ED patients [7]. In contrast to these results, a recent study by Carlson, et al. (2023) found no difference in median time to initiation of analgesia or sedation in a sample of 200 ED patients receiving succinylcholine vs rocuronium for RSI (10 mins vs 8.5 mins; p=0.82) [8].

The purpose of this study is to examine the impact of paralytic agent choice on time to initiation of analgesia and/or sedation after RSI in the ED of a large tertiary care hospital with an anticipated larger cohort of patients compared to prior studies.

2. Materials and Methods

This study was an Institutional Review Board-approved, single center, retrospective cohort evaluation of adult patients who received succinylcholine or rocuronium in the ED for RSI from October 1, 2021 through September 30, 2023. Patients were consecutively screened in reverse chronological order until 200 patients were included in each group. All data was extracted from the hospital electronic medical record database. Patients were excluded if they were intubated prior to ED arrival, experienced cardiac arrest prior to or during their ED stay, or were administered NMBA for any reason other than RSI. Data collection included baseline characteristics as well as medication regimen details.

The primary outcome was time to initiation of post-intubation analgesia and/or sedation after RSI. Time to initiation was defined as the difference in minutes between paralytic administration and first documented administration of continuous or intermittent post-intubation analgesia and/or sedation. Secondary outcomes included the median dose of induction and paralytic agents used and the length of ED stay. Induction agents included etomidate, ketamine, midazolam, propofol, and methohexital. Post-intubation analgesia and/or sedation was defined as the use of: dexmedetomidine, diazepam, fentanyl, hydromorphone, ketamine, lorazepam, midazolam, morphine, and propofol.

Continuous data was analyzed using the Mann Whitney U or student's T-test, and categorical data was analyzed using the Chi Square test or Fisher's Exact test. A p-value of < 0.05 was considered statistically significant. An inter-rater blinded to the study performed an audit of the primary outcome for 10% of a randomly selected sample. An inter-rater agreement level of 90% or greater was accepted.

3. Results

A total of 1215 charts were screened, and 400 patients were included for analysis. Study subjects were mostly male with a median age of 67 years in both groups. No statistically significant differences in baseline characteristics were detected between groups (Table 1). Etomidate was the most

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frequently used induction agent regardless of paralytic choice, and all patients in this study received continuous post-intubation sedation. Additional details regarding RSI and post-RSI sedation and analgesia can be found in Table 2. The median time to initiation of post-intubation sedation and/or analgesia was significantly longer in the rocuronium group compared to the succinylcholine group (14 mins vs 9 mins, respectively; $p<0.01$) (Table 3). The median dose of etomidate administered was 0.3 mg/kg in both groups, and the median doses of rocuronium and succinylcholine were 1 mg/kg and 1.4 mg/kg, respectively. ED length of stay was similar between groups with a median duration of 265 minutes with succinylcholine administration and 244 minutes with rocuronium administration ($p=0.81$).

Table 1. Baseline characteristics.

	Rocuronium (n=200)	Succinylcholine (n=200)	*P*-value
Age (years)	67 (56 – 75)	67 (52 – 77)	0.82
Female sex, n(%)	90 (45)	91 (45.5)	0.92
Weight (kg)	78 (66 – 98)	84 (66 – 100)	0.47
GCS at presentation	13 (8 – 15)	13 (8 – 15)	0.33

* Expressed as median (IQR) unless otherwise noted.

Table 2. Rapid sequence intubation and post-intubation sedation.

	Rocuronium (n=200)	Succinylcholine (n=200)	*P*-value
Pre-medication used			
Lidocaine	*0 (0)*	*2 (1)*	0.50
Induction agent used			
Etomidate	*189 (94.5)*	*187 (93.5)*	0.67
Other	*11 (5.5)*	*13 (6.5)*	--
Continuous analgosedation	200 (100)	200 (100)	1.00
Sedative + analgesic	*98 (49)*	*145 (72.5)*	<0.01
Sedative only	*79 (39.5)*	*47 (23.5)*	<0.01
Analgesic only	*23 (11.5)*	*8 (4)*	<0.01
Intermittent analgosedation	13 (6.5)	29 (14.5)	<0.01
Midazolam	*9 / 13 (69)*	*20 / 29 (69)*	1.00
Ketamine	*2 / 13 (15)*	*8 / 29 (28)*	0.47
Lorazepam	*1 / 13 (8)*	*1 / 29 (3)*	0.53
Fentanyl	*1 / 13 (8)*	*0 / 29 (0)*	0.31

* Expressed as n (%) unless otherwise noted.

Table 3. Outcomes.

	Rocuronium (n=200)	Succinylcholine (n=200)	*P*-value
Time to initiation of sedation and/or analgesia (minutes)	14 (7 – 28)	9 (5 – 16)	<0.01
Induction agent dose (mg/kg)			
Etomidate	*0.3 (0.2 – 0.3)*	*0.3 (0.2 – 0.3)*	<0.01
Other	--	--	--
Paralytic agent dose (mg/kg)	1.0 (1.0 – 1.3)	1.4 (1.1 – 1.6)	--
Length of ED stay (minutes)	244 (182 – 314)	265 (176 – 356)	0.33

* Expressed as median (IQR) unless otherwise noted.

4. Discussion

This is the largest study to date assessing the difference in time to post-intubation sedation in patients given rocuronium or succinylcholine for RSI in the ED. This study reports a median time to

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post-intubation analgesia and/or sedation use of 14 minutes in the rocuronium group, which is longer than the approximately 5-minute duration of action of the most commonly used induction agent, etomidate [9]. With over 90% of patients receiving etomidate for induction in RSI, this leaves a sizeable portion of patients at risk for awareness with paralysis.

Several factors may delay initiation of analgesia and sedation in patients who receive rocuronium for RSI. Healthcare providers may have a false perception of adequate sedation in patients given long-acting paralytics as they may not show signs of discomfort even after the sedative used for RSI has worn off. Time to sedation can be influenced by logistical factors such as availability of staff, time needed to retrieve medications, and programming medication pumps. Additionally, patient-specific characteristics may decrease the likelihood of receiving sedation. Lembersky, et al. (2019) performed a retrospective analysis of data from the National Emergency Airway Registry with the goal of identifying patient populations that may be at risk for omission of post-intubation sedation [10]. The investigators found that the use of short-acting paralytics (i.e. succinylcholine) was associated with increased odds of receiving post-intubation sedation compared to long-acting NMBA (i.e. rocuronium and vecuronium) (1.89; 1.68-2.12). Other factors associated with significantly lower odds of receiving post-intubation sedation were pre- and post-intubation hypotension and cardiac or traumatic arrest.

The studies by Watt and Johnson [6, 7] included younger patients (30s-40s), a majority of which presented as trauma alerts. These patients likely had less comorbidities at baseline but may have been a more tenuous population due to their need for intubation being traumatic in nature. The present study tended to exclude trauma patients as medication administration documentation is recorded in a trauma alert form rather than the medication administration record used to identify the study population. This study and that conducted by Carlson and colleagues [8] included an older patient population (60s), which may influence induction and paralytic agent choice and dosing.

Watt was the only study that required etomidate as the induction agent for inclusion; however, in the other three studies, it was the most common induction agent administered (75-95%). Johnson required the use of continuous sedation to meet the primary outcome; all other studies included use of intermittent sedation as well, which better represents real-world practice. It is possible that this may have affected their primary outcome if patients received adequate intermittent sedation but were not immediately started on continuous sedation. Watt used the time from etomidate administration, rather than paralytic administration, to sedation as their primary outcome. In RSI, these should be given nearly simultaneously, and therefore would not be expected to significantly affect the primary outcome.

While the present study excluded pediatric patients, previous studies conducted in this population have shown similar results. Kendrick, et al. (2009) found in their study of 84 pediatric patients intubated with etomidate and rocuronium or vecuronium a mean time from etomidate to the administration of additional sedation of 46 minutes, and only 23.8% of patients received additional sedation within 15 minutes of initial etomidate administration [11].

Johnson and colleagues assessed the impact of ED pharmacist presence and found that time to sedation or analgesia was significantly shorter when an ED pharmacist was present. In their study, the presence of an ED pharmacist reduced time to sedation or analgesia from 49 ± 45 mins to 20 ± 21 mins ($p < 0.001$). At the study institution, ED pharmacist coverage is not available at all times. This factor may have affected the primary outcome; however, the impact of the ED pharmacist was not assessed in the present study.

This study was limited by its retrospective nature as it relied heavily on the accuracy of documentation in the medical record. Pediatric patients were excluded; therefore, these results are unable to be generalized to that patient population. Finally, information on post-intubation vital signs and adequacy of sedation were not collected; therefore, conclusions cannot be made about the optimization of care after intubation.

5. Conclusions

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The use of rocuronium for RSI resulted in a longer time to post-intubation sedation and/or analgesia compared with succinylcholine in the ED setting. These results add to the existing literature supporting that paralytic choice for RSI has implications for post-intubation management. Emergency medicine provider awareness is essential towards optimizing post-intubation sedation practices and minimizing the risks associated with inadequate sedation.

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Abbreviations

The following abbreviations are used in this manuscript:

ACh	Acetylcholine
ED	Emergency department
GCS	Glasgow Coma Scale
IQR	Interquartile range
IRB	Institutional review board
NMBA	Neuromuscular blocking agent
RSI	Rapid sequence intubation

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