Patient Safety during Rapid Sequence Intubation When Using Succinylcholine Instead of Nondepolarizing Paralytic Agents: Should We Change a Common Rapid Sequence Intubation Pathway?

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Background: Succinylcholine is a depolarizing agent used for rapid sequence intubation (RIS). While the agent is the most widely used drug of choice in most emergency departments (EDs), the adverse effect profile is lengthy compared to nondepolarizing paralytic agents included rocuronium and vecuronium. Objectives: Our objective in this analysis is to detect potential safety signals and differences in safety related outcomes between patients that received succinylcholine compared to those that received rocuronium or vecuronium when undergoing RSI. Specifically, we asked whether there was a difference in all-cause mortality, whether succinylcholine was used in patient later found to have contraindications to the medication, as well as differences in the rates of rescue airway or difficult airway algorithms utilized. Methods: We utilize two clinical cases as a framework to review adverse events among ED patients undergoing RSI when using succinylcholine compared to nondepolarizing agents over a 7 years’ period at our institution as part of a quality review project. The review is retrospective and does not allow us to link adverse events specifically with drug but, instead, considers aggregate level event frequency. Results: From January 31, 2013, to January 31, 2018, there were 36,059 intubations with paralytics in the ED (75.39% with succinylcholine and 24.61% with rocuronium or vecuronium). There was no evidence of death or associated adverse events in 98.49% of patients. Of 36,059 intubations, 14 patients expired, representing 0.039% of all RSI encounters. There were 39/100,000 total deaths during RSI events. There was a higher rate of mortality in the combined rocuronium/vecuronium group (90/100,000) compared to the sample of patients intubated with succinylcholine (22/100,000). Conclusions: While the succinylcholine adverse effect profile is concerning, data from our institution does not support removal of the agent as an available option for RSI as the mortality rate among patients receiving succinylcholine was lower than that of patients receiving non-depolarizing agents. Patient level data will be needed in future work to further understand why the all-cause mortality rate was higher in the group receiving rocuronium or vecuronium and whether those patients had increased risk of mortality from underlying disease at time of presentation.

Keywords: Intubation, rapid sequence intubation, succinylcholine

INTRODUCTION

Rapid sequence intubation (RSI) usually involves the use of a paralytic agent. Widely available choices include depolarizing (succinylcholine) or nondepolarizing agents (rocuronium and vecuronium).

Succinylcholine is used more often by most emergency medicine providers even though there are more known adverse events documented.[1,2] The drug is still frequently used, likely secondary to a perceived decreased risk gained from a shorter half-life during high risk airway intubation compared to the nondepolarizing agents.

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Currently, the added benefits of the drug with a short half-life and the known risks of the same drug in patients that are likely to present to the emergency department (ED) (e.g., those that may have hyperkalemia) compared to the nondepolarizing class of agents, which have a longer half-life but less complex set of contraindications, remains unclear.

In this analysis, we examine 6 years of data from RSI events in our ED and ask whether the risk profile of succinylcholine utilization outweighs benefits when another class of paralytic agents is equally and readily available.

This is a retrospective review of data and only examines patterns of mortality associated with paralytic use to identify potential hypotheses for future prospective study.

**Succinylcholine pharmacology**

Succinylcholine acts by binding nicotinic acetylcholine receptors (AChRs) that are located at the neuromuscular junction and cause depolarization at that junction. Succinylcholine differs from other paralytics used in RSI in that succinylcholine binds to the AChR causing depolarization with an immediate resistance to repeated depolarization facilitating paralysis. Other classes of paralytics used in RSI function to compete with the native acetylcholine for the AChRs, resulting in paralysis secondary to lack of neuromuscular junction depolarization.\(^{[4,5]}\)

The difference in these two mechanisms accounts for the associated rise in serum potassium 0.05–1.0 mEq/L after succinylcholine administration.\(^{[4,5]}\)

A literature search for comparisons of reported adverse events in patients undergoing RSI with succinylcholine compared to rocuronium/vecuronium was performed. Using the search terms of “adverse events,” “rapid sequence intubation,” and “succinylcholine” there were 100 papers found. A second search using the search criteria of “adverse events,” “rapid sequence intubation,” and “rocuronium” resulted in 57 papers. A third search using the search criteria of “adverse events,” “rapid sequence intubation,” and “vecuronium” resulted in 25 papers. A total of 20 papers were fully reviewed as they were found to most relevant to the paralytics being examined for adverse events in various patient populations.

One comparison study found that “although succinylcholine has a faster onset and provided more relaxation, the difference has no clinical significance.”\(^{[3]}\) A review article compared four studies and concluded that succinylcholine should remain the drug of choice for ED RSI unless there are contraindications to its usage because of the perceived risk of gastric content aspiration with the nondepolarizing paralytics, secondary to prolonged bag-valve-mask use.\(^{[4]}\)

Three of the reviewed papers detailed the perceived risk of using nondepolarizing neuromuscular blockers instead of succinylcholine in RSI. Laurin et al. conclude that rocuronium is not ideal for use in the ED because of the 2 min delayed onset of action compared to succinylcholine. The perceived risk of this slow onset is the need to provide bag-valve-mask ventilations for longer to prevent desaturation. There were no clinically relevant data presented to support this claim.

Also noted by this article was the increased risk of gastric insufflation, vomiting, and pulmonary aspiration secondary to the increased amount of time spent provide bag-valve-mask ventilations prior to intubations, though this was not quantified in the study.\(^{[3]}\) The authors also noted that the effects of vecuronium are longer than succinylcholine and would leave the patient unable to initiate spontaneous respiration for longer period of time compared to succinylcholine in the event of a failed intubation.\(^{[3]}\)

Most experts agree that bag-valve-mask ventilation should not be a part of standard RSI procedure and not performed prior to laryngoscopy once paralysis has been achieved.

**Succinylcholine prescriber information**

Review of the package insert for succinylcholine identified adverse events and contraindications to the drugs’ use. The adverse events documented were apnea, bradycardia, asystole, anaphylaxis, and hyperkalemia.\(^{[2,3]}\)

Absolute contraindications include: Hypersensitivity to drug, malignant hyperthermia history, myopathy, major trauma or acute burns, extensive muscular denervation, upper motor neuron injury, angle closure glaucoma, or penetrating eye injury.

Relative contraindications include: Pseudocholinesterase deficiency, neuromuscular disease, myasthenia gravis, Eaton-Lambert Syndrome, pulmonary disease, severe anaphylactic reaction by history, severe renal impairment, electrolyte abnormalities, hyperkalemia, cardiovascular disease, arrhythmias, severe hypothermia, febrile, chronic abdominal infections, subarachnoid hemorrhage, nerve degeneration, spinal cord injury, paraplegia, fractures, muscle spasm, or pediatric patients.\(^{[4,6,7]}\)

**METHODS**

We initiated a quality review project to ensure Tampa General Hospital ED patients undergo best practice RSI with appropriate drug selection.

Patients who underwent RSI with succinylcholine, rocuronium, or vecuronium over a 5 years’ time period between January 31, 2013, and January 31, 2018 were included in the review. We asked, what is the rate of adverse events, including death, when using succinylcholine as a paralytic agent in RIS compared to the rate of adverse events, including death, when compared to rocuronium and vecuronium in RIS? Given the complex adverse event profile and list of contraindications, we wanted to know if there was any remaining clinical value in continuing use of succinylcholine in the ED during RSI when other paralytics are available. If there is any clinically significant value-add to succinylcholine utilization given that these other paralytic agents are available.

In addition, we examined the rate of other adverse events, such as the utilization of the difficult airway pathway.
using escalation of the intubation procedure to the use of a bronchoscopy cart with video monitor for assistance. We also reviewed the pretest probability of contraindications to succinylcholine use in the ED patient population and examine whether the presence of a contraindication to succinylcholine increased the rate of all-cause mortality in our ED sample.

More specifically, we asked the following questions:

**Question 1: All-cause mortality rate associated with use of paralytic agent**

What is the rate of all-cause mortality during RIS when succinylcholine is used as a paralytic in ED patients from January 31, 2013 to January 31, 2018 (a 5-year period)? What is the rate of all-cause mortality during RIS when rocuronium is used as a paralytic in ED patients from January 31, 2013, to January 31, 2018? What is the rate of all-cause mortality during RIS when vecuronium is used as a paralytic in ED patients from January 31, 2013, to January 31, 2018?

**Question 2: Utilization of succinylcholine in contraindicated patients**

Succinylcholine has a complex profile of contraindications that were discussed above. Often during RSI, the intubating provider does not know the medical history of the patient. Downstream of the intubation, the medical history may become clearer with time to examine the medical record. At times, the revealed medical history includes contraindications to succinylcholine utilization that could increase the likelihood of adverse events that were not known during intubation and selection of paralytic agent.

We determined the contraindicated succinylcholine utilization rate, defined as the rate of succinylcholine use in patients with end stage renal disease (ESRD) or hyperkalemia, as well as the number of cases in which succinylcholine was used in the setting of known contraindications.

**Question 3: Need for rescue airway**

The utilization of ultimate rescue airway may be a proxy marker for a difficult intubation secondary to paralytic agent. While many factors may be associated with cricothyroidotomy during RSI, one of those might be the chosen paralytic. To look for general patterns in risk, we asked what the rate of cricothyroidotomy was in patients receiving succinylcholine during RSI compared to those who received rocuronium or vecuronium.

We examined, as a proxy for rescue airway, the rate of all bronchoscopy use during endotracheal intubation by emergency medicine physician in patients that received succinylcholine, from January 31, 2013, to January 31, 2018 (a 5-year period) as well as the rate of all bronchoscopy use during endotracheal intubation by emergency medicine physician in patients that received succinylcholine, cricothyroidotomy during RIS when succinylcholine is used as a paralytic in ED patients from January 31, 2013, to January 31, 2018 (a 5-year period).

**RESULTS**

From January 31, 2013, to January 31, 2018, there were 36,059 intubations with paralytics in the ED. 75.39% of these intubations were completed with succinylcholine and 24.61% with rocuronium or vecuronium [Table 1]. Overall, there is no evidence of death or associated adverse events in 98.49% of patients. Of 36,059 intubations, 14 patients expired, representing 0.039% of all RSI encounters. There were 39/100,000 total deaths during RSI events.

**Question 1: All-cause mortality rate associated with use of paralytic agent**

The overall mortality rate during RSI was 39/100,000 RSI encounters. RSI events with succinylcholine were associated with 22 mortality events/100,000 RSI encounters, while rocuronium was associated with 75 mortality events/100,000 RSI encounters and vecuronium was 230 events/100,000 encounters. Combining rocuronium and vecuronium, the associated mortality rate during intubation was 90 events/100,000 encounters [Table 1 and Figure 1].

**Question 2: Utilization of succinylcholine in contraindicated patients**

We identified 2713 patients that presented to the ED with a history of ESRD and requiring intubation, approximately 7.52% of all intubated patients.

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**Figure 1: Boxed warning[6]**

**WARNING**

Risk of cardiac arrest from hyperkalemic rhabdomyolysis

There have been rare reports of acute rhabdomyolysis with hyperkalemia by ventricular dysrhythmias, cardiac arrest, and death after the administration of succinylcholine to apparently healthy children who were subsequently found to have undiagnosed skeletal muscle myopathy, most frequently Duchenne’s muscular dystrophy. This syndrome often presents as peaked T-waves and sudden cardiac arrest within minutes after the administration of the drug in healthy appearing children (usually, but not exclusively, males, and most frequently 8 years of age or younger). There have also been reports in adolescents. Therefore, when a healthy appearing infant or child develops cardiac arrest soon after the administration of succinylcholine not felt to be due to inadequate ventilation, oxygenation, or anesthetic overdose, immediate treatment for hyperkalemia should be instituted. This should include administration of intravenous calcium, bicarbonate, and glucose with insulin, with hyperventilation. Due to the abrupt onset of this syndrome, routine resuscitative measures are likely to be unsuccessful. However, extraordinary and prolonged resuscitative efforts have resulted in successful resuscitation in some reported cases. In addition, in the presence of signs of malignant hyperthermia, appropriate treatment should be instituted concurrently. Since there may be no signs or symptoms to alert the practitioner to which patients are at risk, it is recommended that the use of succinylcholine in children should be reserved for emergency intubation or instances where immediate securing of the airway is necessary, for example, laryngospasm, difficult airway, full stomach, or for intramuscular use when a suitable vein is inaccessible (see precautions: pediatric use and dosage and administration).
Eight percent of the patients intubated with succinylcholine also had ESRD, while 15% of the patients intubated with rocuronium had ESRD. 6% of patients with vecuronium had ESRD and when vecuronium and rocuronium are combined, 6% of the nondepolarizing group also had ESRD. Of all ESRD patients, 80% were intubated using succinylcholine while 20% of all ESRD patients that required RSI underwent intubation with rocuronium or vecuronium [Table 2].

One thousand six hundred and ninety-six individual adult ED patients out of 204,123 individual adult ED patients (0.83% of all ED encounters or 830/100,000) were diagnosed with hyperkalemia in the ED during the study.

Eight hundred and forty-five patients presented to the ED during the period of analysis and also had hyperkalemia diagnosed during the same ED encounter (2.34% of all patients that underwent RSI or 2340/100,000).

Of these patients 76% were intubated using succinylcholine and 24% were intubated with rocuronium or vecuronium.

**Question 3: Need for rescue airway**
The total number patients that required the utilization of a difficult airway algorithm as measured by the utilization of video bronchoscopy was 530 patients during RSI encounter (1.5% of all intubated patient or 1500/100,000). Of the 27,186 patients intubated using succinylcholine 219 required an emergent airway this was 0.81% of all succinylcholine intubations. Of the 8873 patients intubated with rocuronium or vecuronium 311 required an emergent airway, this was 3.5% of all intubations using rocuronium or vecuronium [Table 3].

**DISCUSSION**
Patients undergoing RSI in the ED represent many of the most critical patients seen in the department. The decision to intubate a patient in the ED is often made quickly with very little information regarding the past medical history. Currently, emergency medicine physicians chose between depolarizing (succinylcholine) and nondepolarizing paralytic agents (rocuronium and vecuronium) at the time of intubation. At our institution, all three medications are readily available during resuscitation.

Out of 36,059 number of patients intubated in 5 years, 27,186 patients received succinylcholine and 8873 patients received rocuronium or vecuronium. The culture among ED physicians and staff at this institution is often to use succinylcholine as a default paralytic agent, often with the pharmacist at bedside in the resuscitation bay already holding a vile of succinylcholine and awaiting the order from the physician to prepare drug.

The readily available default nature of succinylcholine utilization at our facility likely accounts for the lower rates of adverse outcomes when comparing patients intubated with either succinylcholine (22/100,000 deaths) to rocuronium (75/100,000 deaths) at our site. Rocuronium and vecuronium appear reserved for only the known sickest patients or are preferably used by only a handful of physicians as the default agent, creating a significant selection bias.

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**Table 1: All-cause mortality associated with paralytic agent during rapid sequence intubation**

| Paralytic Agent     | Total Intubations | Intubation by Paralytic | Number of Deaths | Percentage Mortality | Rate per 100,000 |
|---------------------|-------------------|-------------------------|------------------|----------------------|-----------------|
| Succinylcholine     | 27186             | 75.39                   | 6                | 0.02                 | 22              |
| Rocuronium          | 8003              | 24.61                   | 6                | 0.07                 | 75              |
| Vecuronium          | 870               | 2.41                    | 2                | 0.23                 | 230             |
| Rocuronium or Vecuronium | 8873       | 24.61                   | 8                | 0.09                 | 90              |
| Total               | 36059             | 100                     | 14               | 0.04                 | 39              |

**Table 2: The association between end-stage renal disease and rapid sequence intubation**

| Paralytic Agent     | Number of Patients with ESRD | Percent of Patients With ESRD | Percent of Patients With ESRD Intubated with Each Paralytic |
|---------------------|-----------------------------|-------------------------------|-------------------------------------------------------------|
| Succinylcholine     | 2173                        | 7.99                          | 80.1                                                        |
| Rocuronium          | 402                         | 5.02                          | 14.82                                                       |
| Vecuronium          | 138                         | 15.86                         | 5.09                                                        |
| Rocuronium or Vecuronium | 540               | 6.09                          | 19.9                                                        |
| Total               | 2713                        | 7.52                          | 100                                                         |

ESRD: End-stage renal disease

**Table 3: Rescue airway and paralytic**

| Paralytic Agent     | Percent of Patients Requiring Bronchoscopy per Paralytic | Bronchoscopy Rate per 100,000 Encounters |
|---------------------|----------------------------------------------------------|-----------------------------------------|
| Succinylcholine     | 0.81                                                     | 800                                     |
| Rocuronium          | 0.9                                                      | 890                                     |
| Vecuronium          | 27.47                                                    | 27000                                   |
| Rocuronium or Vecuronium | 3.51                  | 3500                                   |
| Total               | 1.47                                                     | 1460                                    |
toward succinylcholine adverse events appearing more favorable.

The purpose of this review was to look for patterns in retrospective data, not to formally disprove a specific hypothesis. Instead, this analysis generates hypotheses to explain the data we observed, such as an appearance that succinylcholine utilization was not associated with more adverse outcomes than rocuronium and inferences as to why the associated mortality rate associated with rocuronium use was higher.

Further analysis should include data abstracted in a similar manner from other EDs, prospective observation to observe correlation between drug choice and adverse events, and a review of physician ordering behavior over the same retrospective 5 years’ period. In addition, the patient level case review might reveal decision making strategies employed by the ordering provider when using rocuronium instead of succinylcholine.

The pretest probability of ESRD and possible hyperkalemia in the peri-intubation period as well as the complex and lengthy adverse event profile detailed in the boxed warning continue to concern these authors when nondepolarizing agents are also available in the setting of RSI, especially as video intubation devices become more readily available. The option for awake intubations in patients where concern exists for the length of paralytic period should also be considered. More patient safety-oriented analysis of succinylcholine use compared to nondepolarizing agents is needed to support the continued inclusion of succinylcholine in RSI pathways.

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Conflicts of interest
There are no conflicts of interest.

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