JPPT | Retrospective Multicenter Observational Study

Current Practices and Safety of Medication Use During Pediatric Rapid Sequence Intubation

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OBJECTIVES This study aimed to characterize medication-related practices during and immediately following rapid sequence intubation (RSI) in pediatric care units across the United States and to evaluate adverse drug events.

METHODS This was a multicenter, observational study of medication practices surrounding intubation in pediatric and neonatal intensive care unit (NICU) and emergency department patients across the United States.

RESULTS A total of 172 patients from 13 geographically diverse institutions were included. Overall, 24%, 69%, and 50% received preinduction, induction, and neuromuscular blockade, respectively. Induction and neuromuscular blocking agent (NMBA) use was low in NICU patients (52% and 23%, respectively), whereas nearly all patients intubated outside of the NICU received both (98% and 95%, respectively). NICU patients who received RSI medications were older and weighed more. Despite infrequent use of atropine (21%), only 3 patients developed bradycardia after RSI. Of the 119 patients who received an induction agent, fentanyl (67%) and midazolam (34%) were administered most frequently. Hypotension and hypertension occurred in 23% and 24% of patients, respectively, but were not associated with a single induction agent. Etomidate use was low and not associated with development of adrenal insufficiency. Rocuronium was the most used NMBA (78%). Succinylcholine use was low (11%) and administered despite hyperkalemia in 2 patients. Postintubation sedation and analgesia were not used or inadequate based on timing of initiation in many patients who received a non-depolarizing NMBA.

CONCLUSIONS Medication practices surrounding pediatric RSI vary across the United States and may be influenced by patient location, age, and weight.

ABBREVIATIONS AHA, American Heart Association; CRF, case report form; ED, emergency department; MAP, mean arterial pressure; NICU, neonatal intensive care units; NMBA, neuromuscular blocking agent; RSI, rapid sequence intubation; SBP, systolic blood pressure

KEYWORDS analgesia; anesthesia; child; hypnotics and sedatives; neonatal; neuromuscular blocking agents; rapid sequence induction and intubation

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Introduction

Rapid sequence intubation (RSI) is an advanced airway management technique that most often involves synchronized administration of a sedative and neuromuscular blocking agent (NMBA) to induce unconsciousness and motor paralysis for the purpose of endotracheal intubation.[1,2] Administration of these agents is recommended to facilitate endotracheal intubation by providing an optimal airway environment for the endotracheal tube to be inserted quickly and successfully, while mitigating the risk of complications.

Several controversies exist regarding the most suitable agents and medication doses warranted during each step of RSI.[2–5] Medications given prior to the induction agent, or preinduction medications, like atropine, have historically been used to prevent the deleterious effects of RSI medications or to attenuate the hemodynamic response elicited by direct stimulation of the airway.[1] A lack of robust data supporting this practice and literature disputing its clinical utility led to a recent change in the American Heart Association (AHA) guidelines for pediatric patients.[6–8] Furthermore, medications used for induction and neuromuscular blockade are often selected based on theoretic benefits or drawbacks that have insufficient supporting data to be either accepted or refuted.[1] Agent selection may also be influenced by previous clinician practices that are no longer supported by current literature.

A recent multicenter, cross-sectional study of 34 sites evaluating RSI practices across the United States

found variability in medication use practices between institutions and among intubating clinicians.[1] Although pediatric patients were captured in this study, the pediatric population accounted for less than 10% (34 of 404) of the entire cohort. As such, a more comprehensive evaluation of RSI practices in this patient population was not possible. Because of the number of controversies related to pediatric RSI, understanding the current practice variability and the effect on outcomes is a necessary step to develop future guidance. This study was conducted to target a pediatric cohort undergoing RSI that was larger than previously reported to characterize medication-related practices during and immediately following RSI across the United States and to investigate associations between outcomes and adverse events based on medication selection when possible.

Materials and Methods

Patients and Study Design. This was a multicenter, retrospective evaluation of pediatric RSI practices across the United States. Recruitment of study sites occurred between September 2020 and December 2020 via electronic mail to pharmacy and pediatric organizations (the complete list can be found in the Supplemental Material).

On the research study date, February 17, 2021, all pediatric patients (birth to age 18 years on the day of endotracheal intubation) admitted to a study institution who were currently intubated on or who had undergone endotracheal intubation earlier in their current hospital admission (on or prior to the study date) were screened for inclusion. Those intubated in the delivery room, operating room, or outside of the study institution were excluded. If multiple endotracheal intubation events occurred during the patient's hospitalization, only data from the first qualifying intubation were included for analysis. Medical records of all eligible patients were retrospectively reviewed and data collection surrounding the patient's endotracheal intubation event occurred during a month-long period by participating sites.

Outcomes. The primary outcome was to describe medication use practices, including the medications administered, dose, and timing and frequency of administration, both during and immediately following RSI in pediatric patients undergoing endotracheal intubation. Secondary objectives were to assess the incidence of post-RSI adverse effects, investigate associations between medication selection and adverse events, and assess post-RSI sedation and analgesia practices.

Data Collection. Institutional demographics were collected for participating sites to characterize hospital size, level of acuity, availability of RSI kits, and effect of national drug shortages and the COVID-19 pandemic on medication use. Patient demographics were collected for individual study patients and included age, sex, and past or current diagnoses/disease states that may have influenced RSI agent selection (i.e., congenital heart disease, sepsis, status epilepticus, renal failure, traumatic brain injury, elevated intracranial pressure, cirrhosis, rhabdomyolysis, stroke, or trauma).

Data points to assess primary and secondary outcomes included medical specialty of the intubating clinician during the first endotracheal intubation attempt, number of intubation attempts, location at time of intubation, reason for intubation, and all medications administered for RSI, including preinduction, induction, and NMBA. Atropine use per current and previous AHA Pediatric Advanced Life Support Guidelines was also collected.[7,8] Current guidelines report there is no evidence to support the routine use of atropine as preinduction to prevent bradycardia in emergency pediatric intubations.[7] However, it may be considered in situations when there is an increased risk of bradycardia.[7] Prior to 2015, atropine was recommended as a preinduction agent for infants younger than 1 year, children ages 1 to 5 years of age receiving succinylcholine, or adolescents receiving a second dose of succinylcholine.[8] Dose and timing of administration for RSI medications were collected. Study sites were instructed to use their medication administration record or code/RSI narrator for nursing documentation of administration times. Sedation and analgesia medications administered within the first 120 minutes after RSI were collected to evaluate for variability and occurrence of delays, especially in those who received a non-depolarizing NMBA during RSI given their extended duration of action beyond that of the induction agents used.

Vital signs were collected and patients were evaluated for hemodynamic derangements at baseline (immediately prior to intubation) and within 60 minutes after intubation (highest and lowest systolic blood pressure [SBP], mean arterial pressure [MAP], and heart rate). Hypotension was defined as SBP or MAP less than the fifth percentile for patient age/sex/height (Supplemental Table S1), administration of a fluid bolus >5 mL/kg, or requiring the initiation of vasopressors. Hypertension was defined as a SBP or MAP increase of 20% from baseline or requiring the initiation of an antihypertensive agent. Hypertension is less well defined in the pediatric population, and therefore this definition was chosen to be consistent with the previous published cross-sectional RSI study evaluating medication selection.[1] Bradycardia was defined as heart rate <100 bpm for patients ages 0 to <3 years; <60 bpm for patients ages 3 to <9 years; and <50 bpm for patients ages 9 to 17 years.[9] Tachycardia/tachyarrhythmia was defined as requiring antiarrhythmics or cardioversion. Additional adverse events collected during the first 60 minutes after RSI were the occurrence of chest wall rigidity or cardiac arrest.

Adverse events assessed during the first 24 hours after RSI were the occurrence of hyperkalemia or adrenal

insufficiency that was not present at baseline, or the occurrence of malignant hyperthermia. Hyperkalemia was defined as a potassium concentration of 5.6 to 6.9 mEq/L if age was greater than 1 month or a potassium concentration of 6.1 to 6.9 mEq/L if age was less than or equal to 1 month. Severe hyperkalemia was defined as a potassium concentration ≥7 mEq/L. Adrenal insufficiency was defined as a failure of cosyntropin stimulation test to increase baseline cortisol by 9 mcg/dL, the need for stress dose corticosteroids, or the need for the initiation of continuous vasopressors after RSI.

Data were collected using a standardized case report form (CRF) in a secure REDCap (research electronic data capture) database that was developed and maintained by the coordinating site. Prior to the study date, study investigators from all study sites tested the CRF and provided feedback. Also, conference calls were held with all site investigators to review the data collection tool and discuss each individual data collection point to prevent heterogeneity in data collection between individual study investigators and/or sites. The CRF was refined and clarifications were made as a result of the feedback provided and discussion from conference call sessions prior to the study date. The final CRF was available to all investigators on the study date. Throughout the study data collection period, the coordinating site investigators were available for questions and clarifications. Any clarifications were immediately disseminated to all study sites via email to reduce variability in data collection.

Data Analysis. Data are reported using descriptive statistics with number (%) for categoric data and mean (± SD) or median (IQR) for continuous data. Continuous variables were assessed for normality. Differences between continuous data were compared using Wilcoxon rank sum. Differences between categoric variables between groups were compared using χ^2 analysis or Fisher exact test when appropriate. All data were analyzed using Stata, version 17.0 (StataCorp, College Station, TX).

Results

A total of 172 patients from 13 geographically diverse institutions were included for analysis. Nearly all participating hospitals were university teaching hospitals (84.6%) and trauma centers (91%). Most institutions were either a children's hospital within an adult hospital (46.2%) or a stand-alone children's hospital (46.2%). All sites had a pediatric intensive care unit and pediatric emergency department (ED). Eleven sites (85%) had a neonatal intensive care unit (NICU), and 10 sites (77%) had a pediatric cardiac intensive care unit. Nearly half (45%) of the patients were age <4 weeks at the time of intubation, and 63% were intubated in the NICU. Critical care clinicians intubated patients most frequently (84%), and respiratory failure was the most common reason for intubation (74%). Complete institution, patient, and intubation demographics are included in Tables 1, 2, and 3, respectively.

Preinduction, Induction, and NMBA. Of the 172 patients included, 24%, 69%, and 50% received preinduction, induction, and an NMBA, respectively. All patients who received an NMBA received an induction agent; however, 34 patients (20%) received an induction agent alone. Details regarding induction agents used alone or in combination can be found in Supplemental Table S2. In general, medication doses were consistent with the usual recommendations provided in medication references and prescribing information. Among the 68 patients (40%) who required multiple intubation attempts, only 10 patients required repeat doses of RSI medications or an alternative RSI medication. Therefore, data were analyzed and are presented for RSI medications used during the first intubation attempt only. Details related to all RSI medications administered and medication doses can be found in Table 4.

In the 41 patients who received preinduction, atropine was administered most frequently (36 of 41; 88%) at a median dose of 0.02 mg/kg (IQR, 0.02–0.02). In this cohort, 136 patients met the prior AHA Pediatric Advanced Life Support atropine recommendations,[8] of whom 35 (26%) received atropine (all meeting criteria for age <1 year). One patient not meeting criteria received atropine. Using the current recommendations (atropine may be considered in situations when there is an increased risk of bradycardia [e.g., when giving succinylcholine as an NMBA to facilitate intubation]),[7] 9 patients received succinylcholine, of whom 5 (55.5%) received atropine for preinduction. Further, among the 8 patients who had bradycardia at baseline, only 2 patients (25%) received atropine for preinduction.

Of the 119 patients who received an induction agent, fentanyl was administered most frequently (80 of 119; 67%) at a median dose of 1.16 mcg/kg (IQR, 0.99–2.0), followed by midazolam (40 of 119; 34%) at a median dose of 0.09 mg/kg (IQR, 0.05–0.1). Ketamine was administered to 18 patients, of whom 4 (22%) had a diagnosis of congenital heart disease, 3 (17%) had a diagnosis of sepsis, and 1 (6%) had a diagnosis of status epilepticus. Of the 10 patients who had hypotension at baseline, only 1 patient received ketamine for induction. No patients who had a diagnosis of traumatic brain injury or elevated intracranial pressure at the time of RSI received ketamine for induction. Etomidate was administered to 11 patients, of whom 1 patient (9%) had a diagnosis of sepsis.

In the 86 patients who received an NMBA, a nondepolarizing NMBA was administered most frequently (79 of 86; 92%). Specifically, rocuronium was administered in 67 patients (78%) at a median dose of 1.03 mg/kg (IQR, 0.99–1.2). Overall use of succinylcholine was low in only 9 patients (11%); however, 2 of these patients (22%) had a contraindication for use, which was

Table 1. Institution Demographics

Variable	Value, n (%)
Total	13
Type of institution	
University teaching	11 (84.6)
Community teaching	1 (7.8)
Community	1 (7.8)
Institution patient population	
Children's hospital within an adult hospital	6 (46.2)
Stand-alone children's hospital	6 (46.2)
Other*	1 (7.8)
Total pediatric and neonatal beds	
≤150	7 (53.8)
151–300	2 (15.4)
>300	4 (30.8)
NICU beds	
None	2 (15.4)
21–50	3 (23.1)
>50	8 (61.5)
PICU beds	
1–20	6 (46.2)
21–50	6 (46.2)
>50	1 (7.8)
PCICU beds	
None	3 (23.1)
0–10	1 (7.8)
11–20	7 (53.8)
21–50	2 (15.4)
Pediatric ED beds	
1–20	4 (30.8)
21–50	6 (46.2)
>50	3 (23.1)
Trauma designation (n = 12)†	12 (90.9)
Level I	9 (75)
Level II	3 (25)
Neonatal care unit designation (n = 11)	
Level II	1 (9.1)
Level III	2 (18.2)
Level IV	8 (72.7)
RSI kits available	
General pediatric ward	5 (38.5)
ICU (PICU, PCICU, NICU)	8 (61.5)
ED	10 (76.9)
Do you feel usual RSI practices have been affected by:	
COVID-19‡	9 (69.2)
Drug shortages in the last 12 mo	0 (0)

ED, emergency department; ICU, intensive care unit; NICU, neonatal intensive care unit; PCICU, pediatric cardiac intensive care unit; PICU, pediatric intensive care unit; RSI, rapid sequence intubation

* One institution included patients from a pediatric hospital and an adult hospital that admits pediatrics patients within their health care system.

† American College of Surgeons Designation.

‡ Reasons included: units converted to adult units, limited number of staff in the room during RSI, change in RSI kit medications (added controlled substances), more standardized RSI medications, delays in RSI due to personal protective equipment garbing, delayed admissions.

baseline hyperkalemia at the time of RSI. No patients with baseline bradycardia received succinylcholine.

A high proportion of patients in the NICU did not receive medications for RSI; therefore, intubation events were separated into those events occurring in the NICU (n = 108) and events occurring in areas outside of the NICU (n = 64). Of the NICU patients who received at least 1 RSI medication (56 of 108; 52%), 29%, 52%, and 23% of patients received preinduction, induction, and an NMBA, respectively. Of the non-NICU patients who received at least 1 RSI medication (63 of 64; 98%), 16%, 98%, and 95% of patients received preinduction, induction, and an NMBA, respectively. In the NICU, patients who received at least 1 RSI medication were older based on postnatal age (median, 22 days [IQR, 4.5–60] vs 2 days [IQR, 1–16]) and corrected gestational age (median, 34.5 days [IQR, 30–38] vs 29.5 days [IQR, 27–33]) and weighed more (median, 2.6 kg [IQR, 1.3–3.6] vs 1.1 kg [IQR, 0.8–1.9]) compared with patients who did not receive a medication for RSI ($p < 0.01$ for all comparisons). Moreover, NICU patients who received both an induction and an NMBA in combination (25 of 56; 45%) were older based on postnatal age only (median, 35 days [IQR, 16–120] vs 8 days [IQR, 1–35]) and weighed more (median, 3.3 kg [IQR, 2.1–4] vs 1.7 days [IQR, 1.2–2.9]), compared with patients who received induction alone (31 of 56; 55%; $p < 0.01$ for both comparisons). The RSI medications administered in NICU and non-NICU patients are further described in Table 4.

Adverse Events. An adverse event occurred in 76 of 172 patients (44.2%), and 26 of 76 patients (34.2%) had more than 1 adverse event reported (Table 5). There was no association between age and number of adverse events ($p = 0.62$); however, initial diagnosis of congenital heart disease was associated with a higher number of adverse events occurring ($p = 0.04$). Patients in the NICU had fewer adverse events occurring than non-NICU patients, 36 of 108 (33%) vs 4 of 64 (67%), respectively, $p < 0.001$. Hypotension occurred in 39 of 172 patients (23%); however, no single induction agent was associated with the occurrence of hypotension ($p > 0.05$ for comparisons between those who received fentanyl, midazolam, ketamine, etomidate, propofol, or morphine). Hypertension occurred in 42 of 172 patients (24%). Once again, no single induction agent was associated with the occurrence of hypertension, and only 1 patient required an antihypertensive medication (this patient did not receive RSI medications). Despite the infrequent use of atropine in our study population, only 3 patients developed bradycardia after RSI, all of whom were younger than 3 years. None of these patients received succinylcholine for neuromuscular blockade, and 1 patient received atropine for preinduction. Immediately following RSI, 1 patient was reported to have developed chest wall rigidity; however, no medications were given at the time of RSI. Two patients

Table 2. Patient Demographics

Variables	Value
Total patients, n	172
Age, median (IQR)*	
<4 wk (n = 78; 45.3%), days	2 (1–9)
4 to <8 wk (n = 19; 11%), wk	5 (4–6)
2 to <12 mo (n = 39; 22.7%), mo	4 (3–5)
≥1 yr (n = 36; 20.9%), yr	6.5 (3–14)
Premature at the time of intubation, n (%)†	85 (49.4)
Weight, median (IQR), kg	3 (1.3–7)
Sex, n (%)	
Male	88 (51.2)
Female	84 (48.8)
Diagnosis, n (%)‡	105 (61.0)
Congenital heart disease	40 (38.1)
Sepsis	36 (34.3)
Status epilepticus	10 (9.5)
Renal failure	7 (6.7)
Traumatic brain injury	4 (3.8)
Elevated intracranial pressure	3 (2.9)
Cirrhosis	2 (1.9)
Rhabdomyolysis	1 (1)
Stroke	1 (1)
Trauma	1 (1)
Clinical characteristics, n (%)	
Receiving corticosteroids at time of RSI	32 (18.6)
Receiving vasopressors at time of RSI	14 (8.1)
Cardiac arrest at time of RSI	4 (2.3)
Baseline vital signs, n (%)	
Hypotension (n = 155)§	10 (6.5)
Bradycardia, n (%)	8 (4.7)
Age 0 to <3 yr (<100 bpm)	8 of 143 (5.6)
Age 3 to <9 yr (< 60 bpm)	0 of 10
Age 9–17 yr (<50 bpm)	0 of 19
Glasgow Coma Scale, median (IQR) (n = 14)	12.5 (7–14)

RSI, rapid sequence intubation

* Age reported as postnatal age.
† Corrected gestational age <40 weeks at the time of intubation.
‡ Multiple diagnoses were present in some patients.
§ Hypotension defined by patient's age (Supplemental Table S1).

Table 3. Intubation Demographics

Variable	Value, n (%)
Total	172
Location	
NICU	108 (62.8)
PICU	34 (19.8)
PCICU	21 (12.2)
ED	9 (5.2)
Intubating disciplines (n = 171)	
Critical care clinician/intensivist	144 (84.2)
Emergency medicine clinician	10 (5.8)
NICU transport nurse	5 (2.9)
Anesthesiology clinician	5 (2.9)
Respiratory therapist	3 (1.8)
Other	4 (2.3)
Reasons for intubation	
Respiratory failure	128 (74.4)
Inability to protect airway	22 (12.8)
Hemodynamic compromise	10 (5.8)
Surfactant administration	7 (4.1)
Other	5 (2.9)
Number of intubation attempts (n = 171)*	
1	103 (60.2)
2	42 (24.6)
≥3	26 (15.2)

ED, emergency department; NICU, neonatal intensive care unit; PCICU = pediatric cardiac intensive care unit; PICU, pediatric intensive care unit

* Median intubation attempts (IQR) for patients in the NICU was 2 attempts (1–2) and for non-NICU patients was 1 attempt (1–1), p < 0.001.

experienced cardiac arrest after RSI, and no patients experienced malignant hyperthermia.

Within 24 hours of RSI, 7 of 166 patients (4%) experienced new hyperkalemia/severe hyperkalemia. One of these patients received succinylcholine for RSI, and 1 patient was actively in cardiac arrest at the time of intubation. Although 21 patients (12%) had new adrenal insufficiency after RSI, there was no difference between those patients who received etomidate for induction and those who did not. Specifically, 1 of the 11 patients (9%) who received etomidate had new adrenal insufficiency compared with 20 of 131 patients (15%) receiving other induction agents, p = 0.99.

Post-RSI Medication Administration. A total of 81 of 172 patients (47%) received an analgesic or sedative agent within the first 120 minutes after RSI. Specifically, patients in the NICU received an analgesia or sedative agent within the first 120 minutes after RSI less often than non-NICU patients, 25 of 108 (23%) vs 57 of 64 (89%), respectively, p < 0.001. Of the 81 patients who did receive an agent, 32 patients (39.5%) received both a sedative and analgesic, 30 (37%) received an analgesic alone, and 19 (23%) received a sedative alone. The median times from intubation to sedation and/or analgesia administration were 42 minutes (IQR, 15–89) and 37 minutes (IQR, 12–66), respectively. Of the 79 patients who received a non-depolarizing NMBA for RSI, 28 patients (35%) received both a sedative and analgesic, 21 (27%) received an analgesic alone, and 16 (20%) received a sedative alone. The median times from intubation to sedation and analgesia in patients who received a non-depolarizing NMBA were 42 minutes (IQR, 15.5–83) and 41 minutes (IQR, 13–66), respectively. Details regarding post-RSI sedation and analgesia can be found in Supplemental Table S3.

Table 4. Medications Administered During Rapid Sequence Intubation

Medications Used	Total Population, n (%) (N = 172)	NICU, n (%) (n = 108)	Non-NICU, n (%) (n = 64)	Median (IQR) Dose, mg/kg/dose*
Preinduction	41 of 172 (23.8)	31 of 108 (29.2)	10 of 64 (15.6)†	
Atropine	36 of 41(87.8)	30 of 31 (96.8)	6 of 10 (60)	0.02 (0.02–0.02)
Glycopyrrolate	3 of 41 (7.3)	—	3 of 10 (30)	0.005 (0.002–0.01)
Lidocaine	3 of 41 (7.3)	1 of 31 (3.2)	2 of 10 (20)	
IV	2 of 3 (66.7)	—	2 of 10 (20)	0.99 (0.99–1)
ET	1 of 3 (33.3)	1 of 31 (3.2)	—	2.4
Induction	119 of 172 (69.2)	56 of 108 (51.9)‡	63 of 64 (98.4)§	
Fentanyl	80 of 119 (67.2)	46 of 56 (82.1)	34 of 63 (54)	1.16 (0.99–2)¶
Midazolam	40 of 119 (33.6)	24 of 56 (42.9)	16 of 63 (25.4)	0.09 (0.05–0.1)
Ketamine	18 of 119 (15.1)	—	18 of 63 (28.6)	1 (0.99–1.14)
Etomidate	11 of 119 (9.2)	—	11 of 63 (17.5)	0.3 (0.29–0.3)
Propofol	9 of 119 (7.6)	—	9 of 63 (14.3)	0.99 (0.91–1.1)
Morphine	5 of 119 (4.2)	5 of 56 (8.9)	—	0.05 (0.47–0.1)
Lorazepam	1 of 119 (0.8)	1 of 56 (1.8)	—	0.09
NMBA	86 of 172 (50)	25 of 108 (23.1)	61 of 64 (95.3)**	
Rocuronium	67 of 86 (77.9)	11 of 25 (44)	56 of 61 (91.8)	1.03 (0.99–1.2)
Vecuronium	10 of 86 (11.6)	9 of 25 (36)	1 of 61 (1.6)	0.1 (0.1–0.1)
Succinylcholine	9 of 86 (10.5)	5 of 25 (20)	4 of 61 (6.6)	1.8 (1.5–2.1)
Cisatracurium	2 of 86 (2.3)	—	2 of 61 (3.3)	0.2 (0.2–0.3)

ET, endotracheal; IV, intravenous; NICU, neonatal intensive care unit; NMBA, neuromuscular blocking agent

* Weight-based doses were calculated for all patients.
† One patient received both atropine and lidocaine for preinduction.
‡ Induction agents were used alone in 37 cases and in combination in 19 cases (Supplemental Table S2).
§ Induction agents were used alone in 39 cases and in combination in 24 cases (Supplemental Table S2).
¶ Dose in mcg/kg/dose.
** Two patients received both succinylcholine and rocuronium for NMBA administration.

Discussion

This multicenter study confirmed there is significant variability in medication practices for pediatric RSI across the United States. This is likely related to the lack of established best practices, presence of clinical controversies, and a paucity of conclusive data surrounding medication selection during pediatric RSI. We found that medication use and selection often differ based on the patient's location at time of RSI (NICU or non-NICU), age, and weight. Despite the infrequent use of atropine, only 3 patients developed new bradycardia after RSI. The overall use of induction and neuromuscular blockade in the NICU population was low, whereas nearly all patients intubated outside of the NICU received both induction and an NMBA at the time of RSI. Fentanyl and midazolam were the most common induction agents used, and when an NMBA was used it was often a non-depolarizing NMBA, specifically rocuronium. Postintubation sedation and analgesia use was lacking in those who received a non-depolarizing NMBA and, when administered, was often inadequate based on the timing of initiation after RSI.

We identified significant differences in the use of RSI medications for patients in the NICU compared with those outside of the NICU. In the NICU, less than half received induction therapy and less than a quarter received an NMBA, whereas nearly all patients in non-NICU locations received both. The NICU patients who received induction and/or an NMBA were older and weighed more compared with patients who did not receive medications. These results are consistent with a previous retrospective evaluation of the Emergency Airway Registry for Neonates, which found that patients who received both sedation and neuromuscular blockade had older chronologic age, older gestational age, and greater weight at the time of intubation compared with patients who received sedation only or no medications at all.[10] Similarly, another report of 75 pediatric patients found the likelihood of receiving RSI medications increased with increasing age.[11] Specifically, in the neonatal population medication use was more frequent in full-term neonates compared with premature neonates, and within the preterm neonatal population use was associated with greater age and weight.[11] We speculate that the lack of medication administration in patients who are younger and weigh less may be due to the known anatomic complexity of the infant's airway, anticipated difficulty with oxygenation or intubation, or deemed urgency of the endotracheal intubation.[12] There also may be concern that medication-related complications, such as hemodynamic instability or oxygen desaturation, could lead to rapid patient decompensation if the patient is unable to be intubated.[12] However, several reports have indicated that using RSI

Table 5. Adverse Events

Variable	Value, n (%)
Total	172
Any adverse event*	76 of 172 (44.2)
Bradycardia	3 of 162 (1.9)
Age 0 to <3 yr (<100 bpm)	3 of 134 (2.2)
Age 3 to <9 yr (<60 bpm)	0 of 10
Age 9–17 yr (<50 bpm)	0 of 18
Hypotension†	39 of 172 (22.7)
SBP and age definition	25 of 39 (64.1)
Fluid bolus (>5 mL/kg)	19 of 39 (48.7)
Vasopressor initiation	9 of 39 (23.1)
Hypertension	42 of 172 (24.4)
SBP or MAP increase by 20%‡	41 of 116 (35.3)
Antihypertensive initiated	1 of 172 (0.6)
Adrenal insufficiency	21 of 172 (12.2)
Hyperkalemia	3 of 166 (1.8)
Severe hyperkalemia	4 of 166 (2.4)
Cardiac arrest	2 of 172 (1.2)
Chest wall rigidity	1 of 172 (0.6)

MAP, mean arterial pressure; SBP, systolic blood pressure

* Some patients had multiple adverse events occur.
† Some met multiple criteria.
‡ SBP or MAP at baseline and within 60 minutes after RSI was only available in 116 patients.

medications for neonatal intubation improves overall success rates.[10,12,13] Medication use has been shown to improve glottic visualization, decrease the number of attempts needed to intubate, decrease airway trauma, and reduce adverse events. Although heterogeneity in medication administration was noted in our NICU population, we did not identify any consequences of administering RSI medications. It is possible that our sample size was not large enough to detect these differences, resulting in type II error, and therefore our data should be interpreted with caution in relation to patient outcomes and adverse events. However, our data are consistent with other reports and do show that NICU patients received RSI medications without issue, which may help clinicians feel more comfortable using RSI medications.

The previously reported cross-sectional study of RSI medication practices in adult and pediatric (accounting for less than 10% of the population) patients across the United States also found variability in medication practices similar to our study.[1] Although we found that 98% of non-NICU patients received induction and paralytic agents, the previous study found less overall use, 87% and 77%, respectively.[1] Fentanyl use was common in both studies; however, it was used as a preinduction agent more often in the previous study compared with an induction agent in our study. The lack of standardization of fentanyl use and differing categorization limit direct comparisons between studies and patient populations. Etomidate use in general and specifically in sepsis patients was low (1 of 36; 3%) in our study, which differed from the previous study, in which more than half of the patients with sepsis received etomidate (68 of 117; 58%).[1] Non-depolarizing NMBAs were used more frequently in our study, and overall succinylcholine use was low (11%), which is different from the previous report of almost half (47%) of the patients receiving succinylcholine.[1] However, in the pediatric cohort of the previous study, almost all pediatric patients received rocuronium (29 of 31; 94%), which was similar to our non-NICU population (95%) but not our NICU population, where 44% who received an NMBA received rocuronium.[1]

Pediatric patients, and infants in particular, are known to have a more pronounced vagal response to intubation than adults, leading to bradycardia. Although previous recommendations were to use atropine in specific populations, retrospective data have shown no difference in the incidence of bradycardia comparing those who received atropine and those who did not.[8,14] Overall atropine use in our cohort was low despite previous or current criteria for use,[7,8] and only 3 patients had post-RSI bradycardia. Although the current recommendations are to consider atropine with the use of succinylcholine,[7] we found only half of the patients receiving succinylcholine also received atropine, and again, none of these patients developed post-RSI bradycardia.

Despite their potential to cause hypotension, fentanyl and midazolam were the most commonly administered medications for induction, and 24 patients received these agents concomitantly. However, we did not find an association between use of these agents and post-RSI hypotension. Ketamine, etomidate, and propofol were only used outside of the NICU, and morphine was only used in the NICU. Etomidate may be a favorable induction agent given its rapid onset and hemodynamic stability, but is known to cause adrenal insufficiency, particularly with repeated use. There is uncertainty regarding etomidate's effect on patient outcomes, which could explain the limited use in this cohort.[5] There was no difference in the incidence of new adrenal insufficiency in patients who received etomidate compared with those who did not; however, overall etomidate use was low.

Succinylcholine may be a favorable NMBA given its rapid onset and short duration of action; however, its use is not without limitations, especially in the pediatric population. Administration may cause bradycardia and asystole (in extreme cases), hyperkalemia, malignant hyperthermia, and fasciculations. Also, acute rhabdomyolysis with hyperkalemia followed by ventricular dysrhythmias, cardiac arrest, and death have occurred

after use in apparently healthy pediatric patients who were subsequently found to have undiagnosed skeletal muscle myopathy resulting in a boxed warning in the prescribing information.[15] However, the initiation of this boxed warning is also controversial based on a low number of patients reported, confounding use of halothane induction, and variable baseline potassium concentrations, most with hyperkalemia.[16] Regardless, in both our study and the previous cross-sectional study, succinylcholine was given despite contraindications to its use, most commonly hyperkalemia.[1] Because of the retrospective nature of both of these studies, it is difficult to discern whether the presence of hyperkalemia was known at the time of RSI. Overall, it appears that most clinicians are more comfortable with using rocuronium as an alternative because this was commonly used in both studies.

One major concern with rocuronium use is the potential for inadequate post-RSI sedation and analgesia, leading to awareness with paralysis.[1,17] This is particularly concerning in that rocuronium was the most common NMBA used in our study; however, post-RSI sedation was suboptimal. Of those who received a non-depolarizing NMBA, only 35% received both a sedative and analgesic and 20% received a sedative alone (analgesic administration alone does not provide necessary deep sedation) within the first 120 minutes after RSI (55% total). Even more concerning is that the time to medication administration was significantly delayed, at approximately 40 minutes, which likely coincides with the time that the non-depolarizing NMBA was wearing off (duration of action is approximately 30–60 minutes). Because the induction agents most commonly used in this cohort only provide adequate sedation for approximately 15 to 30 minutes, it is likely a time period of awareness with paralysis occurred in several patients. Fewer patients in our study received a sedative following non-depolarizing NMBA for RSI compared with other reports.[1,18] Groth et al[1] reported 72% of patients who received a non-depolarizing NMBA received a sedative within 120 minutes of RSI. Additionally, in a retrospective study of post-RSI sedation in pediatric patients who received etomidate and a non-depolarizing NMBA, Kendrick et al[18] reported 24% of patients received a sedative agent within 15 minutes of etomidate administration, 63% received a sedative agent after 15 minutes but while in the ED, and 13% of patients did not receive any sedative at all. Similarly to our study, median time to additional sedation after induction was approximately 45 minutes, which is inadequate based on the duration of action of the induction agent and concomitant non-depolarizing NMBA.[18] Ensuring adequate sedation during neuromuscular blockade is essential given the known long-term and deleterious effects of awareness with paralysis, such as posttraumatic stress disorder, clinical depression, and complex phobias.[17] Although we did not assess for negative sequelae associated with awareness during paralysis, reports from the ED-AWARENESS study indicate that patients experiencing this phenomenon have a higher degree of perceived threat and vulnerability during their hospital stay and after discharge.[17] Although this study only included adult patients, it seems reasonable to extrapolate these findings to the pediatric and neonatal population. It is a misconception that neonatal patients, particularly premature neonates, will not have negative sequelae from early life events. The negative neurobiologic effects of pain and stress in preterm infants are now well documented, displaying their associations with brain dysmaturation on neuroimaging and effects on neurobehavioral outcomes later in life.[19]

To our knowledge, this is the only study that characterizes medication practices surrounding pediatric RSI across the United States. Strengths of our study include a multicenter design, wide spectrum of children's hospitals across the United States, and distinct analysis of NICU vs non-NICU intubation locations. Our study has limitations, many of which can be attributed to its retrospective nature. In particular, because of the acute care setting and often stressful environment during intubation, medication record documentation during these events may not always be precise or timely. This may have decreased the accuracy of data, especially related to the timing of medication administration, available for collection.

Also, vital sign information immediately prior to intubation may have been obtained in a wide range of time prior to RSI. A limited time prior to RSI was not followed in an effort to limit missing data. However, the information obtained may not be most reflective of the exact hemodynamics prior to RSI. Missing data also existed, limiting the ability to adequately assess every end point for all patients. For example, cortisol concentrations were not available for all patients and were drawn at the discretion of the participating site. Although we had discrete and thought-out definitions to attempt to capture adverse events that may have been associated with RSI medication administration, it is not known if a change in hemodynamics or escalation of care, in some cases, may have occurred because of continuation of a disease process and were not directly related to use of a particular medication. It is also possible that potassium concentrations were reported from a hemolyzed sample, which may have affected this result at baseline or after RSI. Moreover, it is difficult to ensure data integrity at all sites because several different investigators were collecting data across sites. However, we received REDCap administrator support as the coordinating site to build an extensive, detailed, and user-friendly database for data collection and also provided investigators access to the database for testing, held conference calls to review the tool, received

investigator feedback, refined the tool, and answered questions prior to the study date, all to reduce data collection variability.

Based on the cross-sectional nature of the study, it is possible that selection bias occurred based on the clinicians that worked during the study time frame. Also, clinician years of practice experience may have influenced medication selection. There was a significant number of patients who did not receive RSI medications. There are many reasons, previously discussed, that may have led to this occurrence, particularly in the NICU. Additionally, it is possible that some patients did not require RSI medications because of endotracheal intubation occurring during cardiac arrest or in those who are deeply comatose. We did not exclude these patients because our intent was to provide a real-world cross-sectional evaluation of all patients undergoing intubation to report on current RSI medication practices. Exclusion of these patients had the potential to bias the results because some patients meeting these scenarios still received medications.

Study sites reported that the COVID-19 pandemic did alter patient census and staff availability during RSI (limited number of people in the room, therefore usual medication recommendations provided by team members may have been altered by not being directly at the bedside). Also, there were changes made to RSI kits, and standardization of RSI medications occurred that could affect RSI medication selection. However, other influences that may affect drug selection, like drug shortages, were not occurring at the study sites during the study time period. We did not collect information regarding the content of RSI kits for each study site, which limits evaluation of agent selection based on medication availability. Lastly, most of the patients included in the study were intubated in the NICU, which may have skewed our results. To mitigate this, we separated NICU and non-NICU locations in several of our analyses to investigate differences in these populations.

Conclusions

We found that medication practices vary during pediatric RSI across the United States. Medication selection may be influenced by patient location at time of RSI, age, and weight. Moreover, our study highlights the need for improvement in timely sedation and analgesia after RSI given the negative consequences associated with awareness during paralysis. Although guidelines may not account for every situation, the creation of an RSI guideline may diminish the variability in RSI administration and improve overall patient care.

Article Information

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