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ARTICLE

Premedication with neuromuscular blockade and sedation during neonatal intubation is associated with fewer adverse events

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Abstract

Objective To determine the impact of premedication for tracheal intubation (TI) on adverse TI associated events, severe oxygen desaturations, and first attempt success

Study design Retrospective cohort study in neonatal intensive care units (NICU) participating in the National Emergency Airway Registry for Neonates from 10/2014 to 6/2017. Premedication for TI was categorized as sedation with neuromuscular blockade, sedation only, or no medication.

Results 2260 TIs were reported from 11 NICUs. Adverse TI associated events occurred less often in sedation with neuromuscular blockade group (10%) as compared to sedation only (29%), or no medication group (23%), $p < 0.001$. The adjusted odds ratio (aOR) for adverse TI associated events were: sedation with neuromuscular blockade aOR 0.48 (95%CI 0.34–0.65, $p < 0.001$) compared to no medication.

Conclusion Use of sedation with neuromuscular blockade was associated with favorable TI outcomes. This study supports the recommendation for the standard use of sedation with neuromuscular blockade in non-emergency TIs.

Introduction

Neonatal tracheal intubation (TI) is a life-saving, yet high risk, procedure for neonates with respiratory failure. While TI is one of the most common procedures performed in neonatal intensive care units (NICU), limited literature is available to describe current neonatal TI practice, safety and procedural outcomes across NICUs [1–4]. As a result, there are controversies in the practices surrounding TI in NICUs. One of these controversies includes the use of premedication [5].

Tracheal intubations in neonates may be associated with adverse physiologic changes including bradycardia, hypertension, and increases in intracranial pressure. In addition, multiple attempts at TI has been tied to an increased risk for intraventricular hemorrhage for premature infants [6]. A few small studies have shown the use of premedication for TI decreases these adverse physiologic changes during TI [1, 2, 7, 8]. Subsequently, the American Academy of Pediatrics recommended the use of premedication for non-emergent neonatal TI in 2010 [9]. However, the adoption of routine premedication use for neonatal TI remains highly variable among NICUs despite this recommendation. In some NICUs, providers have minimally adopted this practice, while in other NICUs providers routinely use premedication for TI [10–15].

We sought to evaluate the clinical impact of premedication use during neonatal TI on safety and procedural outcomes using a multicenter quality improvement database: National Emergency Airway Registry for Neonates (NEAR4NEOS). Our specific hypotheses were the use of premedication categorized as sedation and neuromuscular blockade use, or sedation only, was associated with a lower occurrence of adverse TI associated events, fewer severe desaturation, and greater first attempt success, as compared to no medication.

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Methods

Setting

This was a retrospective cohort study utilizing a prospectively collected multicenter neonatal TI quality improvement database, NEAR4NEOS, from 11 academic NICUs in North America, 1 NICU from Europe, and 1 NICU from Asia.

Patient selection

Each participating NEAR4NEOS sites obtained their institutional review board approval or exemption as quality improvement. Tracheal intubation data from NICUs between October 2014 and June 2017 were included. The NEAR4NEOS defines encounter as an episode of airway management; course as one approach for intubation defined by device used and/or premedication [1, 4]. For the current study, we only included the first course of each encounter because the characteristics and outcomes of subsequent courses were not independent from the first course. Thus if during an encounter of tracheal intubation, if the first attempt (s) were made without the use of premedication, followed by premedication, only the first course without premedication were included for the analysis. Exclusion criteria were as follows: neonatal TIs performed in the delivery room or outside the NICU, and TIs performed for tracheal tube change (i.e., non-primary TI Encounter). In addition, TIs utilizing only neuromuscular blockade without sedation were excluded.

Data collection and definitions

The NEAR4NEOS collects the patient, provider, and practice characteristics in TI as well as process of care and outcomes including adverse TI associated events (defined below) and oxygen desaturations following standard operational definitions. We consider a TI associated events as an unwanted event (not necessarily avoidable) which occurred as a consequence of intubation, or simply seen during or after the intubation. This needs to be a change from pre-intubation status. The time frame for TI associated events is from the beginning of the course until 20 min after securing airway. Adverse TI associated events were classified into two categories: severe TI associated events and non-severe events [1, 4]. Severe TI associated events were defined as acute significant patient deterioration during TI which included cardiac arrest with/without return of spontaneous circulation, esophageal intubation with delayed recognition (defined as esophageal intubation leading to deterioration in patient condition), emesis with aspiration, hypotension requiring intervention, laryngospasm, pneumothorax/pneumomediastinum, chest compression < 1 min, gum/dental trauma, and direct airway injury. Non-severe TI associated events included mainstem bronchial intubation, esophageal intubation with immediate recognition, emesis without aspiration, hypertension requiring therapy, epistaxis, lip trauma, medication error, dysrhythmia including bradycardia with heart rate less than 60 per minute without chest compressions, and pain and/or agitation requiring additional medication and causing delay in intubation. Mainstem bronchial intubation was considered only when it was confirmed on chest radiograph or recognized after the clinical team secured the tracheal tube. The definition of adverse TI associated events were described in the shared NEAR4NEOS operational definition documents, and each site PI and data coordinator received the training by the Data Coordinating Center. These definitions are available with more details in a prior publication [4].

Severe oxygen desaturations were defined as greater than 20% absolute decrease in oxygen saturation from the highest level [4]. The highest pulse oximetry saturation (SpO2) measurement immediately prior to the first intubation attempt and the lowest measured SpO2 during the first TI course were recorded. This data is collected by the care team at the time of TI on a NEAR4NEOS data form. Each NICU developed their local compliance plan which describes the process for complete and accurate TI data capture in their NICU. The data were entered into secure Research Electronic Data Capture (REDCap) system hosted by Data Coordinating Center [16].

Premedication use was categorized as follows: (1) Sedation with neuromuscular blockade: sedative/narcotic and neuromuscular blockade, (2) Sedation only: sedative/narcotic use without neuromuscular blockade, or (3) No medication. The use of premedication for TI was at the discretion of the care team. If given, the name and dosage of each medication was recorded.

Outcome measures

Our primary outcome was a composite of any adverse TI associated event. This included both severe and non-severe TI associated events. Secondary outcomes were severe oxygen desaturation (≥20% absolute decline in SpO_2) and first attempt success rate.

Statistical methods

No sample size calculation was performed. The study dates were selected to generate the largest possible cohort from the inception of the registry. Statistical analysis was performed using STATA 14.2 (Stata Corp., College Station TX, USA). Summary statistics for patient, provider and practice characteristics were described with frequencies for

categorical variables or median with interquartile range for continuous variables. Chi-square and Kruskal–Wallis tests were applied to compare categorical and continuous variables between three groups- sedation with neuromuscular blockade, sedation only, and no medication.

We developed a generalized estimating equation (GEE) logistic regression model to compare the probability of the primary outcome (occurrence of adverse TI associated events) between the three groups while adjusting for patient, provider and practice factors associated with premedication use. In this model, the dependent variable was the occurrence of adverse TI associated events and the primary exposure variables were sedation with neuromuscular blockade and sedation only. No medication was treated as the reference group. Site level clustering was accounted for by applying an identity correlation structure in the GEE model with adjustment to the standard errors to account for clustering by site. Variables that were associated with premedication use ($p < 0.1$) were included in the multivariable GEE logistic regression models. A two-sided p-value < 0.05 was considered statistically significant.

Sensitivity analyses were further conducted in the following order to address the imbalance in covariates between the three groups (sedation with neuromuscular blockade, sedation only, no medication). First, we limited our analyses to a sub-cohort that included patients with a weight less than 1500 g at the time of TI Encounter. Second, we limited our analyses to a sub-cohort with a birth gestational age < 28 weeks. Third, we excluded the TIs for surfactant administration.

We also addressed the imbalance in patient characteristics by performing a propensity score based analyses. Here we evaluated two groups: sedation with neuromuscular blockade versus no medication. The propensity score model allowed us to control for a large number of covariates. We first performed a logistic regression of sedation with neuromuscular blockade (versus no medication) on age category, weight, birth gestational age, sex, TI indication (ventilation failure, procedure, shock/unstable hemodynamics, surfactant administration, unplanned extubation), provider level (pediatric resident, neonatology fellow, neonatology attending), device type (direct laryngoscopy, video laryngoscopy), oral vs. nasal intubation. The propensity scores were then calculated for each patient as the predicted probability of sedation with neuromuscular blockade, obtained using the fitted logistic regression model. We then performed two analyses [11]. The first analysis utilized the multivariable logistic regression model with the dependent variable as the occurrence of adverse TI associated events and primary exposure variable as the premedication category (sedation with neuromuscular blockade versus no medication). The logistic model also included indicator variables for the second through fourth quantiles of the propensity score. In addition, device was also included as a covariate in the logistic regression model to achieve a sufficient balance on this variable in the statistical model. The second analysis utilized a propensity score matched analysis. With the calculated propensity score, nearest one to one neighbor matching without replacement was performed with a caliper width no greater than 0.2 times the standard deviation of the logit of the propensity score to generate matched cohorts (sedation and neuromuscular blockade vs. no medication) in which covariates are balanced [17]. The sample size for the matched analysis was substantially reduced because of the difficulty in obtaining a match for older infants intubated with video laryngoscopy. After confirming that we had achieved acceptable balance in the covariates, the association between the exposure and the occurrence of adverse TI associated events were assessed using the matched cohort. We presented the most conservative estimate from these sensitivity analyses in the main body of this manuscript while other analyses results were presented as online only contents.

Results

A total of 2736 TI encounters were reported in the study period across the 11 NICUs. Among these, 465 TI encounters were endotracheal tube changes, and 11 TIs documented utilization of paralytics only, resulting 2260 met inclusion criteria. Sedation with neuromuscular blockade was used in 1058 TIs (47%), sedation alone was used in 394 (17%), and no medication was used in 808 (36%). The most commonly used sedative/narcotic was fentanyl (96%) in the sedation with neuromuscular blockade group. There was a broader distribution of medications in the sedation only group: fentanyl only (42%), morphine only (34%), and fentanyl and midazolam (12%). One NICU did not have any TIs which utilized neuromuscular blockade while one NICU utilized sedation with neuromuscular blockade in the majority (83%) of TIs (Fig. 1).

Patient, provider, and practice characteristics

The sedation and neuromuscular blockade group had older chronological age, older gestational age, and larger weight at the time of TI (Table 1). The indications for TI varied significantly between the three groups: The sedation with neuromuscular blockade group included more ventilation failure as a TI indication while the no medication group included more TIs performed for the indications of surfactant administration and unstable hemodynamics. The sedation only group were more likely intubated by resident providers compared to other two groups. The no medication group patients were more likely to be intubated by a neonatology attending despite that only 56% of TIs had

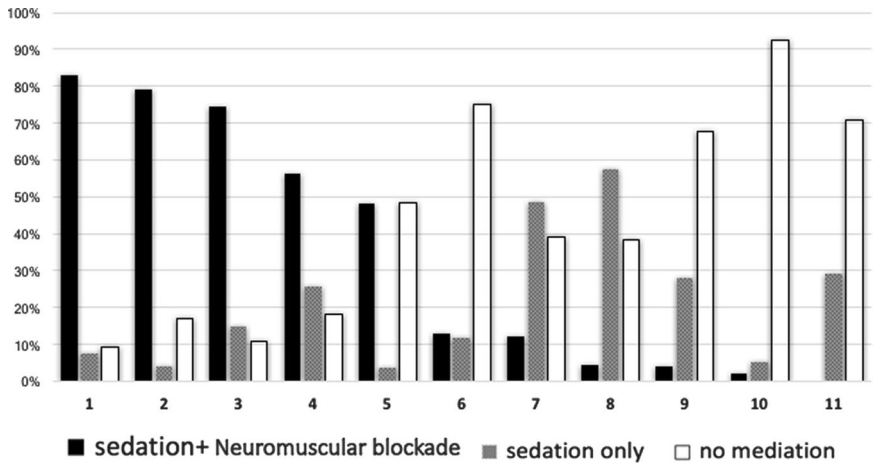

Fig. 1 Site variance in premedication use for tracheal intubation. Footnote NEAR4NEOS site (11 NICUs) variance of using premedication, each number demonstrates individual sites, which are arranged in descending order for percentage of using sedation with neuromuscular blockade

neonatology attending presence, and less frequently had video laryngoscopy. End-tidal carbon dioxide detection was used to confirm endotracheal tube placement in 88% (1994/2260) of TIs.

Primary outcomes

The sedation with neuromuscular blockade group had fewer occurrence of any adverse TI associated events compare to sedation only and no medication group ($p < 0.001$) (Table 2). After adjusting for patient, practice and provider factors associated with the use of sedation with neuromuscular blockade, the use of sedation with neuromuscular blockade remained significantly associated with a lower likelihood for adverse TI associated events (adjust odds ratio: aOR 0.47, 95% confidence interval: CI 0.34–0.65, $p < 0.001$), when compared to no medication group (Table 3). The sedation only group had higher likelihood of adverse TI associated events (aOR 1.48; 95% CI 1.11–1.96, $p = 0.007$) when compared to no medication group. There was a difference in the frequency of esophageal intubation (sedation with neuromuscular blockade: 5.8% vs. sedation only: 15.5%, vs. no medication: 10.4%, $p < 0.001$), Supplemental Table A.

Secondary outcomes

Severe oxygen desaturation rates in the sedation with neuromuscular blockade group was similar to the no medication group (44%: 95% CI 41–47 vs. 42%: 95% CI 38–45, $p = 0.72$), Table 2. Sedation only group had the highest occurrence of severe oxygen desaturation (60%, 95% CI 55–65) compared to other two groups, $p < 0.001$. The sedation with neuromuscular blockade group had the highest first attempt success rate and lowest number of attempts among the three groups ($p < 0.001$ for both outcomes).

Sensitivity analyses

Sensitivity analysis with sub-cohorts with current weight < 1500 g ($n = 703$), birth gestational age less than 28 weeks ($n = 990$), and sub-cohort excluding intubations for surfactant administration ($n = 1830$) showed a similar lower aOR for the occurrence of adverse TI associated events in the sedation with neuromuscular blockade group versus the no medication group (Supplemental Table B, C). Logistic regression with the propensity score as covariates ($n = 1838$) showed a similar OR for the occurrence of adverse TI associated events (aOR 0.45, 95% CI 0.31–0.65), as shown in Supplemental Table D. The analysis of propensity matched cohort ($n = 898$, Table 4) showed the smallest estimate in effect size: OR for adverse TI associated events was 0.91 (95% CI 0.86–0.98, $p = 0.001$) in sedation with neuromuscular blockade vs. no medication group.

Discussion

Our study evaluated the current practice in premedication use for TI procedure across 11 academic NICUs. Our results show wide variability in the premedication practices, with some NICUs using premedication at a minimal frequency and others routinely utilizing premedication. While premedication of sedation with neuromuscular blockade was more frequently used in older patients, after adjusting for patient, provider, and practice factors, the use of sedation with neuromuscular blockade was significantly associated with a lower occurrence of adverse TI associated events and a higher first attempt success rate. Sensitivity analyses by restricting study cohorts and utilizing propensity scores showed results consistent with the primary analysis, while propensity score matched analysis showed the smallest effect size given the sample size was substantially reduced.

Table 1 Patient demographics / provider characteristic

Patient characteristic	Sedation + neuromuscular blockade $n = 1058$	Sedation only $n = 394$	No medication $n = 808$	*P*-value
Age at the time of intubation (days)[a]	29 (4, 70)	6 (1, 34)	3 (1, 26)	<0.001
Gestational age (week) [a]	30 (25, 36)	28 (25, 35)	28 (25, 32)	<0.001
Current weight (gram)[a]	2504 (1300, 3443)	1629 (900, 2800)	1200 (818, 2120)	<0.001
Sex (male)	629 (59.5)	208 (52.8)	474 (58.7)	0.12
Diagnosis[b]				
Acute respiratory failure	525 (49.7)	239 (60.7)	566 (70.1)	<0.001
Chronic respiratory failure	290 (27.4)	86 (21.8)	167 (20.7)	0.002
Sepsis	64 (6.1)	25 (6.4)	63 (7.8)	0.31
Neurological failure	85 (8.0)	27 (6.9)	52 (6.4)	0.40
Cardiac disease	106 (10.0)	24 (6.1)	29 (3.6)	<0.001
Indication for tracheal intubation				
Oxygen failure	334 (31.6)	115 (29.2)	257 (31.8)	0.62
Ventilation failure	474 (44.8)	150 (38.1)	233 (28.8)	<0.001
Frequent apnea & desaturations	198 (18.7)	93 (23.6)	166 (20.5)	0.11
Upper airway obstruction	66 (6.2)	22 (5.6)	33 (4.1)	0.12
Surfactant administration	91 (8.6)	83 (21.1)	250 (30.9)	<0.001
Procedure	175 (16.5)	38 (9.6)	19 (2.4)	<0.001
Unstable hemodynamics	16 (1.5)	5 (1.3)	32 (4.0)	<0.001
Reintubation after unexpected extubation	120 (11.3)	32 (8.1)	119 (14.7)	0.003
History of difficult airway	100 (9.5)	42 (10.7)	62 (7.7)	0.19
Difficult airway feature[c]	232 (21.9)	73 (18.5)	174 (21.5)	0.35
Provider characteristic				<0.001
Pediatric resident	141 (13.3)	91 (23.1)	108 (13.4)	
Neonatology Fellow	304 (28.7)	125 (31.8)	243 (30.0)	
Neonatology Attending	33 (3.1)	13 (3.3)	105 (13.0)	
Nurse Practitioner/Physician Assistant/ Hospitalist	429 (40.6)	128 (32.5)	324 (40.1)	
Respiratory therapist	51 (4.8)	5 (1.2)	8 (1.0)	
Other[d]	100 (9.5)	32 (8.1)	20 (2.5)	
Attending presence	773 (73%)	196 (50%)	450 (56%)	<0.001
Practice characteristics				
Method				<0.001
Oral	1038 (98.1)	368 (93.4)	718 (88.9)	
Nasal	18 (1.7)	24 (6.1)	87 (10.8)	
Missing	2 (0.2)	2 (0.5)	3 (0.4)	
Device				<0.001
Direct laryngoscopy	649 (61.3)	345 (87.6)	775 (95.9)	
Video laryngoscopy	409 (38.7)	49 (12.4)	33 (4.1)	

[a]Median and interquartile range (25th,75th percentile) were reported.

Otherwise counts (*n*) and proportion (%) were reported

[b]Method was missing in six encounters

[c]Difficult airway feature was reported by providers for the presence of any of the followings: limited mouth opening, limited neck extension, small thyromental space, finding of airway obstruction, mid-facial hypoplasia, micrognathia, and cleft palate

[d]Other Provider category includes physicians from non-neonatal specialties (e.g., otolaryngology, surgery)

Underlying diagnosis at the time of airway management. Acute respiratory failure includes (not limited to) respiratory distress syndrome, transient tachypnea of newborn, meconium aspiration syndrome. Neurological failure includes hypoxemic ischemic encephalopathy, seizures, stroke, intraventricular hemorrhage (grade 3 and 4), hydrocephalus with ventricular shunt, for example. Cardiac disease include congenital heart disease excluding isolated patent ductus arteriosus

Table 2 Adverse tracheal intubation associated events, oxygen desaturation, multiple attempts among three groups

Outcomes	Sedation + neuromuscular blockade $n = 1058$	Sedation only $n = 394$	No medication $n = 808$	p-value
Any adverse TI associated events	103 (9.7)	113 (28.7)	189 (23.4)	<0.001
Severe TI associated events	23 (2.2)	24 (6.1)	56 (6.9)	<0.001
Severe oxygen desaturation	470 (44.4)	237 (60.1)	337 (41.7)	<0.001
Oxygen desaturation (Median, IQR)	17% (4–39)	27% (12–42)	19% (8–36)	<0.001
First attempt success	597 (56.4)	133 (33.8)	381 (47.2)	<0.001[a]
Number of attempt (Median, IQR)	1 (1–2)	2 (1–3)	2 (1–3)	<0.001[a]

Counts (n) and proportion (%) were reported except for the oxygen desaturation (absolute % change) number of attempts.

Oxygen desaturation (%) value was calculated as the absolute change in oxygen saturation

TI denotes tracheal intubation. Severe oxygen desaturation is defined as 20% or more absolute decrease from the highest oxygen saturation during the airway management. IQR denotes interquartile range

[a]There were statistically significant differences in first attempt success and number of attempts when sedation + neuromuscular blockade group was compared to no medication group (both $p < 0.001$)

Table 3 Multivariable analysis: association between the medication use and adverse tracheal intubation associated events ($n = 2253$)

Patient, provider, practice factors	Odds ratio	95% CI	p-value
Medication			
No medication	Reference		
Sedation only	1.48	1.11–1.96	0.007
Sedation and Neuromuscular blockade	0.47	0.34–0.65	<0.001
Patient weight (<1500 g)	0.71	0.52–0.97	0.031
Indication			
Ventilation failure	0.94	0.74–1.19	0.597
Shock	2.67	1.45–4.93	0.002
Procedure	0.51	0.35–0.75	0.001
Surfactant administration	0.73	0.60–0.90	0.003
Unplanned extubation	1.10	0.83–1.47	0.502
Nasal intubation (vs. oral)	0.41	0.25–0.68	0.001
Video laryngoscope use (vs. direct laryngoscope)	0.41	0.30–0.57	<0.001
Provider			
Resident	1.12	0.84–1.50	0.45
Fellow	0.78	0.66–0.92	0.004
Attending	0.86	0.49–1.53	0.618
Other[a]	Reference		

Generalized Estimate Equation (GEE) with independent correlation structure was used to develop a multivariable model with a logit link. See details in Method of the manuscript. Seven cases were not included into this model due to missing values

[a]Other includes non-neonatal providers, physician assistants and nurse practitioners

To our knowledge, this is the largest study to date investigating the impact of premedication use for neonatal TI.

Our large multicenter study confirmed the results reported in a few small studies. A single site cohort study demonstrated neuromuscular blockade medications were used less frequently in TIs with adverse TI associated events than TIs without adverse events [1]. We speculate the use of sedation with neuromuscular blockade optimizes intubation conditions allowing for better visualization of airway anatomy and accurate identification of the glottis. This facilitates placement of the endotracheal tube through the vocal cords.

We found the sedation only group had higher occurrence of adverse TI associated events compared to no medication group, even after adjusting for patient, provider and device factors. There are a few potential explanations for this unexpected finding. First, the sedation dosages and medications used may not be sufficient to provide optimal intubation condition. This may be compounded by potential adverse effects of the medication: decrease in pharyngeal tone leading to upper airway obstruction and reduction in functional residual capacity leading to rapid oxygen desaturation during laryngoscopy. It is also possible that the

Table 4 Comparison of cohorts after propensity score matching: Sedation with paralysis versus No medication

Patient, provider, practice characteristics	After matching		
	Sedation with paralysis ($N = 449$)	No medication ($N = 449$)	Standardized difference, %
Age, days			
0	61 (14%)	58 (13%)	N/A
1–6	145 (32%)	135 (30%)	5.0
7–27	105 (23%)	94 (21%)	6.2
≥28	138 (31%)	162 (36%)	11.5
Weight (<1500 g)	236 (53%)	234 (52%)	0.9
Gestational age at birth (week, IQR)	28 (25–34)	27 (25–34)	4.4
Sex (Male)	270 (60%)	264 (59%)	2.7
Indication of intubation			
Ventilation failure	173 (39%)	159 (35%)	6.6
Procedure	7 (1.6%)	17 (3.8%)	7.8[a]
Unstable hemodynamics	12 (2.7%)	10 (2.2%)	2.8
Surfactant administration	83 (18%)	74 (16%)	5.2
Reintubation unplanned extubation	71 (16%)	80 (18%)	5.9
Provider training level			
Pediatric Resident	66 (15%)	58 (13%)	3.4
Neonatology Fellow	138 (31%)	149 (33%)	5.4
Neonatology Attending	25 (5.6%)	21 (4.7%)	5.2
Device (DL)	438 (98%)	417 (93%)	12.5[a]
Approach (Oral)	441 (98%)	444 (99%)	3.0

DL direct laryngoscopy, *IQR* interquartile range

Summaries presented as median (25th, 75th percentile) or count (%)

Refer to Table 1 for before match comparison of two groups

[a]These standardized differences (%) indicate that balance was not achieved between the groups (p-value < 0.05)

commonly used sedation regimens might make the intubation condition paradoxically more difficult; for example, fentanyl is known to cause rigid chest syndrome [18]. In our study the sedation only group commonly utilized morphine. The onset of morphine-induced analgesia after intravenous administration is relatively slow (6–30 min) [19]. Therefore the use of morphine for TI might not provide an optimal intubation condition given its time to onset of action and peak effect. This might lead to stress response such as higher blood pressure, oxygen desaturation, and neurological depression 6 h later [20–22]. Future study should evaluate whether investigation into agents that would allow for adequate sedation without neuromuscular blockade is warranted for those patients where neuromuscular blockade is contraindicated.

One of our sensitivity analyses using propensity matching showed smaller effect size (aOR 0.91) compared to that (aOR = 0.47) from our primary analysis. This can be explained by under-adjustment of covariates in the main model and smaller sample size in propensity score matched analysis. As shown in the Table 1, older neonates with heavier weights received sedation with neuromuscular blockade and were intubated using video laryngoscopy more often that smaller neonates. In the propensity score matched analysis, the effect size was smaller to some extent due to difficulty in obtaining a match in smaller neonates intubated with video laryngoscopy, which resulted in substantially fewer neonates in the matched groups. In contrast, the majority of other sensitivity analyses showed a similar effect size to our primary analysis. Therefore, it is prudent to state that sedation with neuromuscular blockade was significantly associated with lower occurrence of adverse TI associated events, however, the effect size shown in our primary analysis should be interpreted with caution.

We found that premedication with sedation and neuromuscular blockade was associated with greater first attempt success. Similar to our study result, a small randomized study of term infants showed higher first attempt success in neonates that received fentanyl and rocuronium compared to those that received fentanyl alone (35 vs 8%, $p = 0.029$) [23]. Another study including 2694 TI attempts by 169 trainees showed that the premedication with neuromuscular blockade was associated with significantly higher TI attempt success (45 vs. 25%, $p = 0.036$) [8]. We speculate the use of sedation with neuromuscular blockade improves first attempt success by optimizing intubation conditions and allowing for better visualization of the airway anatomy.

Despite these benefits of premedication, there are some reasons why it has not been universally used. There is concern for removing patient's spontaneous respiratory effort especially in neonates who are potentially identified as having a "difficult airway" or are difficult to ventilate with face mask. In addition, there is also concern for neurotoxicity from sedative or narcotic use in neonates in general [24, 25]. However, there is currently no compelling evidence to support severe long-term harm from short term narcotic use in neonates [26, 27]. We speculate that the strongest drivers for premedication practice are local NICU practice habits, rather than data-driven decisions. Based on our result, we suggest the standard use of sedation and neuromuscular blockade as premedication for TI, while taking into account individual patient and provider factors (i.e., no routine neuromuscular blockade use for patient with known or suspected difficult airway).

This study has several limitations. First, this is an observational study and the result we showed here does not pertain causal inference. Future prospective trial or multicenter quality improvement intervention will evaluate

whether the standard use of sedative and neuromuscular blockade would improve the TI safety. Second, the study data were obtained from the multicenter TI quality improvement database. Although the inaccuracy of the data and information biases were minimized with site specific compliance plan and data verification processes, it remains possible to have errors in data acquisition and entry. All adverse TIAEs were self-reported by the clinical team at the time of intubation. It is possible that this led to under-reporting of TIAEs. Clinical teams were not aware of the current analysis of the impact of premedication on TIAEs. Third, site-level clustering (i.e., inter-ICU variability) might bias the result, since premedication practice was variable across the sites while other patient, provider, and practice variables are also different across the sites. We accounted for site-level clustering by fitting generalized estimate equation model to minimize this source of bias.

Conclusion

The use of premedication with sedation and neuromuscular blockade for neonatal TI in the NICU was associated with lower occurrence of adverse TI associated events after adjusting for confounders and clustering by sites. Use of premedication with neuromuscular blockade was also associated with lower oxygen desaturation rate and increased first attempt success rates. The same benefit was not seen in the sedation only group. Premedication with both sedation and neuromuscular blockade should be considered during neonatal TI unless there is a compelling reason not use them.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Foglia EE, Ades A, Napolitano N, Leffelman J, Nadkarni V, Nishisaki A. Factors associated with adverse events during tracheal intubation in the NICU. Neonatology. 2015;108:23–29.
2. Maheshwari R, Tracy M, Badawi N, Hinder M. Neonatal endotracheal intubation: how to make it more baby friendly. J Paediatr Child Health. 2016;52:480–6.
3. Venkatesh V, Ponnusamy V, Anandaraj J, Chaudhary R, Malviya M, Clarke P, et al. Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events. Eur J Pediatr. 2011;170:223–7.
4. Foglia EAA, Sawyer T, Glass K, Singh N, Jung P, Quek BH, et al. Neonatal intubation practice and outcomes: an international registry study. Pediatrics. 2019;143:e20180902.
5. van Hasselt TJ. Question 1 What is the best sedative to give as premedication for neonatal intubation? Arch Dis Child. 2017; 102:780–3.
6. Sauer CW, Kong JY, Vaucher YE, Finer N, Proudfoot JA, Boutin MA, et al. Intubation attempts increase the risk for severe intraventricular hemorrhage in preterm infants-A retrospective cohort study. J Pediatr. 2016;177:108–13.
7. Krick J, Gray M, Umoren R, Lee G, Sawyer T. Premedication with paralysis improves intubation success and decreases adverse events in very low birth weight infants: a prospective cohort study. J Perinatol. 2018;38:681–6.
8. Le CN, Garey DM, Leone TA, Goodmar JK, Rich W, Finer NN. Impact of premedication on neonatal intubations by pediatric and neonatal trainees. J Perinatol. 2014;34:458–60.
9. Kumar P, Denson SE, Mancuso TJ, Committee on F, Newborn SoA, Pain M. Premedication for nonemergency endotracheal intubation in the neonate. Pediatrics. 2010;125:608–15.
10. Bissuel M, Deguines C, Tourneux P. A national survey on pain management before tracheal intubation in neonates in French type III maternity units. Arch Pediatr. 2013;20:123–9.
11. Chaudhary R, Chonat S, Gowda H, Clarke P, Curley A. Use of premedication for intubation in tertiary neonatal units in the United Kingdom. Paediatr Anaesth. 2009;19:653–8.
12. Raban MS, Joolay Y, Horn AR, Harrison MC. Newborns should be receiving premedication before elective intubation. South African Med J. 2014;104:846–9.
13. Wheeler B, Broadbent R, Reith D. Premedication for neonatal intubation in Australia and New Zealand: a survey of current practice. J Paediatr Child Health. 2012;48:997–1000.
14. Durrmeyer X, Daoud P, Decobert F, Boileau P, Renolleau S, Zana-Taieb E, et al. Premedication for neonatal endotracheal intubation: results from the epidemiology of procedural pain in neonates study. Pediatr Crit Care Med. 2013;14:e169–175.
15. Barrington K. Premedication for endotracheal intubation in the newborn infant. Paediatrics & child health. 2011;16:159–71.
16. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42: 377–81.
17. Kurth T, Walker AM, Glynn RJ, Chan KA, Gaziano JM, Berger K, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. Am J Epidemiol. 2006; 163:262–70.
18. Fahnenstich H, Steffan J, Kau N, Bartmann P. Fentanyl-induced chest wall rigidity and laryngospasm in preterm and term infants. Crit Care Med. 2000;28:836–9.
19. Pacifici GM. Metabolism and pharmacokinetics of morphine in neonates: a review. Clinics. 2016;71:474–80.
20. Norman E, Wikstrom S, Hellstrom-Westas L, Turpeinen U, Hamalainen E, Fellman V. Rapid sequence induction is superior to morphine for intubation of preterm infants: a randomized controlled trial. J Pediatr. 2011;159:893–9 e891.
21. Ghanta S, Abdel-Latif ME, Lui K, Ravindranathan H, Awad J, Oei J. Propofol compared with the morphine, atropine, and suxamethonium

regimen as induction agents for neonatal endotracheal intubation: a randomized, controlled trial. Pediatrics. 2007;119:e1248–1255.
22. Avino D, Zhang WH, De Ville A, Johansson AB. Remifentanil versus morphine-midazolam premedication on the quality of endotracheal intubation in neonates: a noninferiority randomized trial. J Pediatr. 2014;164:1032–7.
23. Feltman DM, Weiss MG, Nicoski P, Sinacore J. Rocuronium for nonemergent intubation of term and preterm infants. J Perinatol. 2011;31:38–43.
24. Ing CH, DiMaggio CJ, Malacova E, Whitehouse AJ, Hegarty MK, Feng T, et al. Comparative analysis of outcome measures used in examining neurodevelopmental effects of early childhood anesthesia exposure. Anesthesiology. 2014;120:1319–32.
25. Morriss FH Jr., Saha S, Bell EF, Colaizy TT, Stoll BJ, Hintz SR, et al. Surgery and neurodevelopmental outcome of very low-birth-weight infants. JAMA Pediatr. 2014;168:746–54.
26. Wallenstein MB, Birnie KL, Arain YH, Yang W, Yamada NK, Huffman LC, et al. Failed endotracheal intubation and adverse outcomes among extremely low birth weight infants. J Perinatol. 2016;36:112–5.
27. Attarian S, Tran LC, Moore A, Stanton G, Meyer E, Moore RP. The neurodevelopmental impact of neonatal morphine administration. Brain Sci. 2014;4:321–34.

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