Original Contribution

Apneic oxygenation reduces hypoxemia during endotracheal intubation in the pediatric emergency department☆

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ABSTRACT

Background: Apneic oxygenation (AO) has been evaluated in adult patients as a means of reducing hypoxemia during endotracheal intubation (ETI). While less studied in pediatric patients, its practice has been largely adopted.
Objective: Determine association between AO and hypoxemia in pediatric patients undergoing ETI.
Methods: Observational study at an urban, tertiary children's hospital emergency department. Pediatric patients undergoing ETI were examined during eras without (January 2011–June 2011) and with (August 2014–March 2017) apneic oxygenation. The primary outcome was hypoxemia, defined as pulse oximetry (SpO_2) < 90%. The χ^2 and Wilcoxon rank-sum tests examined differences between cohorts. Multivariable regression models examined adjusted associations between covariates and hypoxemia.
Results: 149 patients were included. Cohorts were similar except for greater incidence of altered mental status in those receiving AO (26% vs. 7%, $p = 0.03$). Nearly 50% of the pre-AO cohort experienced hypoxemia during ETI, versus <25% in the AO cohort. Median [IQR] lowest SpO_2 during ETI was 93 (69, 99) for pre-AO and 100 [95, 100] for the AO cohort ($p < 0.001$). In a multivariable logistic regression model, hypoxemia during ETI was associated with AO (aOR 0.3, 95% confidence interval [CI] 0.1–0.8), increased age (for 1 year, aOR 0.8, 95% CI 0.7–1.0), lowest SpO_2 before ETI (for 1% increase, aOR 0.9, 95% CI 0.8–1.0), and each additional intubation attempt (aOR 4.0, 95% CI 2.2–7.2).
Conclusions: Apneic oxygenation is an easily-applied intervention associated with decreases in hypoxemia during pediatric ETI. Nearly 50% of children not receiving AO experienced hypoxemia.

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1. Introduction

1.1. Background

Endotracheal intubation (ETI) is the most common critical procedure performed in the pediatric emergency department (PED) [1], with efforts focused on performance optimization and process improvement using rapid sequence intubation [2-5]. A fundamental principle in this focus is the prevention and correction of hypoxemia during ETI, which has been associated with increased morbidity [6-11] and risk of mortality [12-14].

Apneic oxygenation (AO), the application of high-flow oxygen by nasal cannula during the apneic period of ETI, has been proposed as a measure to reduce the occurrence of hypoxemia in adult patients [15]. During apnea, reduced barometric pressure in the alveoli results in a pressure gradient and increased gas transfer between upper and lower airways. The application of oxygen during the apneic period of ETI increases the oxygen content in lower airways, resulting in alveolar oxygen uptake via diffusion, even without active breaths, allowing a longer period of "safe apnea" [15-17]. AO has been described as both successful in reducing the incidence of hypoxemia [16,18-24] and ineffective in this objective [25-27]. To our knowledge, the association of AO

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with hypoxemia during ETI has not been examined in pediatric patients in the PED.

Pediatric patients have critically-important physiologic differences from adults. Oxygen consumption is at least twice that of adults [28]. Children have reduced apnea tolerance and can develop hypoxemia more quickly than adults during rapid sequence intubation [11,28,29]. Additionally, ETI is infrequently performed by individual providers [1,29], which can heighten anxiety and potentiate procedural difficulty [30].

1.2. Importance

AO using high-flow oxygen by nasal cannula during the apneic period of endotracheal intubation decreases the incidence of hypoxemia in adults but has not been sufficiently studied in children.

1.3. Goal of this investigation

Our overall goal is to optimize ETI for pediatric patients in the PED and reduce the incidence of hypoxemia during this critical procedure. The objective of this study was to determine if AO is associated with reduction of hypoxemia in patients undergoing ETI in the PED.

2. Methods

2.1. Study design and setting

We performed an observational study with a before-and-after model design. This study was aimed at identifying the lowest oxygen saturation that occurred during ETI, measured using continuous pulse oximetry (SpO_2). The "before" arm took place during an era in which AO was not used. The "after" arm followed this era when AO was adopted as standard of care for all ETI performed in our PED. This study design was chosen over a randomized controlled trial because the intervention was non-invasive and the practice of applying AO was accepted as standard of practice and therefore we felt that there was no longer clinical equipoise. This study was performed at a Level 1 Trauma Center in an urban, tertiary-care children's hospital PED. The study protocol was reviewed and approved by our IRB (protocol #140381).

2.2. Selection of participants

All subjects <22 years of age who presented to the PED requiring ETI were eligible for inclusion. Patients requiring rapid sequence intubation as well as those in whom ETI was performed without sedative or paralytic adjuncts were eligible for inclusion. Patients undergoing active cardiopulmonary resuscitation were excluded. Patients were ultimately included in the study if a dedicated nurse-scribe completed a standardized data collection form at the time of ETI.

2.3. Measurements

2.3.1. Pre-AO cohort

We performed a review of all patients who underwent ETI in our PED between January and June 2011. Patients were identified using a respiratory therapy database that includes all ETI performed within our PED. This database includes variables that were recorded prospectively at the time of ETI and on a standardized data collection form. This information is kept in a centralized quality improvement (QI) database for clinical and research purposes. Demographics (age and gender), date of PED visit, reason for ETI, pre-existing medical conditions, lowest SpO_2 before, during, and after ETI, method of ETI (direct or video laryngoscopy), number of ETI attempts, and level of training of first proceduralist (medical student, resident, fellow, or attending) were recorded. The time periods "before", "during", and "after" ETI were pre-defined. "Before" ETI describes the time point immediately prior to sedation and paralysis or immediately prior to mouth opening if rapid sequence ETI was not performed. "During" ETI describes the time from mouth opening by the proceduralist until the laryngoscopy blade was removed from the mouth. "After" ETI describes the time immediately after the laryngoscopy blade was removed from the mouth until confirmation of endotracheal tube placement.

2.3.2. AO cohort

We performed a prospective, observational review of all patients who underwent ETI in our PED between August 2014 and March 2017, after AO was adopted as standard of care. All patients received 100% oxygen by nasal cannula during ETI. Children up to 2 years received 4 liters/minute (LPM), >2 years to ≤12 years received 6 LPM, and >12 years received 8 LPM. These flow rates were determined by our institution-specific guidelines. Respiratory therapists initiated nasal cannula oxygenation at the time the decision was made to perform ETI. Pre-oxygenation method (non-rebreather, bag-valve mask) and method of ETI (direct or video laryngoscopy and blade size/type) was left to the discretion of the medical team performing the procedure. The same data collection form used for the pre-AO cohort was used to collect data for these patients. Patients in whom it was unclear whether AO was utilized were excluded from analysis. Data from patients, during this era, who did not receive AO were included in the pre-AO cohort for analyses.

2.4. Outcomes

Our primary outcome was hypoxemia, defined as $SpO_2 < 90\%$, during ETI, with this time period defined above. Secondarily, we sought to examine if patient- and procedure-specific predictor variables were independently associated with hypoxemia when comparing the pre-AO and AO cohorts.

2.4.1. Predictor variables

Predictor variables examined for associations with hypoxemia during ETI included age, lowest SpO_2 prior to ETI, level of proceduralist-completed training, method of ETI, or number of attempts.

2.5. Analysis

Differences between the pre-AO and AO cohorts were analyzed using χ^2 for categorical data and Wilcoxon rank-sum test for continuous data. Although the Wilcoxon rank-sum tests for a difference of medians between cohorts, we considered the 25th percentile of lowest SpO_2 during ETI as the most clinically-relevant outcome variable in each group, because by definition 25% of patients experienced an SpO_2 value at or below this level. Multivariable regression models were used to provide adjusted associations of relevant covariates with hypoxemia. Additionally, we performed a sensitivity analysis to examine whether the above analyses were sensitive to inclusion of AO-era patients, who did not receive AO, in the pre-AO cohort. This analysis was performed because the reason for not using AO in these patients might confound the association of our primary predictor variable, AO, with the outcome of hypoxemia.

We used data from the pre-AO cohort to determine the sample size for the AO cohort. With a standard deviation for lowest SpO_2 of 24.3%, alpha of 0.05, our sample size of 59 subjects in the pre-AO cohort and 90 subjects in the AO cohort who were included in analyses was calculated to have power of approximately 0.80 to detect a median oxygen saturation difference of ≥13%. We present continuous data as median [interquartile range, IQR], dichotomous and categorical data as proportions (95% confidence interval, CI), and the output of our logistic regression models as adjusted odds ratios with 95% confidence interval (OR; 95% CI). We considered a p-value of <0.05 as
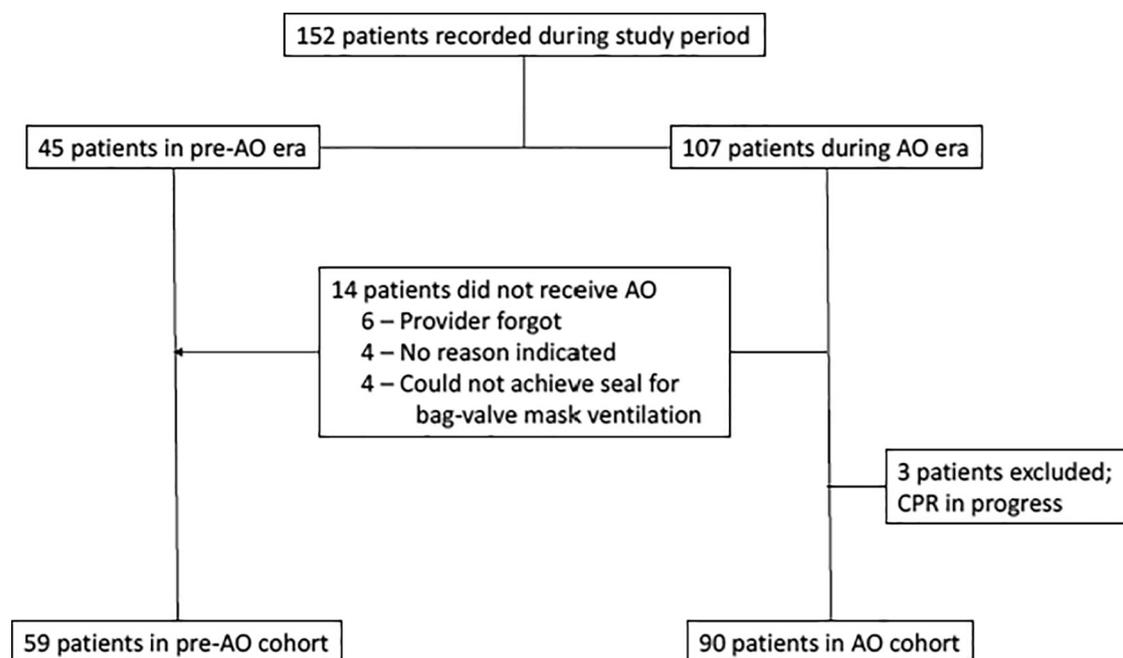
Fig. 1. Flow diagram of patient inclusion.

statistically significant. STATA IC 14.1 (Stata Corp., College Station, TX) was used for all analyses.

3. Results

3.1. Characteristics of the study subjects

There were 152 patients for whom ETI data were collected. Three patients were excluded from the analysis given active cardiopulmonary resuscitation at the time of ETI. Therefore, 59 patients were included in the pre-AO cohort and 90 in the AO cohort (Fig. 1). Fourteen patients identified during the AO era were subsequently included in the pre-AO cohort.

Patient characteristics, including underlying medical conditions and indication for ETI, are shown in Table 1. Three patients between both groups were aged ≥18 years, while 63 patients were aged <1 year, including 28 in the pre-AO cohort and 35 in the AO cohort ($p = 0.44$). Demographic characteristics were similar between groups, with only history of prematurity approaching a statistically-significant difference ($p = 0.051$). Altered mental status as an indication for intubation differed between groups ($p = 0.03$), as did proceduralist level of training ($p = 0.01$).

3.2. Main results

Data regarding the lowest documented SpO_2 before, during and after ETI, as well as the proceduralist level of training, method of ETI, and number of attempts, are additionally presented in Table 1. There was a significant but clinically meaningless difference in the lowest recorded median pre-ETI SpO_2 between cohorts ($p = 0.003$). Video-laryngoscopy was used more frequently in the AO cohort (31% vs. 10%, $p = 0.003$). The median [IQR] SpO_2 during ETI was significantly lower in the pre-AO (93% [69, 99]) in comparison with the AO cohort (100 [95, 100], $p \leq 0.001$). Proceduralist level of training ($p = 0.01$) as well as method of ETI ($p = 0.003$) both also demonstrate statistically significant differences in univariate analysis.

Fig. 2 depicts the proportion of patients in the pre-AO and AO cohorts at each level of lowest-SpO_2 during ETI. Whereas nearly 50% of patients in the pre-AO cohort experienced hypoxemia during ETI, less than

one quarter of patients in the AO cohort experienced hypoxemia. One quarter of patients (the 25th percentile) in the pre-AO cohort experienced a lowest SpO_2 of ≤69%, compared with ≤95% in the AO cohort.

Table 1
Demographic and clinical characteristics of patients with and without apneic oxygenation during endotracheal intubation.

Patient characteristic	Pre-AO N = 59	AO N = 90	p-Value
Age, median (IQR), years[a]	1 (0.1, 5)	2 (0.2, 10)	0.3
Gender, male (%)[b]	36 (61)	53 (59)	0.80
Underlying medical conditions, n (%)[b,c]			
None (healthy)	37 (60)	57 (63)	0.84
Asthma	1 (2)	1 (1)	0.77
Congenital heart disease	1 (2)	0 (0)	0.22
Chronic lung disease	2 (3)	2 (2)	0.68
Multiple (complex medical history)	8 (13)	18 (20)	0.29
Prematurity (<37 weeks)	11(18)	7 (8)	0.051
Epilepsy	6 (10)	11 (12)	0.67
Indication for ETI, n (%)[b,c]			
Respiratory failure	38 (61)	52 (58)	0.50
Cardiopulmonary failure[d]	3 (5)	2 (2)	0.35
Altered mental status	4 (7)	23 (26)	0.03
Diabetic ketoacidosis	0 (0)	2 (2)	0.25
Status epilepticus	7 (11)	14 (16)	0.50
Traumatic injury (GCS < 8)	3 (5)	3 (3)	0.61
Toxidrome/overdose	3 (5)	2 (2)	0.35
Other	10 (16)	9 (10)	0.23
Proceduralist level of training[b,e]			0.01
Pediatrics resident	4 (7)	21 (23)	
Emergency medicine resident	30 (51)	34 (38)	
Pediatric emergency medicine fellow	18 (31)	32 (36)	
Attending	7 (12)	3 (3)	
Video-laryngoscope used for ETI[f]	6 (10)	28 (31)	0.003
Lowest SpO_2 pre-ETI, median (IQR), %[a]	100 (97, 100)	100 (100, 100)	0.003
Lowest SpO_2 during ETI, median (IQR), %[a]	93 (69, 99)	100 (95, 100)	<0.001
Lowest SpO_2 after ETI, median (IQR), %[a]	100 (99, 100)	100 (99, 100)	0.67
ETI attempts, median (IQR)[b]	1 (1, 2)	1 (1, 1)	0.07

Abbreviations: AO, apneic oxygenation; IQR, interquartile range.
[a] Wilcoxon rank-sum test.
[b] χ^2 test.
[c] Variables are not mutually exclusive.
[d] This does not include patients undergoing active cardiopulmonary resuscitation.
[e] Percentages in pre-AO group in excess of 100% due to rounding.
[f] Storz video-laryngoscope or direct laryngoscopy available for ETI.

A multivariable logistic regression model was used to examine adjusted associations of our variables of interest with hypoxemia during ETI (Table 2). Patients receiving AO had 0.3 adjusted odds (95% CI 0.1–0.8) of hypoxemia in comparison with those not receiving AO. Older patients and those with greater SpO_2 before ETI also had decreased adjusted odds of hypoxemia during ETI. Regarding patient age, for every 1-year increase in age, there was a 0.8 (95% CI 0.7–1.0) adjusted odds of hypoxemia during ETI. Similarly, for every 1% increase in pre-ETI SpO_2, there was a 0.9 (95% CI 0.8–1.0) adjusted odds of hypoxemia during ETI. Number of attempts was also independently associated with hypoxemia during ETI, such that for every additional attempt at ETI, there was a 4.0 (95% CI 2.2–7.2) adjusted odds of hypoxemia during the procedure. A sensitivity analysis was performed in which patients enrolled during the AO era who did not receive the intervention (included in the pre-AO group in initial multivariable linear regression model) were removed from the pre-AO group, yielding no change in adjusted odds of hypoxemia from the original model.

4. Limitations

There are several limitations to this study. While the primary intervention in this study was the application of AO during ETI, the pre-AO and AO cohorts were from different time eras, due to inconsistencies in documentation in the period between the pre-AO and AO cohorts owing from a change in QI forms, and unrecognized confounders may exist. For example, video laryngoscopy was used in a greater proportion of AO-era patients. We attempted to mitigate this risk by considering and including factors associated with hypoxemia in our multivariable analysis, though not all factors could be anticipated or included [31]. Additionally, data collected in both arms of this study were based on the report of a dedicated nursing scribe, with potential for measurement errors [32]. An additional limitation was that patients included in the study after the initiation of AO therapy for ETI did not always receive the intervention, and in these cases, were included in the pre-AO group for analysis. To account for possible inclusion bias we performed a sensitivity analysis in which these patients were included in their intended AO group, and found no difference in the results of the multivariable analysis.

5. Discussion

With a goal of optimizing the performance of ETI in the PED, we sought to measure the association of AO with hypoxemia during this critical procedure. In this study, the application of AO during ETI was independently-associated with reduced odds of hypoxemia that were clinically meaningful after adjustment for relevant covariates. Patients in the pre-AO cohort had a higher incidence of hypoxemia, including 25% of patients who experienced markedly reduced SpO_2 (≤69%) during ETI attempts. Additional factors, including age, lowest SpO_2 prior to ETI attempt, and number of attempts at ETI, were independently-associated with hypoxemia during the procedure.

To our knowledge, this is the first study evaluating the application of AO as a method of reducing hypoxemia during ETI in pediatric patients. Adult studies regarding AO during ETI initially showed utility in its application to reduce the incidence of hypoxemia, however with recent studies demonstrating mixed results, its effect has been called into question [16,19-22,24,26,27,33]. Recent efforts at reduction of hypoxemia during pediatric ETI have focused on process standardization, limiting providers performing the procedure, and use of video laryngoscopy [2]. In measuring factors associated with hypoxemia, patient age, respiratory indication for ETI, esophageal intubation and cumulative time of laryngoscopy have been reported as independent
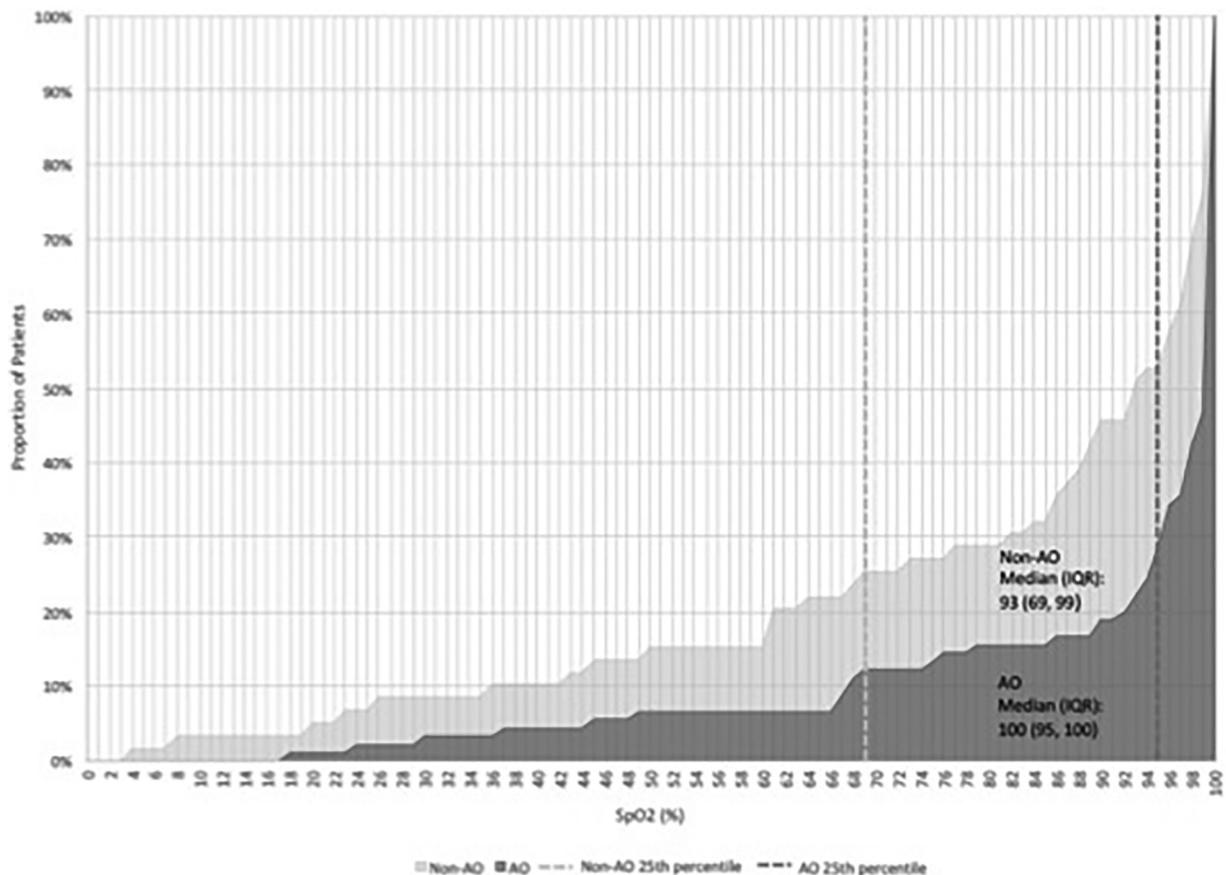

Fig. 2. Lowest oxygen saturation experienced, by proportion, with and without apneic oxygenation during endotracheal intubation. Abbreviations: AO, apneic oxygenation; IQR, interquartile range.

Table 2
Multivariable logistic regression model for hypoxemia during endotracheal intubation in 150 pediatric patients.

Variable	Complete case analysis[a]		Sensitivity analysis[a]	
	aOR (95% CI)	p-Value	aOR (95% CI)	p-Value
Use of AO	0.3 (0.1–0.8)	0.02	0.3 (0.1–0.9)	0.04
Age (1-year increase)	0.8 (0.7–1.0)	0.02	0.8 (0.6–1.0)	0.03
SpO$_2$ before ETI[b]	0.9 (0.8–1.0)	0.01	0.9 (0.8–1.0)	0.03
Each additional ETI attempt	4.0 (2.2–7.2)	<0.001	3.9 (2.1–7.1)	<0.001
Proceduralist training level[c]	0.7 (0.4–1.3)	0.27	0.8 (0.4–1.6)	0.45
Method of intubation[d]	0.6 (0.1–2.7)	0.51	0.4 (0.06–2.5)	0.32

Abbreviations: aOR, adjusted odds ratio; AO, apneic oxygenation; SpO$_2$, oxygen saturation by pulse oximetry; ETI, endotracheal intubation.

[a] Complete case analysis includes 149 patients total with 14 AO-era patients who did not receive AO included in pre-AO group for analysis. Sensitivity analysis excludes these 15 patients from analysis.

[b] 1% increase of SpO$_2$.

[c] Training level: pediatric resident; emergency medicine resident; pediatric emergency medicine fellow; attending.

[d] Method of intubation: direct laryngoscopy versus indirect using Storz video laryngoscope.

predictors of hypoxemia [31]. While the same study did not find an association between the number of attempts and incidence of hypoxemia, this relationship has been shown elsewhere [31,34].

AO is a non-invasive intervention to apply during ETI, and its use may confer benefit to patients in reducing the occurrence of hypoxemia during this procedure. While low-risk, its application was noted to present one unanticipated consequence during ETI. Four patients in whom AO was intended did not receive the intervention because of inability of providers to obtain an effective seal during bag-valve mask ventilation prior to ETI. This could become problematic in the setting of patients presenting in respiratory failure, who already have an increased risk of hypoxemia during ETI and require bag-valve mask to maintain oxygenation and ventilation [31]. As lowest SpO$_2$ prior to ETI was also independently-associated with hypoxemia in this study, it might be reasonable to forgo AO when it prevents an adequate seal during bag-valve mask ventilation resulting in suboptimal SpO$_2$ prior to ETI [15].

Additionally, the reason for a portion of patients not receiving AO during ETI was related to providers forgetting to apply the intervention. Noted previously, standardization of ETI has been associated with reduced incidence of hypoxemia during the procedure [2]. Including AO in ETI standardization will ensure its application and reduce the frequency that patients undergoing ETI do not receive the intervention.

In summary, in this observational analysis, utilizing AO was associated with reduced odds of hypoxemia during ETI. Further, although a subset of patients in the AO group did experience hypoxemia, a larger proportion of patients not receiving the intervention experienced marked hypoxemia, with one quarter of patients having SpO$_2$ ≤ 69% during ETI. Providers should recognize the potential importance of this easily-applied intervention at reducing the incidence of hypoxemia during ETI. Future studies should aim at optimizing ETI attempts and reducing hypoxemia using randomized, controlled methodologies, as well as identifying other potentially modifiable interventions associated with this outcome.

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Author contributions

DM and DHA conceived the study and designed the trial. DHA supervised the conduct of the trial and data collection. AAV, HRH, SLM, DM, and CAS performed data collection and managed the data, including quality control. DHA provided statistical advice on study design and analyzed the data. AAV and HRH drafted the manuscript, while SLM and DHA contributed substantially to its revision. DHA takes responsibility for the paper as a whole. Given their equal contributions to the study, the authors of this study would like to recognize AAV and HRH as joint first authors.

Conflicts of interest

The authors have no conflicts of interest to disclose.

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