PEDIATRIC EMERGENCY MEDICINE CRITICAL ARTICLE REVIEW (PEMCAR)	
QUESTION	In pediatric patients undergoing endotracheal intubation in the emergency department, is apneic oxygenation (high flow oxygen through a standard nasal cannula without ventilation), when compared to intubation without apneic oxygenation, associated with a decrease in hypoxemia (SpO_2 < 90%) during the procedure?
TYPE	Harm
TOPIC	Airway Procedures: Endotracheal Intubation
DATE	June 2019
REVIEWER	Michael Mojica, MD
CITATION	Vukovic AA, Hanson HR, Murphy SL, Mercurio D, Sheedy CA, Arnold DH. Apneic Oxygenation Reduces Hypoxemia During Endotracheal Intubation in the Pediatric Emergency Department Am J Emerg Med. 2019 Jan;37(1):27-32., PubMed ID: 29699900

STUDY DEFINITIONS	
POPULATION	Inclusion: < 22 years of age Presenting to the emergency department Requiring endotracheal intubation (ETI) with/without rapid sequence medications Exclusion: Active cardiopulmonary resuscitation Unclear if apneic oxygenation received (After Apneic oxygenation group only) Setting: Single US Children's Hospital Before Apneic oxygenation cohort (Retrospective): 1/2011-6/2011 After Apneic oxygenation cohort (Prospective): 8/2014-3/2017
EXPOSURE	Apneic oxygenation: 100% FiO_2: ≤ 2 years: 4 Liters/min, > 2 to ≤ 12 years: 6 Liters/min, > 12 years: 8 Liters/min Delivered by a standard nasal cannula with wall oxygen Started by respiratory therapist as the standard of care at time of the decision to perform endotracheal intubation
NO EXPOSURE	No apneic oxygenation
CO-EXPOSURES	At discretion of treating physicians: 1. Preoxygenation method: Non-rebreather mask or bag-valve mask ventilation 2. Endotracheal intubation method: Direct/Video laryngoscopy, blade size/type
OUTCOME	Primary Outcome: Hypoxemia: SpO_2 < 90% during endotracheal intubation (ETI) Before ETI: Prior to sedation/paralysis OR Prior to mouth opening if without RSI During ETI: Mouth opening until the laryngoscope blade removed from mouth After ETI: Laryngoscope blade removal until confirmation of ET placement Multiple logistic regression: Potential patient/procedure confounding variables: Age, lowest SpO2 prior to ETI, proceduralist level of training/specialty, method of ETI (direct vs video laryngoscopy), number of ETI attempts
DESIGN	Observational: Retrospective cohort (before), prospective cohort (after)

CRITICAL REVIEW FORM FOR A HARM ARTICLE (OBSERVATIONAL STUDY)

HOW SERIOUS WAS THE RISK OF BIAS? (COHORT STUDY)

DID THE EXPOSED AND CONTROL GROUPS START AND FINISH WITH THE SAME RISK FOR THE OUTCOME?

Were patients similar for prognostic factors that are known to be associated with the outcome (or were adjustments made using statistical methods)	Yes and No (Table 1). Patients in the before and after cohorts were similar with regard to age, gender, underlying medical conditions, lowest SpO_2 after ETI and number of ETI attempts. Patients were also similar with regard to indication for the ETI with the exception of altered mental status which was more frequent in the after apneic oxygenation group. Pediatric residents more commonly preformed ETI than emergency medicine residents and video laryngoscopy was performed more frequently in the after apneic oxygenation group. A logistic regression analysis was performed to account for the differences in potential confounders. It would have been helpful to include a comparison of patients moved from the after AO group to the before AO group because apneic oxygenation was not performed. However, a sensitivity analysis was performed excluding these patients and the study results did not change.
Were the circumstances and methods for detecting the outcome similar?	Yes. The same data collection form was used for both cohorts. A dedicated recording nurse completed the form at the time of the procedure. The data was kept in a standardized quality improvement database.
Was follow-up sufficiently complete?	Yes. The primary outcome was evaluated at the time of the procedure in the Emergency Department.

WHAT ARE THE RESULTS?

HOW STRONG IS THE ASSOCIATION BETWEEN EXPOSURE AND OUTCOME?

N=149, 42% < 1 year of age
Before AO cohort: n=59 (including 14 who did not receive AO in the after AO time period)
After AO cohort: n=90

PRIMARY OUTCOME: HYPOXIA DURING ENDOTRACHEAL INTUBATION

	Before Apneic Oxygenation	After Apneic Oxygenation
Lowest SpO_2 (Median (IQR))	93% (69, 99%)	100% (95, 100%)
Hypoxemia (%)	50%	25%
25^{th}% of Lowest SpO_2*	≤ 69%	≤ 95%
*The authors considered a difference of ≥ 13% to be clinically significant		

REGRESSION: HYPOXIA DURING ENDOTRACHEAL INTUBATION

Independent Predictors	Adjusted Odds Ratio (95% CI)
Use of Apneic Oxygenation	0.3 (0.1, 0.8)
Age (every 1-year increase)	0.8 (0.7, 1.0)
SpO_2 before ETI (every 1% increase)	0.9 (0.8, 1.0)
Each addition attempt at ETI	4.0 (2.2, 7.2)
Proceduralist level of Training	0.7 (0.4, 1.3)
Method of Intubation (Direct/Video)	0.6 (0.1, 2.7)

RED = Not statistically significant, GREEN = Statistically significant
Beta coefficients not presented to allow for direct comparison of each variables predictive effect
Sensitivity analysis excluding patients transferred from the After AO cohort to the Before AO cohort resulted in similar adjusted odds ratios (Table 2)

HOW PRECISE IS THE ESTIMATE OF THE RISK?

The confidence intervals for the adjusted odds ratios are presented above. Risk and mean differences for the unadjusted analyses were not presented and not calculable from the data presented.

HOW CAN I APPLY THE RESULTS TO PATIENT CARE?	
Were the study patients similar to the patients in my practice?	Likely. This was a single center study at a children's hospital in the US. In the after AO cohort the study center averaged approximately 3 intubations a month which is higher than our volume. It is unclear which sedatives and paralytics were used for those undergoing rapid sequence intubation.
Was follow-up sufficiently long?	Yes. The Primary outcome was hypoxemia during endotracheal intubation occurring in the ED.
Is the exposure similar to what might occur in my patient?	Yes. Endotracheal intubation is a rare but potentially life preserving procedure in the emergency department
What is the magnitude of the risk?	In the regression analysis patients in the after AO cohort were approximately 1/3 as likely to experience hypoxia (Adjusted odds ratio: 0.3, 95% CI (0.1, 0.8)).
Are there any benefits that offset the risks associated with exposure?	Only a single efficacy and no safety outcomes were presented. 4 patients were transferred to the before AO cohort from the after AO cohort because a seal could not be obtained for bag-valve mask ventilation. It is unclear if this was related to the presence of the nasal cannula. Risk differences for the primary outcome were not presented or calculable from the data presented so that a number needed to treat could not be determined.

CLINICAL BOTTOM LINE

BACKGROUND: Preoxygenation prior to intubation provides on oxygen reservoir during intubation in order to avoid hypoxemia. This is particularly important in children who have higher oxygen consumption than adults and become hypoxemic more quickly with rapid sequence intubation. Preoxygenation can be delivered with a non-rebreather face mask with or without bag-valve mask ventilation. Apneic oxygenation is the process of providing a high flow rate of oxygen through a standard nasal cannula prior to intubation without bag-valve mask ventilation. This should be distinguished from high flow, heated and humidified oxygen delivered by a proprietary devise. It is thought that the high flow rate results in nitrogen washout (replacing nitrogen with oxygen) which provides an oxygen reservoir as well as provides some degree of positive end expiratory pressure keeping airways open. Apneic oxygenation with a standard nasal cannula has the advantage of using readily available airway equipment, does not require removal prior to intubation (non-rebreather mask, noninvasive ventilation machines) and avoids the complications that can be associated with bag-valve-mask ventilation (abdominal distension resulting in vomiting and

aspiration as well as limiting tidal volume due to increased intra-abdominal pressure due to gastric distension). Apneic oxygenation was been shown to be beneficial in adults but pediatric data is limited.

CLINICAL QUESTION: In pediatric patients undergoing endotracheal intubation in the emergency department, is apneic oxygenation (high flow oxygen through a standard nasal cannula without ventilation), when compared to intubation without apneic oxygenation, associated with a decrease in hypoxemia (SpO_2 < 90%) during the procedure?

DESIGN/RISK OF BIAS: This was a single-center observational study utilizing a retrospective "Before" apneic oxygenation (AO) cohort and prospective "After" AO cohort with a three-year interval between cohorts. The standard of care in the after AO cohort was apneic oxygenation defined as the delivery of 100% FiO_2 by a standard nasal cannula with wall oxygen and started by the respiratory therapist at the time that the decision to perform endotracheal intubation was made. The oxygen flow rate was determined by age. The preoxygenation method (non-rebreather mask or bag-valve mask ventilation) and endotracheal intubation method (direct or video laryngoscopy and the laryngoscope blade size and type) was at discretion of treating physicians. The primary outcome was the occurrence of hypoxemia (SpO_2 < 90%) during endotracheal intubation (ETI). During ETI was defined as the interval from mouth opening until the laryngoscope blade was removed from mouth.

Patients in the before and after cohorts were similar with regard to age, gender, underlying medical conditions, lowest SpO_2 after ETI and number of ETI attempts. Patients were also similar with regard to indication for the ETI with the exception that altered mental status which was more frequent in the after apneic oxygenation group. Pediatric residents more commonly performed ETI than emergency medicine residents and video laryngoscopy was performed more frequently in the after apneic oxygenation group. Multiple logistic regression was performed to account for the effect of patient and procedure specific confounding variables on the study outcome (Table 2).

13% (14/107) of the patients in the after apneic oxygenation era did not receive apneic oxygenation despite AO being defined as the standard or care. These patients were included in the before AO cohort. It would have been helpful to include a column in Table 1 comparing these patients to those who did receive AO in the after cohort and those in the before AO period. A sensitivity analysis excluding these patients did not reveal a difference in the study outcomes (Table 2). 4 of these patients did not receive AO because a seal could not be obtained for bag-valve mask (BVM) ventilation. It is unclear if this was related to the presence of the nasal cannula. The proportion of patients successfully undergoing BVM ventilation with the cannula in place was not presented.

As with any before and after intervention design, there is a concern that something other than the intervention of interest changed between the study intervals. Pediatric resident intubation and video laryngoscopy were more common in the after AO cohort those there were not found to be independent predictors of hypoxia in the regression analysis.

PRIMARY RESULTS: 149 patients were included in the primary analysis of which 42% were less than 1 year of age. There were 59 patients on the Before AO cohort (including 14 who did not

receive AO in the after AO time period) and 90 patients in the After AO cohort. Hypoxemia during endotracheal intubation was less common in the After AO cohort in both the univariable (unadjusted) analysis and the regression (adjusted) analysis (see tables below). The difference in the proportion with hypoxia was greater than the 13% difference indicated by the authors as clinically significant. Age, SpO_2 before endotracheal intubation and additional attempts at endotracheal intubation were also independent predictors of hypoxia during ETI.

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APPLICABILITY: This was a single center study at a children's hospital in the US. It is likely that the study's results are applicable to those pediatric patients meeting the study's inclusion and exclusion criteria in that setting. However, in the after AO cohort the study center averaged approximately 3 intubations a month which is higher than our volume. It is also unclear which sedatives and paralytics were used for those undergoing rapid sequence intubation.

AUTHOR'S CONCLUSION: "In summary, in this observational analysis, utilizing apneic oxygenation was associated with reduced odds of hypoxemia during endotracheal intubation. Further, although a subset of patients in the apneic oxygenation 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 endotracheal intubation. Providers should recognize the potential importance of this easily-applied intervention at reducing the incidence of hypoxemia during endotracheal intubation. Future studies should aim at optimizing endotracheal intubation attempts and reducing hypoxemia using randomized, controlled methodologies, as well as identifying other potentially modifiable interventions associated with this outcome."

POTENTIAL IMPACT: Apneic oxygenation is simple to perform and readily available in the Emergency Department. Its use in this study was associated with a statistical and clinical improvement in the proportion of patients with hypoxia during ETI. Since there are few if any adverse effects associated with its use it would seem prudent to recommend its routine use in the

pediatric population. The potential for the nasal cannula to prevent an adequate seal during bag-valve mask ventilation merits further study. It is important to acknowledge that approximately one quarter of the patients in the after apneic oxygenation cohort experienced hypoxia leaving room for improvement and further evaluation of the other variables in the regression analysis that were found to be independent predictors of hypoxia during ETI. This question would benefit from a larger or multicenter clinical trial in the pediatric population.