Emergency Department use of Apneic Oxygenation Versus Usual Care During Rapid Sequence Intubation: A Randomized Controlled Trial (The ENDAO Trial)

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ABSTRACT

Objectives: Desaturation leading to hypoxemia may occur during rapid sequence intubation (RSI). Apneic oxygenation (AO) was developed to prevent the occurrence of oxygen desaturation during the apnea period. The purpose of this study was to determine if the application of AO increases the average lowest oxygen saturation during RSI when compared to usual care (UC) in the emergency setting.

Methods: A randomized controlled trial was conducted at an academic, urban, Level I trauma center. All patients requiring intubation were included. Exclusion criteria were patients in cardiac or traumatic arrest or if preoxygenation was not performed. An observer, blinded to study outcomes and who was not involved in the procedure, recorded all times, while all saturations were recorded in real time by monitors on a secured server. Two-hundred patients were allocated to receive AO (n = 100) or UC (n = 100) by predetermined randomization in a 1:1 ratio.

Results: A total of 206 patients were enrolled. There was no difference in lowest mean oxygen saturation between the two groups (92, 95% confidence interval [CI] = 91 to 93 in AO vs. 93, 95% CI = 92 to 94 in UC; p = 0.11).

Conclusion: There was no difference in lowest mean oxygen saturation between the two groups. The application of AO during RSI did not prevent desaturation of patients in this study population.

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Hypoxia may occur during emergent endotracheal intubation of patients.[1–4] Hypoxia, in general, is a condition that may increase the risk of patients suffering from cardiac arrest. An important part of rapid sequence intubation (RSI) is preoxygenation, which is defined as placing the patient on supplemental oxygen with a goal of administering 100% FiO_2 for 3 minutes prior to administering the induction agent and paralytic (i.e., sedative and neuromuscular blocker [NMB]) to increase the amount of oxygen present in the functional residual capacity of the patients lungs to prolong the maintenance of acceptable oxygen saturation during the apneic period of endotracheal intubation.[5–8] In the past decade, physicians have developed a technique known as apneic oxygenation (AO), which is theorized to prevent the occurrence of desaturation during the apneic period. The process entails leaving the patient on nasal cannula (NC) oxygen during the act of visualizing the vocal cords and placing the endotracheal tube.[8,9] The practice has become increasingly utilized in emergency and critical care departments in the United States and Australia.[10–15] A recent randomized controlled trial (The FELLOW Trial) demonstrated no difference in desaturation rates between those patients that received AO and those that did not (usual practice) in patients in the intensive care unit.[10] AO has been retrospectively and prospectively studied in prehospital, emergency department (ED), critical care, and operating room settings, and these studies refute the results of the FELLOW Trial.[11–15]

Although studies have begun investigate the efficacy of AO in preventing desaturation during RSI, randomized controlled trial evidence is still lacking in the ED patient population. Therefore, acquiring a further understanding of the implications of this technique on patient care by performing a randomized controlled trial can help clarify its place in RSI.

The primary outcome of this investigation was to determine if the use of AO increases the average lowest oxygen saturation during RSI when compared to usual care (UC). We also sought to determine if the use of AO not only increased first pass success rates, but decreased the rates of desaturation, time to desaturation, and mortality.

METHODS

Study Design and Setting

A randomized controlled trial was conducted at an urban, academic, Level I trauma center in New York City. The annual census of the ED is approximately 175,000 patients. The department performs approximately 450 intubations a year. This study was approved with waiver of consent by the institutional review board. Waiver was obtained as the intervention was deemed to be minimal risk and every patient was receiving standard of care RSI regardless of group allotment. This study was registered with ClinicalTrials.gov (NCT02737917).

Selection of Participants

Any adult patient (age > 18 years old) presenting to the ED requiring endotracheal intubation was screened for inclusion into the study. Patients were excluded from the study if they were not preoxygenated to the standard RSI protocol of a goal of 3 minutes with 100% FiO_2 by means of BVM, BiPAP, and/or NRB; if they were in cardiac or traumatic arrest; or if they were intubated without an apneic period (i.e., awake intubation). Patients who did not undergo preoxygenation were excluded to avoid a potential confounding variable.

Eligible patients were randomly assigned in a 1:1 ratio to receive AO (intervention) or UC (control). The sequence of study group assignments was generated via a computerized algorithm using permuted blocks of 4, 8, and 12.[16] Study group assignments were placed in a secured binder and sequentially numbered in opaque envelopes. The data collectors were blinded to our study design and outcome, and we feel that no bias was introduced by the use of these trained data collectors.

Interventions

All adult patients undergoing endotracheal intubation in the ED were randomized to receive supplemental oxygen via NC; CareFusion AirLife) and NC $EtCO_2$ (Phillips, Smart Capnoline), both at flush flow rates ≥15 LPM (providing intra and extra nasal oxygen) during laryngoscopy (AO) or no supplemental oxygen during laryngoscopy (UC). All patients received standard of care for endotracheal intubation that is RSI. An internally validated intubation checklist was used on all intubations. Choice of preoxygenation technique (flush flow rate NRB vs. BiPAP vs. BVM), RSI medications and technique (video vs. direct laryngoscopy) was left to the discretion of the attending physician caring for the patient. Preoxygenation was conducted with flush flow rate NRB, with BVM connected to 100% oxygen wall supply, or with BiPAP on 100% FiO_2. Patients on BiPAP or BVM had the masks removed after

administration of induction agents. A jaw thrust was given to patients after administration of induction agents and prior to laryngoscopy. Patients randomized to receive AO had the NC oxygen started with the initiation of preoxygenation.

Methods and Measurements

To minimize observer bias, data collection during intubation was performed by independent observers (research assistants, nurses, and residents) who underwent training for data collection and were not directly involved in the performance of the procedure. The observers used a data collection tool to collect data in real time (see Data Supplement S1, available as supporting information in the online version of this paper, which is available at https://doi.org/onlinelibrary.wiley.com/doi/10.1111/acem.13274/full, for data collection sheet). Vital signs were obtained from the patient's monitor (Philips Intellivue), which is transmitted to a central monitoring system that can be accessed to print out timed reports. The time of O_2 saturations and the saturations themselves were collected and written down on the data collection sheet and then reconciled with the centrally stored monitor data to confirm accuracy. Apnea time was defined as time from first look (defined as insertion of the laryngoscope blade into the patients mouth) to confirmation of endotracheal tube placement by waveform capnography ($EtCO_2$). Insertion of blade into the patients mouth was used as the starting point for apnea time instead of administration of NMB because this is the most distinct sign that the patient is paralyzed (i.e., it would be difficult to determine the exact onset of paralysis after administration of the NMB before the initiation of the first look). Intubation attempts (number of times the patient had the endotracheal tube placed in their mouth) were counted for each patient. In those patients where first pass failed and subsequent attempts were made without assisted ventilation, the apnea time was defined as above. In those attempts where first-pass intubation failed and the patient was ventilated prior to subsequent attempt (i.e., the laryngoscope was taken out of the mouth and the patient ventilated), the apnea time was defined as time of first look to time of assisted ventilation. To confirm the accuracy of data collected by the independent observers, the primary investigators conducted a concurrent assessment of the same outcomes for a convenience sample of the first 20 consecutively enrolled patients (10% of study intubations).

Subjective assessments of Cormack-Lehane grade of view, difficulty of intubation, and airway complications during the procedure were self-reported by the operator to the observer for recording on the data collection tool. All other data on baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes were collected from the medical record by study personnel.

Outcomes

The primary outcome was the average lowest oxygen saturation recorded during the apnea period or in the 2 minutes after. The secondary outcomes were to determine the difference, if any, in rates of first-pass success, desaturation below SpO_2 90%, and desaturation below SpO_2 80%. The final endpoint was to determine the difference, if any, of the average time to desaturation between the two groups.

Data Analysis

Based on a previous study of desaturation during RSI by the FELLOW trial, which demonstrated a difference of the median lowest arterial saturation of 2% between the intervention and control group, and not knowing whether our data set would be abnormally distributed; we calculated a Cohen's d statistic of 0.4 for moderate effect size to detect a difference in oxygen saturation of 5% in our study.[10] With this, an enrollment of 200 patients (100 in each arm) provided a 80% statistical power (at a two-sided alpha level of 0.05) to detect a moderate difference between groups for the primary outcome.

Continuous variables were reported as mean with 95% confidence interval [CI] or median with interquartile range, and categorical variables were reported as frequencies and proportions. Between-group differences were analyzed with the Student's t-tests for continuous variables and Mann-Whitney rank sum tests for ordinal and nonnormally distributed continuous variables.

The primary analysis was a comparison of patients randomized to AO versus UC with regard to the primary outcome of lowest arterial oxygen saturation. A repeated measures analysis of variance (ANOVA) was performed on saturation at different time intervals to determine if there was a difference between the treatment group and control group over time. A two-sided p-value of less than 0.05 and 95% CIs are reported. All analyses were performed using XLStat (Addinsoft).

RESULTS

Characteristics of the Study Subjects

A total of 206 (79%) patients were enrolled out of a possible 262 during the study period between May and December of 2016. Figure 1 demonstrates the enrollment flow of the patients. Six patients received the wrong intervention early in the study period (two patients assigned to the UC group received AO, and four patients assigned to the AO group received UC), but were excluded from the analysis because data collection was incomplete as the observers stopped recording. The remaining 56 patients were excluded per criteria.

Baseline demographics of the two groups were similar in all instances (see Table 1). Patients were intubated a majority of the time in both groups for primary pulmonary etiologies (Table 1). There was no difference in operator experience between the groups (Table 1). There was a kappa of 0.9 ± 1.6 for agreement between the observers for the first 10% of cases enrolled for observer quality assurance.

Main Results

There was no difference in lowest average oxygen saturation during the periprocedural period (Table 2). Figure 2 demonstrates the average SpO_2 and successful intubations over time. The repeated-measures ANOVA demonstrated no difference overtime between the groups (see Table 2, Mauchly's statistic 0.08, Huynt-Feldt Epsilon 0.58, between-group effect p = 0.1). Over 70% of patients were successfully intubated by 60 seconds, 80% by 80 seconds, 90% by 100 seconds, and 100% by 195 seconds. There was a subgroup of

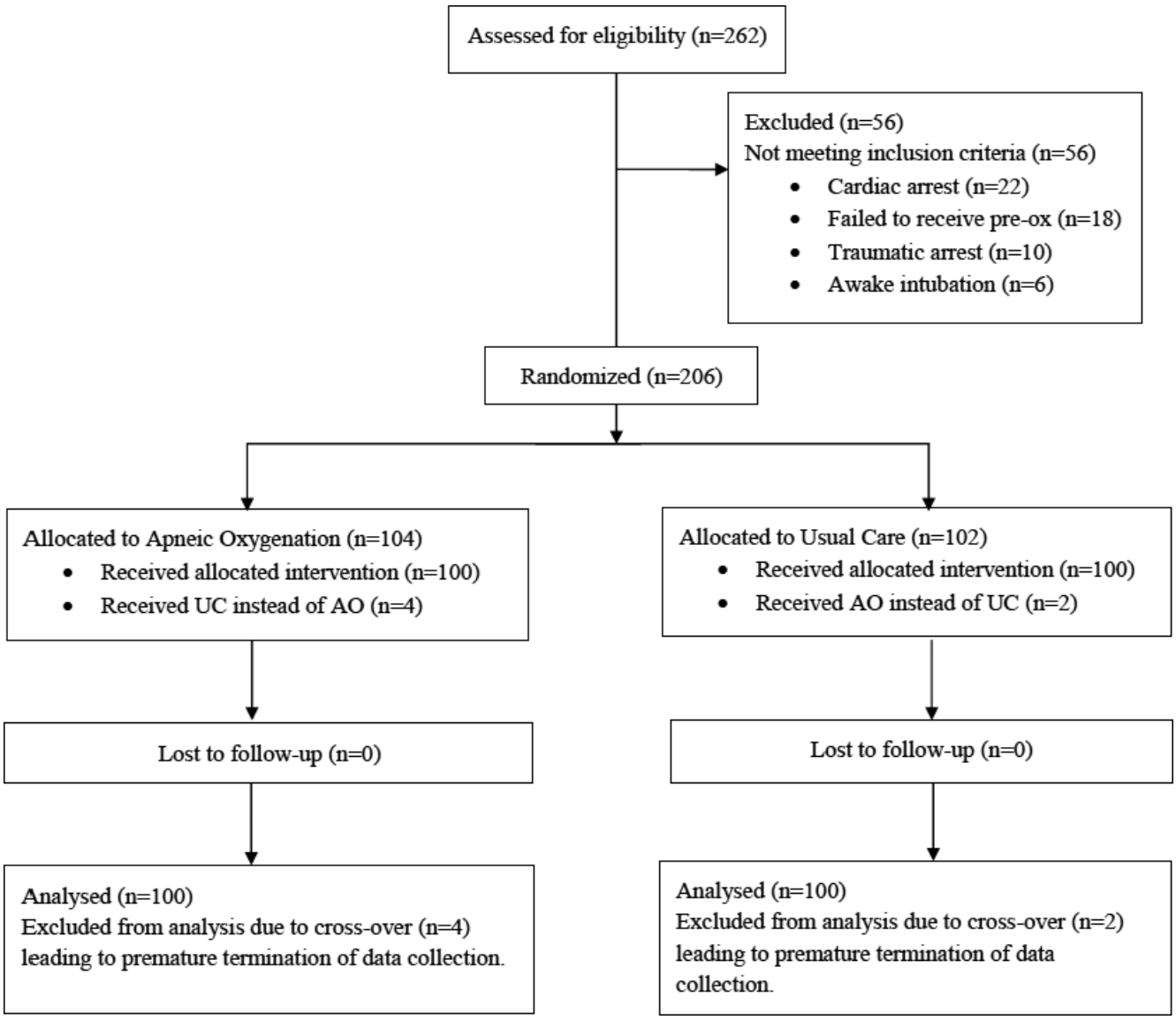

Figure 1. Enrollment flow diagram for the study. AO = apneic oxygenation; UC = usual care.

Table 1
Patient Demographics

	AO (*n* = 100)	95% CI	UC (*n* = 100)	95% CI
Age (y), mean	54.2	51.3–57	55.1	53.8–60
Sex (% male)	58	48–67	59	49–68
Indication for intubation (%)				
Pulmonary	61	50–70	59	48–68
Trauma	13	5–19	11	7–21
Neurologic	7	3–14	8	3–15
Cardiac	2	0–7	3	0–9
Other	17	10–26	19	12–28
Level of training				
EM PGY-1	11	5–19	13	7–21
EM PGY-2	36	26–46	31	22–41
EM PGY-3	22	14–31	24	16–33
EM PGY-4	25	16–33	29	20–39
Attending	5	1–11	3	0–9
Device used (%)				
Direct laryngoscopy	52	42–62	54	44–63
Video laryngoscopy	48	38–58	46	36–56
ASA (mean)	2.67	2.43–2.9	2.69	2.47–2.9
Predicted DA (%)	47	37–47	49	38–59
(L)ook	15	8–23	17	10–26
(E)3:3:2 Rule	27	18–36	24	16–33
(M)allampati, mean	2.2	2–2.3	2.25	2–2.4
(O)bstruction/(O)besity	2.5	0–8	3	0–9
(N)eck mobility	30	21–40	29	20–39
Preoxygenation technique (%)				
NRB (flush rate)	84	72–88	82	70–87
BiPAP	14	8–22	15	8–23
BVM	2	0–8	3	0–9
Preoxygenation duration (min)	13	2–19	13	2–19
C-L view, mean	1.41	1.31–1.5	1.48	1.34–1.61

AO = apneic oxygenation; ASA = American Society of Anesthesia; BVM = bag-valve mask; C-L = Cormack-Lehane; DA = difficult airway; NRB = nonrebreather; PGY = postgraduate year.

patients with prolonged apnea times (>130 seconds) that did not desaturate to an average SpO_2 less than 90 (*n* = 22). There was no difference in oxygen saturation between the groups at any of these time intervals. First-pass intubation success was not obtained in 22 patients. Fifteen patients in this group had multiple subsequent attempts made without assisted ventilation between attempts. Interestingly, all 15 patients had prolonged apnea times (mean = 144 seconds) without desaturation and indications for intubation were for etiologies other than pulmonary.

DISCUSSION

In this first randomized controlled trial investigating the use of AO during the intubation of ED patients, we found that the application of AO offered no benefit in terms of preventing desaturation, increasing the time to desaturation, or the lowest mean oxygen saturation. The demographics of our patient population and of the physicians who performed the intubations, as well as the first-pass success rates, are similar to other reported studies.[17,18] The indications for intubation, mainly pulmonary, were also similar to other studies.[19] We found similar results of desaturation as has been previously reported with about one in four patients desaturating (defined as SpO2 < 93% in a recent cross-sectional study utilizing continuous vital signs during the peri-intubation period).[20] The results of the primary outcome are similar to the FELLOW trial, the only other randomized controlled trial of similar size. This study is different from the FELLOW

Table 2
Difference in Outcomes for the Groups

	AO (n = 100)	95% CI	UC (n = 100)	95% CI	Repeated-measure ANOVA p-value
Apnea time (sec)	64	58–70	58	50–66	–
Mean SpO_2 prior–preoxygenation	92	90–93	92	91to 94	0.08
Mean SpO_2 at NMB paralysis	98	97–99	98	97–99	0.96
Mean SpO_2 at first look	98	97–99	98	97–99	0.7
Mean lowest SpO_2	92	91–93	93	92–94	0.08
SpO_2 at 2 minutes	99	98–99	99	98–99	0.4
Decrease in SpO_2	6	5–8	6	4–7	–
% SpO_2 < 90	17	10–25	15	9–23	–
% SpO_2 < 80	3	1–8	4	2–10	–
Mortality within 24 h (%)	4	2–10	2	0–7	–
Total mortality (%)	14	9–22	16	10–24	–

ANOVA = analysis of variance; NMB = neuromuscular blocker.

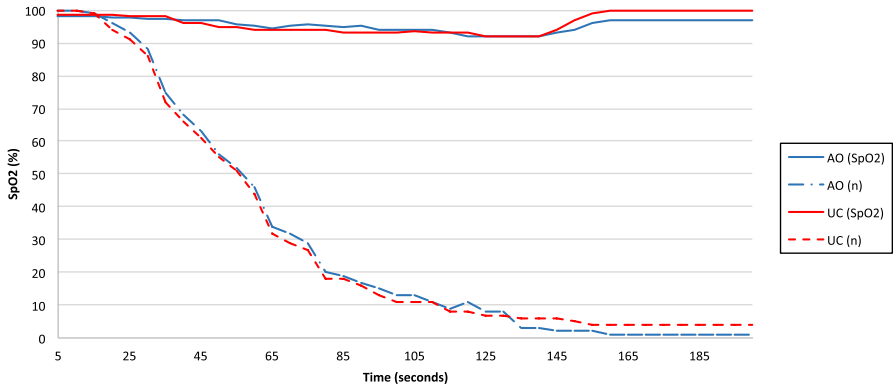

Figure 2. Mean SpO_2 and number of patients intubated over time. AO = apneic oxygenation; UC = usual care. [Color figure can be viewed at wileyonlinelibrary.com]

trial in that all patients received preoxygenation to accepted standards to minimize impact of failure to denitrogenate the lungs on apnea time and control for this confounding variable, which affects periprocedural desaturation rates.

Previous studies on the use of AO in the prehospital and ED settings have been retrospective or observational.[13–15] These studies used self-reporting by the intubating physician, and we chose to use real-time data collection by trained independent observers to eliminate the underestimation of periprocedural adverse events. Furthermore, our limited exclusion criteria prior to randomization support the generalizability of our findings to any ED patient who can be adequately preoxygenated for the standard of care (RSI) for ED patients requiring intubation.

The fact that no difference was found between the two groups does not mean that the application of apneic oxygen does not work, especially for patients with prolonged apnea times. As this was a real-world application of potentially therapeutic supplemental oxygenation during the apneic period, deliberately prolonging apnea time would be unethical, and patients were intubated with the shortest achievable apnea time. The majority of patients were intubated with low C-L graded views within 1 minute after confirmation of apnea, and since all patients received proper preoxygenation, this study demonstrates that AO may not be useful in the majority of patients that can be fully preoxygenated and intubated in a reasonable amount of time. Our results also demonstrate that patients may not suffer a precipitous a drop in oxygen saturation as was previously thought.[8,9,20] This is further supported by our results that showed no difference in rates of moderate (SpO_2 < 90) or severe (SpO_2 < 80%) desaturation between the two groups. This is an important point because it remains unknown whether apneic oxygen could benefit patients undergoing crash

intubations which preclude preoxygenation with a goal of an FiO_2 of 100% for 3 minutes. As stated earlier, there was a subgroup of patients with prolonged apnea times (>130 seconds) that did not desaturate to an average SpO_2 less than 90 (n = 22). Seven of these patients received assisted ventilations to be resaturated before subsequent attempt. In those 15 patients that did not receive assisted ventilations and had multiple attempts causing apnea times greater than 2 minutes, it remains unclear whether their ability to maintain their oxygenation was a function of the preoxygenation, the lack of pulmonary indication for intubation, or a combination of both.[14] It also remains unclear how these patients age, metabolic rates, whether they were obesity or severity of their underlying illness impacted on this as well.

LIMITATIONS

There are several limitations to this study. First, we utilized a real-time data collection form for most of our study outcomes as self-reporting by emergency providers has been shown to underestimate adverse events and the time to intubation.[20] Furthermore, because this was a single-center study at an academic ED with a residency training program, our results may not be generalizable to nonacademic centers.

CONCLUSION

In summary, this study demonstrated that in patients that are properly preoxygenated during rapid sequence intubation in the ED, the application of apneic oxygenation did not lead to any differences in lowest mean oxygen saturation, desaturation rates between the two groups, or intubation success without hypoxemia. The application of apneic oxygenation during rapid sequence intubation did not prevent oxygen desaturation of patients in the ED who could be preoxygenated appropriately. In light of these findings, apneic oxygenation may be used on all patients requiring rapid sequence intubation in the ED but with the understanding that it likely has little no impact on patient desaturation rates.

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Supporting Information

The following supporting information is available in the online version of this paper available at http://onlinelibrary.wiley.com/doi/10.1111/acem.13274/full

Data Supplement S1. ED intubation checklist.