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Emerge**N**cy **D**epartment use of **A**pneic **O**xygenation 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 1 trauma center. All patients requiring intubation were included. Exclusion criteria were patients in cardiac or traumatic arrest or if pre-oxygenation 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 apneic oxygenation (n=100) or usual care (n=100) by pre-determined randomization in a 1:1 ratio.

Results

Two-hundred and six patients were enrolled. There was no difference in lowest mean oxygen saturation between the two groups (92, 95% 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.

Introduction:

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 pre-oxygenation, 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) in order 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 last 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 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 USA and Australia (10, 13-15). A recent randomized controlled trial (RCT) (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 ICU[10]. Apneic oxygenation has been retrospectively and prospectively studied in pre-hospital, emergency department (ED), critical care, and operating room settings; and these studies refute the results of the FELLOW Trial. [11-15].

Although studies have started to 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-1 trauma center in New York City. The annual census of the emergency department 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 emergency department requiring endotracheal intubation was screened for inclusion into the study. Patients were excluded from the study if they were not pre-oxygenated 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 apneic oxygenation (intervention) or usual care (control). The sequence of study group assignments were 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 emergency department were randomized to receive supplemental oxygen via nasal cannula (NC) (CareFusion AirLife, France) 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 pre-oxygenation technique (flush flow rate NRB vs. BiPAP vs. BVM), RSI medications and technique (video versus direct laryngoscopy) was left to the discretion of the attending physician caring for the patient. Pre-oxygenation was conducted with flush flow rate NRB, BVM connected to 100% oxygen wall supply, or with BiPAP on 100% FiO2. 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 pre-oxygenation.

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 appendix for data collection sheet). Vital signs were obtained from the patient's monitor (Philips Intellivue, Philips USA) which is transmitted to a central monitoring system which 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 in order 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 two minutes following intubation. 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.

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 percent 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 percent 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% 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 non-normally distributed continuous variables.

The primary analysis was a comparison of patients randomized to apneic oxygenation versus usual care with regard to the primary outcome of lowest arterial oxygen saturation. A repeated measures analysis of variance 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 < 0.05 and 95% confidence intervals are reported. All analyses were performed using XLStat (Addinsoft, New York, NY).

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 (2 patients assigned to the UC group received AO, and 4 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 fifty-six 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 ten percent of cases enrolled for observer quality assurance.

Main Results:

There was no difference in lowest average oxygen saturation during the peri-procedural period (Table 2). Figure 2 demonstrates the average SpO_2 and successful intubations over time. The repeated measures analysis of variance demonstrated no difference overtime between the groups

(see table 4, Mauchly's statistic 0.08, Huynt-Feldt Epsilon 0.58, between group effect p=0.1). Over seventy percent of patient were successfully intubated by 60 seconds, 80 percent by eighty seconds, 90 percent by 100 seconds, and 100 percent by 195 seconds. There was a sub-group of 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 twenty-two patients. Fifteen patients in this group had multiple subsequent attempts made without assisted ventilation between attempts. Interestingly, all fifteen patients had prolonged apnea times (average 144 seconds) without desaturation and indications for intubation were for etiologies other than pulmonary.

Limitations

There are several limitations to this study. Firstly, we utilized a real-time data collection form for most of our study outcomes asself-reporting by emergency providers has been shown to underestimate adverse events and the time to intubation[17]. Furthermore, because this was a single center study at an academic emergency department with a residency training program, our results may not be generalizable to non-academic centers.

Discussion

In this first randomized controlled trial investigating the use of apneic oxygenation during the intubation of emergency department 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[18,19]. The indications for intubation, mainly pulmonary, were also similar to other studies[20]. We found similar results of desaturation as has been previously reported with about 1 in four patients desaturating (defined as SpO2 <93% in a recent cross-sectional study utilizing continuous vital signs during the peri-intubation period)[23]. 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 trial in that all patients received pre-oxygenation to accepted standards in order to minimize impact of failure to denitrogenate the lungs on apnea time and control for this confounding variable, which affects peri-procedural desaturation rates. Previous studies on the use of apneic oxygenation in the pre-hospital and ED settings have been retrospective or observational[13,14,15]. 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 peri-procedural adverse events. Furthermore, our limited exclusion criteria prior to randomization support the generalizability of our findings to any ED patient who can be adequately pre-oxygenated 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 pre-oxygenation, this study demonstrates that apneic oxygenation may not be useful in the majority

of patients that can be fully pre-oxygenated 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[8,9,21]. This is further supported by our results which 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 pre-oxygenation with a goal of an FiO_2 of 100% for three minutes. As stated earlier, there was a sub-group 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 fifteen 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 pre-oxygenation, 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.

Conclusion

In summary, this study demonstrated that in patients that are properly pre-oxygenated during RSI in the emergency department, 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 AO during RSI did not prevent oxygen desaturation of patients in the emergency department who could be pre-oxygenated appropriately. In light of these findings, ApOx may be used on all patients requiring RSI in the ED but with the understanding that it likely has little no impact on patient desaturation rates.

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

Table 1: Demonstrates the patient demographics. PGY= post graduate year; ASA= American Society of Anesthesia, NRB= non-rebreather, BVM= bag valve mask, C-L= Cormack-Lehane.

	AO (n=100)	95% CI	UC (n=100)	95% CI	Repeated Measure ANOVA
Apnea Time (sec)	64	58 to 70	58	50 to 66	-
Mean SpO_2 Prior to Pre-Ox	92	90 to 93	92	91to 94	p=0.08
Mean SpO_2 at NMB Paralysis	98	97 to 99	98	97 to 99	p=0.96
Mean SpO_2 at First Look	98	97 to 99	98	97 to 99	p=0.7
Mean Lowest SpO_2	92	91 to 93	93	92 to 94	p=0.08
SpO_2 at 2 minutes	99	98 to 99	99	98 to 99	p=0.4
Decrease in SpO_2	6	5 to 8	6	4 to 7	-
% SpO_2 <90	17	10 to 25	15	9 to 23	-
% SpO_2 <80	3	1 to 8	4	2 to 10	-
Mortality within 24 hours (%)	4	2 to 10	2	0 to 7	-
Total Mortality (%)	14	9 to 22	16	10 to 24	-

Table 2: Demonstrates the difference in outcomes for the groups. NMB= neuromuscular blocker.

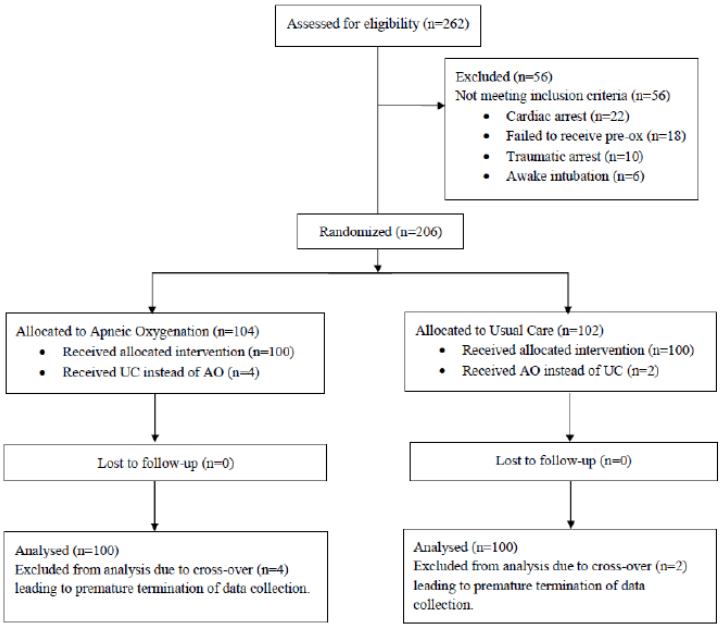

Figure 1: demonstrates the enrollment flow diagram for the study. AO= Apneic Oxygenation.