

EDITORIAL



Preventing Dogma from Driving Practice

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Clinicians generally know that many practices persist in medicine without clear evidence to support them. One such example is the approach to endotracheal intubation of critically ill patients in the intensive care unit (ICU), where intubation is typically fraught with substantially more risk than in the controlled setting of the operating room. Patients in the ICU are often far less clinically stable, and other forms of less invasive support have failed. These patients have a lack of physiological reserve and, as a result, are prone to rapid decompensation in the peri-intubation period. Equally important, they may not be fasting at the time of intubation, which places them at risk for aspiration of gastric contents and the associated complications.

Originally described in 1970,¹ rapid-sequence intubation arose as a tool to shorten the time until intubation and minimize the risk of gastric aspiration. In current practice, a period of pre-oxygenation is followed by the administration of an induction agent, such as propofol or etomidate, and a neuromuscular blocking agent (e.g., succinylcholine or rocuronium). Given the rapid onset of action of these medications (around 60 seconds to onset of paralysis, depending on the dose), the use of these drugs markedly shortens the period of apnea before direct laryngoscopy.

Although some studies²⁻⁴ have called for avoiding manual ventilation after induction to prevent gastric insufflation and aspiration, others have recommended the provision of manual ventilation in specific cohorts of patients.⁵⁻⁷ However, debate around this issue has been limited by a lack of high-quality data documenting the risks of aspiration and other potential benefits of manual ventilation. To address this long-standing

question, Casey and colleagues⁸ now report in the *Journal* the results of the randomized, multicenter PreVent (Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation) trial, which examined the effect of positive-pressure ventilation with a bag-mask device (bag-mask ventilation), as compared with no manual ventilation, on oxygenation and risk of aspiration during the apneic phase of rapid-sequence intubation. In this trial, which enrolled 401 patients in seven ICUs, the primary outcome was the lowest oxygen saturation observed during the interval between induction and 2 minutes after tracheal intubation. Additional outcomes included the number of patients with severe hypoxemia (oxygen saturation, <80% during the same period of monitoring) and other direct and indirect markers of aspiration.

Although the investigators found that the median nadir of oxygen saturation was higher in the bag-mask group than in the control group (96% vs. 93%, $P=0.01$), this difference is probably not clinically relevant. Of greater potential importance is the fact that 45 of the patients in the control group had severe hypoxemia, as compared with 21 in the intervention group. The trial did not show any difference in life-threatening events or deaths associated with these periods of severe hypoxemia but was probably underpowered to detect such differences.

Using multiple measures to detect aspiration (including report by the proceduralist, changes in positive end-expiratory pressure or fraction of inspired oxygen, and development of new radiographic opacities after intubation), the investigators found no significant difference in the incidence of aspiration. Although the trial sample

size is too small to convincingly state that there is no increased risk of aspiration associated with bag-mask ventilation, the findings provide a measure of reassurance that the application of manual ventilation is not likely to cause clinically significant harm.

An important limitation of the trial is the failure to standardize the preoxygenation strategy and the subsequent result that more patients in the bag-mask ventilation group than in the control group received bag-mask ventilation before induction (39.7% vs. 10.9%). The fact that the median oxygen saturation before induction was the same in the two groups (99%) does not preclude marked differences in the arterial partial pressure of oxygen. That is because an oxygen saturation of 100% can be associated with an arterial partial pressure of oxygen that is anywhere from 110 mm Hg to nearly 600 mm Hg, given the shape of the hemoglobin–oxygen dissociation curve.⁹ On the basis of differences in preoxygenation strategies, it is conceivable the bag-mask group had a significantly higher arterial partial pressure of oxygen than the control group and greater reserve protecting against peri-intubation hypoxemia. On the surface, the exclusion of patients with severe hypoxemia at the time of intubation may seem like another important limitation. However, the condition of such patients is often so unstable that more aggressive forms of support, including noninvasive positive-pressure ventilation or bag-mask ventilation, are required in the peri-intubation period to prevent decompensation, regardless of the risk of aspiration.

In the eyes of all clinicians managing airways in the ICU, the results of this rigorous, multi-center trial may not settle the question of the safety of bag-mask ventilation during rapid-sequence intubation. However, the findings provide a strong suggestion that the practice is not harmful. More important, they show the feasibility of conducting a well-designed trial with the goal of questioning one of the long-standing dogmas that too often restrict our clinical practice.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

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ORIGINAL ARTICLE

Bag-Mask Ventilation during Tracheal Intubation of Critically Ill Adults

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ABSTRACT

BACKGROUND

Hypoxemia is the most common complication during tracheal intubation of critically ill adults and may increase the risk of cardiac arrest and death. Whether positive-pressure ventilation with a bag-mask device (bag-mask ventilation) during tracheal intubation of critically ill adults prevents hypoxemia without increasing the risk of aspiration remains controversial.

METHODS

In a multicenter, randomized trial conducted in seven intensive care units in the United States, we randomly assigned adults undergoing tracheal intubation to receive either ventilation with a bag-mask device or no ventilation between induction and laryngoscopy. The primary outcome was the lowest oxygen saturation observed during the interval between induction and 2 minutes after tracheal intubation. The secondary outcome was the incidence of severe hypoxemia, defined as an oxygen saturation of less than 80%.

RESULTS

Among the 401 patients enrolled, the median lowest oxygen saturation was 96% (interquartile range, 87 to 99) in the bag-mask ventilation group and 93% (interquartile range, 81 to 99) in the no-ventilation group ($P=0.01$). A total of 21 patients (10.9%) in the bag-mask ventilation group had severe hypoxemia, as compared with 45 patients (22.8%) in the no-ventilation group (relative risk, 0.48; 95% confidence interval [CI], 0.30 to 0.77). Operator-reported aspiration occurred during 2.5% of intubations in the bag-mask ventilation group and during 4.0% in the no-ventilation group ($P=0.41$). The incidence of new opacity on chest radiography in the 48 hours after tracheal intubation was 16.4% and 14.8%, respectively ($P=0.73$).

CONCLUSIONS

Among critically ill adults undergoing tracheal intubation, patients receiving bag-mask ventilation had higher oxygen saturations and a lower incidence of severe hypoxemia than those receiving no ventilation. (Funded by Vanderbilt Institute for Clinical and Translational Research and others; PreVent ClinicalTrials.gov number, NCT03026322.)

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MORE THAN 1.5 MILLION PATIENTS undergo tracheal intubation each year in the United States.¹ Up to 40% of tracheal intubations in the intensive care unit (ICU) are complicated by hypoxemia, which may lead to cardiac arrest and death.²⁻⁷

For critically ill adults undergoing tracheal intubation, the nearly simultaneous administration of a sedative and a neuromuscular blocking agent (rapid-sequence induction) facilitates intubation on the first laryngoscopy attempt.⁸⁻¹⁰ However, rapid-sequence induction involves an inherent delay of 45 to 90 seconds between medication administration and initiation of laryngoscopy.¹¹ Whether providing positive-pressure ventilation with a bag-mask device (bag-mask ventilation) during this interval prevents hypoxemia without increasing the risk of gastric or oropharyngeal aspiration has been debated for nearly 50 years.¹²⁻¹⁴ Some guidelines recommend providing bag-mask ventilation between induction and laryngoscopy to all patients, including those who are not initially hypoxemic.^{12,15-17} Other guidelines recommend avoiding bag-mask ventilation between induction and laryngoscopy except to treat hypoxemia, a recommendation that prioritizes the perceived risk of aspiration over the potential benefits of preventing hypoxemia.^{11,13,18,19}

To determine the effect of bag-mask ventilation on hypoxemia during tracheal intubation of critically ill adults, we conducted the Preventing Hypoxemia with Manual Ventilation during Endotracheal Intubation (PreVent) trial. We hypothesized that as compared with no ventilation between induction and laryngoscopy, bag-mask ventilation would significantly increase the lowest oxygen saturation during the interval between induction and 2 minutes after tracheal intubation.

METHODS

TRIAL DESIGN AND OVERSIGHT

From March 15, 2017, to May 6, 2018, we conducted a multicenter, parallel-group, unblinded, pragmatic, randomized trial comparing bag-mask ventilation with no ventilation during the interval between induction (administration of a sedative medication) and laryngoscopy during tracheal intubation of critically ill adults. The trial was approved by either the central institutional review board at Vanderbilt University Medical Center or the local institutional review board at

each trial site; the requirement for informed consent was waived. (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

The trial was registered online before initiation and was overseen by an independent data and safety monitoring board. The protocol and statistical analysis plan (also available at NEJM.org) were published before the conclusion of enrollment.²⁰ The authors designed the trial, collected the data, and performed the analyses. The institutions that provided funding to the Vanderbilt Institute for Clinical and Translational Research had no role in the conception, design, or conduct of the trial, nor did their representatives participate in the collection, management, analysis, interpretation, or presentation of the data or in the preparation, review, or approval of the manuscript. All the authors revised the manuscript, vouch for the accuracy and completeness of the data, and approved the decision to submit the manuscript for publication.

TRIAL SITES AND PATIENT POPULATION

The trial was conducted in seven academic ICUs across the United States. (Details regarding the trial sites are provided in the Supplementary Appendix.) Adults (age, ≥ 18 years) undergoing induction and tracheal intubation in a participating ICU were eligible. Patients were excluded if they were pregnant, were incarcerated, or had such an immediate need for tracheal intubation that randomization was precluded or if the treating clinicians had determined that ventilation between induction and laryngoscopy was either required (e.g., as a treatment for hypoxemia or severe acidemia) or contraindicated (e.g., because of an increased risk of aspiration from ongoing emesis, hematemesis, or hemoptysis). Complete lists of inclusion and exclusion criteria are provided in the Supplementary Appendix.

RANDOMIZATION

Patients underwent randomization in a 1:1 ratio to undergo either bag-mask ventilation or no ventilation in permuted blocks of 2, 4, and 6, stratified according to trial site. Trial-group assignments were placed in sequentially numbered opaque envelopes and remained concealed until after enrollment. Given the nature of the intervention, patients, clinicians, and research personnel were aware of trial-group assignments after randomization.

TRIAL INTERVENTIONS

For patients who were assigned to the bag-mask ventilation group, bag-mask ventilation was provided by treating clinicians during the interval from induction until the initiation of laryngoscopy. Structured education regarding best practices in bag-mask ventilation included the use of oxygen flow rates of at least 15 liters per minute, a valve attached to the expiratory port of the bag-mask device to generate a positive end-expiratory pressure of 5 to 10 cm of water, an oropharyngeal airway, a two-handed mask seal performed by the intubating clinician with a head-tilt and chin-lift maneuver, and ventilation at 10 breaths per minute with the smallest volume required to generate a visible chest rise.²¹ Failure to administer bag-mask ventilation at the start of induction was recorded as a protocol violation. (Details regarding bag-mask ventilation practices are provided in the Supplementary Appendix.)

For patients who were assigned to the no-ventilation group, bag-mask ventilation between induction and laryngoscopy was not permitted, except after a failed attempt at laryngoscopy, as treatment for hypoxemia (oxygen saturation, <90%), or at any point if the treating clinicians determined that such treatment was necessary for the safety of the patient. Administration of bag-mask ventilation before the first laryngoscopy attempt in the absence of an oxygen saturation of less than 90% was recorded as a protocol violation.

Noninvasive ventilation during the interval between induction and laryngoscopy was not allowed in either trial group because it could confound the provision of bag-mask ventilation. All other aspects of the procedure were deferred to treating clinicians. Specifically, all methods of pre-oxygenation, including noninvasive ventilation, were allowed in either group before induction. Because a previous trial in a similar setting showed no benefit for the use of supplemental oxygen without ventilation during the interval between induction and tracheal intubation (apneic oxygenation),² apneic oxygenation was not mandated but was allowed in either group.

DATA COLLECTION

A trained nurse or physician who was not involved in the performance of the procedure collected data for periprocedural outcomes, including oxygen saturation and systolic blood pressure at the time of induction, lowest oxygen saturation

and lowest systolic blood pressure during the interval between induction and 2 minutes after tracheal intubation, and the time from induction to intubation. Immediately after each intubation, the operator reported the Cormack–Lehane grade of glottic view,²² subjective difficulty of tracheal intubation, airway complications during the procedure, and the level of operator experience. Trial personnel collected data regarding baseline characteristics, management before and after laryngoscopy, and clinical outcomes from the medical record.

OUTCOMES

The primary outcome was the lowest oxygen saturation (as measured by continuous pulse oximetry) observed during the interval between induction and 2 minutes after tracheal intubation. The single prespecified secondary outcome was the incidence of severe hypoxemia, which was defined as an oxygen saturation of less than 80% during the same interval.

To capture objective clinical manifestations of periprocedural oropharyngeal or gastric aspiration, trial personnel collected measurements of oxygen saturation, fraction of inspired oxygen, and positive end-expiratory pressure, recorded as part of routine care in the 24 hours after intubation. The worst value for each variable between 6 and 24 hours after tracheal intubation was considered to be a main safety outcome.

Additional procedural outcomes included operator-reported oropharyngeal or gastric aspiration and the presence of a new opacity on chest radiography within 48 hours after tracheal intubation. The presence of a new opacity was adjudicated by independent review of chest radiographs by two pulmonary and critical care–medicine attending physicians who were unaware of trial-group assignments and outcomes. (Additional details regarding trial outcomes are provided in the Supplementary Appendix.)

STATISTICAL ANALYSIS

Details regarding the determination of the sample size have been reported previously.²⁰ Assuming a standard deviation of 14% in the lowest oxygen saturation and less than 5% missing data, we determined that the enrollment of 350 patients would provide a power of 90% at a two-sided alpha level of 0.05 to detect an absolute between-group difference of 5 percentage points in the lowest oxygen saturation. As specified in

the initial trial protocol, the standard deviation for the lowest oxygen saturation in the control group was examined at the interim analysis. At that time, the data and safety monitoring board recommended increasing the sample size to 400 patients to maintain the 90% statistical power to detect a between-group difference of 5 percentage points in the lowest oxygen saturation. (Additional details are provided in the Supplementary Appendix.)

The primary analysis was an unadjusted, intention-to-treat comparison of the lowest oxygen saturation among patients in the two trial groups with the use of the Mann–Whitney rank-sum test. Sensitivity analyses used alternate definitions of the lowest oxygen saturation, imputed missing data for the lowest oxygen saturation, and evaluated the marginal effect of the trial group on the lowest oxygen saturation after accounting for prespecified confounders²³ and correlation of measurements within each trial unit with the use of generalized estimating equations. Linear regression models were fit to assess for a possible effect modification by baseline variables. (Additional details are provided in the Supplementary Appendix.)

In a per-protocol analysis, patients who had received bag-mask ventilation to prevent hypoxemia before the first attempt at laryngoscopy were compared with patients who had not received bag-mask ventilation. Patients who had received bag-mask ventilation after a failed attempt at laryngoscopy or as treatment for hypoxemia were assessed with their assigned group.

After the enrollment of 175 patients, the data and safety monitoring board conducted a single interim analysis comparing the lowest oxygen saturation between groups using a Haybittle–Peto stopping boundary for efficacy of $P < 0.001$. For the final analysis of the primary outcome, a two-sided P value of less than 0.05 was considered to indicate statistical significance. Between-group differences in secondary and exploratory outcomes are reported with the use of point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used to infer definitive differences in treatment effects between groups. All analyses were performed with the use of Stata software, version 15.1 (StataCorp), or statistical software R, version 3.3.0 (R Foundation for Statistical Computing).

RESULTS

PATIENTS

Of the 667 screened patients who met the inclusion criteria, 401 (60.1%) met no exclusion criteria and were enrolled (Fig. S1 in the Supplementary Appendix). The median age was 60 years; nearly 50% of patients had sepsis or septic shock, and nearly 60% had hypoxemic respiratory failure as an indication for tracheal intubation. A total of 199 patients were assigned to undergo bag-mask ventilation, and 202 were assigned to undergo no ventilation (Table 1, and Tables S1 through S5 in the Supplementary Appendix).

MANAGEMENT BETWEEN ENROLLMENT AND INDUCTION

Preoxygenation with the use of a bag-mask device before induction was more common among patients in the bag-mask ventilation group than among those in the no-ventilation group (39.7% vs. 10.9%; relative risk, 3.65; 95% confidence interval [CI], 2.37 to 5.60) (Table 2, and Table S6 in the Supplementary Appendix). Conversely, preoxygenation with a noninvasive ventilator or high-flow nasal cannula was less common among patients in the bag-mask ventilation group than among those in the no-ventilation group (27.6% vs. 44.1%; relative risk, 0.63; 95% CI, 0.48 to 0.82). The oxygen saturation at the time of induction did not significantly differ between groups (Table 2, and Tables S6 and S7 and Fig. S2 in the Supplementary Appendix). All the patients received an induction medication, and 97.5% of the patients in each group received a neuromuscular blocking agent; the choice or dose of medication did not differ significantly between groups (Table S8 in the Supplementary Appendix).

MANAGEMENT BETWEEN INDUCTION AND INTUBATION

A total of 198 patients (99.5%) in the bag-mask ventilation group received bag-mask ventilation to prevent hypoxemia before the first attempt at laryngoscopy, as compared with 5 patients (2.5%) in the no-ventilation group (Table 2, and Table S9 and Fig. S1 in the Supplementary Appendix). The time from induction to laryngoscopy during which bag-mask ventilation could be provided was 98 seconds (interquartile range,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Bag-Mask Ventilation (N=199)	No Ventilation (N=202)
Median age (IQR) — yr	59 (45–67)	60 (48–68)
Male sex — no. (%)	118 (59.3)	108 (53.5)
White race — no. (%)†	141 (70.9)	134 (66.3)
Median body-mass index (IQR)‡	27.1 (22.7–32.3)	27.6 (23.4–34.2)
Median APACHE II score (IQR)§	22 (16–29)	22 (16–28)
Receipt of vasopressor — no. (%)	35 (17.6)	40 (19.8)
Active medical conditions — no. (%)¶		
Sepsis or septic shock	98 (49.2)	97 (48.0)
Pneumonia	57 (28.6)	80 (39.6)
Acute respiratory distress syndrome	22 (11.1)	21 (10.4)
Aspiration	14 (7.0)	12 (5.9)
Gastrointestinal bleeding	31 (15.6)	18 (8.9)
Altered mental status	92 (46.2)	82 (40.6)
Indication for intubation — no. (%)¶		
Hypoxemic respiratory failure	117 (58.8)	116 (57.4)
Hypercarbic respiratory failure	39 (19.6)	55 (27.2)
Airway protection for decreased level of consciousness	74 (37.2)	76 (37.6)
Before procedure	21 (10.6)	13 (6.4)
One or more difficult airway characteristics — no. (%)	95 (47.7)	102 (50.5)
One or more risk factors for aspiration — no. (%)**	123 (61.8)	117 (57.9)
Bilevel positive airway pressure in previous 6 hr — no. (%)	44 (22.1)	57 (28.2)
Median highest fraction of inspired oxygen in previous 6 hr (IQR)	0.4 (0.3–1.0)	0.5 (0.3–1.0)
Median lowest oxygen saturation in previous 6 hr (IQR) — %	91 (87–95)	92 (88–95)
Median lowest ratio of oxygen saturation to fraction of inspired oxygen in previous 6 hr (IQR)	202 (94–303)	189 (97–294)

* The only significant differences in baseline characteristics between the two trial groups were the proportion of patients with pneumonia ($P=0.02$) and gastrointestinal bleeding ($P=0.04$). IQR denotes interquartile range.

† Race was reported by patients or their surrogates and recorded in the electronic health record as a part of routine clinical care.

‡ At enrollment, data on body-mass index (the weight in kilograms divided by the square of the height in meters) were missing for five patients (1.2%): three in the bag-mask ventilation group and two in the no-ventilation group.

§ Scores on the Acute Physiology and Chronic Health Evaluation (APACHE) II range from 0 to 71, with higher scores indicating a greater severity of illness.

¶ Patients could have more than one condition or indication.

|| Difficult airway characteristics included a body-mass index of more than 30, obstructive sleep apnea, upper gastrointestinal bleeding, limited mouth opening, limited neck mobility, active vomiting or witnessed aspiration, airway mass or infection, epistaxis or oral bleeding, and head or neck radiation.

** Risk factors for aspiration included narcotic use, functional or mechanical gastrointestinal obstruction, previous esophageal surgery, head injury, active emesis, active upper gastrointestinal bleeding, and gastroesophageal reflux disease.

65 to 135) in the bag-mask ventilation group and 72 seconds (interquartile range, 52 to 120) in the no-ventilation group (mean difference, 13.8 seconds; 95% CI, -1.1 to 28.6) (Table 2, and Table S10 in the Supplementary Appendix). Among the patients who received bag-mask ventilation (198

in the ventilation group and 44 in the no-ventilation group), the percentage of patients in whom an oropharyngeal airway was used (39.4% vs. 47.7%; relative risk, 0.83; 95% CI, 0.58 to 1.18) and the percentage in whom a head-tilt and chin-lift or jaw-thrust maneuver was used (83.3%

Table 2. Characteristics of the Intubation Procedure.

Characteristic	Bag-Mask Ventilation (N = 199)	No Ventilation (N = 202)	Relative Risk or Mean Difference (95% CI)
Before induction			
Preoxygenation method — no. (%) [*]			
Bag-mask device	79 (39.7)	22 (10.9)	3.65 (2.37 to 5.60)
Bilevel positive airway pressure [†]	32 (16.1)	48 (23.8)	0.68 (0.45 to 1.01)
High-flow nasal cannula [‡]	23 (11.6)	41 (20.3)	0.57 (0.36 to 0.91)
Non-rebreather mask	54 (27.1)	62 (30.7)	0.88 (0.65 to 1.20)
Standard nasal cannula [‡]	17 (8.5)	24 (11.9)	0.72 (0.40 to 1.30)
No preoxygenation	3 (1.5)	7 (3.5)	0.44 (0.11 to 1.66)
Preoxygenation with positive pressure — no. (%) [§]	132 (66.3)	111 (55.0)	1.21 (1.03 to 1.42)
Oxygen saturation at induction [¶]			
Median (IQR) — %	99 (95–100)	99 (96–100)	−0.6 (−1.4 to 0.3)
<92% — no./total no. (%)	27/194 (13.9)	17/198 (8.6)	1.62 (0.91 to 2.88)
Median systolic blood pressure at induction (IQR) — mm Hg	122 (105–142)	123 (107–140)	0.0 (−5.5 to 5.6)
New vasopressor before induction — no./total no. (%)	27/197 (13.7)	29/200 (14.5)	0.95 (0.58 to 1.54)
Oxygenation and ventilation between induction and intubation			
Bag-mask ventilation between induction and laryngoscopy to prevent hypoxemia — no. (%) ^{**}	198 (99.5)	5 (2.5)	40.20 (16.91 to 95.53)
Bag-mask ventilation between induction and intubation for any indication — no. (%) ^{††}	198 (99.5)	44 (21.8)	4.57 (3.52 to 5.93)
Supplemental oxygen between induction and laryngoscopy — no. (%) ^{‡‡}	199 (100)	157 (77.7)	1.29 (1.20 to 1.39)
After induction^{§§}			
Median time from induction to laryngoscopy (IQR) — sec	98 (65–135)	72 (52–120)	13.8 (−1.1 to 28.6)
Median time from laryngoscopy to intubation (IQR) — sec	42 (25–72)	45 (30–71)	−11.5 (−30.5 to 7.5)
Median time from induction to intubation (IQR) — sec	158 (110–218)	130 (90–191)	7.7 (−15.6 to 31.0)
Video laryngoscope as initial device — no. (%)	71 (35.7)	65 (32.2)	1.11 (0.84 to 1.46)
Successful intubation on first attempt — no. (%)	167 (83.9)	162 (80.2)	1.05 (0.95 to 1.15)
Use of bougie — no. (%)	33 (16.6)	44 (21.8)	0.76 (0.51 to 1.14)

* More than one method could be used in each patient.

† In patients receiving bilevel positive airway pressure, inspiratory and expiratory settings were determined by the operator.

‡ Among the patients with high-flow nasal cannula, flow rates were up to 70 liters per minute of humidified oxygen. Among those with standard nasal cannula, flow rates were 6 liters per minute or less of nonhumidified oxygen.

§ Preoxygenation with positive pressure was defined as the use of a bag-mask device, bilevel positive airway pressure, or high-flow nasal cannula.

¶ Additional details regarding oxygen saturation at induction are provided in Table S7 and Figure S2 in the Supplementary Appendix.

|| The mean difference is indicated in this category.

** The receipt of bag-mask ventilation by five patients in the no-ventilation group was considered to be a protocol violation. Additional details on protocol violations are provided in Table S9 in the Supplementary Appendix.

†† Therapeutic bag-mask ventilation was allowed in the no-ventilation group after a failed attempt at laryngoscopy or in patients with an oxygen saturation of less than 90%.

‡‡ Supplemental oxygen in the bag-mask group was provided by means of bag-mask ventilation. Supplemental oxygen in the no-ventilation group was provided by means of a non-rebreather mask or a nasal cannula. Details are provided in Table S10 in the Supplementary Appendix.

§§ Data regarding the time from induction to laryngoscopy were missing for 15 patients (3.7%): 8 in the bag-mask ventilation group and 7 in the no-ventilation group; from laryngoscopy to intubation for 11 patients (2.7%): 7 in the bag-mask ventilation group and 4 in the no-ventilation group; and from induction to intubation for 9 patients (2.2%): 6 in the bag-mask ventilation group and 3 in the no-ventilation group.

vs. 88.6%; relative risk, 0.94; 95% CI, 0.83 to 1.06) were similar (Table S10 in the Supplementary Appendix).

A total of 157 patients (77.7%) in the no-ventilation group received supplemental oxygen between induction and laryngoscopy, primarily through a non-rebreather mask or a nasal cannula (Table 2, and Table S10 in the Supplementary Appendix). Additional characteristics of the tracheal intubation procedure are presented in Table 2, and in Table S11 in the Supplementary Appendix.

PRIMARY OUTCOME

The median lowest oxygen saturation was 96% (interquartile range, 87 to 99) in the bag-mask ventilation group and 93% (interquartile range, 81 to 99) in the no-ventilation group ($P=0.01$) (Fig. 1A). The mean difference in the lowest oxygen saturation between the bag-mask ventilation group and the no-ventilation group was 4.7 percentage points (95% CI, 2.5 to 6.8) after adjustment for prespecified covariates and within-unit correlation with the use of multivariable generalized estimating equations (Table S12 in the Supplementary Appendix).

In a post hoc analysis that was performed after adjustment for the provision of preoxygenation, for the preoxygenation device, and for the presence of pneumonia or gastrointestinal bleeding, the mean between-group difference in the lowest oxygen saturation was 5.2 percentage points (95% CI, 2.8 to 7.5) (Table S12 in the Supplementary Appendix). Results were similar in the per-protocol analysis and all sensitivity analyses (Table S13 in the Supplementary Appendix).

In prespecified subgroup analyses, the difference in the lowest oxygen saturation between the bag-mask ventilation group and the no-ventilation group was greater for patients with lower oxygen saturation at induction ($P=0.01$ for interaction) (Fig. 2, and Fig. S3 in the Supplementary Appendix). None of the other prespecified characteristics, including body-mass index, score on the Acute Physiology and Chronic Health Evaluation (APACHE) II, and operator experience, appeared to modify the effect of bag-mask ventilation on the lowest oxygen saturation (Fig. 2, and Figs. S3 through S5 in the Supplementary Appendix).

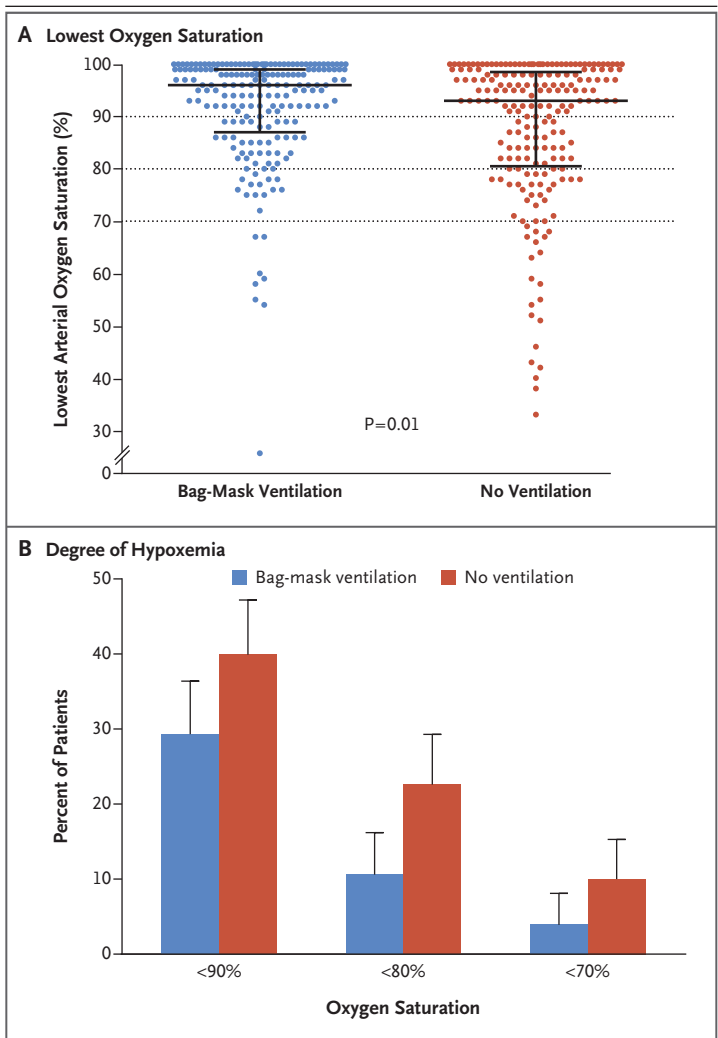


Figure 1. Lowest Oxygen Saturation.

Panel A shows the primary outcome of the lowest oxygen saturation (as measured by continuous pulse oximetry) observed during the interval between induction and 2 minutes after tracheal intubation in patients in the bag-mask ventilation group (blue) and the no-ventilation group (red). The widest horizontal bars represent median values, and the I bars represent the interquartile ranges. The dotted lines represent the thresholds for hypoxemia, severe hypoxemia, and very severe hypoxemia. Panel B shows the percentage of patients who had various degrees of hypoxemia in each group. The T bars represent the upper limit of the 95% confidence interval for the event rate.

SECONDARY OUTCOME

A total of 21 patients (10.9%) in the bag-mask ventilation group had an oxygen saturation of less than 80%, as compared with 45 patients (22.8%) in the no-ventilation group (relative risk, 0.48; 95% CI, 0.30 to 0.77) (Table 3 and Fig. 1B, and Table S14 and Fig. S6 in the Supplementary Appendix).

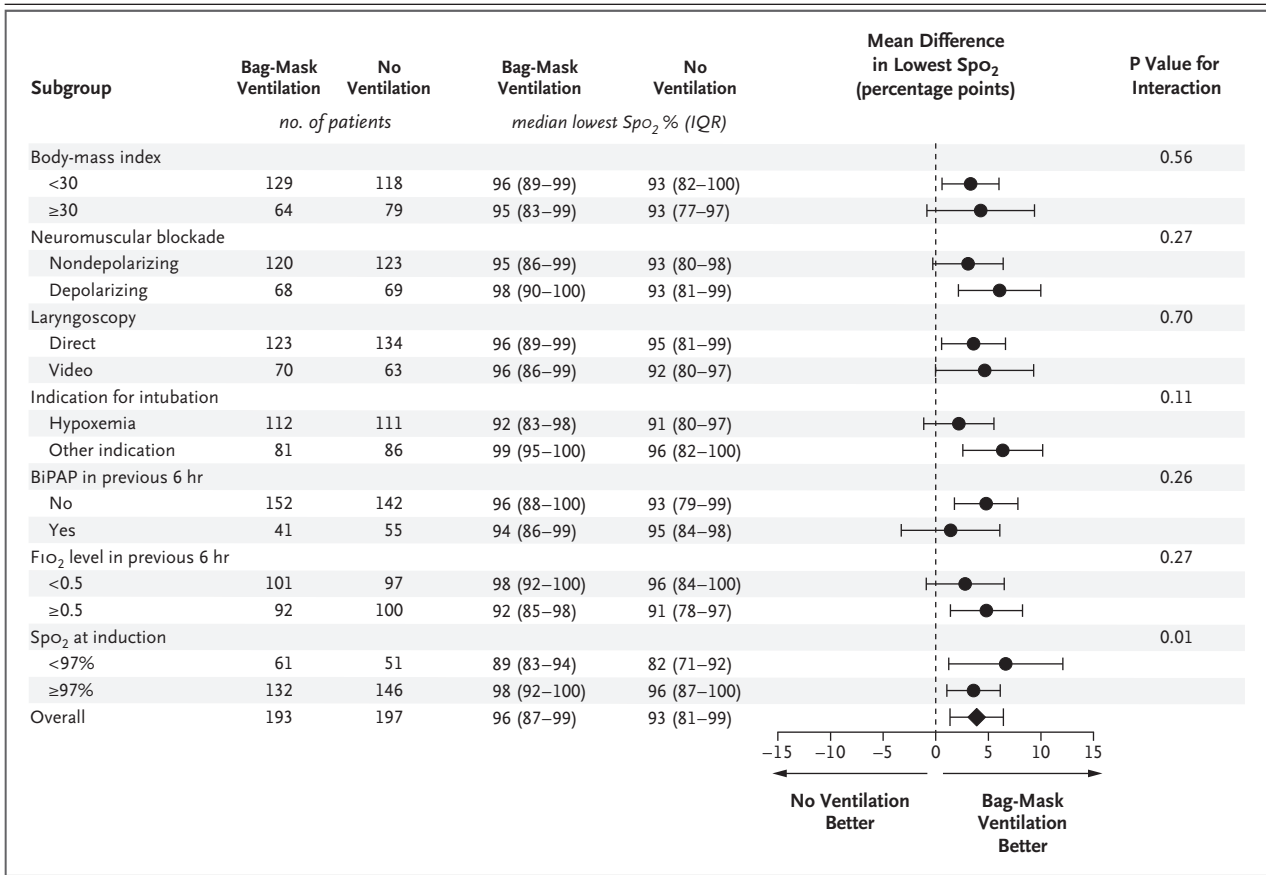


Figure 2. Subgroup Analyses of the Primary Outcome.

Shown is the unadjusted mean difference in the lowest oxygen saturation between patients undergoing bag-mask ventilation and those not undergoing ventilation in prespecified subgroups. The horizontal bars represent the 95% confidence intervals around the mean difference. The number of patients in each group for whom a measure of the lowest oxygen saturation was available is shown. Five patients in each group did not receive a neuromuscular blocking agent. The body-mass index is the weight in kilograms divided by the square of the height in meters. BiPAP denotes bilevel positive airway pressure, Fio₂ highest fraction of inspired oxygen, and SpO₂ oxygen saturation measured by pulse oximetry.

ADDITIONAL OUTCOMES

A lower percentage of patients in the bag-mask ventilation group than in the no-ventilation group had an oxygen saturation of less than 90% (29.5% vs. 40.1%; relative risk, 0.74; 95% CI, 0.56 to 0.97) or an oxygen saturation of less than 70% (4.1% vs. 10.2%; relative risk, 0.41; 95% CI, 0.18 to 0.90) (Table 3). The median decrease in oxygen saturation from induction to the lowest oxygen saturation was 1 percentage point (interquartile range, 0 to 7) in the bag-mask ventilation group and 5 percentage points (interquartile range, 0 to 14) in the no-ventilation group (mean difference, 4.5 percentage points; 95% CI, 2.2 to 6.8).

The bag-mask ventilation group and the no-ventilation group did not significantly differ with regard to the incidence of operator-reported aspiration (2.5% vs. 4.0%; absolute risk difference, -1.5 percentage points; 95% CI, -4.9 to 2.0; P=0.41) or the presence of a new opacity on chest radiography in the 48 hours after tracheal intubation (16.4% vs. 14.8%; absolute risk difference, 1.6 percentage points; 95% CI, -5.6 to 8.9; P=0.73) (Table S15 in the Supplementary Appendix).

In addition, there was no significant between-group difference in oxygen saturation, fraction of inspired oxygen, and positive end-expiratory pressure in the 24 hours after tra-

Table 3. Outcomes of Tracheal Intubation.

Outcome	Bag-Mask Ventilation (N = 199)	No Ventilation (N = 202)	Relative Risk or Mean Difference (95% CI)
Primary: median lowest oxygen saturation (IQR) — %*	96 (87–99)	93 (81–99)	3.9 (1.4 to 6.5)†
Secondary: lowest oxygen saturation of <80% — no./total no. (%)	21/193 (10.9)	45/197 (22.8)	0.48 (0.30 to 0.77)
Exploratory oxygen-saturation outcomes			
Lowest oxygen saturation of <90% — no./total no. (%)	57/193 (29.5)	79/197 (40.1)	0.74 (0.56 to 0.97)
Lowest oxygen saturation of <70% — no./total no. (%)‡	8/193 (4.1)	20/197 (10.2)	0.41 (0.18 to 0.90)
Median decrease in oxygen saturation (IQR) — percentage points	1 (0–7)	5 (0–14)	–4.5 (–6.8 to –2.2)†
Exploratory safety outcomes			
Operator-reported aspiration — no. (%)	5 (2.5)	8 (4.0)	0.63 (0.21 to 1.91)
New opacity on chest radiography — no./total no. (%)	31/189 (16.4)	29/196 (14.8)	1.11 (0.70 to 1.77)
New pneumothorax — no./total no. (%)	2/189 (1.1)	6/196 (3.1)	0.34 (0.07 to 1.66)
New vasopressor after induction — no./total no. (%)	39/196 (19.9)	46/199 (23.1)	0.86 (0.59 to 1.26)
New systolic blood pressure of <65 mm Hg — no./total no. (%)	8/195 (4.1)	17/197 (8.6)	0.48 (0.21 to 1.08)
Cardiac arrest within 1 hr after intubation — no. (%)	2 (1.0)	4 (2.0)	0.51 (0.09 to 2.74)
Exploratory clinical outcomes			
Median no. of ventilator-free days (IQR)	19 (0–25)	18 (0–25)	0.6 (–1.7 to 2.9)†
Median no. of days outside intensive care unit (IQR)	16 (0–22)	14 (0–22)	0.8 (–1.3 to 2.9)†
Death before hospital discharge — no. (%)	71 (35.7)	72 (35.6)	1.00 (0.77 to 1.30)

* Data regarding the lowest oxygen saturation were missing for 11 patients (2.7%): 6 in the bag-mask ventilation group and 5 in the no-ventilation group. In the primary analysis comparing lowest oxygen saturation between groups with the use of a Mann–Whitney rank-sum test, the lowest oxygen saturation was higher in the bag-mask ventilation group than in the no-ventilation group (P=0.01).

† The mean difference is indicated in this category.

‡ This outcome was added post hoc.

cheal intubation (Table S16 in the Supplementary Appendix), nor in in-hospital mortality and in the number of ventilator-free days or days out of the ICU (Table 3, and Table S14 in the Supplementary Appendix). Between-group differences in secondary and exploratory outcomes were similar after adjustment for within-ICU correlation with the use of generalized estimating equations (Tables S6 and S14 in the Supplementary Appendix).

DISCUSSION

In this multicenter, randomized trial, the lowest oxygen saturation during tracheal intubation was 3.9 percentage points higher among patients assigned to receive bag-mask ventilation than among those assigned to receive no ventilation from induction to laryngoscopy. At the same

time, the absolute percentage of patients who had severe hypoxemia was 12 percentage points lower in the bag-mask ventilation group. These results suggest that for every nine critically ill adults undergoing tracheal intubation, providing bag-mask ventilation between induction and laryngoscopy would prevent severe hypoxemia in one patient.

These findings are important because oxygen saturation is an established end point in airway-management trials^{2,3,24–26} and is a contributing factor to periprocedural cardiac arrest and death.^{27,28} The benefit of bag-mask ventilation with regard to oxygen saturation was similar across multiple sensitivity analyses, and the point estimate for lowest oxygen saturation favored bag-mask ventilation in every subgroup.

It has been hypothesized that bag-mask ventilation increases the risk of aspiration during

tracheal intubation.^{11,12,29,30} However, previous studies that have evaluated aspiration during bag-mask ventilation have been limited to the examination of anesthetized healthy volunteers, have used epigastric auscultation to detect gastric insufflation as a surrogate for aspiration, and have reported conflicting results.^{14,31-36} Given the low incidence of operator-reported aspiration during tracheal intubation of critically ill adults,^{7,37,38} determining whether bag-mask ventilation increases the relative risk of aspiration by 50% would require a trial enrolling approximately 4000 patients. However, our trial provides some reassurance, since the incidence of operator-reported aspiration was numerically lower in the bag-mask ventilation group than in the no-ventilation group. Our results suggest that the effect of bag-mask ventilation on the incidence of aspiration lies between an absolute decrease of 4.9 percentage points and an absolute increase of 2.0 percentage points. A total of 49 otherwise eligible patients (7.3%) were excluded from our trial because clinicians thought they were at very high risk for aspiration, and our results do not inform the safety or effectiveness of bag-mask ventilation in such patients.

Our trial has several strengths. The trial design included randomization to balance baseline confounders, concealment of group assignment until enrollment to prevent selection bias, the conduct of the trial at multiple centers to increase generalizability, and the collection of trial end points by an independent observer to minimize observer bias. Rates of protocol noncompliance and missing data were low.

Our trial also has several limitations. The nature of the trial intervention did not allow blinding, and knowledge of group assignment

may have contributed to differences in preoxygenation technique between groups. However, oxygen saturation at induction was numerically lower in the bag-mask ventilation group, and post hoc analyses accounting for preoxygenation methods did not alter the findings that bag-mask ventilation improved oxygen saturation and prevented severe hypoxemia. Furthermore, our trial did not examine the use of noninvasive ventilation during the interval between induction and laryngoscopy and does not inform the choice between noninvasive ventilation and bag-mask ventilation. Because our trial involved only patients in ICUs, it is unclear whether these results can be generalized to patients undergoing tracheal intubation in the emergency department or in a prehospital setting. Whether the effect of bag-mask ventilation on hypoxemia during tracheal intubation translates into differences in other patient-centered outcomes also remains unknown.

In conclusion, in this multicenter, randomized trial involving critically ill adults undergoing tracheal intubation, patients receiving bag-mask ventilation during the interval between induction and laryngoscopy had higher oxygen saturations and lower rates of severe hypoxemia than those receiving no ventilation.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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