ORIGINAL ARTICLE

Nasal High-Flow Therapy during Neonatal Endotracheal Intubation

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ABSTRACT

BACKGROUND

Neonatal endotracheal intubation often involves more than one attempt, and oxygen desaturation is common. It is unclear whether nasal high-flow therapy, which extends the time to desaturation during elective intubation in children and adults receiving general anesthesia, can improve the likelihood of successful neonatal intubation on the first attempt.

METHODS

We performed a randomized, controlled trial to compare nasal high-flow therapy with standard care (no nasal high-flow therapy or supplemental oxygen) in neonates undergoing oral endotracheal intubation at two Australian tertiary neonatal intensive care units. Randomization of intubations to the high-flow group or the standard-care group was stratified according to trial center, the use of premedication for intubation (yes or no), and postmenstrual age of the infant (≤28 or >28 weeks). The primary outcome was successful intubation on the first attempt without physiological instability (defined as an absolute decrease in the peripheral oxygen saturation of >20% from the preintubation baseline level or bradycardia with a heart rate of <100 beats per minute) in the infant.

RESULTS

The primary intention-to-treat analysis included the outcomes of 251 intubations in 202 infants; 124 intubations were assigned to the high-flow group and 127 to the standard-care group. The infants had a median postmenstrual age of 27.9 weeks and a median weight of 920 g at the time of intubation. A successful intubation on the first attempt without physiological instability was achieved in 62 of 124 intubations (50.0%) in the high-flow group and in 40 of 127 intubations (31.5%) in the standard-care group (adjusted risk difference, 17.6 percentage points; 95% confidence interval [CI], 6.0 to 29.2), for a number needed to treat of 6 (95% CI, 4 to 17) for 1 infant to benefit. Successful intubation on the first attempt regardless of physiological stability was accomplished in 68.5% of the intubations in the high-flow group and in 54.3% of the intubations in the standard-care group (adjusted risk difference, 15.8 percentage points; 95% CI, 4.3 to 27.3).

CONCLUSIONS

Among infants undergoing endotracheal intubation at two Australian tertiary neonatal intensive care units, nasal high-flow therapy during the procedure improved the likelihood of successful intubation on the first attempt without physiological instability in the infant. (Funded by the National Health and Medical Research Council; Australian New Zealand Clinical Trials Registry number, ACTRN12618001498280.)

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Opportunities for clinicians to become proficient in neonatal intubation have decreased over time.[1,2] Factors contributing to this trend include the increasing use of noninvasive respiratory support,[3] the availability of less invasive surfactant administration techniques for use in preterm infants,[4] and recommendations against routine endotracheal suctioning in infants born through meconium-stained amniotic fluid.[5] However, intubation is still necessary for the sickest and most immature infants.[6]

Rates of successful neonatal intubation on the first attempt are low. In a large, multicenter, international registry study of more than 2500 intubations, the rate of success on the first attempt was approximately 50%[7]; rates of success as low as 23% have been reported for intubations that are performed by inexperienced operators.[7-9] Furthermore, the duration of an intubation attempt is frequently longer than what is recommended in international guidelines,[10] particularly when performed by an inexperienced operator.[9]

A neonate's condition is often clinically unstable during intubation because neonates have a lower functional residual capacity and greater metabolic demand than older children and adults.[11] In the neonatal unit, an infant's oxygen saturation falls by 20% or more from the preintubation baseline level in approximately half the intubations performed; bradycardia occurs rarely.[7] The most common reason for abandoning an intubation attempt is physiological instability.[12] Repeat intubation attempts are associated with adverse events, including intraventricular hemorrhage and airway injury.[13-15] Therefore, interventions to improve the rates of safe, expeditious, and successful intubation in neonates are urgently needed.

Nasal high-flow therapy (hereafter, high-flow therapy) is a simple form of respiratory support that delivers heated, humidified gas through narrow nasal cannulae.[16] High-flow therapy has been used successfully in older children and adults to aid intubation: a technique termed transnasal humidified rapid insufflation ventilatory exchange.[17] The potential mechanisms of this technique include the generation of continuous distending pressure, enhanced washout of nasopharyngeal dead space, and cardiogenic oscillations, whereby variations in intrathoracic pressure during the cardiac cycle promote gas exchange.[18,19] In adults receiving general anesthesia, high-flow therapy prolongs the time to desaturation during a period of apnea[17]; it may be used in patients in whom intubation is expected to be difficult (because of anatomical features)[17] or cannot be performed (because of upper airway surgery)[20] or in those in whom the time to desaturation is likely to be short (because of coexisting medical conditions).[17] In healthy children receiving general anesthesia, the use of high-flow therapy can extend the safe apneic window by prolonging the time to desaturation.[21]

Data are lacking to support the benefit of high-flow therapy during intubation in neonates, who often undergo intubation urgently and who frequently have underlying lung disease. We performed this randomized trial to assess whether high-flow therapy during oral neonatal endotracheal intubation improves the likelihood of successful intubation on the first attempt without physiological instability in the infant.

METHODS

TRIAL DESIGN AND OVERSIGHT

This trial was conducted at two tertiary neonatal intensive care units in Melbourne, Australia — the Royal Women's Hospital and Monash Children's Hospital. Approval was obtained from the human research ethics committee at each site. An external data and safety monitoring board was convened for trial oversight (Section S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). All the authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, which was published previously[22] and is available at NEJM.org. Vapotherm provided equipment that was used in the trial but had no input in the design of the trial, in the accrual or analysis of the data, or in the preparation of the manuscript and had no access to the trial data. The parents of the infants provided written informed consent. Antenatal or prospective consent was sought whenever possible. In addition, both centers approved a retrospective consent process if criteria were met (Section S2).

PARTICIPANTS

Infants undergoing oral endotracheal intubation in the delivery room or neonatal intensive care unit at the participating centers were eligible for

inclusion in the trial. Exclusion criteria were nasal intubation, urgent intubation as determined by the treating clinician, a heart rate of less than 120 beats per minute immediately before randomization, contraindication to high-flow therapy (e.g., congenital nasal anomaly, congenital diaphragmatic hernia, or abdominal wall defect), cyanotic congenital heart disease, or suspected or proven severe acute respiratory syndrome coronavirus 2 infection in the infant or mother.

RANDOMIZATION

Intubations were randomly assigned to the high-flow group or the standard-care group (no high-flow therapy or supplemental oxygen) before the first intubation attempt. Randomization was performed with the use of a computer-generated random-assignment sequence based on permuted blocks with varying block sizes and was stratified according to trial center, postmenstrual age of the infant (≤28 or >28 weeks), and the use of premedication for intubation (yes or no). Subsequent intubation episodes in the same infant could be included in the analyses if either the randomization stratum of premedication use differed between the intubations or if there was at least 1 week between the intubations in which premedications were used. Repeat intubation episodes meeting these conditions were considered to be independent events. Intubations in multiple-birth siblings were randomly assigned on an individual basis. Electronic randomization was performed at the infant's cot side by means of the Web-based, secure sockets layer–encrypted and password-protected Research Electronic Data Capture randomization tool (REDCap, Vanderbilt University).[23]

TRIAL INTERVENTIONS

The preintubation fraction of inspired oxygen, the use of preoxygenation, the use of video laryngoscopy, and the commencement, duration, and termination of the intubation attempt were at the discretion of the clinician leading the procedure. Except in the case of intubations performed in the delivery room, premedication with atropine, fentanyl, and suxamethonium was standard practice at both centers. All infants were monitored with the use of a pulse oximeter (Masimo) that displayed the real-time peripheral oxygen saturation and heart rate; the device was set to maximum sensitivity and had a 2-second averaging time.

In intubations that were assigned to the high-flow group, an investigator applied appropriately sized binasal cannulae immediately after removing the preexisting respiratory support interface before laryngoscopy (Fig. S1). The tubing circuit was secured behind the infant's head without adhesive tapes, and the gas flow was set to 8 liters per minute. The fraction of inspired oxygen was set at the concentration being delivered before laryngoscopy and was increased to 1.0 (100% oxygen) if the oxygen saturation fell to below 90%. High-flow therapy was continued throughout laryngoscopy; at the conclusion of the first intubation attempt, high-flow therapy was discontinued. In the intubations that were assigned to the standard-care group, the intubation attempt proceeded without high-flow therapy or supplemental oxygen.

TRIAL OUTCOMES

The primary outcome was successful intubation on the first attempt without physiological instability in the infant. An intubation attempt was defined as the insertion of the laryngoscope blade beyond the infant's lips until its removal from the infant's mouth, whether or not an attempt was made to insert an endotracheal tube. Successful intubation was defined as completion of the intubation attempt with correct placement of the endotracheal tube, as confirmed by the detection of expired carbon dioxide with a colorimetric detector. Physiological instability was defined as desaturation (with an absolute decrease in oxygen saturation of >20% from the immediate prelaryngoscopy baseline level for any duration) or bradycardia (with a heart rate of <100 beats per minute for any duration) during the first intubation attempt.

Prespecified secondary outcomes were the median oxygen saturation during the intubation attempt, the time to and duration of desaturation (if applicable), and the duration and number of intubation attempts. The complete list of prespecified secondary outcomes is provided in the trial protocol[22] and Section S3. Prespecified serious adverse events were cardiac compressions or epinephrine administration within 1 hour after the intervention and pneumothorax or death within 72 hours after the intervention.

VIDEO RECORDING

All intubations were recorded on video to ensure the accuracy of data. A GoPro camera was posi-

A video showing nasal high-flow therapy is available at NEJM.org

tioned to provide a clear view of the procedure and the pulse oximeter displaying the oxygen saturation level and heart rate. An intubation in the high-flow group is shown in a video, available at NEJM.org. Data were documented on a case-report form and verified against the video recording. The primary outcome was verified by an independent assessor through video review. In the event that the video could not be used, the primary outcome was determined on the basis of the case-report form. Any discrepancy was resolved by another assessor.

STATISTICAL ANALYSIS

The statistical analysis plan was published before the data were analyzed[24] and is available with the protocol. Previous data from the lead site[25] showed that intubation performed according to standard practice was successful on the first attempt without physiological instability in 29% of the infants. We estimated that 123 intubations in each treatment group would provide the trial with 90% power to detect an increase in the incidence of successful intubation without physiological instability in the infant from 30% to 50%, at a two-sided alpha level of 0.05.

The external data and safety monitoring board performed safety analyses after 25%, 50%, and 75% of the planned sample had been recruited, and one blinded interim efficacy analysis was performed after 50% of the planned sample had been recruited. The data and safety monitoring board could recommend stopping the trial on the basis of safety at any time or if there was a highly significant difference ($P<0.001$) in the interim efficacy analysis of the primary outcome.

The primary analysis was performed on an intention-to-treat basis, with the results of all eligible intubation procedures and with post-randomization exclusion criteria determined a priori.[24] The analysis of the primary outcome was adjusted for the randomization stratification factors; the adjusted analyses of the components of the primary outcome did not include adjustment for trial-center stratification factor as planned owing to collinearity with the other stratification factors. A per-protocol analysis of the primary outcome was planned if there were infants who did not undergo their treatment assignment. Mechanical failure of the nasal high-flow device and dislodgement of the nasal cannulae were documented but not deemed to be protocol violations.

The primary outcome and dichotomous secondary outcomes were compared according to the risk difference and two-sided 95% confidence interval. Generalized linear-regression models with the binomial distribution family and identity link function were used to estimate the difference between the high-flow group and the standard-care group. Continuous secondary outcomes were compared according to the difference in means, with 95% confidence intervals, by means of linear regression (if the distribution of the values was not skewed) or according to the difference in medians, with 95% confidence intervals, by means of quantile regression (if the distribution was skewed). Secondary outcomes were reported as point estimates with 95% confidence intervals; there was no adjustment for multiplicity. In a prespecified sensitivity analysis, multivariable binary regression with robust standard errors to adjust for within-infant correlation was used to account for repeat randomization events in individual infants. Prespecified subgroup analyses of the primary outcomes were performed with the use of logistic-regression models for subgroups defined by postmenstrual age (≤28 or >28 weeks), the use of premedication for intubation (yes or no), and experience level of the operator according to the number of previous intubations performed (<20 [inexperienced] or ≥20 [experienced]) (Section S4). The number needed to treat was calculated as the reciprocal of the risk difference, and the result was rounded to a whole number.

RESULTS

RECRUITMENT

From November 2018 through April 2021, a total of 258 intubations in 209 infants were randomly assigned to the high-flow group (129 intubations) or the standard-care group (129 intubations) (Fig. 1). Seven intubations were excluded after randomization, and 251 intubations (124 in the high-flow group and 127 in the standard-care group) in 202 infants were included in the primary intention-to-treat analysis.

The demographic and clinical characteristics of the infants were similar in the treatment groups (Table 1 and Table S1). Infants had a median postmenstrual age of 27.9 weeks (interquartile range, 26.3 to 32.1) and a median weight of 920 grams (interquartile range, 712 to 1499) at the time of intubation. The median age

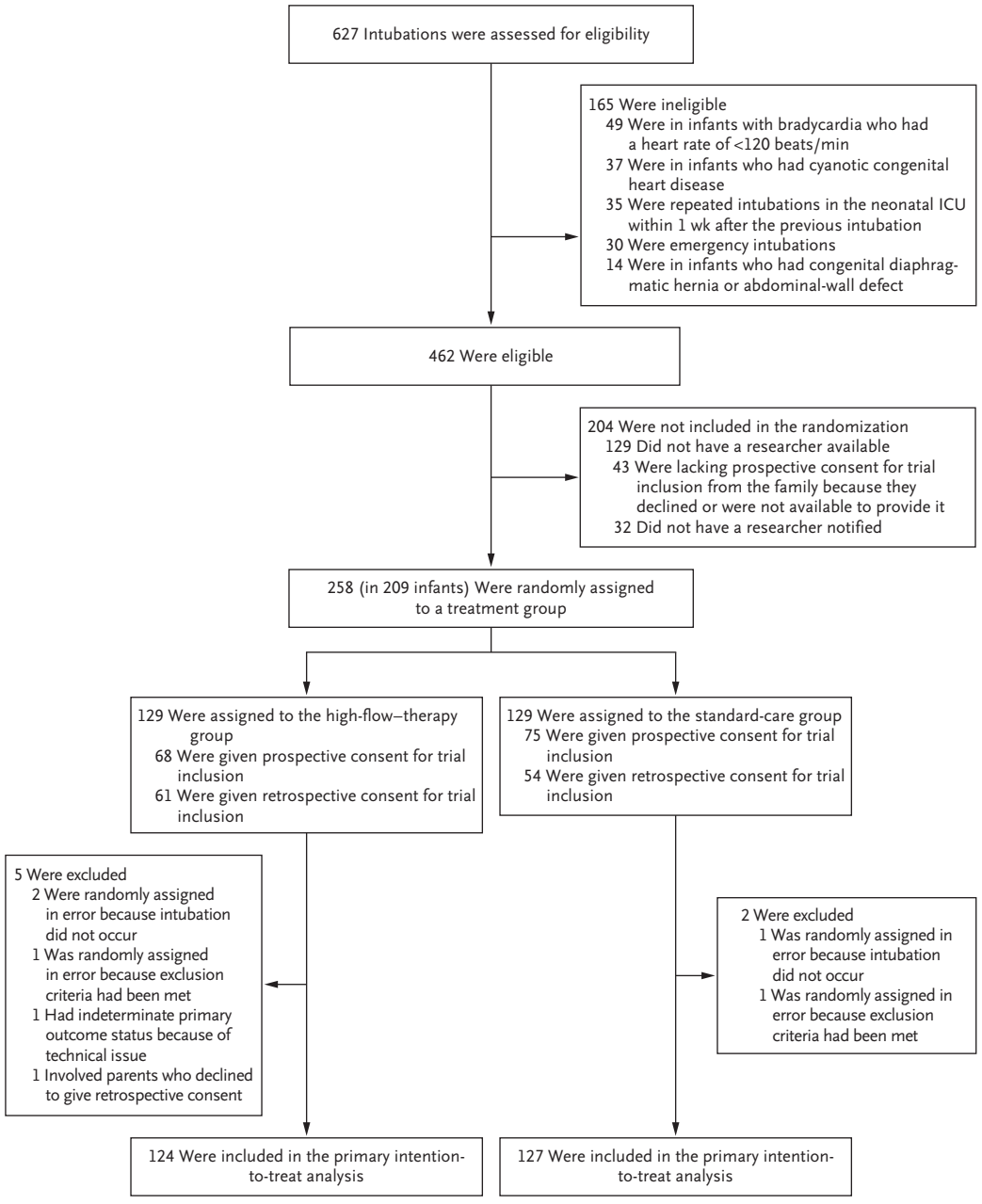

Figure 1. Screening, Randomization, and Analysis.

Intubations were randomly assigned to the high-flow group, in which nasal high-flow therapy was used, or the standard-care group, in which the intubation was performed according to standard clinical practice. ICU denotes intensive care unit.

at the time of randomization was 10 hours (interquartile range, 0 to 215).

PRIMARY OUTCOME

In the primary intention-to-treat analysis, successful intubation on the first attempt without physiological instability in the infant was achieved in 62 of 124 intubations (50.0%) in the high-flow group and in 40 of 127 intubations (31.5%) in the standard-care group (adjusted risk difference, 17.6 percentage points; 95% confidence interval [CI], 6.0 to 29.2; number needed to treat

Table 1. Demographic and Clinical Characteristics of the Infants Undergoing Endotracheal Intubation.*

Characteristic	High-Flow Group (N=124)	Standard-Care Group (N=127)
Median gestational age (IQR) — wk	27.0 (25.0–31.0)	27.0 (25.1–28.9)
Median birth weight (IQR) — g	893 (684–1492)	841 (670–1162)
Delivery by cesarean section — no. (%)	96 (77.4)	96 (75.6)
Multiple birth — no. (%)	41 (33.1)	30 (23.6)
Male sex — no. (%)	71 (57.3)	70 (55.1)
Median Apgar score at 5 min (IQR)	8 (6–9)	7.5 (6–9)
Median age at intubation (IQR) — hr	7.0 (0.0–86.0)	13.0 (0.0–292.0)
Median postmenstrual age at intubation (IQR) — wk	27.9 (26.3–33.4)	27.9 (26.3–31.0)
Median weight at intubation (IQR) — g	976 (712–1835)	907 (713–1320)
Location of intubation — no. (%)		
Delivery room	31 (25.0)	34 (26.8)
Neonatal intensive care unit	93 (75.0)	93 (73.2)
Respiratory support before procedure — no. (%)		
Nasal high-flow therapy	2 (1.6)	5 (3.9)
Continuous positive airway pressure	113 (91.1)	113 (89.0)
Intermittent positive-pressure ventilation	4 (3.2)	6 (4.7)
Low-flow oxygen	1 (0.8)	1 (0.8)
None	4 (3.2)	2 (1.6)
Fraction of inspired oxygen before randomization	0.62±0.28	0.62±0.29
Peripheral oxygen saturation immediately before procedure — %	92.6±12.7	92.3±11.9
Primary indication for intubation — no. (%)		
Hypoxia	73 (58.9)	74 (58.3)
Hypercarbia	3 (2.4)	4 (3.1)
Apnea	26 (21.0)	25 (19.7)
Resuscitation	3 (2.4)	7 (5.5)
Other	19 (15.3)	17 (13.4)
Operator experience level — no. (%)		
Inexperienced: <20 previous intubations	61 (49.2)	51 (40.2)
Experienced: ≥20 previous intubations	63 (50.8)	76 (59.8)

* Plus–minus values are means ±SD. Intubations were randomly assigned to the high-flow group, in which nasal high-flow therapy was used, or the standard-care group, in which the intubation was performed according to standard clinical practice. An infant could undergo more than one intubation during the trial period and be counted more than once in the total number of intubations. IQR denotes interquartile range.

for 1 infant to benefit, 6 [95% CI, 4 to 17]) (Table 2). The results for the components of the primary outcome were consistent with those for the primary outcome (Table 2). In the subgroup analyses, the treatment effect with respect to the primary outcome was similar in the two treatment groups regardless of postmenstrual age or use of premedication, but the results suggested that the effect was larger when the intubation was performed by an inexperienced operator than by an experienced operator (Table 2).

SECONDARY OUTCOMES

The results for the secondary outcomes are shown in Table 3. Additional information regarding the use of video recordings and video laryngoscopy is provided in Sections S5 and S6. Oxygen saturation over time during the first in-

Table 2. Primary Outcome and Subgroup Analyses.

Outcome	High-Flow Group (N=124)	Standard-Care Group (N=127)	Adjusted Risk Difference (95% CI)*
Primary outcome and component analyses			
Primary outcome: successful intubation on first attempt without physiological instability — no. (%)	62 (50.0)	40 (31.5)	17.6 (6.0 to 29.2)†
Successful intubation on first attempt — no. (%)‡	85 (68.5)	69 (54.3)	15.8 (4.3 to 27.3)†
No physiological instability — no. (%)‡	79 (63.7)	64 (50.4)	13.4 (1.3 to 25.5)§
No desaturation¶	89 (71.8)	77 (60.6)	13.1 (4.1 to 22.1)§
No bradycardia‖	113 (91.1)	111 (87.4)	2.4 (–2.1 to 6.9)§
Primary outcome according to prespecified subgroup analyses			
Postmenstrual age — no./total no. (%)			
≤28 wk	34/64 (53.1)	23/66 (34.8)	16.8 (0.3 to 33.2)
>28 wk	28/60 (46.7)	17/61 (27.9)	20.3 (5.8 to 35.7)
Premedication use — no./total no. (%)			
Yes	50/92 (54.3)	30/93 (32.3)	20.1 (7.1 to 34.2)
No	12/32 (37.5)	10/34 (29.4)	13.5 (–7.2 to 34.1)
Operator experience level — no./total no. (%)			
Inexperienced: <20 previous intubations	30/61 (49.2)	8/51 (15.7)	33.3 (18.3 to 48.2)
Experienced: ≥20 previous intubations	32/63 (50.8)	32/76 (42.1)	7.5 (–9.4 to 24.3)

* The 95% confidence intervals in the subgroup analyses have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.
† Adjustment was made for all randomization stratification factors (postmenstrual age, use of premedication for intubation, and trial center).
‡ Infants could have more than one component of the primary outcome.
§ Adjustment was made for postmenstrual age and use of premedication for intubation; trial center was not included owing to collinearity with another stratification variable.
¶ Desaturation was defined as a decrease in oxygen saturation of greater than 20% from the preintubation baseline level.
‖ Bradycardia was defined as heart rate of less than 100 beats per minute at any time.

tubation attempt is shown in Figure S2. The median oxygen saturation during the first intubation attempt was 93.5% in the high-flow group and 88.5% in the standard-care group, with a 5.0 percentage-point difference in the median values (95% CI, 1.1 to 8.9). Among the infants with an episode of oxygen desaturation, the mean time to desaturation was longer in the high-flow group (44.3 seconds) than in the standard-care group (35.5 seconds), for a mean difference of 8.8 seconds (95% CI, 0.2 to 17.4). In the high-flow group, the mean time to apply the nasal prongs was 9.9 seconds. The median number of intubation attempts, the duration of the first and any subsequent intubation attempts, the percentage of intubations that were esophageal intubations, and the percentage of intubations in which a serious adverse event occurred were similar in the two treatment groups (Table 3).

A per-protocol analysis was not performed because the prespecified criteria had not been met. A total of 13 intubations were randomly assigned in multiple-birth siblings. A prespecified sensitivity analysis to account for repeat randomization events in individual infants and a post hoc sensitivity analysis to account for within-sibling correlations yielded results that were similar to those of the primary-outcome analysis (Table S2).

DISCUSSION

In this multicenter, randomized trial, the likelihood of successful intubation on the first attempt without physiological instability in the infant

Table 3. Secondary Outcomes and Adverse Events.*

Outcome	High-Flow Group (N = 124)	Standard-Care Group (N = 127)	Difference (95% CI)
Peripheral oxygen saturation†			
Intubations assessed — no.	120	126	
Median value of outcome (IQR) — %	94 (83–98)	89 (79–95)	5.0 (1.1 to 8.9)
Heart rate†			
Intubations assessed — no.	120	126	
Mean value of outcome — beats/min	166±22	161±24	5.4 (–0.5 to 11.2)
Duration of peripheral oxygen saturation of >97%†‡			
Intubations assessed — no.	119	122	
Median value of outcome (IQR) — sec	2.0 (0.0–20.0)	0 (0.0–16.0)	2.0 (–2.1 to 6.1)
Number of intubation attempts per procedure			
Intubations assessed — no.	124	127	
Median value of outcome (IQR) — no.	1.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	0.0 (–0.2 to 0.2)
Duration of first intubation attempt§			
Intubations assessed — no.	124	127	
Median value of outcome (IQR) — sec	50.5 (33.5–69.0)	46.0 (33.0–66.0)	5.0 (–4.5 to 14.5)
Total duration of all intubation attempts¶			
Intubations assessed — no.	123	127	
Median value of outcome (IQR) — sec	58.0 (36.0–95.0)	68.0 (35.0–125.0)	–10.0 (–27.2 to 7.2)
Esophageal intubation — no. (%)	18 (14.5)	20 (15.7)	–1.2 (–10.1 to 7.6)‖
Time to apply nasal prongs			
Intubations assessed — no.	123	NA	
Mean value of outcome — sec	9.9±5.2	NA	
Intubations in which desaturation occurred — no. (%)**	35 (28.2)	50 (39.4)	
Time to desaturation†			
Intubations assessed — no.	34	50	
Mean value of outcome — sec	44.3±19.5	35.5±19.5	8.8 (0.2 to 17.4)
Duration of desaturation†			
Intubations assessed — no.	34	47	
Mean value of outcome — sec	65.0±35.1	63.6±38.9	1.5 (–15.3 to 18.2)
Intubations in which bradycardia occurred — no. (%)	11 (8.9)	16 (12.6)	
Time to bradycardia†			
Intubations assessed — no.	11	15**	
Mean value of outcome — sec	39.4±22.9	39.9±19.9	–0.5 (–17.9 to 16.9)
Duration of bradycardia — sec†			
Intubations assessed — no.	11	15**	
Mean value of outcome — sec	26.6±20.7	31.3±23.3	–4.6 (–22.9 to 13.6)
Serious adverse events — no. of events (%)			
CPR or epinephrine administration within 1 hr after intubation attempt	0	2 (1.6)	

Table 3. (Continued.)

Outcome	High-Flow Group (N=124)	Standard-Care Group (N=127)	Difference (95% CI)
Pneumothorax diagnosed within 72 hours after randomization			
Any case	2 (1.6)	6 (4.7)	
Cases involving drainage with needle thoracocentesis or intercostal catheter	2 (1.6)	5 (3.9)	
Death within 72 hr after randomization	1 (0.8)	3 (2.4)	

* Plus–minus values are means ±SD. Confidence intervals for secondary outcomes have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Secondary outcomes are reported without adjustment for the three randomization stratification factors. CPR denotes cardiopulmonary resuscitation, and NA not applicable.
† The first intubation attempt was used in the assessment of this outcome.
‡ The median oxygen saturation in each infant was calculated across first intubation attempts.
§ This outcome was added post hoc.
¶ This outcome was measured as the sum of each separate intubation attempt.
‖ The difference is presented in percentage points.
** The result of one intubation was not included in the analysis because of a technical issue with the recording.

was higher with high-flow therapy than with standard care. Successful intubation was more common in the high-flow group than in the standard-care group, and desaturation below the predefined threshold occurred in a lower percentage of intubations in the high-flow group. The effects were consistent across subgroups defined according to postmenstrual age and the use of premedication for intubation.

Despite the use of less mechanical ventilation in neonatal care over recent years, intubation is still needed for the most immature and unwell infants.[6] Intubation is commonly performed in infants with small airways and minimal physiological reserve. Hence, the time available to safely secure the airway is short. Few interventions increase the success of neonatal intubation.[26] Simulation training transiently improves the technical performance of the intubation procedure[27,28] and increases confidence levels reported by trainees in critical care,[29] but it does not consistently translate into improved clinical success.[27,30] Video laryngoscopy allows a supervisor to share the view of the infant's airway and improves the likelihood of success on the first attempt among inexperienced operators.[25,31,32] The current trial showed clinically important improvement in terms of intubation success and the maintenance of physiological stability with high-flow therapy, with a number needed to treat of 6 for 1 infant to benefit. The intervention was quick and simple to apply and was not associated with adverse events.

Inexperienced clinicians are less likely to perform neonatal intubation successfully on the first attempt, and their attempts take longer.[7,9] The results of subgroup analyses according to the experience level of the operator suggested a greater benefit of high-flow therapy in intubations performed by inexperienced operators, among whom the percentage of successful intubations on the first attempt without physiological instability in the infant was similar to that among experienced operators when high-flow therapy was used (Table 2); however, subgroup analyses were not adjusted for multiplicity. A retrospective observational study and mixed-methods survey of trainees suggest that early positive career experience with intubation may have an effect on future success and confidence level.[33,34] Consistent with the findings in previous studies,[35,36] the median duration of the first intubation attempt was more than 45 seconds in both treatment groups, which is longer than the 30-second time limit recommended in guidelines.[10]

We chose a composite primary outcome that reflected the importance of both success on the first attempt (in order to avoid medical complications) and the maintenance of physiological stability in the infant. We hypothesized that maintenance of physiological stability would

safely prolong the time available to complete the procedure. In addition to our observation that intubation success was greater with the use of high-flow therapy, the duration of the intubation attempts was not prolonged as compared with that in the standard-care group. Our results align with those from a previous pediatric randomized trial of high-flow therapy, in which the therapy was shown to prolong the safe apneic window during general anesthesia,[21,37] although that study included only five infants younger than 6 months of age. In our trial, desaturation occurred during 34% of the intubations. The time to desaturation was longer by a mean of 9 seconds among the infants in the high-flow group than among those in the standard-care group. In contrast to pediatric and adult populations, in our newborn infant population, preoxygenation was not routine and was not controlled for. If used, preoxygenation may have influenced the time to desaturation; however, the preintubation fraction of inspired oxygen was the same in the two treatment groups.

Our trial has several limitations. The treatment assignments were not concealed; a sham procedure was not performed owing to concerns that the application of prongs without flow might cause nasal obstruction and that the time taken to apply the nasal prongs could have obscured differences in the duration of the intubation attempt between the treatment groups. However, in order to limit bias, outcomes were determined through video review with objective outcome criteria, and the findings with respect to the primary outcome were corroborated by an independent reviewer. We did not collect information on race or ethnic group, but the participants appeared to be representative — in terms of sex and gestational age at birth — of neonates who undergo intubation. We randomly assigned intubation episodes, rather than infants, because we judged that intubations that were included in different premedication strata or performed more than 1 week apart could be considered to be independent events. Sensitivity analysis showed that the results for the primary outcome were consistent after adjustment for repeat randomization events in individual infants.

In the current trial involving neonates, the use of high-flow therapy during oral endotracheal intubation led to a greater likelihood of successful intubation on the first attempt without physiological instability in the infant.

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