ORIGINAL ARTICLE

A Randomized Trial of Laryngeal Mask Airway in Neonatal Resuscitation

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ABSTRACT

BACKGROUND

Face-mask ventilation is the most common resuscitation method for birth asphyxia. Ventilation with a cuffless laryngeal mask airway (LMA) has potential advantages over face-mask ventilation during neonatal resuscitation in low-income countries, but whether the use of an LMA reduces mortality and morbidity among neonates with asphyxia is unknown.

METHODS

In this phase 3, open-label, superiority trial in Uganda, we randomly assigned neonates who required positive-pressure ventilation to be treated by a midwife with an LMA or with face-mask ventilation. All the neonates had an estimated gestational age of at least 34 weeks, an estimated birth weight of at least 2000 g, or both. The primary outcome was a composite of death within 7 days or admission to the neonatal intensive care unit (NICU) with moderate-to-severe hypoxic–ischemic encephalopathy at day 1 to 5 during hospitalization.

RESULTS

Complete follow-up data were available for 99.2% of the neonates. A primary outcome event occurred in 154 of 563 neonates (27.4%) in the LMA group and 144 of 591 (24.4%) in the face-mask group (adjusted relative risk, 1.16; 95% confidence interval [CI], 0.90 to 1.51; P=0.26). Death within 7 days occurred in 21.7% of the neonates in the LMA group and 18.4% of those in the face-mask group (adjusted relative risk, 1.21; 95% CI, 0.90 to 1.63), and admission to the NICU with moderate-to-severe hypoxic–ischemic encephalopathy at day 1 to 5 during hospitalization occurred in 11.2% and 10.1%, respectively (adjusted relative risk, 1.27; 95% CI, 0.84 to 1.93). Findings were materially unchanged in a sensitivity analysis in which neonates with missing data were counted as having had a primary outcome event in the LMA group and as not having had such an event in the face-mask group. The frequency of predefined intervention-related adverse events was similar in the two groups.

CONCLUSIONS

In neonates with asphyxia, the LMA was safe in the hands of midwives but was not superior to face-mask ventilation with respect to early neonatal death and moderate-to-severe hypoxic–ischemic encephalopathy. (Funded by the Research Council of Norway and the Center for Intervention Science in Maternal and Child Health; NeoSupra ClinicalTrials.gov number, NCT03133572.)

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A complete list of the NeoSupra investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 7 million neonates worldwide need resuscitation at birth.[1] Birth asphyxia is the third leading cause of neonatal death, accounting for approximately 700,000 deaths each year.[2,3] Wide-scale implementation of evidence-based interventions has improved perinatal outcomes, but United Nations Sustainable Development Goal 3 emphasizes the need to accelerate the reduction of neonatal mortality. According to this global goal, each country should aim for a neonatal mortality below 12 per 1000 live births by 2030.[4] Improving outcomes from neonatal resuscitation is crucial to achieve this target.[5]

Effective positive-pressure ventilation is the most important step in neonatal resuscitation.[6,7] A modeling study estimated that proper bag-and-mask ventilation could reduce intrapartum-related mortality by 40%.[8] However, delivering proper tidal volumes with a face mask is difficult. Mask leakage, airway blockage, and poor chest expansion have been reported.[9-11] Ventilation is commonly initiated with a face mask, followed by endotracheal intubation in the event of a failure of face-mask ventilation or a need for prolonged ventilatory support. Endotracheal intubation is the most difficult skill in neonatal resuscitation, and a study showed a success rate of 24% among residents, 78% among fellows, and 86% among consultants.[12]

International guidelines have suggested the use of the laryngeal mask airway (LMA) in cases of failure of positive-pressure ventilation with the use of a face mask during resuscitation of neonates (gestational age of ≥34 weeks, birth weight of ≥2000 g, or both) or if intubation is unsuccessful or not feasible.[13,14] Studies suggest that effective positive-pressure ventilation can be performed safely with the LMA in most neonates (range, 95 to 99%) and thus reduce the need for intubation.[15-18]

Most neonates with asphyxia in low-income countries receive no advanced airway management,[5] so shifting the use of the LMA to nondoctors could improve outcomes. The effectiveness and safety of the LMA as compared with the face mask have been identified as important knowledge gaps.[13,19] In the Neonatal Supraglottic Airway (NeoSupra) trial, we wanted to test the hypothesis that the LMA would be superior to the face mask with respect to mortality and morbidity among neonates with asphyxia when used as a primary device for neonatal resuscitation by midwives in a low-income country.

METHODS

TRIAL OVERSIGHT

Our trial was an investigator-initiated, single-site, randomized, phase 3, open-label, superiority, controlled trial involving neonates who needed positive-pressure ventilation at birth in two parallel groups: resuscitation with an LMA (i-gel, size 1, Intersurgical)[20] or with a face mask (round-shaped, silicone, size 1, Laerdal Medical). The trial was conducted at the Mulago National Referral Hospital in Kampala, Uganda, where practitioners assist in approximately 25,000 deliveries annually. Treatments that were available in the neonatal intensive care unit (NICU) included the use of supplemental oxygen and nasal continuous positive airway pressure; mechanical ventilators and continuous monitoring were not available.

The trial protocol has been published previously.[21] The protocol and statistical analysis plan are available with the full text of this article at NEJM.org. The protocol was approved by the Uganda National Council for Science and Technology and the Regional Committee for Medical and Health Research Ethics in Norway. The manufacturers of the laryngeal mask airway and the face mask did not provide support for the trial and were not involved its design or conduct or in the writing of the manuscript. The sponsors (the Research Council of Norway and the Center for Intervention Science in Maternal and Child Health) had no influence on the design or conduct of the trial and were not involved in data collection or analysis, in the writing of the manuscript, or in the decision to submit it for publication. There were no agreements concerning confidentiality of the data between the sponsors and the authors or their institutions.

A two-tier procedure for consent was used because the trial involved the care of unexpectedly critically ill neonates. Mothers entering the labor ward received brief oral information about the trial and provided oral consent. Mothers whose neonates were found to be eligible were approached for deferred written consent for continuing participation.

An independent data monitoring committee operated according to the procedures used by

the DAMOCLES (Data Monitoring Committees: Lessons, Ethics, Statistics) Study Group.[22] A prespecified interim analysis that was performed in January 2019 allowed the trial to be continued. The trial was conducted in accordance with the principles of the Declaration of Helsinki. The first, second, sixth, tenth, and last authors assume responsibility for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

PARTICIPANTS

Neonates were eligible for inclusion in the trial if they were born in the hospital; had an estimated gestational age of at least 34 weeks, an estimated birth weight of at least 2000 g, or both; and required positive-pressure ventilation at birth. Neonates with major malformations (incompatible with sustained life or affecting the airways) and stillbirths were excluded.

On a daily basis, investigators and trained research assistants consecutively recruited neonates around the clock until the required sample size was reached. Among stillborn neonates (those born with no heart rate and no breathing efforts), fresh stillborn neonates (those without maceration) received at least 10 minutes of ventilation, and stillborn neonates with maceration grade 0 or grade I ("parboiled" reddened skin or skin slippage and peeling) received at least 1 minute of ventilation.[23] Enrolled neonates and their mothers were tagged with a trial identification number on a bracelet.

TRIAL PROCEDURES

Day-by-day cluster randomization was performed for practical reasons; the randomization procedure was prepared by an independent statistician with the use of randomly selected block sizes of four to eight. The assignments remained concealed in opaque, sealed, and dated envelopes, pending the actual date of randomization. The device that was not assigned for the day was available in a sealed box. Midwives were instructed to continue ventilation with the device of the day for 3 minutes and, if ventilation was inadequate, to reposition the LMA or reapply the face mask before a switch to the other device was considered. The decision to switch was based on recommendations from the International Liaison Committee on Resuscitation (ILCOR).[24] A report that specified the reason for switching was filed in every case.

Before the initiation of the trial, all the midwives who were involved in neonatal resuscitation (approximately 200 persons) participated in a 1-day training session based on the second edition of the Helping Babies Breathe (HBB) curriculum, including practice with face-mask ventilation, with an additional module for using the LMA in a mannequin (SimNewB, Laerdal Medical).[25] Two pediatricians who were trained in use of the LMA conducted the training, facilitated by local HBB instructors. Three successful LMA insertions in the mannequins as shown by effective ventilation were required. Repeated HBB and on-site training were given throughout the trial to new providers to correctly recognize the need for positive-pressure ventilation and to support the management of resuscitation, LMA and face-mask use, and adherence to the protocol.

The severity of hypoxic–ischemic encephalopathy was assessed according to the Thompson score, a validated clinical and prognostic tool for hypoxic–ischemic encephalopathy that is used in settings where sophisticated technology is unavailable.[26,27] Scoring is based on nine items including muscle tone, level of consciousness, clinically apparent seizures, posture, the presence of primitive reflexes (Moro, grasp, and suck), respiratory pattern, and fontanel tension; scores ranges from 0 to 22 (with 0 indicating normal, 1 to 10 mild hypoxic–ischemic encephalopathy, 11 to 14 moderate hypoxic–ischemic encephalopathy, and 15 to 22 severe hypoxic–ischemic encephalopathy) (Table S3 in the Supplementary Appendix, available at NEJM.org).[28] Research assistants who extracted data from clinical records and observed each resuscitation were aware of the trial-group assignments, and the data monitoring committee had access to information about trial-group assignments during the interim analysis and the assessment of serious adverse events and adverse events. NICU physicians who assessed outcomes and the statistician who analyzed the data were unaware of the trial-group assignments.

INTERVENTIONS

HBB principles of the Golden Minute were applied to all the neonates in need of positive-pressure ventilation, including drying, stimula-

tion, and assessment.[25,29] A research assistant started a stopwatch at the time of birth. Any infant who was not breathing after the initial steps had the umbilical cord cut and was moved to the resuscitation area for initiation of positive-pressure ventilation. Inflations were administered with ambient air with a 240-ml silicone self-inflating bag and a pressure-relief valve limit at 35 to 40 cm of water (NeoNatalie Resuscitator, Laerdal Medical). All the neonates with a 5-minute Apgar score of less than 7 and persisting respiratory distress or signs of hypoxic–ischemic encephalopathy were transferred to the NICU. Advanced resuscitation (endotracheal intubation, chest compressions, or both) was initiated if a physician was available. Resuscitations were continuously monitored by research assistants and video-recorded with the use of an HD 1080P Black Box AI-IP018 camera (Shenzhen Aishine Electronics), and the recordings were reviewed daily by trial physicians.

OUTCOMES

The primary outcome was a composite of death within 7 days or admission to the NICU with moderate-to-severe hypoxic–ischemic encephalopathy (Thompson score, ≥11) at day 1 to 5 during hospitalization.[28] The secondary outcomes were the safety of the LMA in the hands of midwives, based on clinical and video observations; the need for advanced resuscitation; early neonatal death (within 7 days of life); very early neonatal death (within 24 hours of life); admission to the NICU with moderate-to-severe hypoxic–ischemic encephalopathy at day 1 to 5 during hospitalization; admission to the NICU with mild-to-severe hypoxic–ischemic encephalopathy (Thompson score ≥7) at day 1 to 5 during hospitalization; and any hospital admission during the first 7 days of life.[30] Recorded adverse events included predefined intervention-related adverse events and serious adverse events, as well as other adverse events and serious adverse events.

STATISTICAL ANALYSIS

A relative between-group difference of 25% in the primary outcome measure was considered to be clinically relevant for changing clinical practice. A sample size of 954 neonates was required for a 90% chance of detecting an absolute difference of 10 percentage points in the primary outcome (30% in the LMA group vs. 40% in the face-mask group) at a two-sided significance level of 5%. The sample size was increased to 1150 to account for day-by-day cluster randomization, under the assumption of an intraclass correlation coefficient of 0.10 and an average daily enrollment of 3 neonates.

The statistical analysis was performed on an intention-to-treat basis. Our protocol also specified a per-protocol analysis and a crossover-adjusted intention-to-treat analysis; however, because crossover between the groups (i.e., switch to the other device) occurred for safety reasons at the discretion of the provider and was likely to be associated with poorer outcomes, we decided before unblinding not to perform these analyses.

Categorical data were recorded as frequency and percentage. Continuous data were recorded as median and interquartile range. The statistical analysis included both unadjusted and adjusted analyses. Outcome measures were compared between the groups with the use of the chi-square test or Fisher's exact test (unadjusted analysis). Generalized mixed-effects models were used to estimate the effect of the treatment on outcome measures, with adjustment for clusters (random effect) and unbalanced neonate characteristics (adjusted analysis). Effect sizes were reported as relative risk with 95% confidence interval.

Missing data were very rare; hence, the main analysis was based on cases with complete data (available in 99.2% of the neonates). A post hoc sensitivity analysis (in which neonates with missing data were counted as having had a primary outcome event in the LMA group and as not having had such an event in the face-mask group) was also performed.

All tests were two-sided, and a P value of less than 0.05 was considered to indicate statistical significance. Data were analyzed with the use of R software, version 3.5 (R Foundation for Statistical Computing).[31]

RESULTS

CHARACTERISTICS OF THE NEONATES

From May 8, 2018, through August 12, 2019, we determined that of the 16,791 neonates who

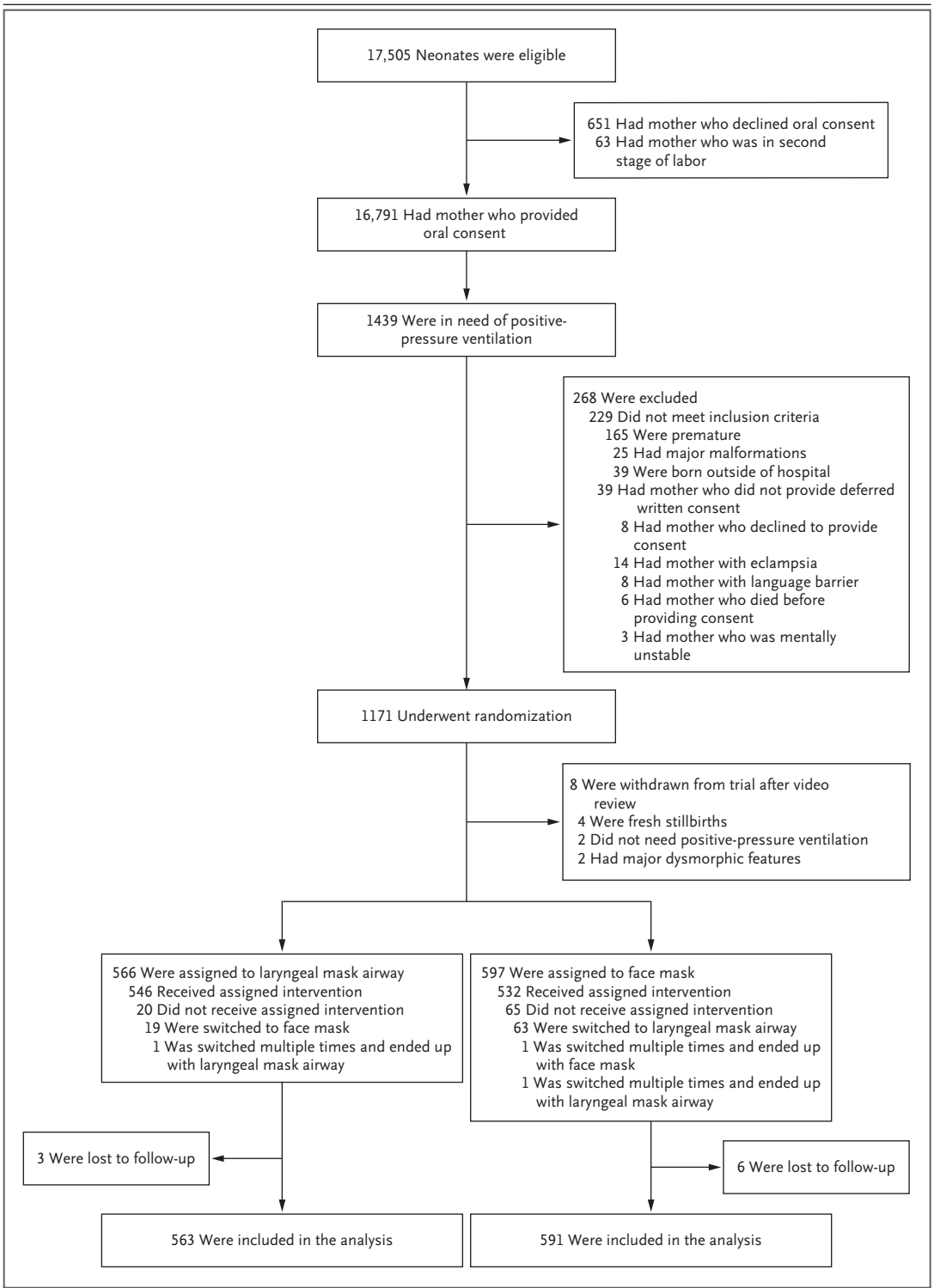

Figure 1. Enrollment and Randomization of the Participants.

were eligible to participate in the trial and for whom the mother had provided oral consent, 1439 (8.6%) needed positive-pressure ventilation, and 1171 who fulfilled the inclusion criteria underwent randomization (Fig. 1). After video review, 8 neonates who did not meet the inclusion criteria were excluded, and 1163 (717 male and 446 female neonates; median birth weight, 3100 g) were assigned to either the LMA group (566 neonates) or the face-mask group (597 neonates). The two groups were well-balanced with respect to all baseline characteristics except for sex (Table 1); sex was thus included as a covariate in the adjusted analyses. Nine neonates were lost to follow-up, so 1154 neonates (563 in the LMA group and 591 in the face-mask group) were included in the primary analysis.

Crossover to the other device occurred in 20 of 566 neonates (3.5%) in the LMA group and 65 of 597 neonates (10.9%) in the face-mask group (relative risk, 0.32; 95% confidence interval [CI], 0.20 to 0.53); after the use of the initial device, these crossovers occurred after a median duration of 11 minutes (interquartile range, 4 to 26) in the LMA group and 8 minutes (interquartile range, 6 to 11) in the face-mask group. The most common reasons for crossover were lack of or poor chest movement (44 of 85 [52%]) and lack of or poor heart-rate improvement (35 of 85 [41%]) (Table S1).

Table 1. Characteristics of the Neonates and Pregnancies at Baseline.*

Characteristic	Laryngeal Mask Airway (N=566)	Face Mask (N=597)
Median maternal age (IQR) — yr	24 (21–29)	23 (20–28)
≥1 Antenatal visit — no. (%)	563 (99.5)	588 (98.5)
Primiparous — no. (%)	255 (45.1)	268 (44.9)
Amniotic fluid — no. (%)		
Clear	205 (36.2)	216 (36.2)
Meconium-stained, foul-smelling, or both	342 (60.4)	370 (62.0)
Unknown	19 (3.4)	11 (1.8)
Type of delivery — no. (%)		
Vaginal delivery	249 (44.0)	268 (44.9)
Vaginal delivery by vacuum extraction	18 (3.2)	28 (4.7)
Cesarean section	299 (52.8)	301 (50.4)
Male sex — no. (%)	368 (65.0)	349 (58.5)
Multiple birth — no. (%)	37 (6.5)	30 (5.0)
Median birth weight (IQR) — g	3100 (2800–3400)	3100 (2800–3400)
Median time to resuscitation table (IQR) — sec†	47 (28–97)	52 (29–103)
Median Apgar score (IQR)		
At 1 min	3 (2–4)	3 (2–4)
At 5 min	5 (4–6)	5 (4–6)
At 10 min	7 (6–8)	7 (6–8)

* IQR denotes interquartile range.
† Data on time to the resuscitation table were unavailable for one participant assigned to the laryngeal mask airway and two participants assigned to the face mask.

PRIMARY OUTCOME

A primary outcome event occurred in 154 of 563 neonates (27.4%) in the LMA group (122 deaths and 32 cases of moderate-to-severe hypoxic–ischemic encephalopathy) and 144 of 591 (24.4%) in the face-mask group (109 deaths and 35 cases of moderate-to-severe hypoxic–ischemic encephalopathy) (unadjusted relative risk, 1.12; 95% CI, 0.92 to 1.37; adjusted relative risk, 1.16; 95% CI, 0.90 to 1.51) (Table 2 and Table S2). Results of the sensitivity analysis (in which neonates with missing data were counted as having had a primary outcome event in the LMA group and as not having had such an event in the face-mask group) were similar to the findings in the primary analysis (unadjusted relative risk, 1.15; 95% CI, 0.95 to 1.40; adjusted relative risk, 1.20; 95% CI, 0.92 to 1.55).

SECONDARY OUTCOMES AND SAFETY

There was no evidence that any of the secondary outcome measures differed substantially between the two groups (Table 2). Early neonatal deaths (within 7 days) according to treatment sequence (including a switch to the other device and advanced resuscitation) are shown in Figure S1. Among the neonates who underwent crossover, the percentage who had a primary outcome event was 90% (18 of 20) for those starting with the LMA who switched to the face mask, as compared with 68% (44 of 65) for those starting with the face mask who switched to the LMA (relative risk, 1.33; 95% CI, 1.06 to 1.66) (Table S1). Few predefined potentially intervention-

Table 2. Unadjusted and Adjusted Analyses of the Primary and Secondary Outcomes.*

Outcome	Laryngeal Mask Airway	Face Mask	Unadjusted Analysis		Adjusted Analysis†	
			Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
	no./total no. (%)					
Primary outcome	154/563 (27.4)	144/591 (24.4)	1.12 (0.92–1.37)	0.27	1.16 (0.90–1.51)	0.26
Secondary outcomes						
Advanced resuscitation	39/566 (6.9)	39/597 (6.5)	1.05 (0.69–1.62)	—	1.08 (0.63–1.86)	—
Early neonatal death	122/563 (21.7)	109/591 (18.4)	1.17 (0.93–1.48)	—	1.21 (0.90–1.63)	—
Very early neonatal death	89/563 (15.8)	85/591 (14.4)	1.10 (0.84–1.45)	—	1.13 (0.80–1.58)	—
Admission to NICU with Thompson score of ≥11 at days 1–5 during hospitalization	53/474 (11.2)	51/504 (10.1)	1.13 (0.89–1.70)	—	1.27 (0.84–1.93)	—
Admission to NICU with Thompson score of ≥7 at days 1–5 during hospitalization	100/474 (21.1)	115/504 (22.8)	0.97 (0.78–1.21)	—	0.94 (0.70–1.27)	—
Any hospital admission during first 7 days of life	496/519 (95.6)	530/554 (95.7)	0.99 (0.97–1.02)	—	—	—

* The primary outcome was a composite of early neonatal death (within 7 days) or admission to the neonatal intensive care unit (NICU) with moderate-to-severe hypoxic–ischemic encephalopathy (Thompson score, ≥11) at day 1 to 5 during hospitalization. Thompson scores range from 0 to 22, with higher scores indicating greater severity of hypoxic–ischemic encephalopathy. Very early neonatal death was defined as death within 24 hours.

† The analysis was adjusted for cluster and sex. Adjusted analysis for hospital admission was not performed owing to the small number of participants not admitted to the hospital. In a sensitivity analysis of the primary outcome measure (in which participants with missing data were counted as having had a primary outcome event in the laryngeal-mask-airway group and as not having had such an event in the face-mask group), the unadjusted relative risk was 1.15 (95% CI, 0.95 to 1.40).

related adverse events occurred overall, with no significant difference between the two groups (Table 3).

DISCUSSION

This randomized trial of the effectiveness and safety of the LMA in neonatal resuscitation conducted by midwives in a low-income country showed the LMA to be safe in the hands of midwives but to confer no benefit over the face mask with respect to the composite of early neonatal death or moderate-to-severe hypoxic–ischemic encephalopathy. The cuffless LMA that was used in this trial is designed to provide an efficient seal to the larynx without the inflatable cuff used in conventional LMAs. Positioning is easy, and the risk of tissue compression or dislodgement is low.[16,32] Thus, the device provides a useful alternative to the face mask and endotracheal intubation, especially in settings where skills in performing positive-pressure ventilation or intubation are insufficient.[5] A study in Uganda that used mannequins showed that after a brief training, midwives could easily insert this LMA, and it was more effective than the face mask in establishing positive-pressure ventilation in a mannequin.[33] A phase 2, randomized, controlled trial at the same site showed that midwives could perform resuscitation in neonates effectively and safely with the cuffless LMA.[34]

Data from previous trials have suggested that LMA use results in shorter ventilation times than use of a face mask and may reduce the hypoxic–ischemic insult.[15,16,34] Resuscitations in these studies were conducted by physicians or supervised midwives. In the present trial, midwives used the LMA unsupervised, and the insertion technique could have been suboptimal, which may have affected the effectiveness of the LMA. The observation of a higher likelihood of treatment failure in the face-mask group than in the LMA group and the suggestion that rescue with the LMA might result in better outcomes than rescue with the face mask in the current trial are consistent with the results from previous trials.[17,18,34] The frequency of failure with the face mask appeared to be lower than in our pilot trial; this may reflect improved skills regarding face-mask ventilation among midwives because of additional and repeated training during the trial.

Although our trial did not show superiority of the LMA over the face mask and the trial was not designed to assess noninferiority, the findings appear consistent with current ILCOR recommendations.[24] Thus, our findings suggest that the LMA can be safely used as an alternative device during newborn resuscitation, including when performed by trained midwives.

Most studies show that 3 to 6% of neonates require positive-pressure ventilation at birth. In our trial, 8.6% needed positive-pressure ventilation, and a large proportion of neonates were severely compromised; 61.2% had meconium-stained or foul-smelling amniotic fluid, and very early neonatal death occurred in 15.1%. This percentage is considerably higher than those in previous reports[35,36] and could reflect the hospital demographics, with large numbers of late referrals and mainly neonates with severe asphyxia; previous reports that showed benefits of the LMA largely involved neonates who had mild asphyxia.[15,17,18,35] Differences between our trial population and those in previous trials are a potential explanation for the discrepancy between our results and the results of previous trials.

This trial extends our knowledge about LMA use among severely compromised neonates in a low-income setting — where more neonatal deaths occur than in higher-income settings and advanced resuscitation is often not available — by having a larger number of participants, relevant outcomes, rigorous methods (including video documentation), and a strong adherence to trial-group assignments with minimal loss to follow-up or exclusions. The trial also has some limitations. It was a single-site trial in a high-volume hospital, where fetal heart-rate monitoring was not routinely available, and there was inconsistent capacity of staff to provide advanced resuscitation; thus, the findings may not be generalizable to better-resourced settings. For trial conduct, we had additional staff on site. Crossovers, which occurred for safety reasons, were more frequent in the face-mask group than in the LMA group (10.9% vs. 3.5%), and this might have improved the outcomes of the neonates initially treated with the face mask. The neurologic outcome (hypoxic–ischemic encephalopathy) was based on the Thompson score without advanced examinations (e.g., electroencephalography or neuroimaging). In addition, it was an open-label trial, but hard outcomes were used and outcome assessors were not aware of the trial-group assignments.

Table 3. Adverse Events and Severe Adverse Events at Resuscitation and in the Hospital within 7 Days.*

Event	Laryngeal Mask Airway	Face Mask	P Value*
	no./total no. (%)		
Adverse events			
At resuscitation			
Blood from mouth†	2/566 (0.4)	2/597 (0.3)	0.99
Vomiting†	0/566	0/597	—
Other adverse event	0/566	0/597	—
In the hospital within 7 days			
Bleeding†	1/472 (0.2)	1/497 (0.2)	0.99
Localized infection†	1/472 (0.2)	1/497 (0.2)	0.99
Severe adverse events			
At resuscitation			
Laryngospasm†	0/566	0/597	—
In the hospital within 7 days			
Stridor†	0/472	0/497	—
Airway obstruction†	0/472	0/497	—
Visible trauma†	0/472	0/497	—
Sepsis†‡	1/472 (0.2)	0/497	0.49
Omphalitis	1/472 (0.2)	0/497	0.49

* P values are unadjusted. Adjusted analysis was not performed owing to the small number of occurrences of the outcomes.
† This event was prespecified in the trial protocol.
‡ Sepsis was based on clinical report. Antibiotics were routinely prescribed to neonates with asphyxia, and there was limited diagnostic testing capacity to evaluate for sepsis.

In our trial, the LMA was safe in the hands of midwives but did not result in a lower incidence of early neonatal death or moderate-to-severe hypoxic–ischemic encephalopathy than face-mask ventilation among neonates with asphyxia.

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

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

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